SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-098732- -00000-0000

Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 613

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** Inhibidores del Virus de la Hepatitis C

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** Bristol- Myers Squibb Company

DOMICILIO Princeton, New Jersey, Estados Unidos

74. **APODERADO** Alvaro Correa Ordoñez

22. **BOGOTÁ, D.C.,** Agosto 4, 2011

(FORMA P-10)

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-098732- -00000-0000

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Act. 411 PRESENTACION Folios: 613

Industria y Comercio
SUPERINTENDENCIA

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

(1) **SOLICITUD DE :**

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[X]	Capítulo I.	[ ]	Capítulo II.

(2) **SOLICITANTE** (71)	Nombre: **BRISTOL-MYERS SQUIBB COMPANY** Dirección: Route 206 and Province Line Road Princeton, New Jersey 08543-4000, U.S.A. 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@bakermckenzie.com	**IDENTIFICACION** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número 79.143.366 Usaquén TP 20281
(4) **INVENTOR (ES)** (72)	Nombre: ROMINE, Jeffrey Lee; ST. LAURENT, Denis R.; BELEMA, Makonen; SNYDER, Lawrence B.; HAMANN, Lawrence G.; KADOW, John F.; KAPUR, Jayne; GOOD, Andrew C.; LOPEZ, Omar D.; LAVOIE, Rico; BENDER, John A. Dirección: 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); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); Novartis Institutes for BioMedical Research 250 Massachusetts Avenue Cambridge, Massachusetts 02139 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); 4046 Merrick Street Houston, Texas 77025 (US); 52 High Hill Road Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); 16 Avenue de Bercy Candiac , Québec J5R 4B7 (CA); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US) Nacionalidad o Domicilio: Estados unidos de América y Canadá (Respectivamente)	

(5) **PCT (85)**

Solicitud Internacional No.	PCT/US2010/023582	Fecha	09-02-2010
Publicación Internacional No.	WO2010/096302	Fecha	26-08-2010

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

(7) **Clasificación Internacional (51)** C07D 403/14; A61K 31/4184; A61K 31/4178; A61P 31/12; C07D 413/14

(8) **Prioridad**	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	17-02-2009	61/153,186
SI [X] NO [ ]	US	08-02-2010	12/701,919

(9) **Comprobante de pago No.** 11-0070224 – 11-0070179 – 11-0064161 – 11-0070117 – 11-0053509 **Fecha** 01-07-11 / 19-07-11 / 02-06-11

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

(11) **FIGURA CARATERISTICA**

(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

RECIBO DE PAGO

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0070224

Bogotá D.C., Julio 19 de 2011 - 16:46.48

RECIBIDO DE : BAKER & CKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325068763	18/07/2011	82.912.000.00

*** Conceptos Pagados ***

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

SON: **QUINIENTOS SETE TA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al pediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-098732- -00000-0000
Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
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2011/012 4

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0070179

Bogotá D.C., Julio 19 de 2011 - 16:46:48

RECIBIDO DE : BAKER & CKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	NCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANC DE BOGOTA	062754387	325068763	18/07/2011	82.912.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE A SOLICITUDES	ERVACIONES 12 MARCAS Y LEMAS COMERCIALES	304.000.00	304.000.00
				$304.000.00

SON: TRESCIENTOS CU TRO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al pediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-098732- -00000-0000
Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 613

2011/011 5

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

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SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0064161

Bogotá D.C., Julio 01 de 2011 - 14:27:42

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325065742	01/07/2011	95.266.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACION NO N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODOFICA	118.000.00	118.000.00
				$118.000.00

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

Responsable: _____
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Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-098732- -00000-0000
Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
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Act. 411 PRESENTACION Folios: 613

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0070117

Bogotá D.C., Julio 19 de 2011 - 16:46:48

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325068763	18/07/2011	82.012.000.00

*** Conceptos Pagados ***

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

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

Responsable: ******

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-098732- -00000-0000

Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
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Act. 411 PRESENTACION Folios: 613

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0053509

Bogotá D.C., Junio 02 de 2011 - 16:48:12

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	403018361	02/06/2011	62.500.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	10.000.00	10.000.00
				$10.000.00

ON: **DIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-098732- -00000-0000

Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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EXTRACTOS

Industria y Comercio
SUPERINTENDENCIA

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

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

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

(51) Clasificación Internacional: C07D 403/14; A61K 31/4184; A61K 31/4178; A61P 31/12; C07D 413/14

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

(72) Inventor(es): ROMINE, Jeffrey Lee; ST. LAURENT, Denis R.; BELEMA, Makonen; SNYDER, Lawrence B.; HAMANN, Lawrence G.; KADOW, John F.; KAPUR, Jayne; GOOD, Andrew C.; LOPEZ, Omar D.; LAVOIE, Rico; BENDER, John A.

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/153,186	17-02-2009	US
	12/701,919	08-02-2010	US

(85) Fecha inicio fase nacional: 17-09-2011

(86) Datos relativos a la presentación de la solicitud PCT
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No. de solicitud: PCT/US2010/023582

(87) Publicación internacional
Fecha: 26-08-2010
N° publicación: WO2010/096302

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

Industria y Comercio
SUPERINTENDENCIA

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

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 31/4184; A61K 31/4178; A61P 31/12; C07D 413/14

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(72) Inventor(es) ROMINE, Jeffrey Lee; ST. LAURENT, Denis R.; BELEMA, Makonen; SNYDER, Lawrence B.; HAMANN, Lawrence G.; KADOW, John F.; KAPUR, Jayne; GOOD, Andrew C.; LOPEZ, Omar D.; LAVOIE, Rico; BENDER, John A.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/153,186	17-02-2009	US
	12/701,919	08-02-2010	US

(85) Fecha límite inicio fase nacional: 17-09-2011
(86) Datos relativos a la presentación de la solic. PCT
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(87) Publicación internacional:
Fecha: 26-08-2010
No. Publicación: WO2010/096302

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

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

CONTINUA AL RESPALDO

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

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad	(31) *No.*	32) *Fecha*	(33) *País*
	61/153,186	17-02-2009	US
	12/701,919	08-02-2010	US

(51) Int Cl: C07D 403/14; A61K 31/4184; A61K 31/4178; A61P 31/12; C07D 413/14

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

(72) Inventor(es) ROMINE, Jeffrey Lee; ST. LAURENT, Denis R.; BELEMA, Makonen; SNYDER, Lawrence B.; HAMANN, Lawrence G.; KADOW, John F.; KAPUR, Jayne; GOOD, Andrew C.; LOPEZ, Omar D.; LAVOIE, Rico; BENDER, John A.

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

(85) Fecha limite inicio fase nacional: 17-09-2011

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 09-02-2010
No. de solicitud PCT/US2010/023582

(87) Publicación internacional
Fecha: 26-08-2010
N° publicación: WO2010/096302

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

RESUMEN: La presente exposición se refiere a compuestos, composiciones y procedimientos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se exponen composiciones farmacéuticas que contienen tales compuestos y procedimientos para usar estos compuestos en el tratamiento de infección por VHC.


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

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12/701,919 8 February 2010 (08.02.2010) US

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

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ROMINE, Jeffrey Lee** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US). **ST. LAURENT, Denis R.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US). **BELEMA, Makonen** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **SNYDER, Lawrence B.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HAMANN, Lawrence G.** [US/US]; c/o Novartis Institutes for BioMedical Research, 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **KADOW, John F.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **KAPUR, Jayne** [GB/US]; 4046 Merrick Street, Houston, Texas 77025 (US). **GOOD, Andrew C.** [US/US]; 52 High Hill Road, Wallingford, Connecticut 06492 (US). **LOPEZ, Omar D.** [AR/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **LAVOIE, Rico** [CA/CA]; 16 Avenue de Bercy, Candiac, Québec J5R 4B7 (CA). **BENDER, John A.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US).

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

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

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

Published:

— *with international search report (Art. 21(3))*

WO 2010/096302 A1

(54) Title: HEPATITIS C VIRUS INHIBITORS

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

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 61/153,186 filed February 17, 2009.

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.

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

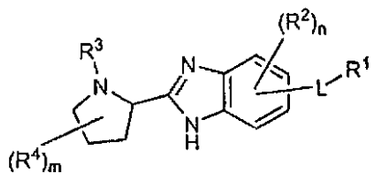
HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain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

Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome due to the high error rate of the encoded RNA dependent RNA polymerase which lacks a proof-reading capability. At least six major genotypes have been characterized, and more than 50 subtypes have been described with distribution worldwide. The clinical significance of the genetic heterogeneity of HCV has demonstrated a propensity for mutations to arise during monotherapy treatment, thus additional treatment options for use are desired. The possible modulator effect of genotypes on pathogenesis and therapy remains elusive.

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

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in the following references: S. L. Tan, et al., *Virology*, 284:1-12 (2001); K.-J. Park, et al., *J. Biol. Chem.*, 30711-30718 (2003); T. L. Tellinghuisen, et al., *Nature*, **435**, 374 (2005); R. A. Love, et al., *J. Virol*, **83**, 4395 (2009); N. Appel, et al., *J. Biol. Chem.*, **281**, 9833 (2006); L. Huang, *J. Biol. Chem.*, **280**, 36417 (2005); C. Rice, et al., WO2006093867.

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

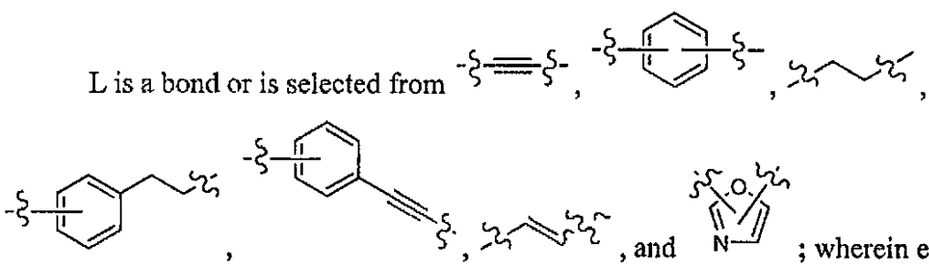


(I),

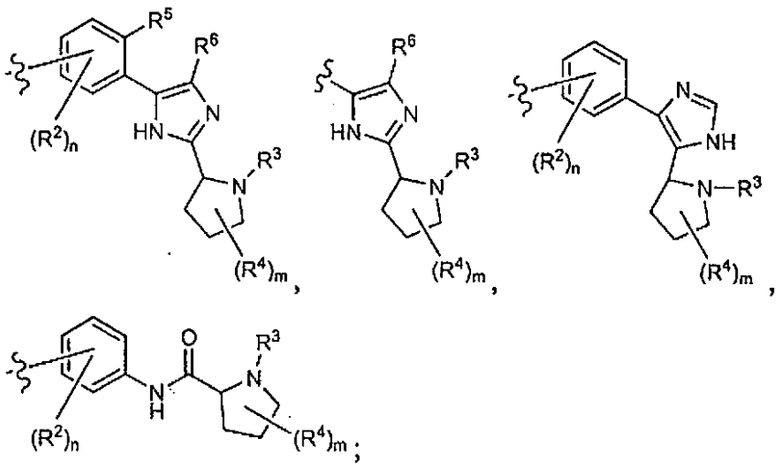
or a pharmaceutically acceptable salt thereof, wherein

each m is independently 0 or 1;

each n is independently 0 or 1;

L is a bond or is selected from  ; wherein each group is drawn with its left end attached to the benzimidazole and its right end attached to R^1;

R^1 is selected from



each R^2 is independently selected from alkyl and halo;

each R^3 is independently selected from hydrogen and $-C(O)R^7$;

R^4 is alkyl;

R^5 and R^6 are independently selected from hydrogen, alkyl, cyanoalkyl, and halo, or

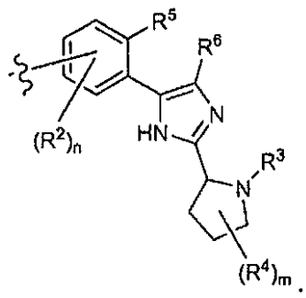
R^5 and R^6, together with the carbon atoms to which they are attached, form a six- or seven-membered ring optionally containing one heteroatom selected from nitrogen and oxygen and optionally containing an additional double bond; and

each R^7 is independently selected from alkoxy, alkyl, arylalkoxy, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl.

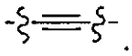
In a first embodiment of the first aspect the present disclosure provides a

compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein L is a bond.

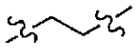
In a second embodiment of the first aspect R^1 is



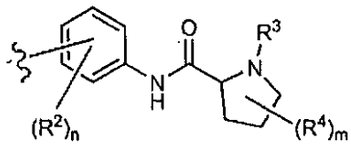
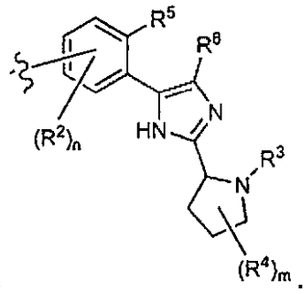
In a third embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein L is



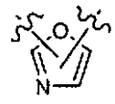
In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein L is

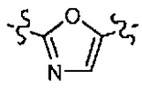
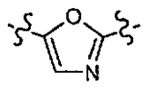


In a fifth embodiment R^1 is selected from

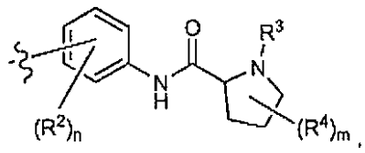
 and 

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

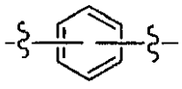


In a seventh embodiment L is selected from  and  .

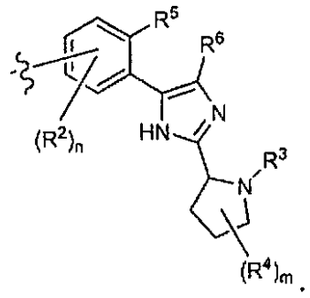
In an eighth embodiment R^1 is

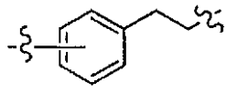
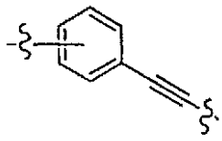


In a ninth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein L is

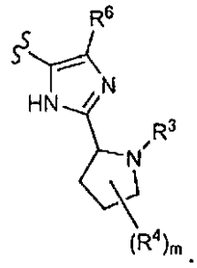


In a tenth embodiment R^1 is

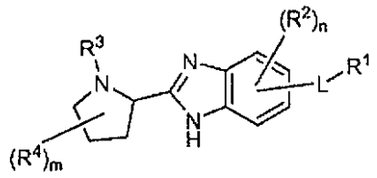


In an eleventh embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein L is wherein L is selected from  and  ; wherein each group is drawn with its left end attached to the benzimidazole and its right end attached to R^1.

In a twelfth embodiment R^1 is



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



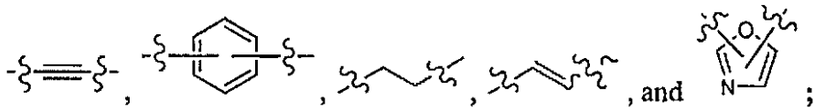
(II),

or a pharmaceutically acceptable salt thereof, wherein

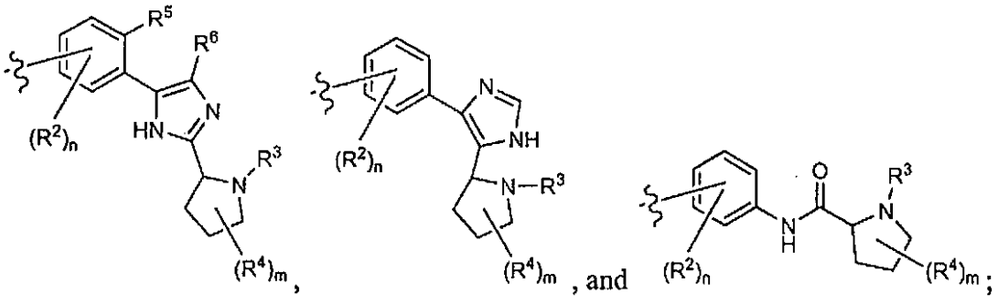
each m is independently 0 or 1;

each n is independently 0 or 1;

L is a bond or is selected from



R^1 is selected from



each R^2 is independently selected from alkyl and halo;

each R^3 is independently selected from hydrogen and $-C(O)R^7$;

R^4 is alkyl;

R^5 and R^6 are independently hydrogen or halo, or

R^5 and R^6, together with the carbon atoms to which they are attached, form a six- or seven-membered ring optionally containing one heteroatom selected from nitrogen and oxygen and optionally containing an additional double bond; and

each R^7 is independently selected from alkoxy, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl.

In a third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a first embodiment of the third aspect the composition further comprises one or two additional compounds having anti-HCV activity. In a second embodiment of the third aspect at least one of the additional

compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and one or two additional compounds having anti-HCV activity, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

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

In a fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the fourth aspect the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment of the fourth aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the fourth aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or two additional compounds

having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and 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.

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^2 and R^4) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when n is 2, each of the two R^2 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:

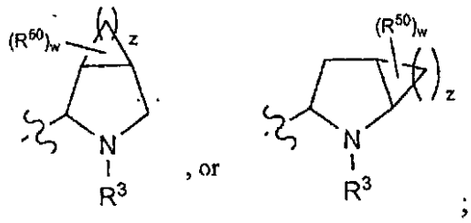
As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

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

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

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when m is 1 and R^4 is alkyl, the alkyl can optionally form a fused three- or four-membered ring with an adjacent carbon atom to provide one of the structures shown below:



;

where z is 1 or 2, 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 "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 "arylalkoxy," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through an oxygen atom.

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, $-NR^xR^y$, and oxo.

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

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

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, cyclobutyl, 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)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups.

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

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

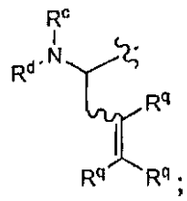
The terms "halo" and "halogen," as used herein, refer to F, Br, Cl, or I.

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]oct-2-yl, and 2-azabicyclo[2.2.2]oct-3-yl. 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, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, quinolinyl, thiazolyl, thienyl, and thiomorpholinyl. 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 "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 "$-NR^cR^d$," 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, cycloalkyloxycarbonyl, 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



wherein R^c and R^d are as defined herein and each R^q is independently hydrogen or C_{1-3} alkyl.

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, arylalkoxycarbonyl, carboxy, cycloalkyl, 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 "$-NR^eR^f$," 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 "$-NR^xR^y$," 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.

Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products

followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

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

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

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

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication

commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, 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 Debio-025		Cyclophilin inhibitors	Novartis Debiopharm
Zadaxin		Immunomodulator	SciClone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-Tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	Antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV inhibitor	Achillion / Gilead

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Pyrazolopyrimidine compounds and salts From WO 2005/047288 May 26, 2005	Antiviral	HCV inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	Monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA / Eli Lilly and Co., Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B replicase inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B replicase inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B replicase inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B replicase inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B replicase inhibitor	Gilead
PSI 6130	Antiviral	NS5B replicase inhibitor	Roche
R1626	Antiviral	NS5B replicase inhibitor	Roche

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
2'C Methyl adenosine	Antiviral	NS5B replicase inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	Ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	Ribavirin	Schering-Plough Corporation, Kenilworth, NJ
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

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

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
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
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	Antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	Caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B replicase inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
Boceprevir	Antiviral	Serine protease inhibitor	Schering-Plough
TMS-435	Antiviral	Serine protease inhibitor	Tibotec BVBA, Mechelen, Belgium

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
BI-201335	Antiviral	Serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
MK-7009	Antiviral	Serine protease inhibitor	Merck
PF-00868554	Antiviral	Replicase inhibitor	Pfizer
ANA598	Antiviral	Non-Nucleoside NS5B polymerase inhibitor	Anadys Pharmaceuticals, Inc., San Diego, CA, USA
IDX375	Antiviral	Non-Nucleoside replicase inhibitor	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	NS5B polymerase inhibitor	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada
PSI-7851	Antiviral	Nucleoside polymerase inhibitor	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	NS5B polymerase inhibitor	ViroChem Pharma
VCH-916	Antiviral	NS5B polymerase inhibitor	ViroChem Pharma
GS-9190	Antiviral	NS5B polymerase inhibitor	Gilead
Peg-interferon lamda	Antiviral	Interferon	ZymoGenetics / Bristol-Myers Squibb

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

The compounds of this disclosure may also be used to treat or prevent viral

contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

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

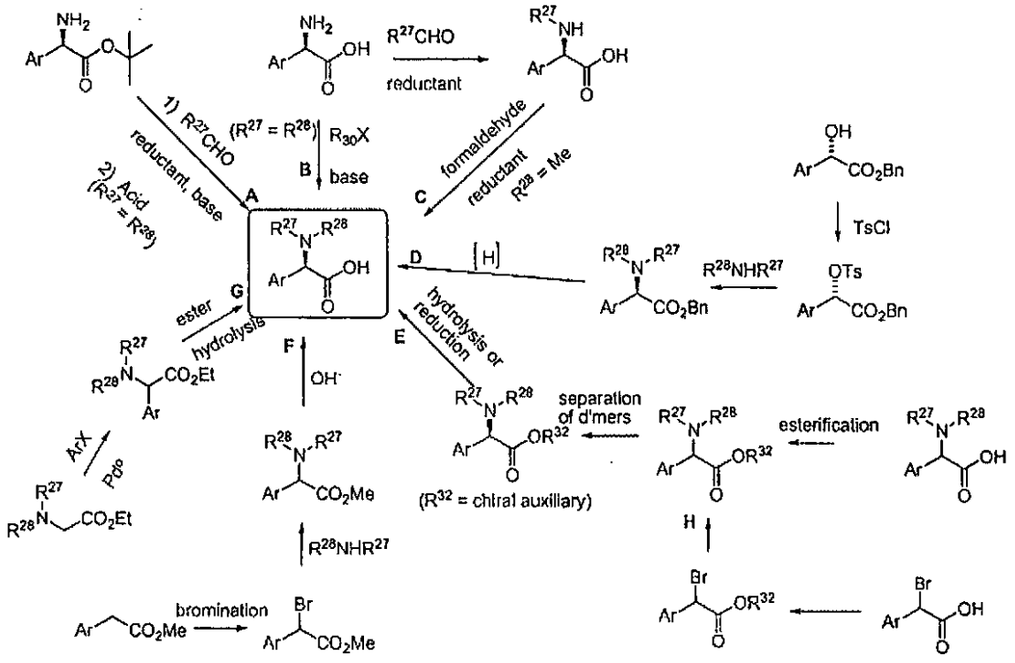
The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: RT for room temperature or retention time (context will dictate); R_t for retention time; min for minutes; TFA for trifluoroacetic acid; DMSO for dimethylsulfoxide; Ph for phenyl; THF for tetrahydrofuran; Et_2O for diethyl ether; Boc or BOC for tert-butoxycarbonyl; MeOH for methanol; Et for ethyl; DMF for dimethylformamide; h or hr for hours; TBDPS for tert-butyldiphenylsilyl; DMAP for N,N-dimethylaminopyridine; TBAF for tetrabutylammonium fluoride; Et_3N or TEA for triethylamine; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; Ac for acetate or acetyl; SEM for 2-trimethylsilylethoxymethoxy; EDC or EDCI for 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; EEDQ for N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; MeOH for methanol; i-Bu for isobutyl; Bn for benzyl; and Me for methyl.

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: Substituted Phenylglycine Derivatives

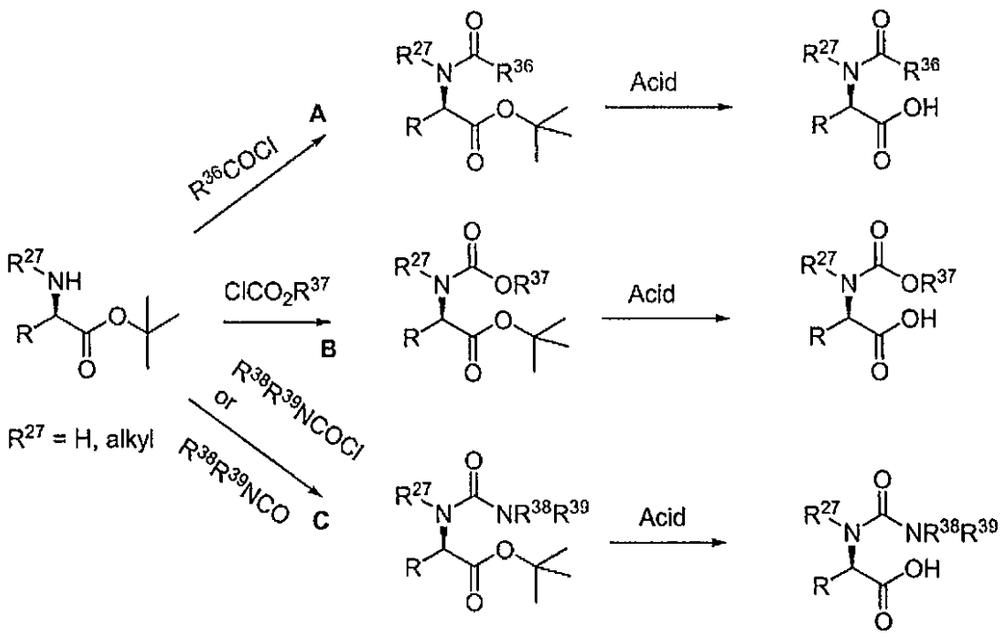
Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished 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.



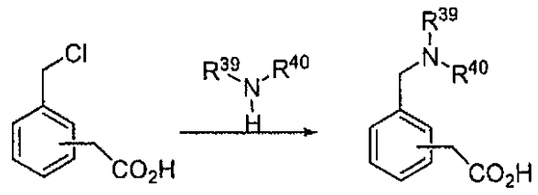
Scheme 2: Acylated Amino Acid Derivatives

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 3

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



Synthesis of common caps

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

Cond.-MS-W1

Column	= XTERRA 3.0 X 50 mm S7
Start %B	= 0
Final %B	= 100
Gradient time	= 2 min
Stop time	= 3 min

Flow Rate	= 5 mL/min
Wavelength	= 220 nm
Solvent A	= 0.1% TFA in 10% methanol/90%H_2O
Solvent B	= 0.1% TFA in 90% methanol/10% H_2O

Cond.-MS-W2

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

Cond.-MS-W5

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

Cond.-D1

Column	= XTERRA C18 3.0 X 50 mm S7
Start %B	= 0
Final %B	= 100
Gradient time	= 3 min
Stop time	= 4 min

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

Cond.-D2

Column	= Phenomenex-Luna 4.6 X 50 mm S10
Start %B	= 0
Final %B	= 100
Gradient time	= 3 min
Stop time	= 4 min
Flow Rate	= 4 mL/min
Wavelength	= 220 nm
Solvent A	= 0.1% TFA in 10% methanol/90%H_2O
Solvent B	= 0.1% TFA in 90% methanol/10% H_2O

Cond.-MD1

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

Cond.-M3

Column	= XTERRA C18 3.0 X 50 mm S7
Start %B	= 0
Final %B	= 40
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 OL1

Column = Phenomenex-Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 4 min
Stop time = 5 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition OL2

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

Condition I

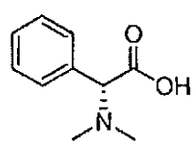
Column = Phenomenex-Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min

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

Condition II
Column = Phenomenex-Luna 4.6 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

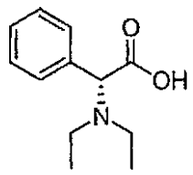
Condition III
Column = XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cap-1



A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of Cap-1 as a white needle (4.0 g). Optical rotation: -117.1° [c=9.95 mg/mL in H_2O; λ=589 nm]. ^{1}H NMR (DMSO-d_6, δ=2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. I): RT=0.25; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

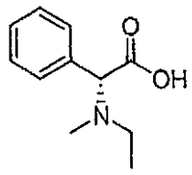
Cap-2



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

Cap-3

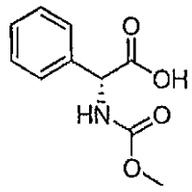


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under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

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

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

Cap-4

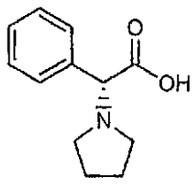


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-*tert*-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component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

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

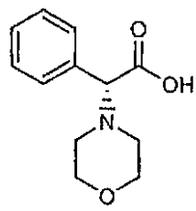
index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

Cap-5



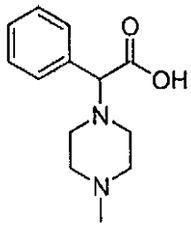
A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated *in vacuo*. The residue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

Cap-6



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

Cap-7



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

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

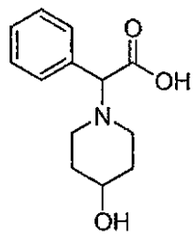
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *in vacuo*. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the enantiomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min,

and monitored at 220 nm. Enantiomer-1 (1.474 g) and enantiomer-2 (2.2149 g) were retrieved as viscous oil. ^{1}H NMR ($CDCl_3$, δ=7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, *J*=12.5, 1H), 5.08 (d, *J*=12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT=2.10 (Cond. III); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

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

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

Cap-8

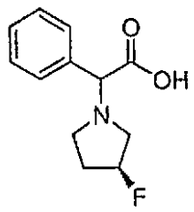


8a: enantiomer-1
8b: enantiomer-2

The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following

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

Cap-9

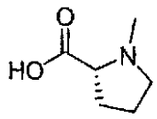


9a: diastereomer-1
9b: diastereomer-2

The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective 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. I); >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; Cap-9b (diastereomer-2): ^{1}H NMR (DMSO-d_6, δ=2.5, 400 MHz) 7.43-7.21

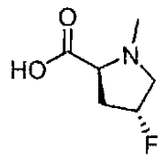
(m, 5H), 5.19 (d of m, J=55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT=0.44 (Cond. I); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

Cap-10



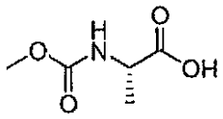
To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide Cap-10 as an off-white solid (2.15 g). ^{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. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

Cap-11



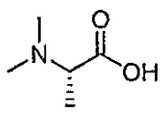
A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®)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

Cap-12 (same as cap 52)



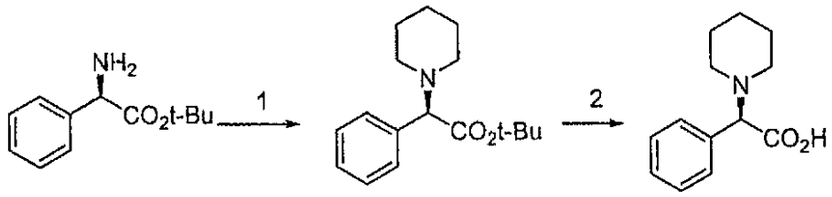
L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was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

Cap-13



A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide the HCl salt of Cap-13 as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, *J*=7.4, 1H), 2.76 (s, 6H), 1.46 (d, *J*=7.3, 3H).

Cap-14



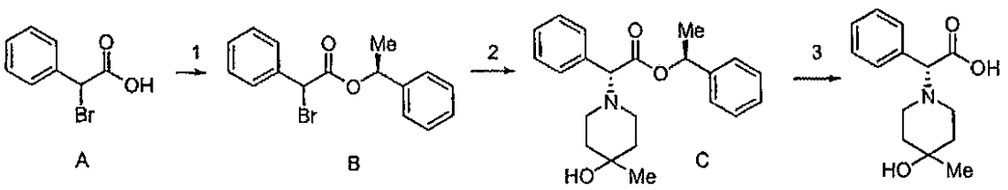
Cap-14

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

Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492

g, 78%) as a light yellow solid. ^{1}H NMR (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-15



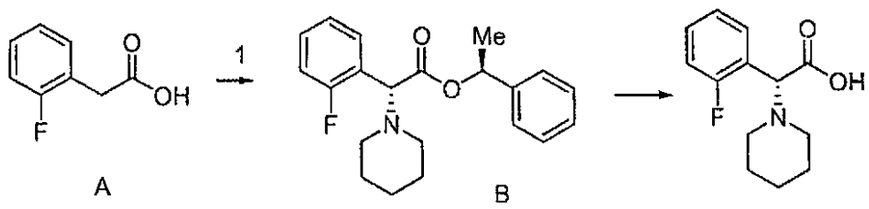
Step 1: (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred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

Step 2: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ^{1}H NMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q,

J=6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, J=6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: ^{1}H NMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, J=6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, J=6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, J=6.8 Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

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

Cap-16



(R)-Cap-16

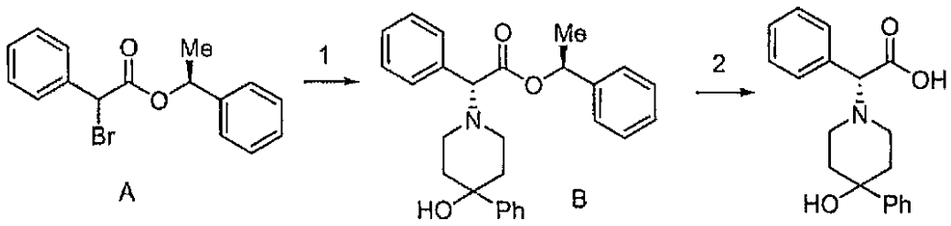
Step 1: (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O-ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil

(8.38 g, 92%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.32-7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, *J*=6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, *J*=6.5 Hz, 3H).

Step 2: (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate: To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0 °C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of CBr_4 (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH_4Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated *in vacuo* and the residue was purified by silica gel chromatography (Biotage/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ^{1}H NMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (ddd, *J*=9.4, 7.6, 1.8 Hz, 1H), 7.33 – 7.40 (m, 1), 7.23 – 7.23 (m, 4H), 7.02 – 7.23 (m, 4H), 5.86 (q, *J*=6.6 Hz, 1H), 4.45 (s, 1H), 2.39 – 2.45 (m, 4H), 1.52 – 1.58 (m, 4H), 1.40 – 1.42 (m, 1H), 1.38 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

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

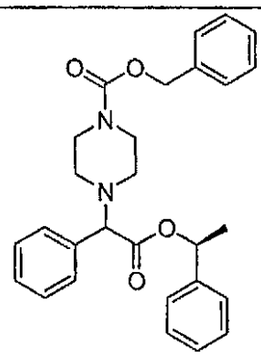
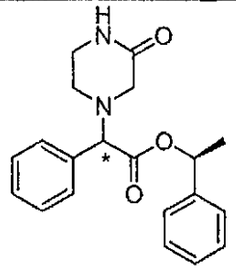
Cap-17

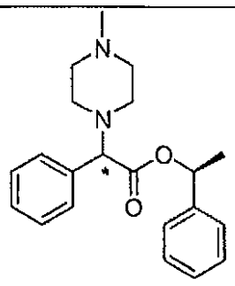
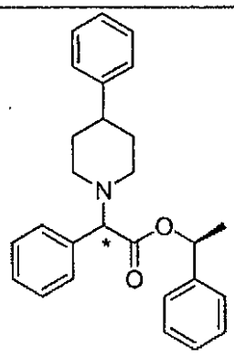


(R)-Cap-17

Step 1: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ^1H NMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30 x 250mm; 20% ethanol in CO_2 at 35 °C), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. (S,R)-isomer: ^1H NMR (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, *J*=11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, *J*=11.1, 2.5 Hz, 1H), 2.20 (dt, *J*=12.1, 4.6 Hz, 1H), 2.10 (dt, *J*=12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, *J*=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; (S,S)-isomer: H^1NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, *J*=11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, *J*=11.1, 2.5 Hz, 1H), 2.25 (dt, *J*=12.1, 4.6 Hz, 1H), 2.12 (dt, *J*=12.1, 4.6 Hz, 1H), 1.73 (dd, *J*=13.6, 3.0 Hz, 1H), 1.64 (dd, *J*=13.6, 3.0 Hz, 1H), 1.40 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

The following esters were prepared in similar fashion:

Intermediate-17a		Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.36 (d, *J*=6.41 Hz, 3H) 2.23-2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, *J*=6.71 Hz, 1H) 7.15-7.52 (m, 15H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; Found: 459.44 $(M+H)^+$. Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27-2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19-7.27 (m, 3H) 7.27-7.44 (m, 10H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; Found: 459.44 $(M+H)^+$.
Intermediate -17b		Diasteromer 1: RT=11.76 minutes (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16 Found: 339.39 $(M+H)^+$; Diastereomer 2:

		RT=10.05 minutes (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16; Found: 339.39 $(M+H)^+$.
Intermediate -17c		Diastereomer 1: T_R=4.55 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20 Found: 339.45 $(M+H)^+$; Diastereomer 2: T_R=6.00 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20 Found: 339.45 $(M+H)^+$.
Intermediate -17d		Diastereomer 1: RT=7.19 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT=9.76 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22 Found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time

Condition I

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

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

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored @ 220 nm

Injection: 1.0 mg/3mL methanol

Condition II

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

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

Temp: 35 °C

Pressure: 150 bar

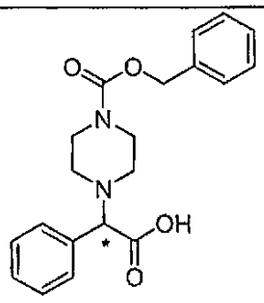
Flow rate: 2.0 mL/min.

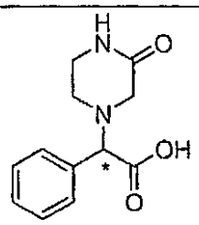
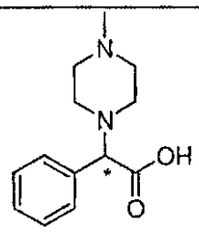
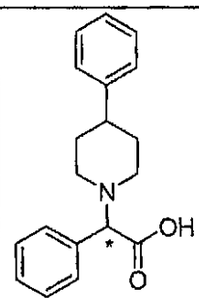
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

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

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

Cap-17a		RT=2.21 (Cond'n II); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.20-2.35 (m, 2H) 2.34-2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06-7.53 (m, 10H). LCMS: Anal.

		Calcd. for: $C_{20}H_{22}N_2O_4$ 354.16; Found: 355.38 $(M+H)^+$.
Cap-17b		RT=0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.10; Found: 235.22 $(M+H)^+$.
Cap-17c		RT=0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.14; Found: 235.31 $(M+H)^+$.
Cap-17d		RT=2.21 (Cond'n I); LCMS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.16; Found: 296.33 $(M+H)^+$.

LCMS Conditions for determining retention time

Condition I

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B=0

Fianl % B=100

Gradient Time=4 min

Flow Rate=4 mL/min

Wavelength=220

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

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

Condition II

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B=0

Fianl % B=100

Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

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

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

Condition III

Column: Phenomenex 10μ 3.0 X 50 mm

Start % B=0

Fianl % B=100

Gradient Time=2 min

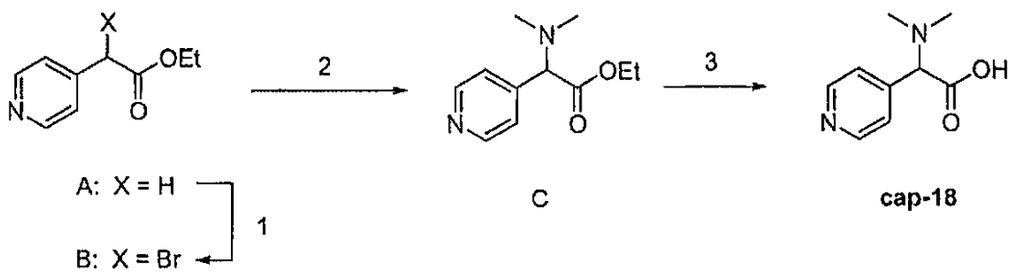
Flow Rate=4 mL/min

Wavelength=220

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

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

Cap-18



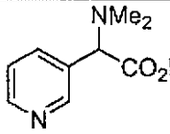
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr_4 (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours.

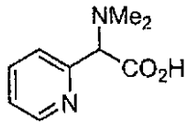
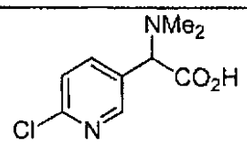
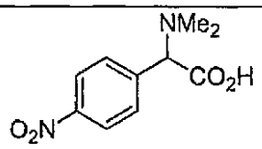
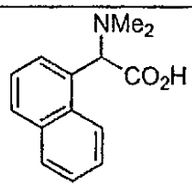
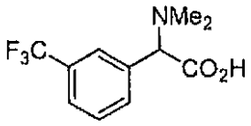
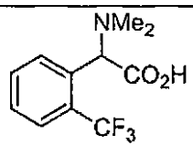
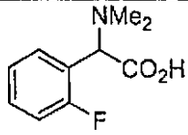
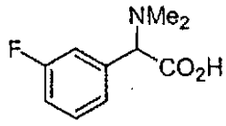
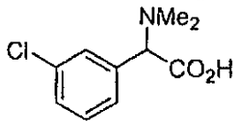
The reaction mixture was then quenched with sat. aq. NH_4Cl and the phases were separated. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J*=4.6, 1.8 Hz, 2H), 7.45 (dd, *J*=4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, *J*=7.1 Hz, 3H). LCMS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

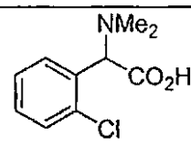
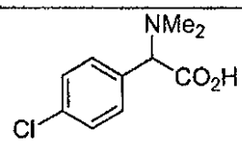
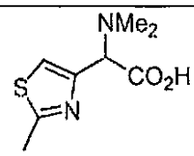
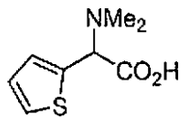
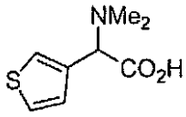
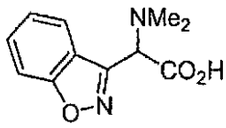
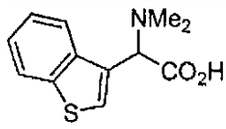
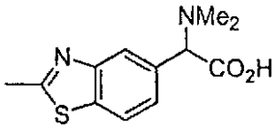
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography)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

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

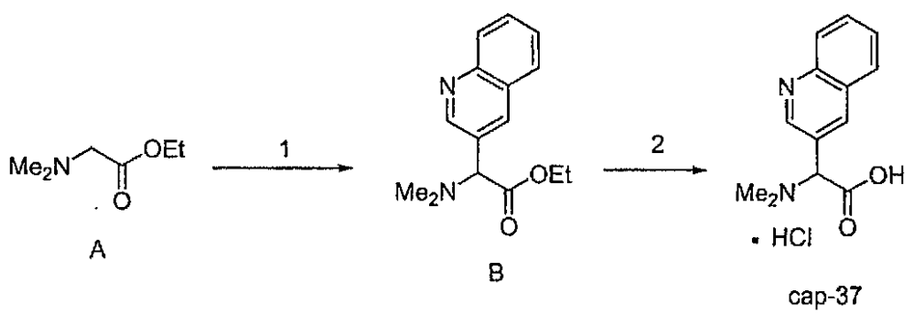
The following examples were prepared in similar fashion using the method described above;

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.

Cap-20		LCMS: no ionization. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (d, *J*=4.3 Hz, 1H), 7.84 (app t, *J*=5.3 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.37 (app t, *J*=5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.
Cap-22		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-23		LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 229; found: 230 $(M+H)^+$.
Cap-24		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.

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

Cap-37

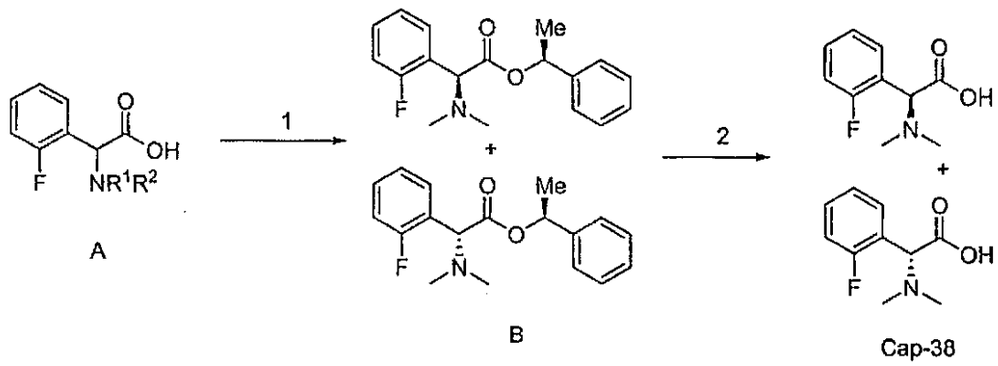


A B cap-37

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

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

Cap-38



Step 1; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a

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

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

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

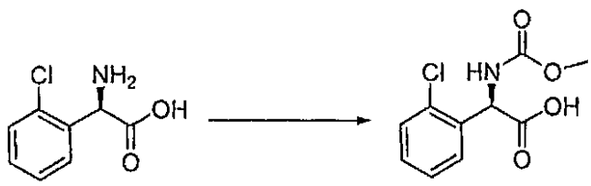
Cap-39



cap-39

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

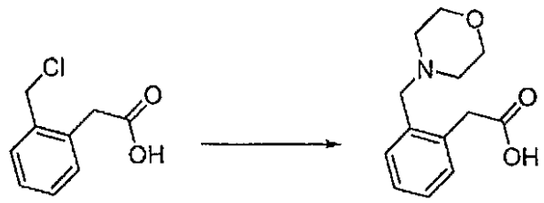
Cap-40



cap-40

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

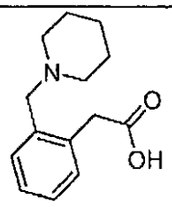
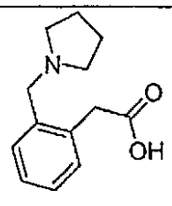
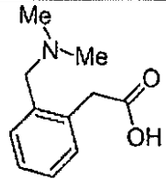
Cap-41

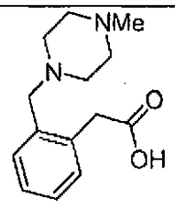


cap-41

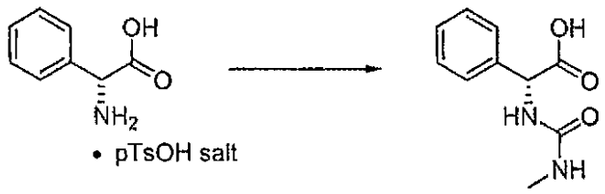
To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/ 0-10% methanol-CH_2Cl_2) to give the title compound 2-(2-(Morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

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

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

Cap-45		LCMS: Anal. Calcd. for $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$.

Cap-45a

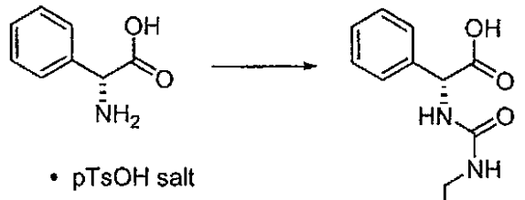


• pTsOH salt

Cap-45a

HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used without further purification. ^1H 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

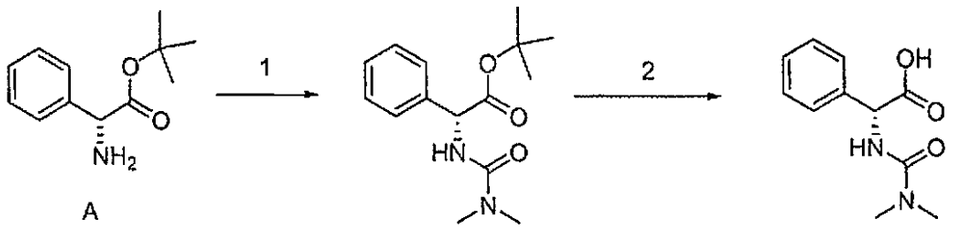


• pTsOH salt

cap-46

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

Cap-47

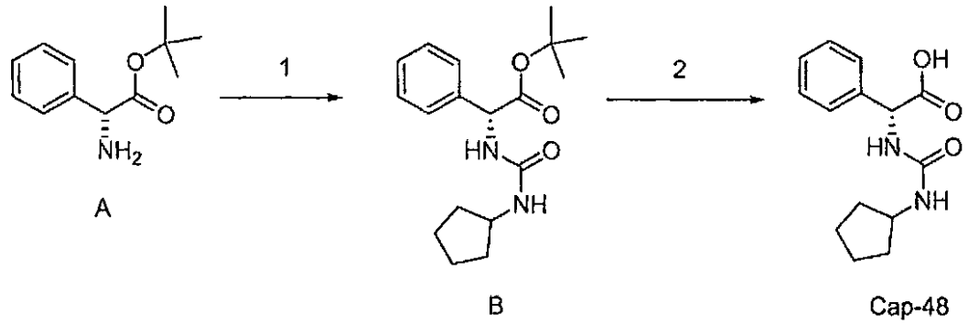


Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at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

Step 2; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of ((R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH_2Cl_2 (250 mL) was added TFA (15 mL) dropwise and the resulting solution was

stirred at rt for 3 hours. The desired compound was then precipitated out of solution with a mixture of EtOAC:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28 (t, *J*=7.17 Hz, 1H) 7.33 (t, *J*=7.32 Hz, 2H) 7.38-7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=0.75 min, 93% homogeneity index.

Cap-48



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

Step 2; (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH_2Cl_2 (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17-1.35 (m, 2H) 1.42-1.52 (m, 2H) 1.53-1.64 (m, 2H) 1.67-1.80 (m, 2H) 3.75-3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24-7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for $C_{14}H_{18}N_2O_3$: 262.31; found: 263.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=1.24 min, 100% homogeneity index.

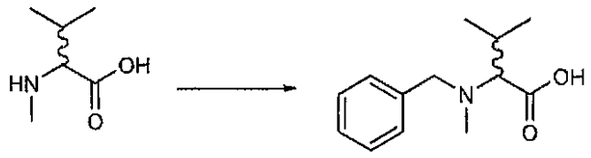
Cap-49



cap-49

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

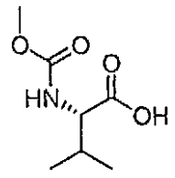
Cap-50



Cap-50

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

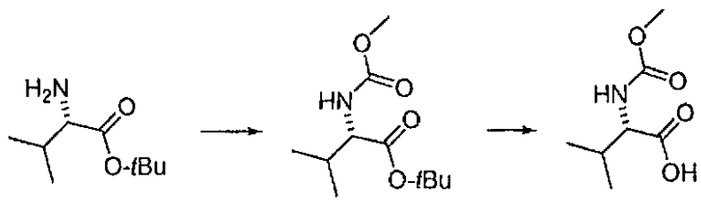
Cap-51



Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added dropwise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford Cap-51 as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, 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 51 (alternate route).



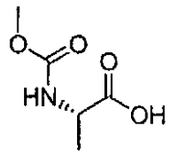
DIEA (137.5 mL, 0.766 mol) was added to a suspension of (*S*)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride (75.0 g, 0.357 mol) in THF (900 mL), and the mixture was cooled to 0 °C (ice/water bath). Methyl chloroformate (29.0 mL, 0.375 mol) was added dropwise over 45 min, the cooling bath was removed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

Trifluoroacetic acid (343 mL, 4.62 mol) and Et_3SiH (142 mL, 0.887 mol) were added sequentially to a solution of (S)-tert-butyl 2-(methoxycarbonylamino)-3-methylbutanoate (82.0 g, 0.355 mol) in CH_2Cl_2 (675 mL), and the mixture was stirred at ambient temperature for 4 h. The volatile component was removed under diminished pressure and the resultant oil triturated with petroleum ether (600 mL) to afford a white solid, which was filtered and washed with hexanes (500 mL) and petroleum ether (500 mL). Recrystallization from EtOAc/petroleum ether afforded *Cap-51* as white flaky crystals (54.8 g, 88 % yield). MP = 108.5-109.5 °C. ^{1}H NMR

(500 MHz, DMSO-d_6, δ = 2.5 ppm) 12.52 (s, 1 H), 7.31 (d, J = 8.6, 1 H), 3.83 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.07 (m, 1 H), 0.86 (dd, J = 8.9, 7.0, 6 H). ^{13}C NMR (126 MHz, DMSO-d_6, δ = 39.2 ppm) 173.30, 156.94, 59.48, 51.37, 29.52, 19.15, 17.98. LC/MS: $[M+H]^+$ = 176.11. Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 48.17; H, 7.55; N, 7.99. Optical Rotation: $[\alpha]_D$ = -4.16 (12.02 mg/mL; MeOH). Optical purity: >99.5 % ee. Note: the optical purity assessment was made on the methyl ester derivative of *Cap-51*, which was prepared under a standard $TMSCHN_2$ (benzene/MeOH) esterification protocol. HPLC analytical conditions: column, ChiralPak AD-H (4.6 x 250mm, 5μm); solvent, 95% heptane / 5% IPA (isocratic); flow rate, 1 mL/min; temperature, 35 °C; UV monitored at 205 nm.

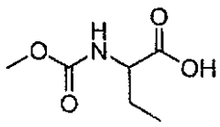
[Note: Cap 51 could also be purchased from Flamm.]

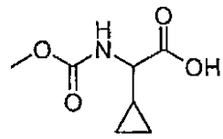
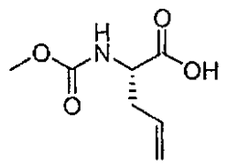
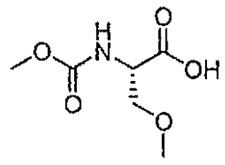
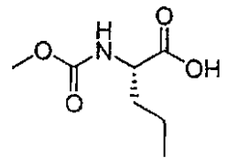
Cap-52 (Same as Cap-12)

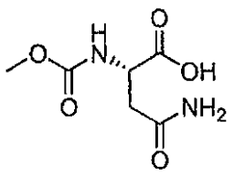
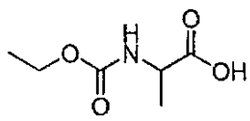
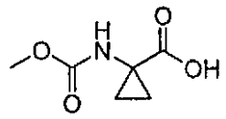
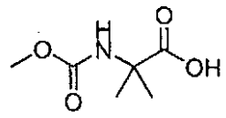


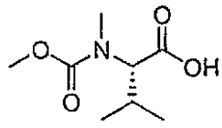
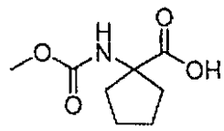
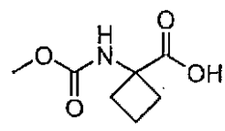
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to afford Cap-52 as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ=2.5 ppm,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

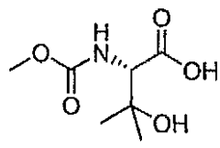
Cap	Structure	Data
Cap-53a: (R) *Cap-53b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, J = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, J = 7.3, 3H). RT =

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

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

Cap-65

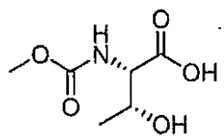


Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-2-amino-3-hydroxy-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was removed and stirring was continued for an additional 3.75 hr. The reaction mixture

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

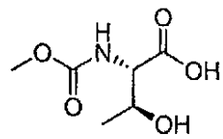
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



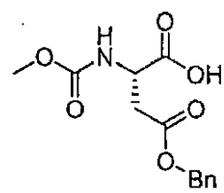
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, J = 8.3, 0.13H), 6.81 (d, J = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, J = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, J = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



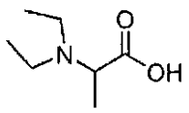
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, J = 8.4, 0.75H), 7.12 (br d, J = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, J = 6.3, 3H). [Note: only the dominant signals of NH were noted].

Cap-68



Methyl chloroformate (0.38 ml, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M $NaHCO_3$ (aq) (9.0 ml, 9.0 mol), L-aspartic acid β-benzyl ester (1.0 g, 4.5 mmol) and Dioxane (9 ml). The reaction mixture was stirred at ambient conditions for 3 hr, and then washed with Ethyl acetate (50 ml, 3x). The aqueous layer was acidified with 12N HCl to a pH ~ 1-2, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford *Cap*-68 as a light yellow oil (1.37g; mass is above theoretical yield, and the product was used without further purification). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, *J* = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, *J* = 12.8, 1H), 5.10 (d, *J* = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 16.2, 5.5, 1H), 2.71 (dd, *J* =16.2, 8.3, 1H). LC (Cond. 2): RT = 1.90 min; LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; found 282.12.

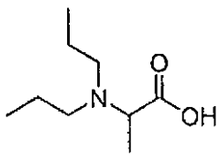
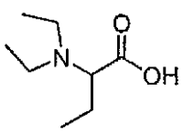
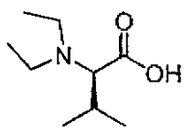
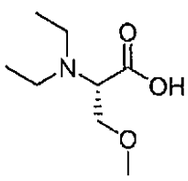
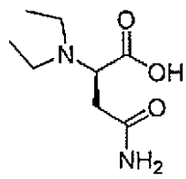
Cap-69a and -69b

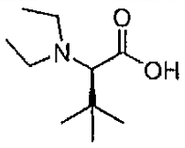


Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

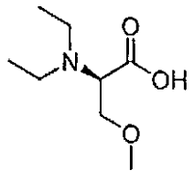
$NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a Dowex® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford *Cap*-69 (2.0 g) as an off-white soft hygroscopic solid. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, *J* = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, *J* = 7.1, 3H), 1.13 (t, *J* = 7.3, 6H).

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

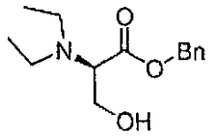
Cap-70a: (R) *Cap-70b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, *J* = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, *J* = 7.3, 3H), 0.85 (t, *J* = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) *Cap-71b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06.
Cap-72		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 6H), 0.91 (d, *J* = 6.5, 3H), 0.85 (d, *J* = 6.5, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15.
Cap-73		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, *J* = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, *J* = 7.2, 6H).
Cap-74		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, *J* = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, *J* = 15.6, 7.0, 1H), 2.36 (dd, *J* = 15.4, 6.3, 1H), 1.09 (t, *J* = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$:

		189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21

Cap-75



Cap-75, step a



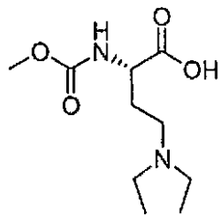
$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC ($MeOH/H_2O$/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min.

Methyl iodide (56 μL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH_3/Methanol. Removal of the volatile component *in vacuo* afforded *Cap*-75, contaminated with (R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

Cap-76

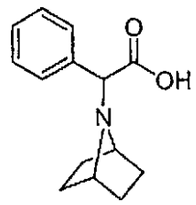


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed *in vacuo*, and the remaining mixture was treated with concentrated HCl until its pH reached ~ 1.0 and then heated for 2 hr at 40 °C. The volatile component was removed *in vacuo*, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed *in vacuo* and the residue was purified with Dowex ® 50WX8-100 ion-exchange resin (column was washed with water and the compound was eluted with dilute NH_4OH, prepared from 18 ml of NH_4OH and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/H_2O, 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued

for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with CH_2Cl_2 (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M NH_3/MeOH) to afford impure *Cap*-76 as an off-white solid (704 mg). ^{1}H NMR (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, J = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, J = 7.3, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; found 233.24.

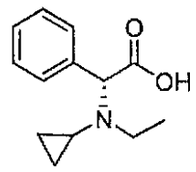
Cap-77a and -77b



Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

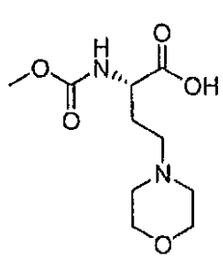
The synthesis of *Cap*-77 was conducted according to the procedure described for *Cap*-7 by using 7-azabicyclo[2.2.1]heptane for the SN_2 displacement step, and by effecting the enantiomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was injected on a chiral HPLC column (Chiracel AD-H column, 30 x 250 mm, 5 um) eluting with 90% CO_2-10% EtOH at 70 mL/min, and a temperature of 35 °C to provide 124.5 mg of enantiomer-1 and 133.8 mg of enantiomer-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap*-7 to provide *Cap*-77: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; found 232.1340.

Cap-78



$NaCNBH_3$ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (*R*)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of *Cap*-3; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40 mmol) in MeOH (10 mL), and the semi-heterogeneous mixture was heated at 50 °C with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and $NaCNBH_3$ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~ pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotervaped. The resulting crude material was taken up in *i*-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated *in vacuo*. About 1/3 of the resultant crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of *Cap*-78 as a colorless viscous oil (353 mg). ^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



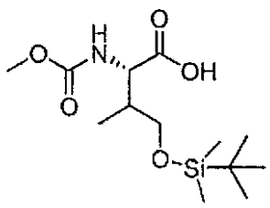
Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of

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). ^{1}H 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). ^{1}H 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 (^{1}H NMR). The stereochemistry of the dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ^{1}H NMR data (DMSO-d_6, 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.

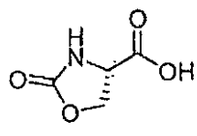
TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a CH_2Cl_2 (3 ml) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture 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

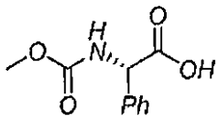


Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

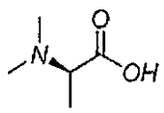
Cap-82 to Cap-85

Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51 or *Cap*-13. The samples exhibited

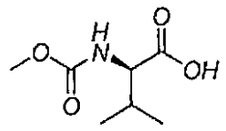
similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively).



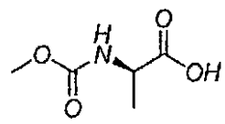
Cap-82



Cap-83

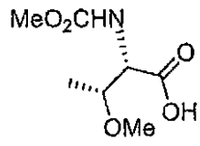


Cap-84



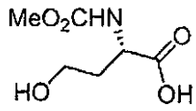
Cap-85

Cap-86



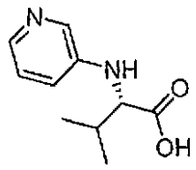
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in CH_2Cl_2 (250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, J = 7.7 Hz, 3H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 $(M-H)^-$.

Cap-87



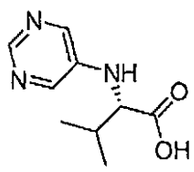
To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated *in vacuo* to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.23 (dd, J = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 – 2.14 (m, 1H), 1.82 – 1.89 (m, 1H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 $(M+H)^+$.

Cap-88



A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2X200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.00 (s, br, 1H), 7.68 – 7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04 – 2.06 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{10}H_{14}N_2O_2$: 194; found: 195 $(M+H)^+$.

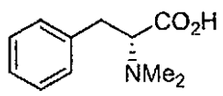
Cap-89



A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and

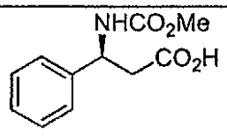
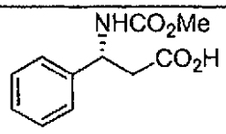
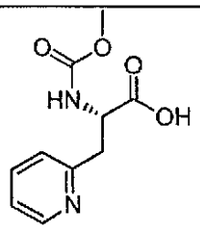
loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, CD_3OD) showed the mixture to contain valine and the purity could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

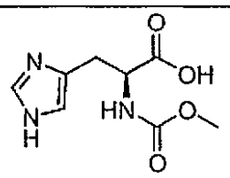
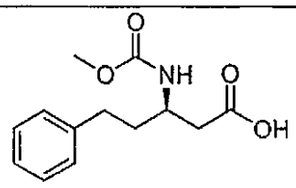
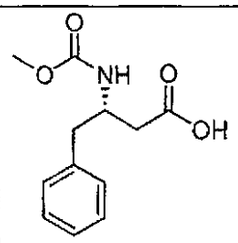
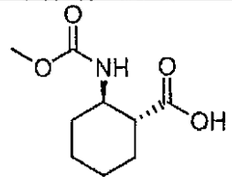
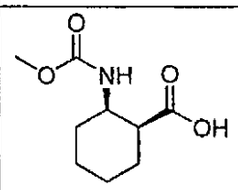
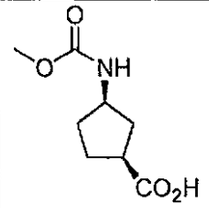
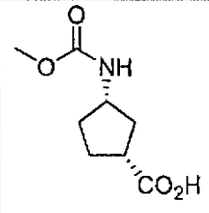
Cap–90

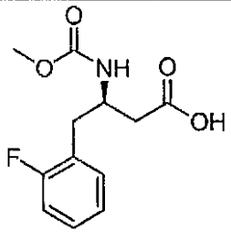
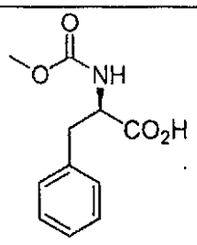
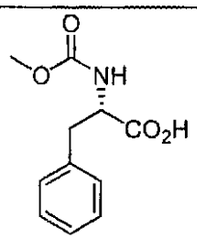
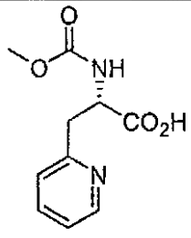
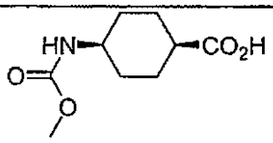
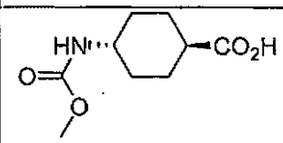


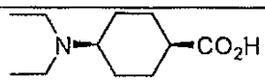
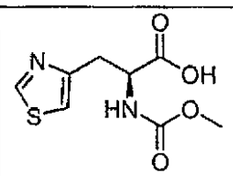
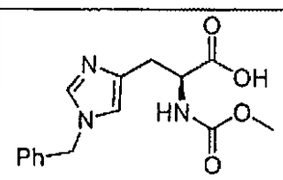
Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

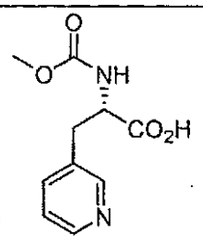
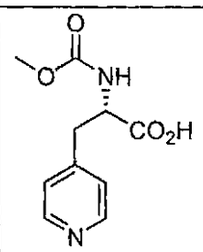
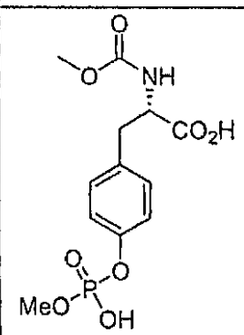
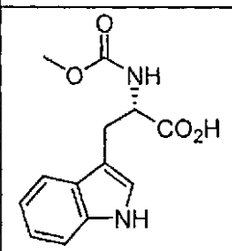
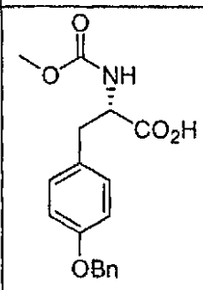
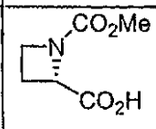
The following caps were prepared according to the method used for preparation of cap 51 unless noted otherwise:

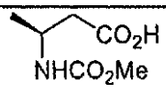
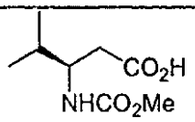
Cap	Structure	LCMS
Cap-91		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-92		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-93		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.

Cap-94		LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.
Cap-95		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 $(M-H)^-$.
Cap-96		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 $(M-H)^-$.
Cap-97		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 200 $(M-H)^-$.
Cap-98		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 $(M+H)^+$.
Cap-99		^{1}HNMR (400 MHz, CD_3OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
Cap-99a		^{1}HNMR (400 MHz, CD_3OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45

		– 1.71 (m, 2H).
Cap-100		LCMS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 $(M+H)^+$.
Cap-101		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 – 3.53 (m, 1H), 2.66 – 2.69 and 2.44 – 2.49 (m, 1H), 1.91 – 2.01 (m, 2H), 1.62 – 1.74 (m, 4H), 1.51 – 1.62 (m, 2H).
Cap-105		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H,

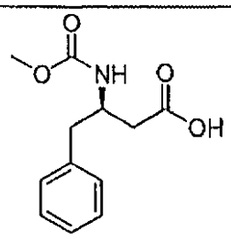
		partially obscured by solvent), 2.37 – 2.41 and 2.16 – 2.23 (m, 1H), 1.94 – 2.01 (m, 4H), 1.43 – 1.53 (m, 2H), 1.17 – 1.29 (m, 2H).
Cap-106	 Prepared from cis-4-aminocyclohexane carboxylic acid and acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX ($MeOH/H_2O/CH_2Cl_2$ wash; 2 N NH_3/MeOH elution) to afford an oil, which was dissolved in CH_3CN/H_2O and lyophilized to afford a tan solid.	^{1}HNMR (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 – 2.31 (m, 2H), 1.79 – 1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H)
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.

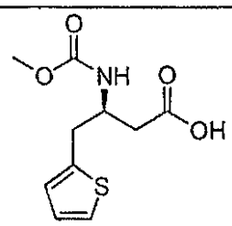
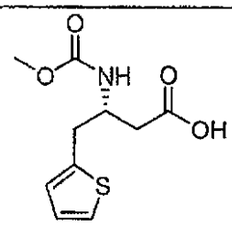
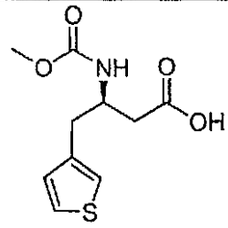
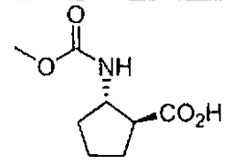
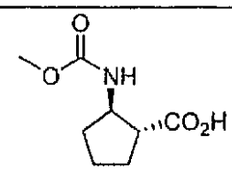
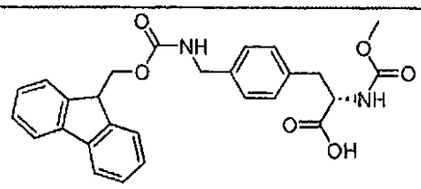
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$.
Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$.
Cap-114		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br,

		2H)
Cap-115		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, J = 5.0 Hz, 2H), 1.28 (d, J = 9.1 Hz, 3H).
Cap-116		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.10 (d, J = 8.6 Hz, 1H), 3.74 – 3.83 (m, 1H), 3.69 (s, 3H), 2.54 – 2.61 (m, 2H), 1.88 (sept, J = 7.0 Hz, 1H), 0.95 (d, J = 7.0 Hz, 6H).

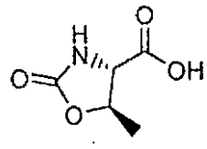
Cap-117 to Cap-123

For the preparation of *Cap*-117 to *Cap*-123 the Boc amino acids were obtained from commercially sources and were deprotected by treatment with 25% TFA in CH_2Cl_2. After complete reaction as judged by LCMS the solvents were removed *in vacuo* and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure described for *Cap*-51.

Cap	Structure	LCMS
Cap-117		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 238 $(M+H)^+$.

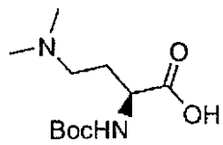
Cap-118		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-119		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-120		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-121		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.06 – 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 and 2.66 (s, br, 1H), 1.86 – 2.10 (m, 3H), 1.64 – 1.76 (m, 2H), 1.44 – 1.53 (m, 1H).
Cap-122		^{1}HNMR profile is similar to that of its enantiomer, Cap-121.
Cap-123		LCMS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$.

Cap-124



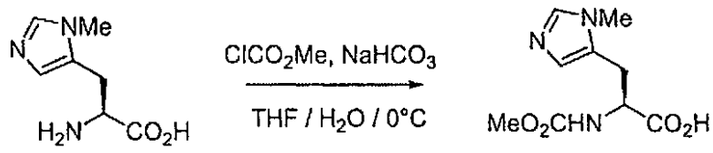
The hydrochloride salt of L-threonine tert-butyl ester was carbamoylated according to the procedure for *Cap*-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless oil which solidified on standing. The aqueous layer was concentrated *in vacuo* and the resulting mixture of product and inorganic salts was triturated with EtOAc-CH_2Cl_2-MeOH (1:1:0.1) and then the organic phase concentrated *in vacuo* to give a colorless oil which was shown by LCMS to be the desired product. Both crops were combined to give 0.52 g of a solid. ^{1}HNMR (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). LCMS: Anal. Calcd. for $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

Cap-125



To a suspension of $Pd(OH)_2$, (20%, 100 mg), aqueous formaldehyde (37% wt, 4 ml), acetic acid, (0.5 mL) in methanol (15 mL) was added (S)-4-amino-2-(tert-butoxycarbonylamino)butanoic acid (1 g, 4.48 mmol). The reaction was purged several times with hydrogen and was stirred overnight with an hydrogen balloon room temp. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®), and the volatile component was removed in vacuo. The resulting crude material was used as is for the next step. LC/MS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

Cap-126

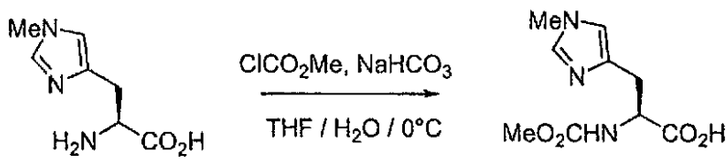


cj-25 *cap-126*

This procedure is a modification of that used to prepare *Cap*-51. To a suspension of 3-methyl-L-histidine (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0°C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 5.20 mmol) and the mixture allowed to stir at 0°C. After stirring for ca. 2h LCMS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2. The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LCMS and ^{1}H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10mL) and H_2O (10mL), cooled to 0°C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LCMS and ^{1}H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification. ^{1}HNMR (400 MHz, CD_3OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, J = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, J = 4.5, 15.6 Hz, 1H, partially obscured by solvent), 3.12 (dd, J = 9.0, 15.6 Hz, 1H).LCMS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228.09 $(M+H)^+$.

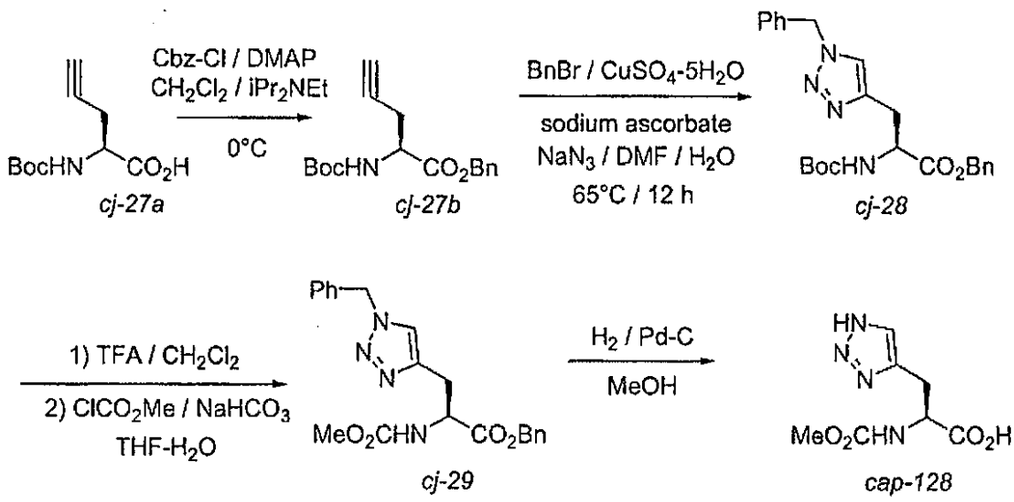
Cap-127



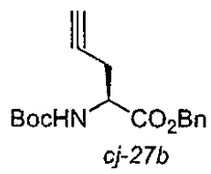
cj-26 *cap-127*

Cap-127 was prepared according to the method for *Cap*-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and ^1H NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification. ^{1}HNMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, J = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H); LCMS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228 $(M+H)^+$.

Preparation of Cap-128



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

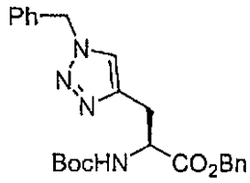


cj-27b

To a solution of *cj-27a* (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and iPr_2NEt (1.7 mL, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0°C was added Cbz-Cl (0.68 mL, 4.83 mmol). The solution was allowed to stir for 4 h at 0°C, washed (1N $KHSO_4$, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound

(1.30 g, 91%) as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d, br, J = 8.1 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.48 – 4.53 (m, 1H), 2.68 – 2.81 (m, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.44 (s, 9H). LCMS: Anal. Calcd. for $C_{17}H_{21}NO_4$: 303; found: 304 $(M+H)^+$.

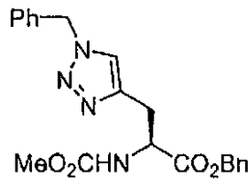
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28).



cj-28

To a mixture of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) and NaN_3 (0.13 g, 2.1 mmol) in DMF-H_2O (5 mL, 4:1) at rt was added BnBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65°C. After 5h LCMS indicated low conversion. A further portion of NaN_3 (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and H_2O and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed (H_2O x3, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in CH_2Cl_2; TLC 3% MeOH in CH_2Cl_2) to afford a light yellow oil which solidified on standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, J = 1.0, 5.3 Hz, 1H), 3.06 (dd, J = 5.3, 14.7 Hz), 2.96 (dd, J = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H).
LCMS: Anal. Calcd. for $C_{24}H_{28}N_4O_4$: 436; found: 437 $(M+H)^+$.

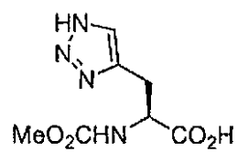
Step 3. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



cj-29

A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in CH_2Cl_2 was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2h. The mixture was concentrated *in vacuo* to give a colorless oil which solidified on standing. This material was dissolved in THF-H_2O and cooled to 0°C. Solid $NaHCO_3$ (0.25 g, 3.00 mmol) was added followed by $ClCO_2Me$ (0.25 mL, 3.25 mmol). After stirring for 1.5h the mixture was acidified to pH~2 with 6N HCl and then poured into H_2O-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The combined org layers were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 4.32 – 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J = 5.6, 14.7 Hz, 1H), 2.98 (dd, J = 9.6, 14.7 Hz, 1H). LCMS: Anal. Calcd. for $C_{21}H_{22}N_4O_4$: 394; found: 395 $(M+H)^+$.

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

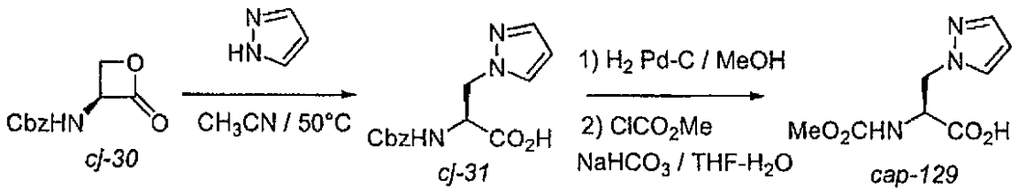


Cap-128

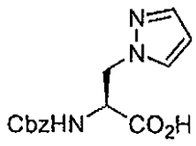
(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The

mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.78 (s, br, 1H), 7.59 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.19 – 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, J = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, J = 9.9, 15.0 Hz, 1H). LCMS: Anal. Calcd. for $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

Preparation of Cap-129



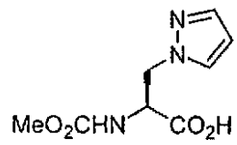
Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



cj-31

A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH_3CN (12 mL) was heated at 50 °C for 24h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated *in vacuo* and then triturated with a small amount of CH_3CN (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%). m.p. 165.5 – 168°C. lit m.p. 168.5 – 169.5 [Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105]. ^{1}HNMR (400 MHz, CD_3OD) δ 7.51 (d, J = 2.0, 1H), 7.48 (s, J = 1.5 Hz, 1H), 7.24 – 7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, J = 12.7 Hz, 1H), 4.59 – 4.66 (m, 2H), 4.42 – 4.49 (m, 1H). LCMS: Anal. Calcd. for $C_{14}H_{15}N_3O_4$: 289; found: 290 $(M+H)^+$.

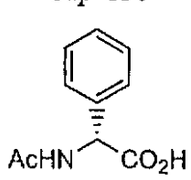
Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap-129*).



cap-129

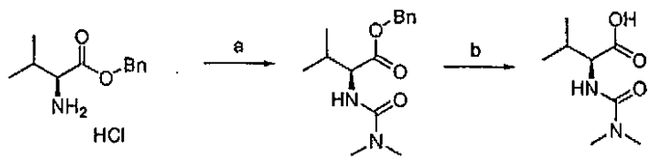
(S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the reaction mixture was diluted with 5mL H_2O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended in THF-H_2O (1:1, 10mL) and then cooled to 0°C. To the cold mixture was added $NaHCO_3$ (146.0 mg, 1.74 mmol) carefully (evolution of CO_2). After gas evolution had ceased (ca. 15 min) $ClCO_2Me$ (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extracted with EtOAC (x5). The combined organic layers were washed (brine), dried (Na_2SO_4), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 6.19 (app t, J = 2.0 Hz, 1H), 4.47 (dd, J = 3.0, 12.9 Hz, 1H), 4.29 – 4.41 (m, 2H), 3.48 (s, 3H). LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.

Cap-130



Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analgous to the procedure given in: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

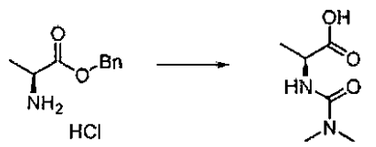
Cap-131



Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:hexanes (1:1). Collected fractions were concentrated under vacuum providing 2.35 g (85%) of clear oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.95 Hz, 3H), 0.89 (d, *J*=6.59 Hz, 3H), 1.98-2.15 (m, 1H), 2.80 (s, 6H), 5.01-5.09 (m, *J*=12.44 Hz, 1H), 5.13 (d, *J*=12.44 Hz, 1H), 6.22 (d, *J*=8.05 Hz, 1H), 7.26-7.42 (m, 5H). LC (Cond. 1): RT = 1.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; found 279.03.

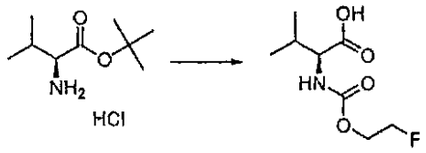
Step b: To a MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N_2 (3x) and placed under 1 atm of H_2. The mixture was stirred at room temperature overnight and filtered though a microfiber filter to remove the catalyst. The resulting clear solution was then concentrated under reduced pressure to obtain 1.43 g (89%) of *Cap-131* as a white foam, which was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (d, *J*=4.27 Hz, 3H), 0.88 (d, *J*=3.97 Hz, 3H), 1.93-2.11 (m, 1H), 2.80 (s, 6H), 3.90 (dd, *J*=8.39, 6.87 Hz, 1H), 5.93 (d, *J*=8.54 Hz, 1H), 12.36 (s, 1H). LC (Cond. 1): RT = 0.33 min; MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.04.

Cap-132



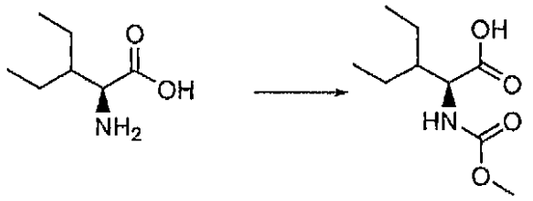
Cap-132 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for *Cap-131*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; found 161.00.

Cap-133



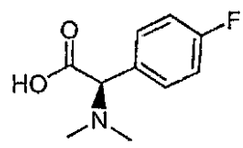
Cap-133 was prepared from (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap-47*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.54 (m, 1H), 4.59-4.65 (m, 1H), 7.51 (d, *J* = 8.54 Hz, 1H), 12.54 (s, 1H).

Cap-134



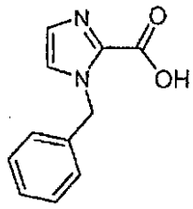
Cap-134 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap-51*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, *J* = 8.85, 5.19 Hz, 1H), 7.24 (d, *J* = 8.85 Hz, 1H), 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$: 204.12; found 204.02.

Cap-135



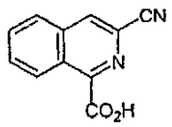
A solution of D-2-amino-(4-fluorophenyl)acetic acid (338 mg, 2.00 mmol), 1*N* HCl in diethylether (2.0 mL, 2.0 mmol) and formalin (37%, 1 mL) in methanol (5 mL) was subjected to balloon hydrogenation over 10% palladium on carbon (60 mg) for 16 h at 25 °C. The mixture was then filtered through Celite to afford the HCl salt of *Cap-135* as a white foam (316 mg, 80%). ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.59 (dd, J = 8.80, 5.10 Hz, 2H), 7.29 (t, J = 8.6 Hz, 2H), 5.17 (s, 1H), 3.05 (v br s, 3H), 2.63 (v br s, 3H); R_t = 0.19 min (Cond.-MS-W5); 95% homogenity index; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; found: 198.10.

Cap-136

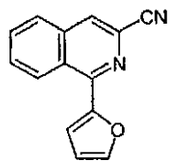


To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -50 °C, dry carbon dioxide (passed through Drierite) was bubbled into the reaction mixture for 10 min before it was allowed to warm up to 25 °C. The heavy precipitate which formed on addition of carbon dioxide to the reaction mixture was filtered to yield a hygroscopic, white solid which was taken up in water (7 mL), acidified to pH = 3, cooled, and induced to crystallize with scratching. Filtration of this precipitate gave a white solid which was suspended in methanol, treated with 1*N* HCl/diethyl ether (4 mL) and concentrated *in vacuo*. Lyophilization of the residue from water (5 mL) afforded the HCl salt of *Cap-136* as a white solid (817 mg, 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.50-7.31 (m, 5H), 5.77 (s, 2H); R_t = 0.51 min (Cond.-MS-W5); 95% homogenity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; found: 203.11.

Cap-137



Cap-137, step a



A suspension of 1-chloro-3-cyanoisoquinoline (188 mg, 1.00 mmol; prepared according to the procedure in WO 2003/ 099274) (188 mg, 1.00 mmol), cesium fluoride (303.8 mg, 2.00 mmol), bis(tri-*tert*-butylphosphine)palladium dichloride (10 mg, 0.02 mmol) and 2-(tributylstannyl)furan (378 µL, 1.20 mmol) in anhydrous dioxane (10 mL) under nitrogen was heated at 80 °C for 16 h before it was cooled to 25 °C and treated with saturated, aqueous potassium fluoride solution with vigorous stirring for 1 h. The mixture was partitioned between ethyl acetate and water and the organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification of the residue on silica gel (elution with 0% to 30% ethyl acetate/hexanes) afforded *Cap-137, step a* (230 mg, 105%) as a white solid which was carried forward directly. R_t = 1.95 min (Cond.-MS-W2); 90% homogeneity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_8N_2O$: 221.07; found: 221.12.

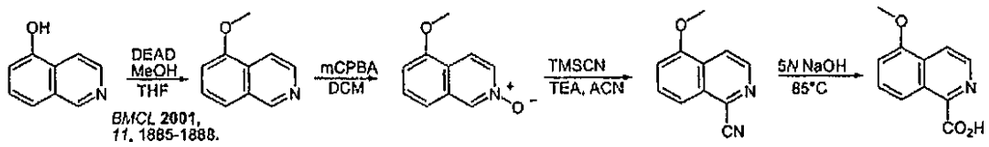
Cap-137

To a suspension of *Cap 137, step a*, (110 mg, 0.50 mmol) and sodium periodate (438 mg, 2.05 mmol) in carbon tetrachloride (1 mL), acetonitrile (1 mL) and water (1.5 mL) was added ruthenium trichloride hydrate (2 mg, 0.011 mmol). The mixture was stirred at 25 °C for 2 h and then partitioned between dichloromethane and water. The aqueous layer was separated, extracted twice more with dichloromethane and the combined dichloromethane extracts were dried over Na_2SO_4, filtered and concentrated. Trituration of the residue with hexanes afforded *Cap-137* (55 mg, 55%) as a grayish-colored solid. R_t = 1.10 min (Cond.-MS-W2);

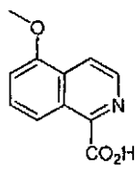
90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_8N_2O_2$: 200.08; found: 200.08.

Caps 138 to *158*

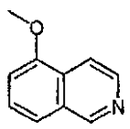
Synthetic Strategy. Method A.



Cap-138

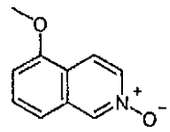


Cap-138, step a



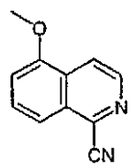
To a stirred suspension of 5-hydroxyisoquinoline (prepared according to the procedure in WO 2003/ 099274) (2.0 g, 13.8 mmol) and triphenylphosphine (4.3 g, 16.5 mmol) in dry tetrahydrofuran (20 mL) was added dry methanol (0.8 mL) and diethyl azodicarboxylate (3.0 mL, 16.5 mmol) portionwise. The mixture was stirred at room temperature for 20 h before it was diluted with ethyl acetate and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was preabsorbed onto silica gel and chromatographed (elution with 40% ethyl acetate/hexanes) to afford *Cap-138, step a* (1.00 g, 45%) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); R_t = 0.66 min (Cond.-D2); 95% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO$: 160.08; found 160.1.

Cap-138, step b



To a stirred solution of *Cap 138, step a* (2.34 g, 14.7 mmol) in anhydrous dichloromethane (50 mL) at room temperature was added *meta*-chloroperbenzoic acid (77%, 3.42 g, 19.8 mmol) in one portion. After being stirred for 20 h, powdered potassium carbonate (2.0 g) was added and the mixture was stirred for 1 h at room temperature before it was filtered and concentrated *in vacuo* to afford *Cap-138, step b* (2.15 g, 83%) as a pale, yellow solid which was sufficiently pure to carry forward directly. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 7.3, 1.7 Hz, 1H), 8.04 (d, J=7.1 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.00 (s, 3H); R_t = 0.92 min, (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO_2$: 176.07; found: 176.0.

Cap-138, step c



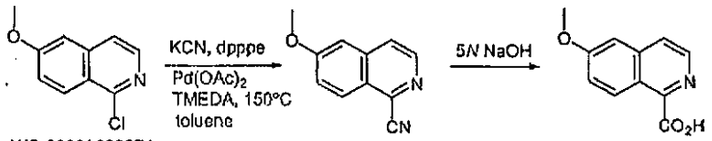
To a stirred solution of *Cap 138, step b* (0.70 g, 4.00 mmol) and triethylamine (1.1 mL, 8.00 mmol) in dry acetonitrile (20 mL) at room temperature under nitrogen was added trimethylsilylcyanide (1.60 mL, 12.00 mmol). The mixture was heated at 75 °C for 20 h before it was cooled to room temperature, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine prior to drying over Na_2SO_4 and solvent concentration. The residue was flash chromatographed on silica gel (gradient elution with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes) to afford *Cap-138, step c* (498.7 mg, 68%) as a white, crystalline solid along with 223 mg (30%) of additional *Cap-138, step c* recovered from the filtrate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 4.04 (s,

3H); R_t = 1.75 min, (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.10.

Cap-138

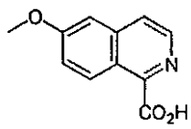
Cap-138, step c (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried over Na_2SO_4, concentrated to ¼ volume and filtered to afford *Cap-138* (0.44g, 88.9%) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.6 (br s, 1H), 8.56 (d, *J* = 6.0 Hz, 1H), 8.16 (d, *J* = 6.0 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H); R_t = 0.70 min (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

Synthetic Strategy. Method B (derived from *Tetrahedron Letters*, **2001**, *42*, 6707).

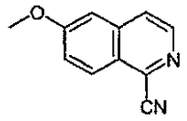


WO 2003/ 099274

Cap-139



Cap-139, step a



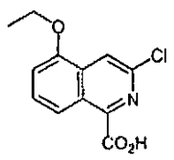
To a thick-walled, screw-top vial containing an argon-degassed suspension of 1-chloro-6-methoxyisoquinoline (1.2 g, 6.2 mmol; prepared according to the procedure in WO 2003/ 099274), potassium cyanide (0.40 g, 6.2 mmol), 1,5-bis(diphenylphosphino)pentane (0.27 g, 0.62 mmol) and palladium (II) acetate (70 mg, 0.31 mmol) in anhydrous toluene (6 mL) was added *N,N,N',N'*-

tetramethylethylenediamine (0.29 mL, 2.48 mmol). The vial was sealed, heated at 150 °C for 22 h and then allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (gradient elution with 5% ethyl acetate/hexanes to 25% ethyl acetate/hexanes) to afford *Cap-139, step a* (669.7 mg, 59%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.54 (d, J = 6.0 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.13 (d, J = 2.0 Hz, 1H), 3.98 (s, 3H); R_t = 1.66 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.2.

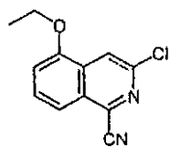
Cap-139

Cap-139 was prepared from the basic hydrolysis of *Cap-139, step a* with 5*N* NaOH according to the procedure described for *Cap 138*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (v br s, 1H), 8.60 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H); R_t = 0.64 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

Cap-140



Cap-140, step a



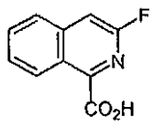
To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/ 051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry dimethylacetamide (2 mL) at 25 °C under nitrogen was added N,N,N',N'-

tetramethylethylenediamine (60 mL, 0.40 mmol). After 10 min, the mixture was heated to 150 °C, and then a stock solution of acetone cyanohydrin (prepared from 457 μL of acetone cyanohydrin in 4.34 mL DMA) was added in 1 mL portions over 18 h using a syringe pump. The mixture was then partitioned between ethyl acetate and water and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (gradient elution with 10% ethyl acetate in hexanes to 40% ethyl acetate in hexanes) to afford *Cap-140, step a* (160 mg, 34%) as a yellow solid. R_t = 2.46 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; found: 233.08.

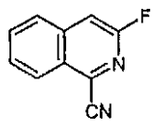
Cap-140

Cap-140 was prepared by the acid hydrolysis of *Cap-140, step a* with 12*N* HCl as described in the procedure for the preparation of *Cap 141*, described below. R_t = 2.24 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; found: 252.02.

Cap-141



Cap-141, step a

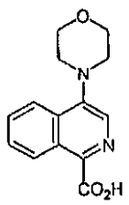


Cap-141, step a was prepared from 1-bromo-3-fluoroisoquinoline (prepared from 3-amino-1-bromoisoquinoline using the procedure outlined in *J. Med. Chem.* **1970**, *13*, 613) as described in the procedure for the preparation of *Cap-140, step a* (*vide supra*). ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.83 (t, *J* = 7.63 Hz, 1H), 7.77-7.73 (m, 1H), 7.55 (s, 1H); R_t = 1.60 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6FN_2$: 173.05; found: 172.99.

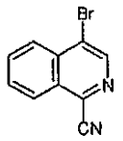
Cap-141

Cap-141, step a (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature and diluted with water (3 mL). The mixture was stirred for 10 min and then filtered to afford *Cap-141* (44.1 mg, 48%) as an off-white solid. The filtrate was diluted with dichloromethane and washed with brine, dried over Na_2SO_4, and concentrated to afford additional *Cap-141* (29.30 mg, 32%) which was sufficiently pure to be carried forward directly. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 14.0 (br s, 1H), 8.59-8.57 (m, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.88-7.85 (m, 2H), 7.74-7.71 (m, 1H); R_t = 1.33 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 191.97.

Cap-142

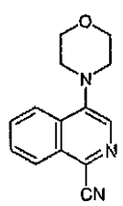


Cap-142, step a



Cap-142, step a was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of *Cap-138, steps b and c*. R_t = 1.45 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

Cap-142, step b

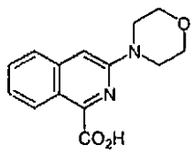


To an argon-degassed suspension of *Cap-142, step a* (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 µL, 0.70 mmol). The mixture was heated at 100 °C for 16 h, cooled to 25 °C, filtered through diatomaceous earth (Celite®) and concentrated. Purification of the residue on silica gel (gradient elution with 10% to 70% ethyl acetate in hexanes) afforded *Cap-142, step b* (38 mg, 32%) as a yellow solid which was carried forward directly. R_t = 1.26 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; found: 240.13.

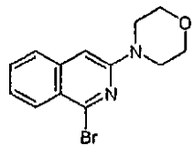
Cap-142

Cap-142 was prepared from *Cap-142, step b* with *5N* sodium hydroxide as described in the procedure for *Cap 138*. R_t = 0.72 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-143



Cap-143, step a



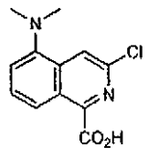
To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 µL, 2.00 mmol) was added. This mixture was stirred further at 25 °C for 5 h and at 75 °C for 72 h before it was cooled to 25 °C, quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The

organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. Purification of the residue on silica gel (gradient elution with 0% to 70% ethyl acetate in hexanes) afforded *Cap-143, step a* (180 mg, 31%) as a yellow solid. R_t = 1.75 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; found: 293.04.

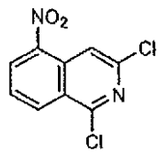
Cap-143

To a cold (-60 °C) solution of *Cap-143, step a* (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 0.25 mL, 0.633 mmol). After 10 min, dry carbon dioxide was bubbled into the reaction mixture for 10 min before it was quenched with 1*N* HCl and allowed to warm to 25 °C. The mixture was then extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were concentrated *in vacuo*. Purification of the residue by reverse phase HPLC (MeOH/water/TFA) afforded *Cap-143* (16 mg, 12%). R_t = 1.10 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-144



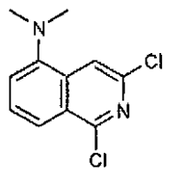
Cap-144, step a



1,3-Dichloroisoquinoline (2.75 g, 13.89 mmol) was added in small portions to a cold (0 °C) solution of fuming nitric acid (10 mL) and concentrated sulfuric acid (10 mL). The mixture was stirred at 0 °C for 0.5 h before it was gradually warmed to 25 °C where it stirred for 16 h. The mixture was then poured into a beaker containing chopped ice and water and the resulting suspension was stirred for 1 h at 0 °C before it was filtered to afford *Cap-144, step a* (2.73 g, 81%) as a yellow solid which was

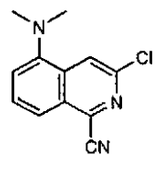
used directly. R_t = 2.01 min (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; found: 242.92.

Cap-144, step b



Cap-144, step a (0.30 g, 1.23 mmol) was taken up in methanol (60 mL) and treated with platinum oxide (30 mg), and the suspension was subjected to Parr hydrogenation at 7 psi H_2 for 1.5 h before formalin (5 mL) and additional platinum oxide (30 mg) were added. The suspension was resubjected to Parr hydrogenation at 45 psi H_2 for 13 h before it was suction-filtered through diatomaceous earth (Celite®) and concentrated down to ¼ volume. Suction-filtration of the ensuing precipitate afforded the title compound as a yellow solid which was flash chromatographed on silica gel (gradient elution with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes) to afford *Cap-144, step b* (231 mg, 78%) as a pale, yellow solid. R_t = 2.36 min (Cond.-D1); 95% homogenity index; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.30 (d, J = 7.3 Hz, 1H), 2.88 (s, 6H); LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.03; found: 241.02. HRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.0299; found: 241.0296.

Cap-144, step c



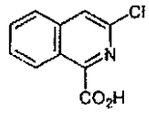
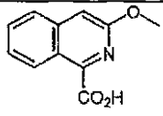
Cap-144, step c was prepared from *Cap-144, step b* according to the procedure described for the preparation of *Cap-139, step a*. R_t = 2.19 min (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.06; found: 232.03. HRMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.0642; found: 232.0631.

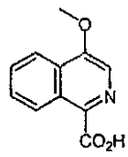
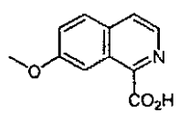
Cap-144

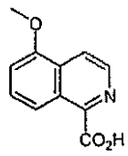
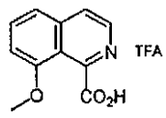
Cap-144 was prepared according to the procedure described for *Cap-141*. R_t = 2.36 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; found: 238.09.

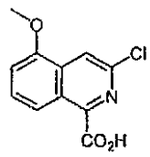
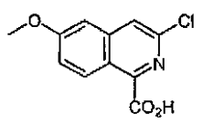
Caps-145 to -162

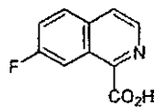
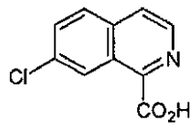
Caps-145 to *162* were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of *Cap-138* (Method A) or *Cap-139* (Method B) unless noted otherwise as outlined below.

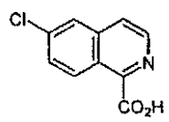
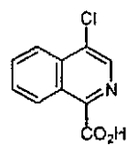
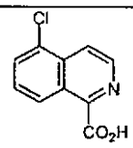
Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-145	 Prepared from commercially available 1,3-dichloroisoquinoline	B	12*N* HCl	1.14 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-146		A	5*N* NaOH	1.40 min (Cond.-

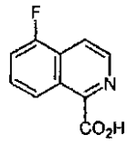
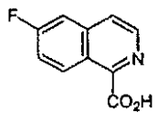
	Prepared from commercially available 3-hydroxyisoquinoline			D1); 95% ; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.06.
Cap-147	 Prepared from commercially available 1-chloro-4-hydroxyisoquinoline	B	5*N* NaOH	0.87 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-148	 Prepared from commercially available 7-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$

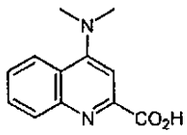
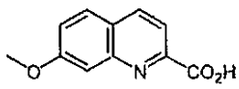
				$C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-149	 Prepared from commercially available 5-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-150	 Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	A	12*N* HCl	0.26 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.04.

Cap-151	 Prepared from 5-methoxy-1,3-dichloroisoquinoline, which can be synthesized following the procedure in WO 2005 / 051410.	B	12*N* HCl	1.78 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; found: 238.09.
Cap-152	 Prepared from commercially available 6-methoxy-1,3-dichloroisoquinoline	B	12*N* HCl	1.65 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00; found: 238.09.
Cap-153	 Prepared from 4-bromoisoquinoline, which can be synthesized	A	6*N* HCl	1.18 min (Cond.-MS-W1); 95%; LCMS: Anal.

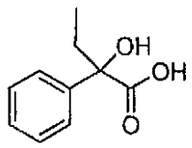
	following the procedure in WO 2003/ 062241			Calc. for $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; found: 251.95.
Cap-154	 Prepared from 7-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.28 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-155	 Prepared from 1,7-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.59 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found:

				208.00.
Cap-156	 Prepared from 1,6-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.60 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.03.
Cap-157	 Prepared from 1,4-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 062241	B	12*N* HCl	1.49 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{17}ClNO$: 208.02; found: 208.00.
Cap-158	 Prepared from 1,5-dichloroisoquinoline,	B	5*N* NaOH	0.69 min (Cond.-MS-W1); 90%; LCMS:

	which can be synthesized following the procedure in WO 2003/ 099274			Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.01.
Cap-159	 Prepared from 5-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.41 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-160	 Prepared from 6-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.30 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05;

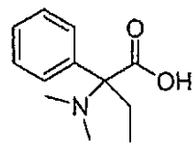
				found: 192.03.
Cap-161	 Prepared from 4-bromoquinoline-2-carboxylic acid and dimethylamine (DMSO, 100 °C)	--	--	0.70 min (Cond. D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217.10; found: 217.06.
Cap-162	 Prepared from *m*-anisidine following the procedure described in *J. Hetero. Chem.* **1993**, 17 and *Heterocycles*, **2003**, *60*, 953.	--	--	0.65 min (Cond.-M3); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 203.94.

Cap-163



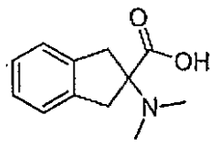
To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water followed by brine and dried over $MgSO_4$. After concentration *in vacuo*, a white solid was obtained. The solid was recrystallized from hexanes/ethyl acetate to afford *Cap-163* as white needles (883.5 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.71 (br s, 1 H), 7.54-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 5.52-5.39 (br s, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 0.79 (app t, J = 7.4 Hz, 3H).

Cap-164



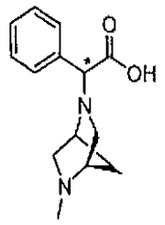
A mixture of 2-amino-2-phenylbutyric acid (1.5 g, 8.4 mmol), formaldehyde (14 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (0.5 mg) in MeOH (40 mL) was exposed to H_2 at 50 psi in a Parr bottle for 42 h. The reaction was filtered over Celite and concentrated *in vacuo*, the residue was taken up in MeOH (36 mL) and the product was purified with a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of *Cap-164* as a white solid (1.7 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.54-7.47 (m, 5H), 2.63 (m, 1H), 2.55 (s, 6H), 2.31 (m, 1H), 0.95 (app t, J = 7.3 Hz, 3H).

Cap-165



To a mixture of 2-amino-2-indanecarboxylic acid (258.6 mg, 1.46 mmol) and formic acid (0.6 ml, 15.9 mmol) in 1,2-dichloroethane (7 ml) was added formaldehyde (0.6 ml, 37% in water). The mixture was stirred at ~25 °C for 15 min then heated at 70 °C for 8h. The volatile component was removed *in vacuo*, and the residue was dissolved in DMF (14 mL) and purified by a reverse phase HPLC ($MeOH/H_2O/TFA$) to afford the TFA salt of *Cap-165* as a viscous oil (120.2 mg). ^1H NMR (DMSO-d_6, $\delta = 2.5$ ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found: 206.07.

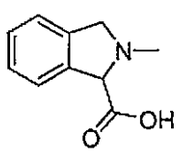
Cap-166a and -166b



Cap-166a: Diastereomer-1
Cap-166b: Diastereomer-2

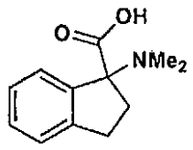
Caps-166a and *-166b* were prepared from (1S, 4S)-(+)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2HBr) according to the method described for the synthesis of *Cap-7a and Cap-7b*, with the exception that the benzyl ester intermediate was separated using a semi-prep Chrialcel OJ column, 20 x 250 mm, 10 μm eluting with 85:15 heptane/ethanol mixture at 10 mL/min elution rate for 25 min. *Cap-166b*: ^1H NMR (DMSO-d_6, $\delta = 2.5$ ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H), 7.27-7.19 (m, 3H), 4.09 (s, 1H), 3.34 (app br s, 1H), 3.16 (app br s, 1H), 2.83 (d, *J*=10.1 Hz, 1H), 2.71 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H), 1.77 (d, J = 9.8 Hz, 1H), 1.63 (d, J = 9.8 Hz, 1H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; found: 247.11.

Cap-167



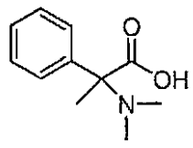
A solution of racemic Boc-1,3-dihydro-2H-isoindole carboxylic acid (1.0g, 3.8 mmol) in 20% TFA/CH_2Cl_2 was stirred at ~25 °C for 4h. All the volatile component was removed *in vacuo*. A mixture of the resultant crude material, formaldehyde (15 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (10 mg) in MeOH was exposed to H_2 (40 PSI) in a Parr bottle for 23 h. The reaction mixture was filtered over Celite and concentrated *in vacuo* to afford *Cap-167* as a yellow foam (873.5 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, J = 14 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.07 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; found: 178.65.

Cap-168



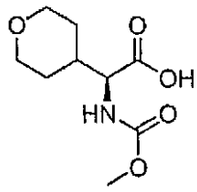
Racemic *Cap-168* was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of *Cap-167*. The crude material was employed as such.

Cap-169



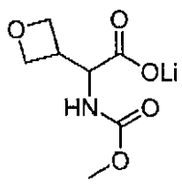
A mixture of 2-amino-2-phenylpropanoic acid hydrochloride (5.0 g, 2.5 mmol), formaldehyde (15 ml, 37% in water), 1N HCl (15 ml), and 10% Pd/C (1.32 g) in MeOH (60 mL) was placed in a Parr bottle and shaken under hydrogen (55 PSI) for 4 days. The reaction mixture was filtered over Celite and concentrated *in vacuo*. The residue was taken up in MeOH and purified by reverse phase prep-HPLC (MeOH/water/TFA) to afford the TFA salt of *Cap-169* as a viscous semi-solid (2.1 g). ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 7.58-7.52 (m, 2 H), 7.39-7.33 (m, 3H), 2.86 (br s, 3H), 2.47 (br s, 3H), 1.93 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found: 194.12.

Cap-170



To (*S*)-2-amino-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (505mg; 3.18mmol; obtained from Astatech) in water (15ml) was added sodium carbonate (673mg; 6.35mmol), and the resultant mixture was cooled to 0 °C and then methyl chloroformate (0.26ml; 3.33mmol) was added dropwise over 5 minutes. The reaction was allowed to stir for 18 hours while allowing the bath to thaw to ambient temperature. The reaction mixture was then partitioned between 1N HCl and ethyl acetate. The organic layer was removed and the aqueous layer was further extracted with 2 additional portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford *Cap-170* a colorless residue. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 12.65 (1 H, br s), 7.44 (1 H, d, *J*=8.24 Hz), 3.77 - 3.95 (3 H, m), 3.54 (3 H, s), 3.11 - 3.26 (2 H, m), 1.82 - 1.95 (1 H, m), 1.41 - 1.55 (2 H, m), 1.21 - 1.39 (2 H, m); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{16}NO_5$: 218.1; found 218.1.

Cap-171

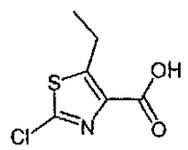


A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (200 mg, 0.721 mmol; Il Farmaco (2001), 56, 609–613) in ethyl acetate (7 ml) and CH_2Cl_2 (4.00 ml) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 ml, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight at which time TLC (95:5 CH_2Cl_2 / MeOH: visulalized with stain made from 1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water) indicated complete conversion. The reaction was

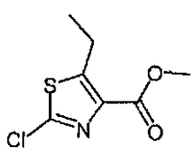
filtered through celite and concentrated. The residue was purified via Biotage® (load with dichloromethane on 25 samplet; elute on 25S column with dichloromethane for 3CV then 0 to 5% MeOH / dichloromethane over 250ml then hold at 5% MeOH / dichloromethane for 250ml; 9ml fractions). Collected fractions containing desired material and concentrated to 120mg (81%) of methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.29 - 3.40 (m, *J*=6.71 Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, *J*=6.41 Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (br s, 1 H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; found 204.0.

To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246 mmol). The resultant solution was allowed to stir overnite at ambient temperature. TLC (1:1 EA / Hex; Hanessian stain [1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water]) indicated ~10% starting material remaining. Added an additional 3mg LiOH and allowed to stir overnight at which time TLC showed no starting material remaining. Concentrated *in vacuo* and placed on high vac overnite providing 55mg lithium 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless solid. ^{1}H NMR (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

Cap-172



Cap-172, step a



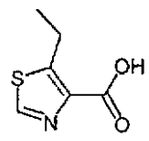
The following diazotization step was adapted from Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**,

159-164: A solution of $NaNO_2$ (166 mg, 2.4 mmol) in water (0.6 mL) was added slowly to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol), $CuSO_4 \cdot 5H_2O$ (330 mg, 1.32 mmol), NaCl (260 mg, 4.45 mmol) and H_2SO_4 (5.5 mL) in water (7.5 mL). The mixture was stirred at 0 °C for 45 min and allowed to warm up to room temperature where it stirred further for 1 h before CuCl (118 mg) was added. This mixture was stirred further at room temperature for 16 h before it was diluted with brine and extracted with ether twice. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 2-chloro-5-ethylthiazole-4-carboxylate (i.e. *Cap-172, step a*) (175 mg, 85%) as an orange oil (80% pure) which was used directly in the next reaction. R_t = 1.99 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_9ClNO_2S$: 206.01; found: 206.05.

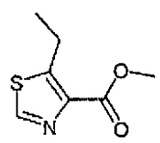
Cap-172

To a solution of methyl 2-chloro-5-ethylthiazole-4-carboxylate (175 mg) in THF/H_2O/MeOH (20 mL/ 3 mL/ 12 mL) was added LiOH (305 mg, 12.76 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield *Cap-172* (60 mg, 74%) as a red solid which was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 13.03-13.42 (1 H, m), 3.16 (2 H, q, *J* = 7.4 Hz), 1.23 (3 H, t, *J* = 7.5 Hz). R_t = 1.78 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_7ClNO_2S$: 191.99; found: 191.99.

Cap-173



Cap-173, step a

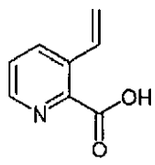


The following diazotization step was adapted from Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: A solution of $NaNO_2$ (150 mg, 2.17 mmol) in water (1.0 mL) was added dropwise to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol) in 50% H_3PO_2 (3.2 mL). The mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature where it stirred further for 2h. After recooling to 0 °C, the mixture was treated slowly with a solution of NaOH (85 mg) in water (10 mL). The mixture was then diluted with saturated $NaHCO_3$ solution and extracted twice with ether. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 5-ethylthiazole-4-carboxylate (i.e. *Cap-173, step a*) (134 mg, 78%) as an orange oil (85% pure) which was used directly in the next reaction. R_t = 1.58 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{10}NO_2S$: 172.05; found: 172.05.

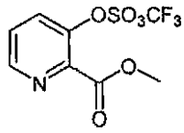
Cap-173

To a solution of methyl 5-ethylthiazole-4-carboxylate (134 mg) in THF/H_2O/MeOH (18 mL/ 2.7 mL/ 11 mL) was added LiOH (281 mg, 11.74 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield *Cap-173* (90 mg, 73%) as an orange solid which was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 12.74-13.04 (1 H, m), 3.20 (2 H, q, *J* = 7.3 Hz), 1.25 (3 H, t, *J* = 7.5 Hz). R_t = 1.27 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_8NO_2S$: 158.03; found: 158.04.

Cap-174



Cap-174, step a

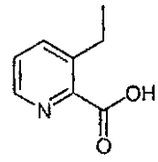


Triflic anhydride (5.0 g, 18.0 mmol) was added dropwise to a cold (0 °C) solution of methyl 3-hydroxypicolinate (2.5 g, 16.3 mmol) and TEA (2.5 mL, 18.0 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at 0 °C for 1h before it was allowed to warm up to room temperature where it stirred for an additional 1 h. The mixture was then quenched with saturated $NaHCO_3$ solution (40 mL) and the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to give methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e. Cap-174, step a*) (3.38 g, 73%) as a dark brown oil (>95% pure) which was used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.72-8.79 (1 H, m), 7.71 (1 H, d, J = 1.5 Hz), 7.58-7.65 (1 H, m), 4.04 (3 H, s). R_t = 1.93 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_7F_3NO_5S$: 286.00; found: 286.08.

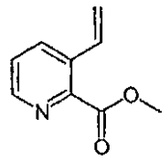
Cap-174

To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (570 mg, 2.0 mmol) in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C overnight before a saturated solution of KF (20 mL) was added to the reaction mixture at room temperature. This mixture was stirred for 4 h before it was filtered through Celite and the pad of Celite was washed with ethyl acetate. The aqueous phase of the filtrate was then separated and concentrated down *in vacuo*. The residue was treated with 4*N* HCl in dioxanes (5 mL) and the resulting mixture was extracted with methanol, filtered and evaporated to afford *Cap-174* (260 mg) as a green solid which was slightly contaminated with inorganic salts but was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.21 (1 H, d, J = 3.7 Hz), 7.81-7.90 (1 H, m), 7.09 (1 H, dd, J = 7.7, 4.8 Hz), 6.98 (1 H, dd, J = 17.9, 11.3 Hz), 5.74 (1 H, dd, J = 17.9, 1.5 Hz), 5.20 (1 H, d, J = 11.0 Hz). R_t = 0.39 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_8NO_2$: 150.06; found: 150.07.

Cap-175

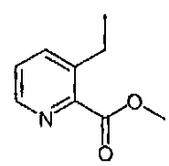


Cap-175, step a



To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e. Cap 173, step a*) (570 mg, 2.0 mmol), an intermediate in the preparation of *Cap-174*, in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C for 4 h before the solvent was removed *in vacuo*. The residue was taken up in acetonitrile (50 mL) and hexanes (50 mL) and the resulting mixture was washed twice with hexanes. The acetonitrile layer was then separated, filtered through Celite, and evaporated. Purification of the residue by flash chromatography on a Horizon instrument (gradient elution with 25% ethyl acetate in hexanes to 65% ethyl acetate in hexanes) afforded methyl 3-vinylpicolinate (i.e. *Cap-175, step a*) (130 mg, 40%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.60 (1 H, dd, J = 4.6, 1.7 Hz), 7.94 (1 H, d, J = 7.7 Hz), 7.33-7.51 (2 H, m), 5.72 (1 H, d, J = 17.2 Hz), 5.47 (1 H, d, J = 11.0 Hz), 3.99 (3 H, s). R_t = 1.29 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{10}NO_2$: 164.07; found: 164.06.

Cap-175, step b



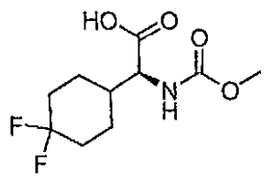
Palladium on carbon (10%, 25 mg) was added to a solution of methyl 3-vinylpicolinate (120 mg, 0.74 mmol) in ethanol (10 mL). The suspension was stirred at room temperature under an atmosphere of hydrogen for 1 h before it was filtered

through Celite and the pad of Celite was washed with methanol. The filtrate was concentrated down to dryness to yield methyl 3-ethylpicolinate (i.e. *Cap-175, step b*) which was taken directly into the next reaction. R_t = 1.15 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{12}NO_2$: 166.09; found: 166.09.

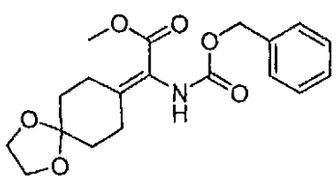
Cap-175

To a solution of methyl 3-ethylpicolinate in THF/H_2O/MeOH (5 mL/ 0.75 mL/ 3 mL) was added LiOH (35 mg, 1.47 mmol). The mixture was stirred at room temperature for 2 d before additional LiOH (80 mg) was added. After an additional 24 h at room temperature, the mixture was filtered and the solvent was removed *in vacuo*. The residue was then treated with 4*N* HCl in dioxanes (5 mL) and the resulting suspension was concentrated down to dryness to yield *Cap-175* as a yellow solid which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.47 (1 H, dd, *J* = 4.8, 1.5 Hz), 7.82-7.89 (1 H, m), 7.53 (1 H, dd, *J* = 7.7, 4.8 Hz), 2.82 (2 H, q, *J* = 7.3 Hz), 1.17 (3 H, t, *J* = 7.5 Hz). R_t = 0.36 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{10}NO_2$: 152.07; found: 152.10.

Cap-176



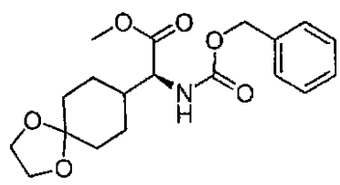
Cap-176, step a



A solution of 1,4-dioxaspiro[4.5]decan-8-one (15 g, 96 mmol) in EtOAc (150 mL) was added to a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (21.21 g, 64.0 mmol) in 1,1,3,3-tetramethylguanidine (10.45 mL, 83 mmol) and EtOAc (150 mL). The resulting solution was the stirred at ambient temperature for 72 h and then it was diluted with EtOAc (25 mL). The

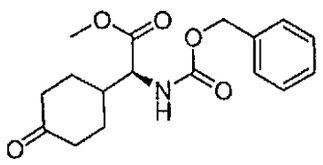
organic layer was washed with 1N HCl (75 mL), H2O (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified via Biotage (5% to 25 % EtOAc/Hexanes; 300g column). The combined fractions containing the product were then concentrated under vacuum and the residue was re-crystallized from hexanes/EtOAc to give white crystals that corresponded to methyl 2-(benzyloxycarbonylamino)-2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (6.2 g) ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.30 - 7.44 (5 H, m), 6.02 (1 H, br. s.), 5.15 (2 H, s), 3.97 (4 H, s), 3.76 (3 H, br. s.), 2.84 - 2.92 (2 H, m), 2.47 (2 H, t, *J*=6.40 Hz), 1.74 - 1.83 (4 H, m). LC (Cond. OL1): R_t = 2.89 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745.21; found: 745.47

Cap 176, step b



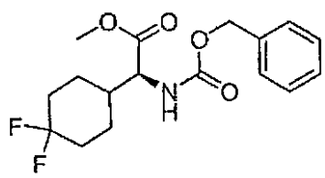
Ester *Cap 176, step b* was prepared from alkene *Cap 176, step a* according to the method of Burk, M. J.; Gross, M. F. and Martinez J. P. (*J. Am. Chem. Soc.*, **1995**, *117*, 9375-9376 and references therein): A 500 mL high-pressure bottle was charged with alkene *Cap 176, step a* (3.5 g, 9.68 mmol) in degassed MeOH (200 mL) under a blanket of N_2. The solution was then charged with (-)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane(cyclooctadiene)rhodium (I) tetrafluoroborate (0.108 g, 0.194 mmol) and the resulting mixture was flushed with N_2 (3x) and charged with H_2 (3x). The solution was shaken vigorously under 70 psi of H_2 at ambient temperature for 72 h. The solvent was removed under reduced pressure and the remaining residue was taken up in EtOAc. The brownish solution was then filtered through a plug of Silica Gel and eluted with EtOAc. The solvent was concentrated under vacuum to afford a clear oil corresponding to ester *Cap 176, step b* (3.4 g) .^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 7.28 - 7.43 (5 H, m), 5.32 (1 H, d, *J*=9.16 Hz), 5.06 - 5.16 (2 H, m), 4.37 (1 H, dd, *J*=9.00, 5.04 Hz), 3.92 (4 H, t, *J*=3.05 Hz), 3.75 (3 H, s), 1.64 - 1.92 (4 H, m), 1.37 - 1.60 (5 H, m). LC (Cond. OL1): R_t = 1.95 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{19}H_{26}NO_6$: 364.18; found: 364.27.

Cap 176, step c



Ester *Cap 176, step b* (4.78 g, 13.15 mmol) was dissolved in THF (15 mL) followed by sequential addition of water (10 mL), glacial acetic acid (26.4 mL, 460 mmol) and dichloroacetic acid (5.44 mL, 65.8 mmol). The resulting mixture was stirred for 72 h at ambient temperature, and the reaction was quenched by slow addition of solid Na_2CO_3 with vigorous stirring until the release of gas was no longer visible. Crude product was extracted into 10% ethyl acetate-dichloromethane and the organic layers were combined, dried ($MgSO_4$) filtered and concentrated. The resulting residue was purified via Biotage (0 to 30% EtOAc/Hex; 25 g column) to afford ketone *Cap 176, step c* (3.86g) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.28 - 7.41 (5 H, m), 5.55 (1 H, d, *J*=8.28 Hz), 5.09 (2 H, s), 4.46 (1 H, dd, *J*=8.16, 5.14 Hz), 3.74 (3 H, s), 2.18 - 2.46 (5 H, m), 1.96 - 2.06 (1 H, m), 1.90 (1 H, ddd, *J*=12.99, 5.96, 2.89 Hz), 1.44 - 1.68 (2 H, m, *J*=12.36, 12.36, 12.36, 12.36, 4.77 Hz). LC (Cond.. OL1): R_t = 1.66 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342.13; found: 342.10.

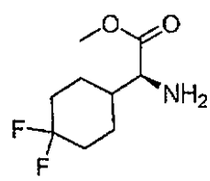
Cap 176, step d



Deoxo-Fluor® (3.13 mL, 16.97 mmol) was added to a solution of ketone *Cap 176, step c* (2.71 g, 8.49 mmol) in CH_2Cl_2 (50 mL) followed by addition of a catalytic ammount of EtOH (0.149 mL, 2.55 mmol). The resulting yellowish solution was stirred at rt overnight. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (25 mL) and the mixture was extracted with EtOAc (3X75 mL)). The combined organic layers were dried ($MgSO_4$), filtered and dried to give a yellowish oil. The residue was purified via Biotage chromatography (2% to 15% EtOAc/Hex; 90g column) and a white solid corresponding to the difluoro amino acid dilforide *Cap*

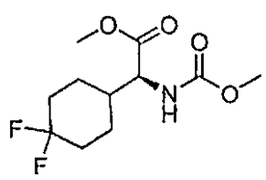
176, step d (1.5 g) was recovered. ^{1}H NMR (400 MHz, , $CDCl_3$-*d*) δ ppm 7.29 - 7.46 (5 H, m), 5.34 (1 H, d, *J*=8.28 Hz), 5.12 (2 H, s), 4.41 (1 H, dd, *J*=8.66, 4.89 Hz), 3.77 (3 H, s), 2.06 - 2.20 (2 H, m), 1.83 - 1.98 (1 H, m), 1.60 - 1.81 (4 H, m), 1.38 - 1.55 (2 H, m). ^{19}F NMR (376 MHz, $CDCl_3$-*d*) δ ppm -92.15 (1 F, d, *J*=237.55 Hz), -102.44 (1 F, d, *J*=235.82 Hz). LC (Cond. OL1): R_t = 1.66 min. LC/MS: Anal. Calcd. For $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705.28; found: 705.18.

Cap 176, step e



Difluoride *Cap 176, step d* (4 g, 11.72 mmol) was dissolved in MeOH (120 mL) and charged with Pd/C (1.247 g, 1.172 mmol). The suspension was flushed with N_2 (3x) and the reaction mixture was placed under 1 atm of H_2 (balloon). The mixture was stirred at ambient temperature for 48 h. The suspension was then filtered though a plug of Celite and concentrated under vacuum to give an oil that corresponded to amino acid *Cap 176, step e* (2.04 g) and that was used without further purification. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 3.62 (3 H, s), 3.20 (1 H, d, *J*=5.77 Hz), 1.91 - 2.09 (2 H, m), 1.50 - 1.88 (7 H, m), 1.20 - 1.45 (2 H, m). ^{19}F NMR (376 MHz, *DMSO-d*$_6$) δ ppm -89.39 (1 F, d, *J*=232.35 Hz), -100.07 (1 F, d, *J*=232.35 Hz). ^{13}C NMR (101 MHz, *DMSO-d*$_6$) δ ppm 175.51 (1 C, s), 124.10 (1 C, t, *J*=241.21, 238.90 Hz), 57.74 (1 C, s), 51.39 (1 C, s), 39.23 (1 C, br. s.), 32.02 - 33.83 (2 C, m), 25.36 (1 C, d, *J*=10.02 Hz), 23.74 (1 C, d, *J*=9.25 Hz). LC (Cond. OL2): R_t = 0.95 min. LC/MS: Anal. Calcd. For $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415.22; found: 415.40.

Cap 176, step f



Methyl chloroformate (1.495 mL, 19.30 mmol) was added to a solution of amino acid *Cap 176, step e* (2 g, 9.65 mmol) and DIEA (6.74 mL, 38.6 mmol) in

CH_2Cl_2 (100 mL). The resulting solution was stirred at rt for 3 h and volatiles were removed under reduced pressure. The residue was purified via Biotage (0% to 20% EtOAc/Hex; 90g column). A clear oil that solidified upon standing under vacuum and corresponding to carbamate *Cap-176, step f* (2.22 g) was recovered. ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 5.27 (1 H, d, *J*=8.55 Hz), 4.39 (1 H, dd, *J*=8.85, 4.88 Hz), 3.77 (3 H, s), 3.70 (3 H, s), 2.07 - 2.20 (2 H, m), 1.84 - 1.96 (1 H, m), 1.64 - 1.82 (4 H, m), 1.39 - 1.51 (2 H, m). ^{19}F NMR (471 MHz, $CDCl_3$-*d*) δ ppm -92.55 (1 F, d, *J*=237.13 Hz), -102.93 (1 F, d, *J*=237.12 Hz). ^{13}C NMR (126 MHz, $CDCl_3$-*d*) δ ppm 171.97 (1 C, s), 156.69 (1 C, s), 119.77 - 125.59 (1 C, m), 57.24 (1 C, br. s.), 52.48 (1 C, br. s.), 52.43 (1 C, s), 39.15 (1 C, s), 32.50 - 33.48 (2 C, m), 25.30 (1 C, d, *J*=9.60 Hz), 24.03 (1 C, d, *J*=9.60 Hz). LC (Cond. OL1): R_t = 1.49 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288.10; found: 288.03.

Cap-176

A solution of LiOH (0.379 g, 15.83 mmol) in Water (25 mL) was added to a solution of carbamate *Cap-176, step f* (2.1 g, 7.92 mmol) in THF (75 mL) and the resulting mixture was stirred at ambient temperature for 4 h. THF was removed under vacuum and the remaining aqueous phase was acidified with 1N HCl solution (2 mL) and then extracted with EtOAc (2 X 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a white foam corresponding to *Cap-176* (1.92 g). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 12.73 (1 H, s), 7.50 (1 H, d, *J*=8.78 Hz), 3.97 (1 H, dd, *J*=8.53, 6.02 Hz), 3.54 (3 H, s), 1.92 - 2.08 (2 H, m), 1.57 - 1.90 (5 H, m), 1.34 - 1.48 (1 H, m), 1.27 (1 H, qd, *J*=12.72, 3.26 Hz). ^{19}F NMR (376 MHz, *DMSO-d*$_6$) δ ppm -89.62 (1 F, d, *J*=232.35 Hz), -99.93 (1 F, d, *J*=232.35 Hz). LC (Cond. OL2): R_t = 0.76 min. LC/MS: Anal. Calcd. For $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250.09; found: 250.10.

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.

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. Unless noted otherwise, the LC conditions employed in determining the retention time (R_t) were:

Cond.-J1

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

Cond.-J2

Column	= Phenomenex-Luna 3.0X 50 mm S10
Start %B	= 0
Final %B	= 100
Gradient time	= 4 min
Stop time	= 5 min
Flow Rate	= 4 mL/min
Wavelength	= 220 nm
Slovent A	= 0.1% TFA in 10% methanol/90%water

	Solvent B	= 0.1% TFA in 90% methanol/10% water
	Cond.-J3	
	Column	= XTERRA C18 S7 (3.0 x 50mm)
	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%water
	Solvent B	= 0.1% TFA in 90% methanol/10% water
	Cond.-D1	
	Column	= Phenomenex-Luna 3.0X50 mm S10
	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%water
	Solvent B	= 0.1% TFA in 90% methanol/10% water
	Cond.-D2	
	Column	= Phenomenex-Luna 4.6X50 mm S10
	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%water

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

Cond.-JB-1

Column = Waters Sunfire 5u C18 4.6x30mm

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

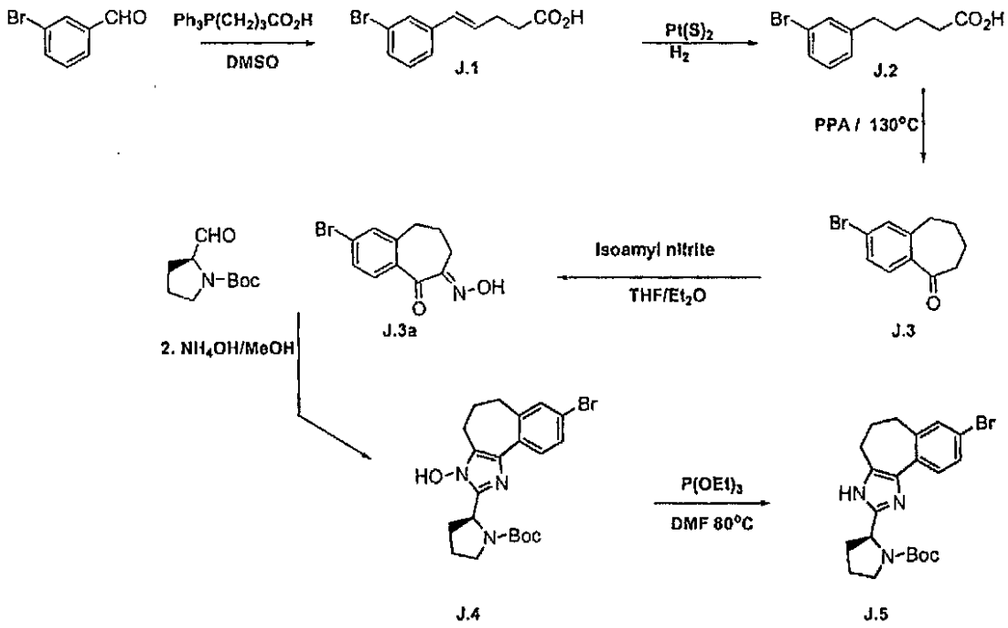
Flow Rate = 4 mL/min

Wavelength = 220 nm

Slovent A = 0.1% TFA in 10%acetonitrile/90%water

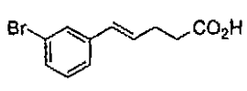
Solvent B = 0.1% TFA in 90% acetonitirle/10% water

Synthetic Route 1:



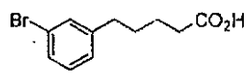
Reference: *J.Med.Chem.* (2005) 48, 7351.

Examples J.1 – J.5



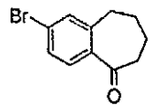
J.1

A 1M solution of potassium tert-butoxide in tetrahydrofuran (80 mL) was added dropwise to (3-carboxypropyl)triphenylphosphonium bromide (17 g, 40 mol) in anhydrous DMSO (20 mL) under nitrogen at 24 °C, and the solution was stirred 30 min. before addition of 3-bromobenzaldehyde (4.7 mL, 40 mmol). After several minutes a precipitate was observed and an additional 20 mL of DMSO was added to aid solvation, and the reaction was stirred 18 h. The solution was poured onto water (120 mL) and washed with chloroform. The aqueous layer was acidified with conc. HCl and extracted with chloroform (3 x 250 mL). The organic phase was concentrated and applied to a 65i Biotage silica gel column, gradient elution from 15-65% B (A = Hexanes; B = ethyl acetate) over 2L to give J.1, (E)-5-(3-bromophenyl)pent-4-enoic acid, 8.2 g (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (t, J = 1.5 Hz, 1H), 7.30 (dt, J = 7.7, 1.5 Hz, 1H), 7.2-7.16 (m, 1H), 7.12 (t, J = 7.7 Hz, 1H), 6.40-6.32 (m, 1H), 6.23-6.14 (m, 1H), 2.52 (s, 4H). LC (Cond.-J1): RT = 2.0 min; LRMS: Anal. Calcd. for [M-H]$^-$ $C_{11}H_{11}BrO_2$: 252.97; found: 252.98.



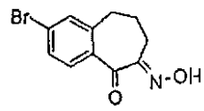
J.2

J.1, (E)-5-(3-Bromophenyl)pent-4-enoic acid (4 g, 15.8 mmol) was dissolved in absolute ethanol (200 mL) and flushed with nitrogen before addition of 5% platinum sulfide on carbon (2.5 g). The solution was flushed with hydrogen at atmospheric pressure and stirred 5 h. The catalyst was removed by filtration over diatomaceous earth (Celite®) and the solvent immediately removed by rotory evaporation (in order to minimized esterification) to give J.2, 5-(3-bromophenyl)pentanoic acid 4 g (99%) which was carried forward without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.30 (m, 2H), 7.13 (t, J = 7.6 Hz, 1H), 7.09-7.07 (d, J = 7.6 Hz, 1H), 2.60 (t, J = 7.0 Hz, 2H), 2.37 (t, J = 7.0 Hz, 2H), 1.68-1.65 (m, 4H). LC (Cond.-J1): RT = 2.1 min; LRMS: Anal. Calcd. for [M-H]$^-$ $C_{11}H_{13}BrO_2$: 255.00; found: 254.99.



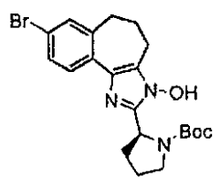
J.3

J.2, 5-(3-bromophenyl)pentanoic acid (4 g, 15.6 mmol) was taken up in polyphosphoric acid (15 g) and heated to 140 °C for 8 h in a 150 mL pressure vessel, capped to prevent product loss due to sublimation. The reaction mixture was partitioned between 150 mL of water and dichloromethane (600 mL). [Caution is necessary to avoid boiling of dichloromethane.] The organic phase was washed with water, brine, and concentrated. The crude product was applied to a 40 (S) Biotage silica gel column and gradient eluted from 5 – 60% (ethyl acetate/hexanes) and gave J.3 2-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 1.7 g (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 1H), 7.41 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 2.86 (t, J = 5.9 Hz, 2H), 2.69 (t, J = 5.8 Hz, 2H), 1.90-1.73 (m, 4H). LC (Cond.-J1): RT = 2.1 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{11}BrO$: 239.00; found: 239.14.



J.3a

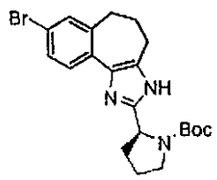
J.3, 2-Bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1.5 g, 5.9 mmol) was dissolved in 2:1 ether/tetrahydrofuran (120 mL) and 1N HCl in ether (9 mL) was added. The solution was cooled to 0 °C before addition of isoamyl nitrite (1.2 mL, 9 mmol) and the reaction was stirred 18 h at 24 °C, concentrated, and applied to 25 (M) Biotage silica gel column. Gradient elution from 15-100% B (A = Hexanes; B = ethyl acetate) over 1L and gave J.3a (E)-2-bromo-6-(hydroxyimino)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 1 g (64%). LC (Cond.-J1); RT = 1.9 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{10}NBrO_2$: 268; found: 268.



J.4

Concentrated ammonium hydroxide (12 mL, 28%) was added to a solution of J.3a(E)-2-bromo-6-(hydroxyimino)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one

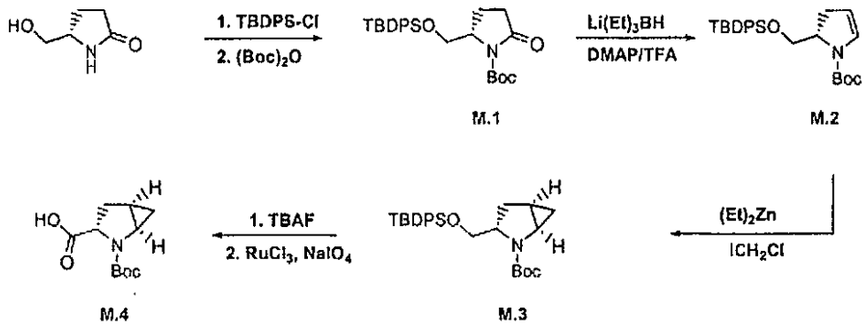
(1g, 3.7 mmol) and N-Boc-L-prolinal (850 mg, 4.3 mmol) in methanol (35 mL) and the reaction stirred 18 h at 24 °C. The reaction mixture was concentrated to remove methanol, the aqueous solution extracted with dichloromethane, and the organic phase washed with water. Application of the crude product in dichloromethane to a 40 (S) Biotage silica gel column and subjection to gradient elution; Segment 1. 15%-30% B over 300 mL; Segment 2. 30%-100% B over 700 mL (A = 1:1 hexanes/dichloromethane; B = ethyl acetate) gave J.4 700 mg (44%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.3 (br. s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4, 1.5 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 5.0/4.87 (m, 1H), 3.51-3.46 (m, 1H), 3.42-3.36 (m, 1H), 2.90-2.70 (m, 4H), 2.27-1.80 (m, 6H), 1.38/1.11 (s, 9H). LC (Cond.-J1): RT = 1.9 min; LRMS: Anal. Calcd. For $[M+H]^+$ $C_{21}H_{26}BrN_3O_3$: 488.12; found: 488.14. HRMS: Anal. Calcd. for $[M+H]^+C_{21}H_{26}BrN_3O_3$: 488.1236; found: 488.1242.



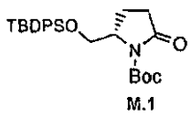
J.5

Triethyl phosphite (0.78 mL, 4.7 mmol) was added to a solution of J.4 (700 mg, 1.57 mmol) in dimethylformamide (2 mL) and the solution heated at 80 °C for 18 h under a nitrogen atmosphere. The reaction mixture was taken up in ethyl acetate (100 mL) and washed with water and brine. After concentration the crude product was applied to a 40 (S) Biotage silica gel column and subjected to gradient elution; Segment 1. 5%-15% B over 300 mL; Segment 2. 15%-100% B over 600 mL (A = dichloromethane; B = ethyl acetate) to give J.5 675 mg (100%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.7 (br. s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 4.78/4.69 (br s, 1H), 3.57-3.48 (m, 1H), 3.38-3.32 (m, 1H), 2.85-2.78 (m, 4H), 2.28-1.77 (m, 6H), 1.39/1.14 (s, 9H). LC (Cond.-J1): RT = 1.9 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{26}BrN_3O_2$: 432.13; found: 432.14.

Synthetic Route 2



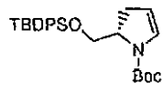
Examples M.1 - M.4



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

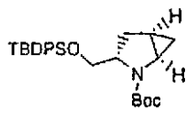
Di-tert-butyl dicarbonate (38.5 g, 177 mmol) was added in portions as a solid over 10 min to a dichloromethane (200 mL) solution of silyl ether (31.2 g, 88.3 mmol), Et_3N (8.93 g, 88 mmol), and DMAP (1.08 g, 8.83 mmol) and stirred for 18 h at 24 °C. Most of the volatile material was removed in vacuo and the crude material taken up in 20% ethyl acetate/hexanes and applied to a 2 L funnel containing 1.3 L of silica gel and then eluted with 3 L of 20% ethyl acetate/hexane and 2 L of 50% ethyl acetate). Upon concentration of the desired fractions in a rotary evaporator, a white slurry of solid formed which was filtered, washed with hexaness and dried in vacuo to afford carbamate M.1 as a white solid (32.65 g, 82% yield). ^{1}H NMR (400 MHz,

DMSO-d_6, δ = 2.5 ppm) 7.61-7.59 (m, 2H), 7.56-7.54 (m, 2H), 7.50-7.38 (m, 6H), 4.18 (m, 1H), 3.90 (dd, J = 10.4, 3.6, 1H), 3.68 (dd, J = 10.4, 2.1, 1H), 2.68-2.58 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.12 (m, 1H), 2.01-1.96 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H). LC/MS $[M\text{-Boc}+H]^+$ = 354.58. Calcd. 454.24.



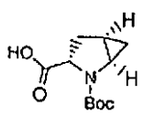
M.2

A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with carbamate M.1 (10.05 g, 22.16 mmol) and toluene (36 mL), and lowered into -55 °C cooling bath. When the internal temperature of the mixture reached -50 °C, lithium triethylborohydride (23 mL of 1.0 M/tetrahydrofuran, 23.00 mmol) was added dropwise over 30 min and the mixture stirred for 35 min while maintaining the internal temperature between -50 °C and -45 °C. Hunig's base (16.5 mL, 94 mmol) was added dropwise over 10 min. Then, DMAP (34 mg, 0.278 mmol) was added in one batch, followed by the addition of trifluoroacetic anhydride (3.6 mL, 25.5 mmol) over 15 min, while maintaining the internal temperature between -50 °C and -45 °C. The bath was removed 10 min later, and the reaction mixture was stirred for 14 h while allowing it to rise to ambient temperature. It was diluted with toluene (15 mL), cooled with an ice-water bath, and treated slowly with water (55 mL) over 5 min. The phases were separated and the organic layer washed with water (50 mL, 2x) and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel; 5% ethyl acetate/hexanes) to afford dihydropyrrole M.2 as a colorless viscous oil (7.947 g, 82% yield). Rt = 2.41 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 methanol/water; B = 0.1% TFA in 9:1 methanol/water) over 2 min and hold for 1 min; detection @ 220 nm; Phenomenex-Luna 3.0X50 mm S10 column. ^{1}H-NMR (400 MHz, DMSO-d_6, δ = 2.5 ppm) 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (br s, 1H), 5.07/5.01 (overlapping br d, 1H), 4.18 (br s, 1H), 3.89 (br s, 0.49H), 3.69 (br s, 1.51H), 2.90-2.58 (br m, 2H), 1.40/1.26 (overlaping br s, 9H), 0.98 (s, 9H). LC/MS: $[M+Na]^+$ = 460.19.



M.3

Diethylzinc (19 mL of ~1.1 M in toluene, 20.9 mmol) was added dropwise over 15 min to a cooled (-30 °C) toluene (27 mL) solution of dihydropyrrole M.2 (3.94 g, 9.0 mmol). Chloroiodomethane (stabilized over copper; 3.0 mL, 41.2 mmol) was added dropwise over 10 min, and stirred while maintaining the bath temperature at -25 °C for 1 h and between -25 °C and -21 °C for 18.5 h. The reaction mixture was opened to the air and quenched by the slow addition of 50% saturated $NaHCO_3$ solution (40 mL), and then removed from the cooling bath and stirred at ambient temperature for 20 min. It was filtered through a filter paper and the white cake was washed with 50 mL of toluene. The organic phase of the filtrate was separated and washed with water (40 mL, 2x), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified using a Biotage system (350 g silica gel; sample was loaded with 7% ethyl acetate/hexanes; eluted with 7-20% ethyl acetate/hexanes) to afford a mixture of methanopyrrolidines (M.3 predominates) as a colorless viscous oil (3.69 g, 90.7%). [Note: the exact cis/trans-isomer ratio was not determined at this stage]. Rt = 2.39 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 methanol/water; B = 0.1% TFA in 9:1 methanol/water) over 2 min, and hold for 1 min; detection @ 220 nm; Phenomenex-Luna 3.0X50 mm S10 column. ^{1}H-NMR (400 MHz, DMSO-d_6, δ= 2.5 ppm) 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.77/3.67 (overlapping br s, 3H), 3.11-3.07 (m, 1H), 2.23 (app br s, 1H), 2.05-2.00 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (very broad s, 9H), 1.00 (s, 9H), 0.80 (m, 1H), 0.30 (m, 1H). LC/MS: $[M+Na]^+$ = 474.14.



M.4

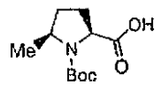
TBAF (7.27 mL of 1.0 M in tetrahydrofuran, 7.27 mmol) was added dropwise over 5 min to a tetrahydrofuran (30 mL) solution of silyl ethers M.3 (3.13 g, 6.93 mmol) and the mixture stirred at ambient temperature for 4.75 h. After the addition

of saturated ammonium chloride solution (5 mL), most of the volatile material was removed in vacuo and the residue partitioned between dichloromethane (70 mL) and 50% saturated ammonium chloride solution (30 mL). The aqueous phase was extracted with dichloromethane (30 mL), and the combined organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo and then exposed to high vacuum overnight. The crude material was purified using a Biotage (silica gel; 40-50% ethyl acetate/hexanes) to afford a mixture of alcohols, contaminated with traces of a lower Rf spot, as a colorless oil (1.39 g, ~94% yield). [Note: the exact cis/trans isomer ratio was not determined at this stage.] ^{1}H-NMR (400 MHz, dimethylsulfoxide-d_6, δ= 2.5 ppm) 4.70 (t, J = 5.7, 1H), 3.62-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.33-3.27 (m, 1H), 3.08-3.04 (m, 1H), 2.07 (br m, 1H), 1.93-1.87 (m, 1H), 1.51-1.44 (m, 1H), 1.40 (s, 9H), 0.76-0.71 (m, 1H), 0.26 (m, 1H). LC/MS $[M+Na]^+$ = 236.20.

A semi-solution of sodium periodate (6.46 g, 30.2 mmol) in water (31 mL) was added to a solution of alcohols (2.15 g, 10.08 mmol) in acetonitrile (20 mL) and carbon tetrachloride (20 mL). Ruthenium trichloride (0.044 g, 0.212 mmol) was added immediately and the heterogeneous reaction mixture was stirred vigorously for 75 min. The reaction mixture was diluted with water (60 mL) and extracted with dichloromethane (50 mL, 3x). The combined organic phase was treated with 1 mL methanol, allowed to stand for about 5 min, and then filtered through diatomaceous earth. The pad was washed with dichloromethane (50 mL), and the filtrate was concentrated in vacuo to afford a light charcoal-colored solid. The crude material was dissolved in ethyl acetate (~10 mL) with heating and allowed to stand at ambient temperature with seeding. About 15 min into the cooling phase, a rapid crystal formation was observed. About 1 h later, hexanes (~6 mL) was added and the mixture refrigerated overnight (it did not appear that additional material precipitated out). The mixture was filtered and washed with ice/water-cooled hexanes/ethyl acetate (2:1 ratio; 20 mL) and dried under high vacuum to afford the first crop of acid M.4 (off-white crystals, 1.222 g). The mother liquor was concentrated in vacuo, and the residue dissolved in ~3 mL of ethyl acetate with heating, allowed to stand at ambient temperature for 1 h, and then 3 mL hexanes was added and stored in a refrigerator for ~15 h. A second crop of acid M.4 was retrieved similarly (grey crystals, 0.133 g), for a combined yield of 59%. Rt = 1.48 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A =

0.1% TFA in 1:9 methanol/water; B = 0.1% TFA in 9:1 methanol/water) over 3 min; detection @ 220 nm; Phenomenex-Luna 3.0X50 mm S10 column. MP (dec.) for the first crop = 147.5-149.5 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, δ = 2.5 ppm) 12.46 (s, 1H), 3.88 (app br s, 1H), 3.27 (app br s, 1H; overlapped with water signal), 2.28 (br m, 1H), 2.07 (app br s, 1H), 1.56 (app s, 1H), 1.40/1.34 (two overlapped s, 9H), 0.71 (m, 1H), 0.45 (m, 1H). ^{13}C-NMR (100.6 MHz, DMSO-d_6, δ = 39.21 ppm) 172.96, 172.60, 154.45, 153.68, 78.74, 59.88, 59.58, 36.91, 31.97, 31.17, 27.77, 27.52, 14.86, 14.53, 13.69. LC/MS $[M+Na]^+$ = 250.22. Anal. Calcd. For C11H17NO4: C, 58.13; H, 7.54; N, 6.16. Found (for first crop): C, 58.24; H, 7.84; N, 6.07. Optical rotation (10 mg/mL in CHCl3): [α] D = -216 and -212 for the first and second crop, respectively.

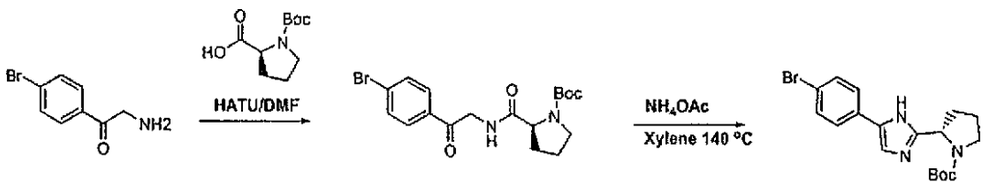
ExampleM.4a



M.4a

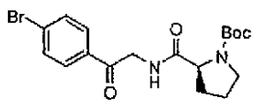
The synthesis of acid M.4a is reported in patent application: US2009/0068140.

Synthetic Route 3



J.6 J.7

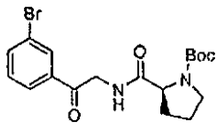
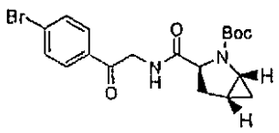
Examples J.6 – J.7b

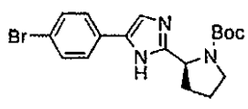


J.6

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-bromo-

phenyl)ethanone (8.127 g, 32.44 mmol), in dimethylformamide (105 mL) and stirred at ambient condition for 55 minutes. Dimethylformamide 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. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 50-60 % ethyl acetate/hexanes) to provide J.6 (S)-tert-butyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)pyrrolidine-1-carboxylate 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.-J1): RT = 1.70 min; LCMS: Anal. Calcd. For $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; found 433.09.

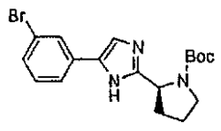
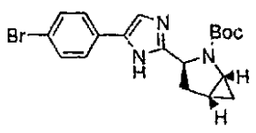
J.6a		LRMS: Anal. Calcd. For $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; found: 433.12
J.6b	 From M.4	LC (Cond.-J1): RT = 1.7 min; Anal. Calcd. For $[M+Na]^+$ $C_{19}H_{23}BrN_2NaO_4$: 445.08; found: 446.93.



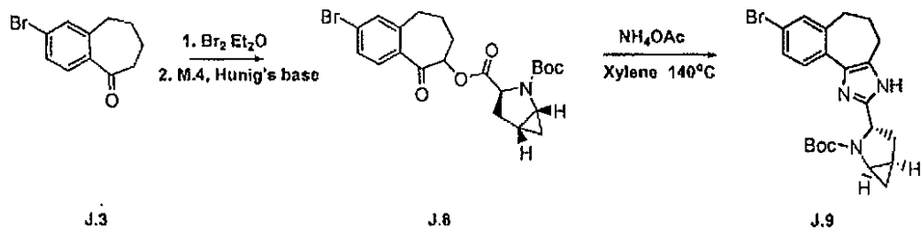
J.7

A mixture J.6 (S)-tert-butyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-pyrrolidine-1-carboxylate (12.8 g, 31.12 mmol) and ammonium acetate (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. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of J.7 (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate, 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. ^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.-J1): RT = 1.71 min; 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.

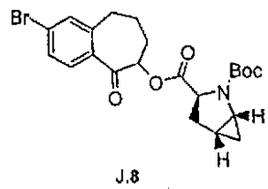
J.7a	 From J.6a	LRMS: Anal. Calcd. For $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; found: 391.96.
J.7b	 From J.6b	LC (Cond.-J1): RT = 1.5 min; Anal. Calcd. For $[M+H]^+$ $C_{19}H_{23}BrN_3O_2$: 405.09; found: 406.04.

Synthetic Route 4



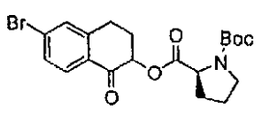
J.3 J.8 J.9

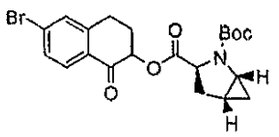
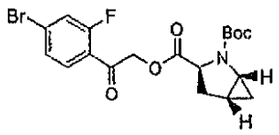
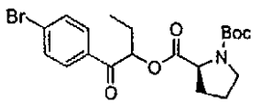
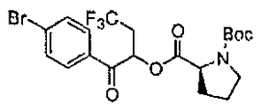
Examples J.8 – J.9e

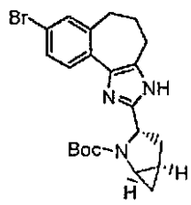


J.8

Bromine (0.23 mL, 4.18 mmol) was added dropwise to a solution of J.3 2-Bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1.0 g, 4.18 mmol) in ether (50 mL), after being cooled to 0 °C. The solution was stirred 3 h and a few drops of additional bromine was and while the reaction was followed by TLC until complete. The solvent was removed by rotory evaporation, the residue was taken up in acetonitrile (25 mL), M.4 (950 mg, 4.18 mmol), and Hunig's base (1.4 mL) added dropwise. The reaction was stirred 18 hours at 60 °C prior to removal of the solvent by rotory evaporation. The crude product charged (dichloromethane) to a 40 g Thompson silica gel cartridge and gradient elution 15 - 100% B over 1L (A/B hexanes/ethyl acetate) gave J.8 (1R,3S,5R)-3-(2-bromo-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl) 2-tert-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate 1 g (51.5 %) as an oil. RT = 2.2 minutes (Cond.-J1). LCMS: Anal. Calcd. for $C_{22}H_{26}BrNO_5Na$: 486.10; found: 486.07 $(M+Na)^+$.

J.8a (Derived from 6-bromo tetral-1-one purchased from *J* & W PharmLab, LLC)		RT = 3.1 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}BrNO_5$: 438; found: 438.

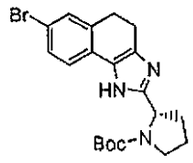
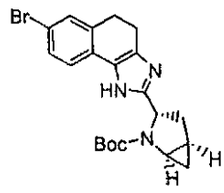
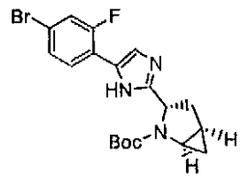
J.8b (Derived from 6-bromo tetral-1-one purchased from *J* & W PharmLab, LLC)	 From M.4	RT = 2.99 min (Cond. D2), LCMS: Calcd for $C_{21}H_{25}BrNO_5$ $[M+Na]^+$ 472.07; found: 472.10
J.8c (Derived from 4-bromo 2-fluoroacetophenone)	 From M.4	RT = 2.87 min (Cond. D2), LCMS: Calcd for $C_{29}H_{22}BrFNO_5$ $[M+H]^+$ 464.05; found: 463.98
J.8d Derived from 1-(4-bromophenyl)butan-1-one)		RT = 2.2 min, (Cond.-J1); Calcd for $C_{20}H_{27}BrNO_5$ $[M-Boc]^+$ 340.11; found: 340.02.
J.8e Derived from 1-(4-bromophenyl)-4,4,4-trifluorobutan-1-one		RT = 2.21 min, (Cond.-J1); Calcd for $C_{20}H_{24}BrF_3NO_5$ $[M-Boc]^+$394.08; found: 394.03.

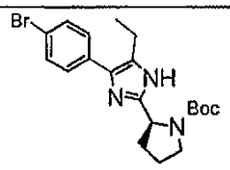
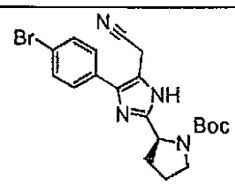


J.9

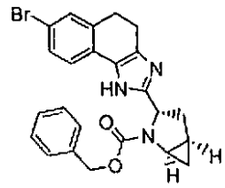
Ammonium acetate (1.7 g, 21.54 mmol) was added to a solution of J.8 (1.0 g, 2.15 mmol) in xylene (15 mL) and the reaction mixture stirred at 140 °C for 3 h in a screw-cap pressure vessel. After being cooled, the reaction mixture was partitioned between ethyl acetate and sat'd $NaHCO_3$ soln, and the aqueous layer was extracted

with ethyl acetate. The combined organic layers were washed with brine, concentrated, and the residue applied to 20 g Thomson silica gel column. Gradient elution (10-50% B over 1 L; A/B hexanes/ethyl acetate). The major and less polar product (oxazole 450 mg) was separated away to afford J.9 192 mg (20 %) as a diastereomeric mixture (favoring J.9; a 3:1 mixture of S/R proline). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6/10.3 (br. s, 1H), 8.06 (d, J = 8.2 Hz, 0.6H), 7.34 (dd, J = 6.4, 1.8 Hz, 1H), 7.28 (s, 0.3H), 7.21 (d, J = 1.8 Hz, 0.7H), 7.11 (d, J = 8.6 Hz, 0.3H), 4.83-4.77 (m, 1H), 3.48 (m, 0.68H), 3.23 (m, 1.2H), 2.98 (t, J = 6.4 Hz, 0.65H), 2.88 (t, H = 6.7 Hz, 1.35H), 2.82-2.79 (m, 2H), 2.33 (t, J = 9.1 Hz, 1H), 2.01-1.95 (m, 2.4H), 1.76-1.72 (m, 1H), 1.57/1. 48 (s, 9H), 0.87-0.83 (m, 1.3H), 0.44 (br. s, 1H). LC (Cond.-J1): RT = 1.7 min; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{26}BrN_3O_2$: 444.13; found: 444.07.

J.9a	 From J.8a	RT = 2.4 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}BrN_3O_2$: 418.11; found: 418.10.
J.9b	 From J.8b	RT = 2.3 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430.11; found: 430.16. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430.1125; found 430.1123.
J.9c	 From J.8c	RT = 2.2 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{22}BrFN_3O_2$: 422.09; found: 422.10. HRMS: Anal. Calcd. for

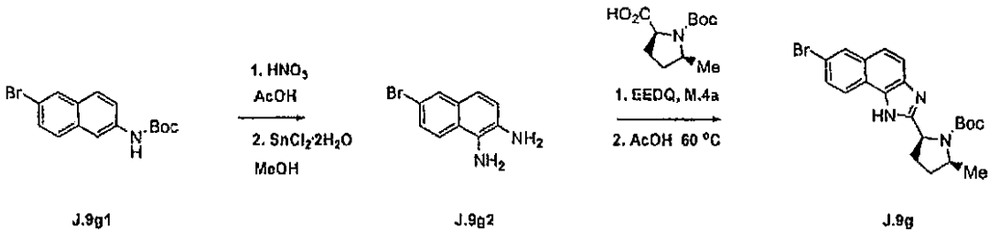
		$[M+H]^+$ $C_{19}H_{22}BrFN_3O_2$: 422.0877; found 422.0874.
J.9d	 From J.8d	RT = 1.69 min, (Cond.-J1); Calcd for $C_{20}H_{27}BrN_3O_2$ $[M+H]^+$ 420.13; found: 420.13.
J.9e Obtained as the more polar product of a ~1:1 mixture containing the CF_3 analog.	 From J.8e	RT = 1.55 min, (Cond.-J1); Calcd for $C_{20}H_{24}BrN_4O_2$ $[M+H]^+$ 431.11; found: 431.15.

Example J.9f



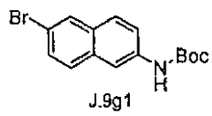
A cold (0 °C) solution of HCl (0.871 mL, 3.49 mmol, 4*N* in dioxanes) was added to a solution of J.9b (1.5 g, 3.49 mmol) in MeOH (20 mL). The mixture was stirred for 2 h before it was concentrated to dryness. The tan solid was taken up in dioxane (20 mL) and water (20 mL), cooled to 0 °C, and treated with sodium carbonate (0.369 g, 3.49 mmol) and CBZ-Cl (0.498 mL, 3.49 mmol). The reaction mixture was allowed to warm up to room temperature, stirred for 5 h, diluted with ethyl acetate, and washed with saturated sodium bicarbonate solution. The organic phase was washed with brine and dried over sodium sulfate to yield J.9f (0.97 g, 60%) as a tan foam, RT = 2.47 min (Cond.-D1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{23}BrN_3O_2$: 464.10 and 466.10; found: 463.95 and 465.98.

Synthetic Route 4.a



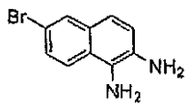
J.9g1 J.9g2 J.9g

Examples J.9g1 – J.9g



J.9g1

Diphenylphosphoryl azide (17.09 mL, 79 mmol) was added to a solution of 6-bromo-2-naphthoic acid (16.5 g, 65.7 mmol), triethylamine (18.32 mL, 131 mmol), and *tert*-butylalcohol (7.54 mL, 79 mmol) in toluene (225 mL) and stirred for 4 h at 100 °C. The volatiles were removed by rotary evaporation and the residue taken up in EtOAc (500 mL) and washed with water and brine. A precipitate formed upon concentration which was isolated by filtration and washed with 1:1 Et_2O/Hex to give Example J.9g1 (10.5 g). A second crop of less pure product was isolated upon concentration of the mother liquor (9.8 g); combined yield (93%). LC/MS (Cond. J2): RT = 3.44 min. LC/MS Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{16}BrNO_2$: 345.02; found 345.03.

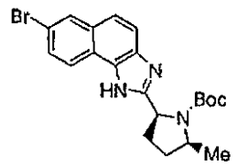


J.9g2

Example J.9g1 (5 g, 15.52 mmol) was diluted in acetic acid (50 mL) and fuming nitric acid (2.3 mL) was added dropwise over 20 min. The reaction was stirred for 2 h and the product, isolated by filtration, was partitioned between CH_2Cl_2 and sat'd $NaHCO_3$ soln. The organic layer was concentrated to provide tert-butyl 6-bromo-1-nitronaphthalen-2-ylcarbamate 5.7 g (quant). LC/MS (Cond. J2): RT = 3.52 min. LC/MS Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{15}BrN_2O_4$: 390.02.; found 390.99.

Tin(II)chloride dehydrate (3 g, 16.34 mmol) was added to a solution of tert-butyl 6-bromo-1-nitronaphthalen-2-ylcarbamate (2 g, 5.47 mmol) in MeOH (100 mL)

and the solution was stirred for 18 h at 70 °C. The solvent was removed by rotary evaporation and Example J.9g2 (assume theoretical 1.25 g) was dried under high vacuum. LC/MS (Cond. J2): RT = 1.49 min. LC/MS Anal. Calcd. for $[M+H]^+$ $C_{10}H_9BrN_2$: 237.00; found 236.96.

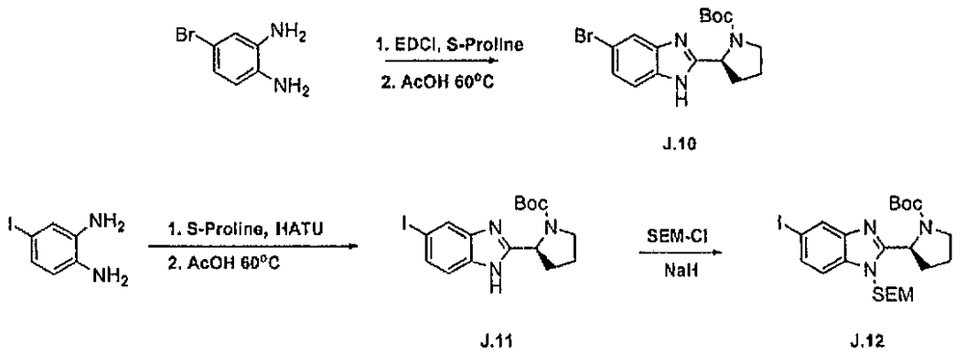


J.9g

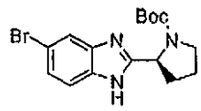
EEDQ (1.67 g, 6.75 mmol) was added to a solution of Example J.9g2 (1.6 g, 6.75 mmol) and M.4a (1.55 g, 6.75 mmol) in DCM (100 mL) and stirred for 6h. (Note: The dianiline was not completely soluble). The reaction mixture was diluted with DCM (1 vol) and washed with half sat'd $NaHCO_3$ soln. Concentration gave a solid (2.5 g). LC/MS (Cond. J2): RT = 3.07 min. LC/MS Anal. Calcd. for $[M+H]^+$ $C_{21}H_{27}BrN_3O_3$: 448.13; found 448.11.

The crude solid (2.5 g, 5.58 mmol) was taken up in AcOH (200 mL) and stirred for 18 h at 60 °C. Concentration under high vacuum removed the solvent. The residue was taken up in DCM, washed with sat'd $NaHCO_3$ soln, and concentrated. The residue was charged (DCM) to a 80 g Thompson silica gel cartridge and gradient elution was performed from 15% to 100% B over 750 mL. (A/B Hex/EtOAc) to give Example J.9g (2.6 g). ^1H NMR (MeOD, 500 MHz, δ): 8.36-8.35 (m, 2H), 8.0 (d, J = 9Hz, 1H), 7.91 (dd, J = 9, 2 Hz, 1H), 7.87 (d, J = 9 Hz, 1H), 5.31-5.28 (m, 1H), 4.17 (br. s, 1H), 2.59-2.56 (m, 1H), 2.39-2.31 (m, 2H) 1.86-1.83 (m, 1H), 1.52-1.19 (m, 12H). LC/MS (Cond. J2): RT = 2.57 min. LC/MS Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430.12; found 430.09.

Synthetic Route 5

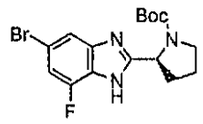
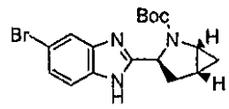
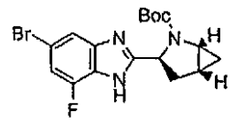
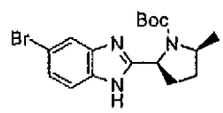


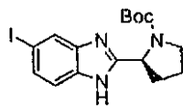
Examples J.10 –J.12



J.10

EDCI•HCl (2.35 g, 12.25 mmol) was added to a mixture of 4-bromobenzene-1,2-diamine (2.078 g, 11.11 mmol), N-Boc-L-proline (2.311 g, 10.74 mmol) and 1-hydroxybenzotriazole (1.742 g, 12.89 mmol) in dichloromethane (40 mL), and stirred at ambient conditions for 19 h. The mixture was then diluted with dichloromethane, washed with water (2x), dried (brine; $MgSO_4$), filtered, and concentrated in vacuo to provide a brown foam. Acetic acid (40 mL) was added to the foam, and the mixture was heated at 65 °C for 90 min. The volatile component was removed in vacuo, and the residue was dissolved in ethyl acetate and washed carefully with saturated $NaHCO_3$ solution (2x), and the organic phase was dried (brine; $MgSO_4$), filtered, and concentrated in vacuo. The resultant crude material was submitted to flash chromatography (silica gel; ethyl acetate) to provide J.10 as a tan foam (2.5 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.49-12.33 (four br s, 1H), 7.71 (d, J = 2, 0.54H), 7.60 (app br s, 0.46H), 7.50 (d, J = 8.6, 0.45H), 7.40 (d, J = 8.4, 0.55H), 7.26 (m, 1H), 4.96-4.87 (m, 1H), 3.64-3.51 (m, 1H), 3.44-3.38 (m, 1H), 2.38-2.21 (m, 1H), 1.99-1.85 (m, 3H), 1.39 (s, 3.7H), 1.06 (s, 5.3H). (Cond.-D2) LC/MS: Anal. Calcd. for [M+H]+ $C_{16}H_{21}BrN_3O_2$: 368.03; found: 368.18.

J.10a		RT = 1.9 min (Cond.-J1) LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{16}H_{20}BrN_3NaFO_2$: 406.06; found: 406.06.
J.10b	 From M.4	RT = 1.7 min (Cond.-D2) LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{20}BrN_3NaO_2$: 400.06; found: 400.09
J.10c	 From M.4	RT = 1.9 min (Cond.-J1) LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{20}BrN_3NaFO_2$: 418.06; found: 418.06.
J.10d	 From M.4a	RT = 2.0 min (Cond.-J2) LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{23}BrN_3O_2$: 380.10; found: 380.03.

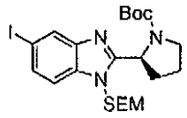


J.11

4-Iodo-2-nitroaniline (35.2 g, 0.133 mol) was added in batches via an open funnel over 25 min to a heated (65 °C) mixture of $SnCl_2.2H_2O$ (106.86 g, 0.465 mol) and 12N HCl (200 ml). An additional 12N HCl (30 ml) was added and the reaction mixture was heated at 65 °C for an additional 1 h, and stirred at room temperature for 1 h. It was placed in a refrigerator for 15 h, and the precipitate was filtered. The resultant solid was transferred into a flask containing water (210 ml), cooled (ice/water), and a solution of NaOH (aq) (35 g in 70 ml of water) was added to it over 10 min with stirring. The cooling bath was removed, and vigorous stirring was continued for 45 min. The mixture was filtered and the solid was washed with water and dried in vacuo to provide 4-iodobenzene-1,2-diamine as a tan solid (25.4 g). The product was used in the next step without further purification. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 500 MHz): 6.79 (d, J = 2,1H), 6.63 (dd, J = 1.9, 8.1, 1H), 6.31 (d, J = 8.1, 1H), 4.65 (br s, 2H), 4.59 (br s, 2H). LC/MS: Anal. Calcd. for [M+H]+ $C_6H_8IN_2$: 234.97; found: 234.9.

HATU (6.5 g, 17.1 mmol) was added to a solution of 4-iodobenzene-1,2-diamine (4 g, 17.1 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (3.67 g, 17.1 mmol), and Hunig's base (3 mL) in dimethylformamide (100 mL). The reaction mixture was stirred for 4 h before being diluted with ethyl acetate (300 mL) and washed with sat'd $NaHCO_3$, brine, and dried (Na_2SO_4). The aqueous phase was extracted twice more with ethyl acetate and combined with the initial organic extract prior to drying. Concentration gave a residue which was taken up in glacial acetic acid (100 mL) and heated at 65 °C for 2h. The cooled mixture was concentrated in vacuo, diluted with ethyl acetate (300 mL) and 1N NaOH solution (to pH = 10), washed with brine, and dried (Na_2SO_4). The crude product was applied applied to a 65 (i) Biotage silica gel cartridge. Segment 1. Hold 15% B for 450 mL; Segment 2. Gradient elution from 15% to 100% B over 4.5 L (A = hexane; B = ethyl acetate); Segment 3. Hold 100% B for 2.5 L to give J.11 tert-butyl 2-(5-iodo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-(S)-carboxylate 7.0 g (99%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (br.s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.34 (br. s, 1H), 4.97-

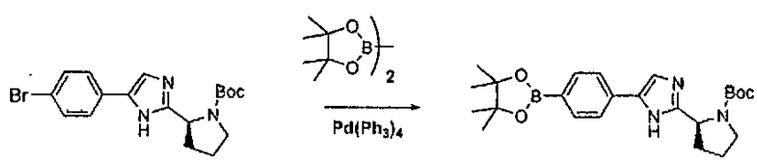
4.84 (m, 1H), 3.6 (br. s, 1H), 3.44-3.40 (m, 1H), 2.37-2.25 (m, 1H), 1.99-1.87 (m, 3H), 1.4/ 1.07 (s, 9H). LC (Cond.-D2): 2.1 min; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{20}IN_3O_2$: 414.07; found: 414.08.



J.12

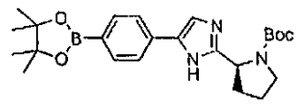
Unwashed 60% sodium hydride (48 mg, 1.21 mmol) was added in one portion to a stirred solution of J.11 tert-butyl 2-(5-iodo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-(S)-carboxylate (500 mg, 1.21 mmol) in dry dimethylformamide (10 mL) under nitrogen. The mixture was stirred 5 min before addition of SEM-Cl (0.21 mL, 1.21 mmol), stirred for 3 h, quenched with sat'd ammonium chloride (1 mL), diluted with ethyl acetate (50 mL), and the organic phase was washed with sat'd $NaHCO_3$ soln and brine. The aqueous phase was extracted twice more with ethyl acetate and combined with the initial organic extract prior to drying. Concentration gave a residue applied which was applied (dichloromethane) to a 40 (i) Biotage silica gel cartridge. Segment 1. Hold 5% B for 150 mL; Segment 2. Gradient elution from 5% to 100% B over 2.5 L (A = hexane; B = ethyl acetate) B to give regioisomeric products (SEM location) J.12 316 mg (48 %). ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 5.8 Hz, 1H), 7.54-7.49 (m, 2H), 5.77-5.64 (m, 2H), 5.20-5.11 (m, 1H), 3.61-3.43 (m, 4H), 2.89-2.05 (m, 2H), 1.98-1.87 (m, 2H), 1.36/1.04 (s, 9H), 0.91-0.81 (m, 2H), -0.06 (s, 9H). LC (Cond.-D2): RT = 3.1 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{34}IN_3O_3Si$: 544.15; found: 544.15.

Synthetic Route 6.



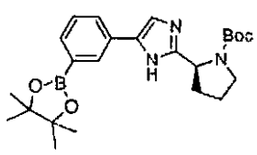
J.7 J.13

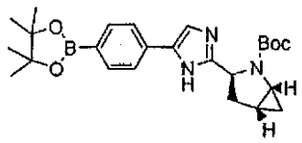
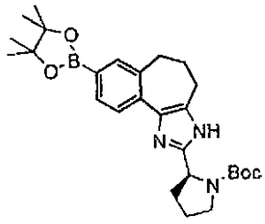
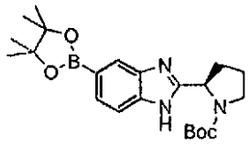
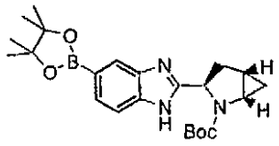
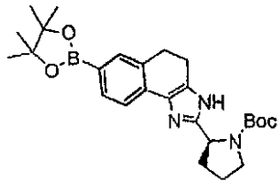
Examples J.13 – J.13f



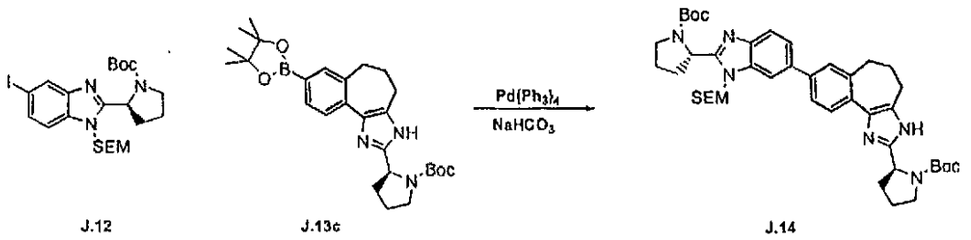
J.13

$Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of J.7 (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (4 g, 10.22 mmol), bis(pinacolato)diboron (5.4 g, 21.35 mmol), potassium acetate (2.6 g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated (oil bath 80 °C) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude material was partitioned carefully between dichloromethane (150 mL) and an aqueous medium (50 mL water + 10 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with dichloromethane, 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/dichloromethane) to provide J.13 (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, contaminated with pinacol, as an off-white dense solid; the relative mole ratio of J.13 to pinacol was about 10:1 (^{1}H NMR). The sample weighed 3.9 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.-J1): RT = 1.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

J.13a	 From J.7a	RT = 1.6 min (Cond.-J1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found: 440.36.

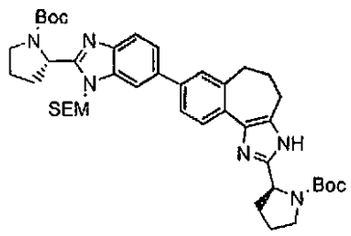
J.13b	 From J.7b	RT = 1.6 min (Cond.-J1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{35}BN_3O_4$: 452.27; found: 452.17.
J.13c	 From J.5	RT = 1.9 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{38}BN_3O_4$: 480; found: 480.
J.13d	 From J.10	RT = 1.7 (Cond.-J1) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{33}BN_3O_4$ 414.25; found: 414.28.
J.13e	 From J.10a	RT = 2.1 (Cond.-D2) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{33}BN_3O_4$ 426.29; found: 426.21.
J.13f	 From J.9a	RT = 2.46 (Cond.-D2) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{37}BN_3O_4$ 466.28; found: 466.33.

Synthetic Route 7



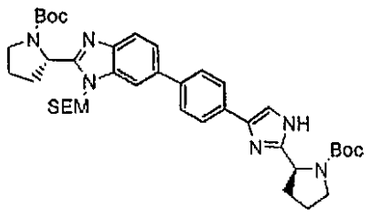
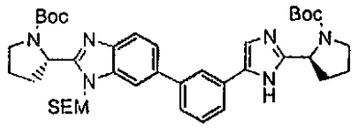
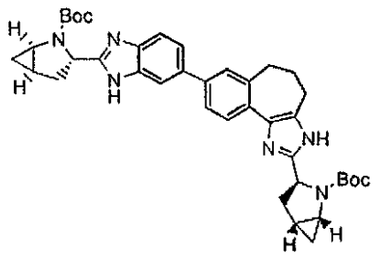
J.12 J.13c J.14

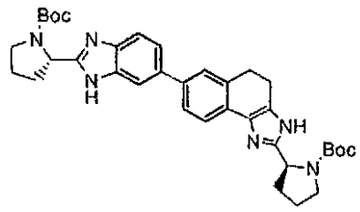
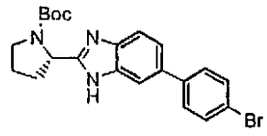
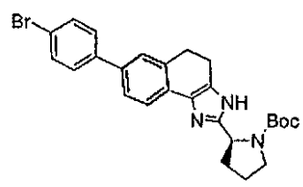
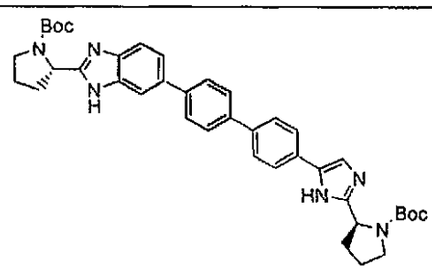
Examples J.14 – J.14f.1

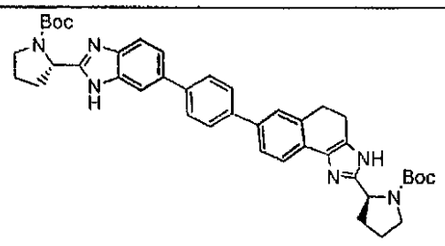


J.14

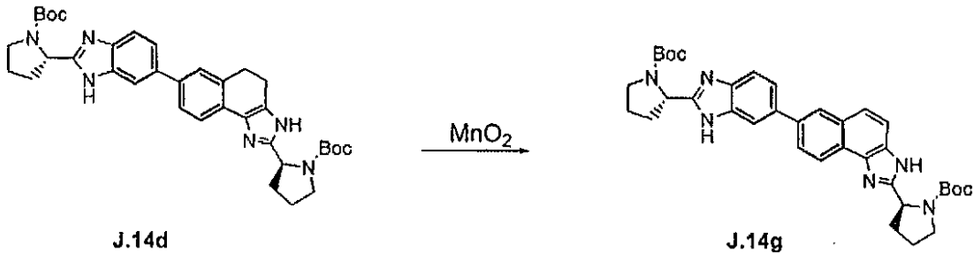
The benzimidazole J.12 (250 mg, 0.46 mmol), boronic ester J.13c (217 mg, 0.46 mmol), and $NaHCO_3$ (95 mg, 1.13 mmol) were dissolved in 1,2-dimethoxyethane (4.5 mL) and water (1.1 mL) was added. The reaction mixture was evacuated and flushed with nitrogen (3x), $Pd(Ph_3P)_4$ (26 mg, 0.022 mmol) was added, and the mixture heated (oil bath at 80°C) in a capped pressure vessel for 14 h. After being cooled, the solution was partitioned into ethyl acetate/water and the organic layer washed with sat'd $NaHCO_3$, brine, and dried (Na_2SO_4). Concentration gave a residue which was applied to a 25M Biotage SiO_2 column pre-equilibrated with 25%B (300 mL). Gradient elution; Segment 1: 25% B (60 mL); Segment 2: 25-100% B (1440 mL); Segment 3: Hold at 100% (600 mL). A = Hexanes; B = ethyl acetate gave J.14, 101.1 mg (29%). ^1H NMR (500 MHz, DMSO-d_6) δ 8.10-8.09 (m, 1H), 7.96/7.91 (s, 1H), 7.65-7.47 (m, 4H), 5.85-5.70 (m, 2H), 5.12/5.14 (s, 1H), 4.83/4.73 (s, 1H), 3.62-3.54 (m, 4H), 3.48-3.26 (m, 2H), 2.90 (br. s, 4H), 2.37-1.84 (m, 10H), 1.42/1.08 (s, 9H), 1.37/1.06 (s, 9H), 0.92-0.83 (m, 2H), 0.06 (s, 9H). LC (Cond.-D2): 2.8 min; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{61}N_6O_5Si$ 769.45; found: 769.43. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{61}N_6O_5Si$: 769.4473; found 769.4484.

J.14a	 From J.12 and J.13	RT = 2.71 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$ 729.42; found: 729.43. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$: 729.4160; found: 729.4188.
J.14b	 From J.12 and J.13a	RT = 2.75 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$ 729.42; found: 729.44. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$: 729.4160; found: 729.4191.
J.14c	 From J.13e and J.9	RT = 1.6 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{46}N_6O_4$ 663.37; found: 663.46. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{46}N_6O_4$ 663.3653;

		found: 663.3648.
J.14d	 From J.13d and J.9a	RT = 2.11 min, (Cond.-D2); Calcd for $C_{36}H_{45}N_6O_4$ $[M+H]^+$ 625.35; found: 625.42. HRMS: Calcd for $C_{36}H_{45}N_6O_4$ $[M+H]^+$ 625.3497; found: 625.3486.
J.14e	 From J.13d and 1,4-dibromobenzene	RT = 1.83 min, (Cond.-J1); Calcd for $C_{22}H_{25}BrN_3O_2$ $[M+H]^+$ 442.12; found: 442.20.
J.14e.1	 From J.13f and 1,4-dibromobenzene	RT = 2.40 min, (Cond.-D2); Calcd for $C_{26}H_{29}BrN_3O_2$ $[M+H]^+$ 494.15; found: 494.14.
J.14f	 From J.14e and J.13	RT = 1.66 min, (Cond.-J1); Calcd for $C_{40}H_{47}N_6O_4$ $[M+H]^+$ 675.36; found: 675.52.

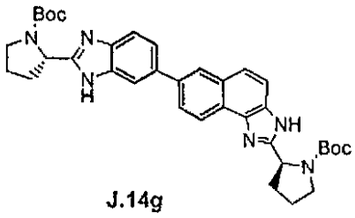
J.14f.1	 From J.13d and J.14e.1	RT: 2.15 min, (Cond.-D1); Calcd for $C_{42}H_{49}N_6O_4$ $[M+H]^+$ 701.38; found: 701.35.

Synthetic Route 8



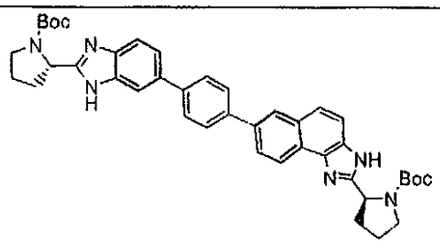
J.14d J.14g

Examples J.14g – J.14g.1

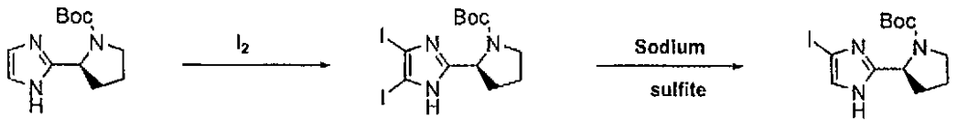


J.14g

Activated manganese dioxide (122 mg, 1.409 mmol) was added in one portion to a stirred solution of J.14d (S)-tert-butyl 2-(7-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (88 mg, 0.141 mmol) in dry dichloromethane (2 mL). The suspension was stirred for 14 h and additional manganese dioxide (1.5 g) was added. The suspension was stirred for 16 h and manganese dioxide (1.5 g) was added again and allowed to continue stirring for 24h. The reaction mixture was filtered through diatomaceous earth (Celite®), concentrated, and placed on high vacuum for 1 h. There was isolated J.14g (85.0 mg, 92 %) as a yellowish-orange solid, LCMS: 2.14 min (Cond.-D2) Calcd. for $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623.33; found: 623.46. HRMS: Calcd for $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623.3340; found: 623.3327.

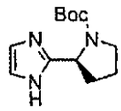
J.14g.1	 From J.14f.1	RT: 2.20 min, (Cond.-D1); Calcd for $C_{42}H_{47}N_6O_4$ $[M+H]^+$ 699.37; found: 699.32.

Synthetic Route 8a



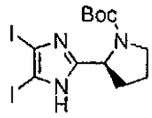
JB.1 JB.2 JB.3

Examples JB.1 – JB.3



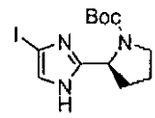
JB.1

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 (8.56 g, 43.0mmol) 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, EtOAc) followed by a recrystallization (EtOAc, room temperature) to provide (S)-tert-butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate (4.43g) as a white fluffy solid. ^1H NMR (DMSO-d_6, 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). RT = 0.87 min (Cond.-JB.1) LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$: 238.16; found 238.22. The compound shown to have a 98.9 ee% when analyzed under the chiral HPLC conditions 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*)



JB.2

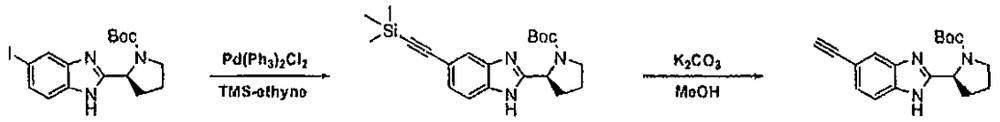
Iodine was (16.17 g, 63.7 mmol) was added to a solution of Example JB.1 (6.87 g, 29.0 mmol) and sodium carbonate (9.21 g, 87 mmol) in dioxane (72 mL) and water (72 mL) at ambient temperature. The flask was covered with aluminum foil and stirred for 16 hours. The reaction mixture was diluted with EtOAc and a saturated aqueous solution of sodium thiosulfate. The mixture was stirred for 15 minutes and the phases were separated. The layers were separated and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford (S)-tert-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (12.5 g) as a tan solid. ^1H NMR (500 MHz, MeOD) δ ppm 4.72 - 4.84 (m, 1H), 3.58 - 3.70 (m, 1H), 3.43 - 3.54 (m, 1H), 2.36 (br s, 1H), 1.88 - 2.08 (m, 3H), 1.47 (br s, 3H), 1.27 (br s, 6H). RT = 1.40 min (Cond.-JB.1) LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{17}I_2N_3O_2$: 488.94 Found; 489.96.



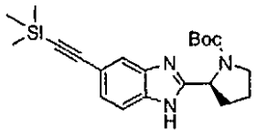
JB.3

Sodium sulfite (10.31 g, 82 mmol) was added to a solution of Example JB.2 (4.0 g, 8.2 mmol) in ethanol (75 mL) and water (75 mL). The suspension was heated with an oil bath at 100°C for 4 hours and at 90°C for 16h. The reaction was diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted several times with EtOAc. The combined organic phases were dried (brine, Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by a flash chromatography (sample was dry loaded on silica gel and eluted with, 0 to 40% ethyl acetate/CH_2Cl_2) to afford (S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (2.17 g) as a white solid. ^1H NMR (500 MHz, MeOD) δ ppm 7.52-7.64 (m, 1H), 4.95 - 5.10 (m, 1H), 3.57 - 3.70 (m, 1H), 3.47 - 3.57 (m, 1H), 2.37 - 2.55 (m, 1H), 1.94 - 2.10 (m, 3H), 1.46 (s, 4H), 1.27 (s, 5H). RT = 0.93 min (Cond.-JB.1) LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}IN_3O_2$ 363.04; Found: 364.06.

Synthetic Route 9

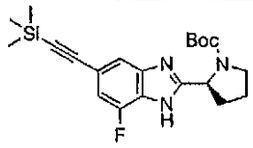
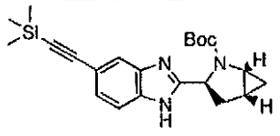


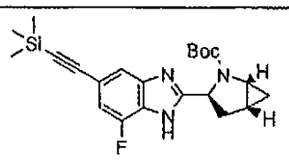
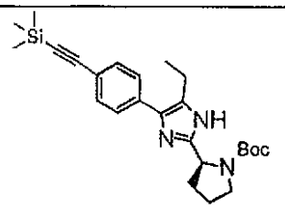
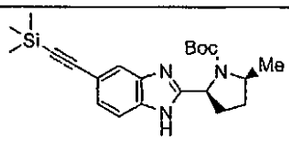
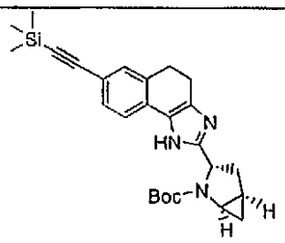
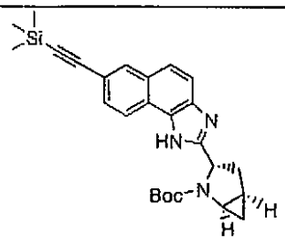
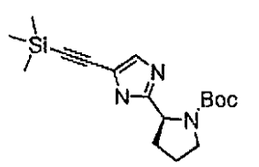
Examples J.15 – JB.4



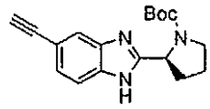
J.15

A mixture of copper iodide (299.6 mg, 48.1 mmol) and $Pd(PPh_3)_2Cl_2$ (1.29 g, 4.41 mmol) was added to a dimethylformamide (200 ml) solution of J.11 (16.0 g, 38.7 mmol), (trimethylsilyl)acetylene (6.8 ml, 48.1 mmol), and triethylamine (16 ml), and the reaction mixture was stirred at ~25 °C for 19.5 h. The volatile component was removed *in vacuo* and a silica gel mesh was prepared from the residue and submitted to a flash chromatography (silica gel; eluting with 40% ethyl acetate/hexanes) to provide alkyne J.15 as a tan foam (13.96 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.52-12.38 (m, 1H), 7.62-7.41(m, 2H), 7.24-7.19 (m, 1H), 5.01-4.85 (m, 1H), 3.64-3.51 (m, 1H), 3.46-3.35 (m, 1H), 2.38-2.21 (m, 1H), 2.07-1.81 (m, 3H), 1.39 (s, 4H), 1.04 (s, 5H), 0.23 (s, 9H). RT = 2.09 min (Cond.-J1) LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{30}N_3O_2Si$: 384.21; found: 384.27.

J.15a	 From J.10a	RT = 1.89 min, (Cond.-J1); Calcd for $C_{21}H_{29}N_3O_2Si$ $[M+H]^+$ 402.20; found: 402.26.
J.15b	 From J.10b	RT = 1.92 min, (Cond.-J1); Calcd for $C_{22}H_{30}N_3O_2Si$ $[M+H]^+$ 396.21; found: 396.22.

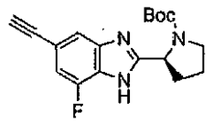
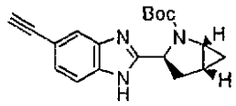
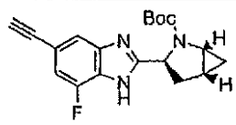
J.15c	 From J.10c	RT = 2.2 min, (Cond.-J1); Calcd for $C_{22}H_{29}FN_3O_2Si$ $[M+H]^+$ 414.20; found: 414.26.
J.15d	 From J.9d	RT = 1.70 min, (Cond.-J1); Calcd for $C_{25}H_{36}N_3O_2Si$ $[M+H]^+$ 438.26; found: 438.33.
J.15d.1	 From J.10.d	RT = 1.70 min, (Cond.-J1); Calcd for $C_{22}H_{32}N_3O_2Si$ $[M+H]^+$ 398.23; found: 398.19.
J.15e	 From J.9b	RT = 2.43 min, (Cond.-D1); Calcd for $C_{26}H_{34}N_3O_2Si$ $[M+H]^+$ 448.24; found: 448.82.
J.15f	 From J.15e according to the procedure described for J.14g.	LCMS: 2.51 min, (Cond.-D1); Calcd for $C_{26}H_{32}N_3O_2Si$ $(M+H)^+$ 446.23; found: 446.05.
JB.4	 From JB.3	LCMS: 1.5 min, (Cond.-JB.1); Calcd for $C_{17}H_{28}N_3O_2Si$ $(M+H)^+$ 334.20; found: 334.14.

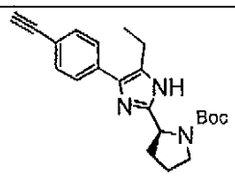
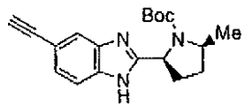
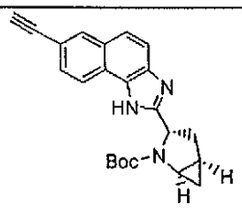
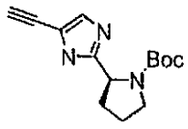
Examples J.16 – JB.5



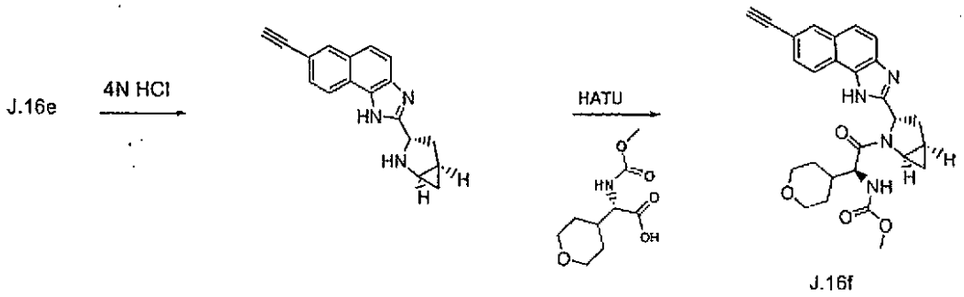
J.16

Potassium carbonate (0.5526 g, 4 mmol) was added to solution of alkyne J.15 (13.9 g, 36 .2 mmol) in methanol (200 ml) and the mixture was stirred at room temperature for 17 h. The volatile component was removed *in vacuo*, and the residue was partitioned between ethyl acetate and saturated ammonium chloride (aq) solution, and the organic layer was separated and washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide alkyne J.16 as a tan foam (9.3 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.58-12.30 (br s, 1H), 7.72-7.36 (two overlapping app br s, 2H), 7.23 (d, J = 8.1, 1H), 4.97-4.88 (m, 1H), 4.02 (s, 1H), 3.64-3.52 (m, 1H), 3.44-3.36 (m, 1H), 2.40-2.20 (m, 1H), 2.06-1.81 (m, 3H), 1.39 (s, 4H), 1.05 (s, 5H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{21}N_3NaO_2$: 334.15; found: 334.24.

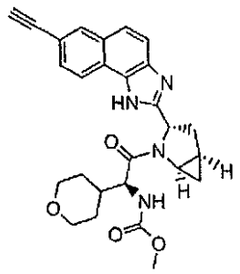
J.16a	 From J.15a	RT = 1.69 min, (Cond.-J1); Calcd for $C_{18}H_{20}N_3O_2$ $[M+Na]^+$ 352.14; found: 352.15.
J.16b	 From J.15b	RT = 1.40 min, (Cond.-J1); Calcd for $C_{19}H_{21}N_3O_2$ $[M+Na]^+$ 346.15; found: 346.19.
J.16c	 From J.15c	RT = 1.36 min, (Cond.-J1); Calcd for $C_{19}H_{20}FN_3O_2$ $[M+Na]^+$ 364.14; found: 364.15.

J.16d	 From J.15d	RT = 1.30 min, (Cond.-J1); Calcd for $C_{22}H_{28}N_3O_2$ $[M+H]^+$ 366.22; found: 366.25.
J.16d.1	 From J.15d.1	RT = 2.74 min, (Cond.-J2); Calcd for $C_{19}H_{24}N_3O_2$ $[M+H]^+$ 326.19; found: 326.13.
J.16e	 From J.15f	LCMS: 1.88 min, (Cond.-D1) Calcd for $C_{23}H_{24}N_3O_2$ $(M+H)^+$ 374.19; found: 374.04.
JB.5	 From JB.4	LCMS: 0.88 min, (Cond.-JB-1) Calcd for $C_{10}H_{11}N_3O_2$ (M+H; -tBu)$^+$ 206.10; found: 206.05.

Synthetic Route 9a



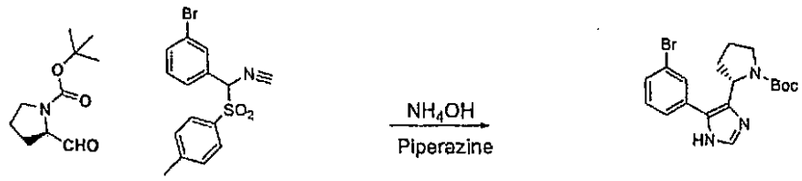
Example J.16f



J.16f

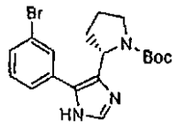
Example J.16f was obtained from Example J.16e according to the two step procedure described below. Deprotection as in the preparation of J.19 to formed an HCl salt which was coupled with cap-170 with HATU according the preparation of J.21 below to give J.16f RT = 1.59 min, (Cond.-D1); Calcd for $C_{27}H_{29}N_4O_4$ $[M+H]^+$ 473.22; found: 473.06.

Synthetic Route 10



J.17

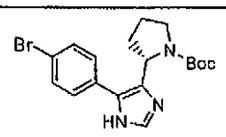
Example J.17 - 17.a



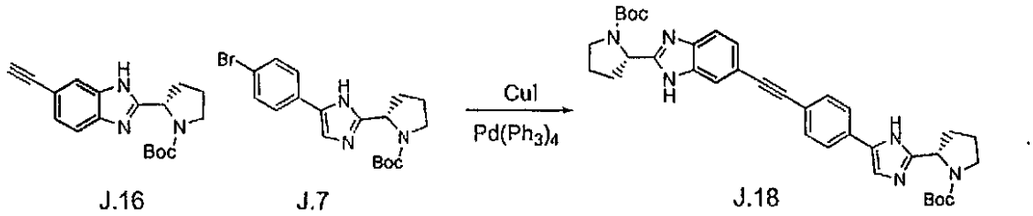
J.17

The ammonium hydroxide (4 mL) was added to a solution of (S)-prolinal (650 mg, 3.26 mmol) in tetrahydrofuran (15 mL) and stirred for 6 h at 48 °C in a sealed pressure vessel. α-tosyl-(3-bromobenzyl) isocyanide (974 mg, 2.77 mmol) and piperazine (281 mg, 3.26 mmol) were added and the reaction mixture stirred 18 h at at 48 °C. After being cooled, the reaction mixture was diluted with ethyl acetate (200 mL) and washed with water and brine and concentrated. The crude product was taken up in dichloromethane and charged to a 40 g Thomson silica gel cartridge.

Gradient elution was performed from 20-100% B over 750 mL gave J.17 (S)-tert-butyl 2-(5-(3-bromophenyl)-1H-imidazol-4-yl)pyrrolidine-1-carboxylate 413 mg (31%). ^{1}H NMR ($CDCl_3$, δ 500 MHz): 10.36/9.90 (br s, 1H), 7.75 (br s, 1H), 7.53 (br. s, 2H), 7.38 (br. s, 1H), 7.24 (br. s, 1H), 5.11 (br. s, 1H), 3.54 (br. s, 2H), 2.32/2.19 (m, 1H), 1.95-1.85 (m, 2H), 1.74 (s, 1H), 1.45/1.18 (s, 9H). RT = 1.7 (Cond.-J1) LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.09; found: 392.13.

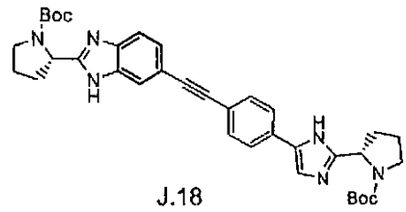
J.17a	 From α-tosyl-(4-bromobenzyl) isocyanide	RT = 1.7 min, (Cond.-J1); Calcd for $C_{18}H_{23}BrN_3O_2$ $[M+H]^+$ 392.09; found: 392.13.

Synthetic Route 11.



J.16 J.7 J.18

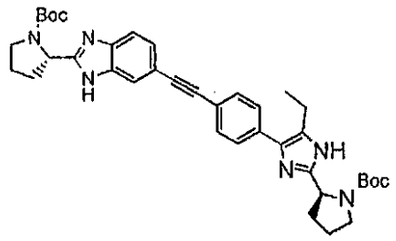
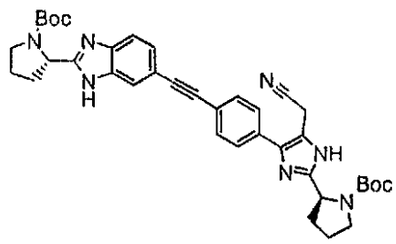
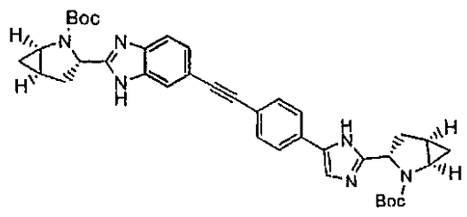
Examples J.18 – JB.6

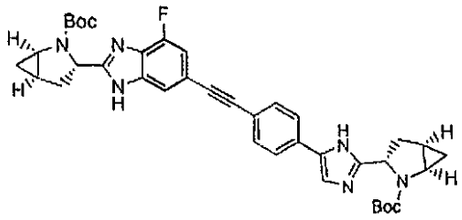
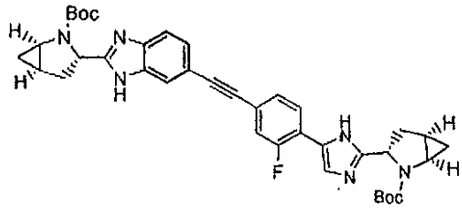
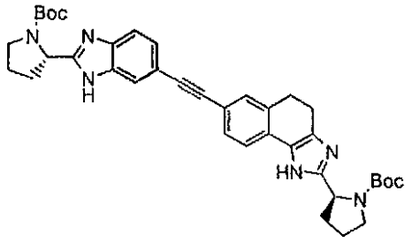


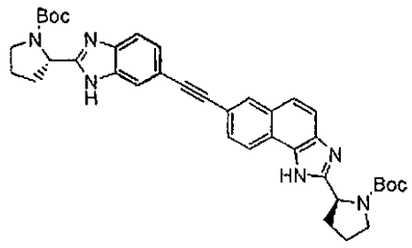
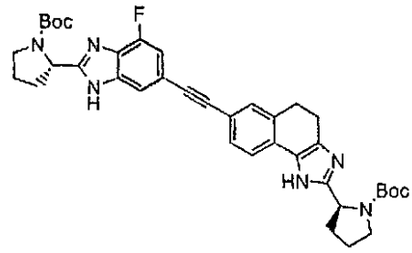
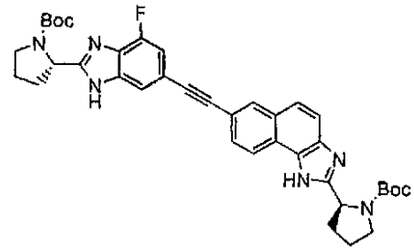
J.18

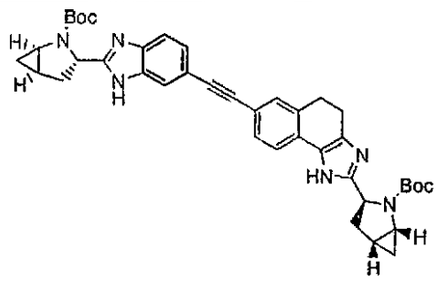
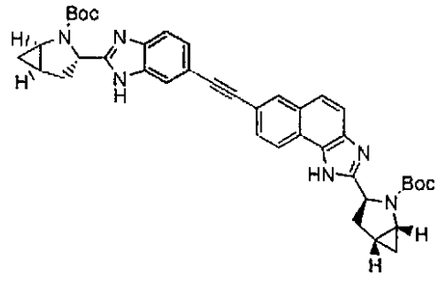
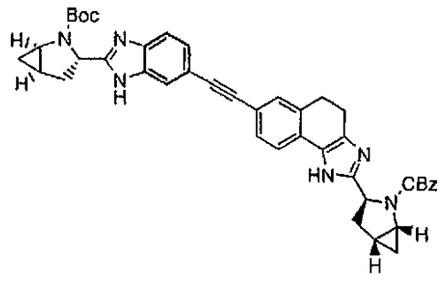
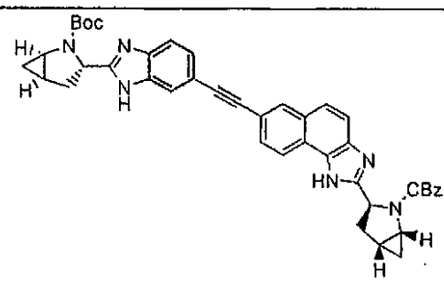
Copper iodide (9.8 mg, 0.051 mmol) and $Pd(PPh_3)_4$ (59.4 mg, 0.051 mmol) were added to a nitrogen purged solution of J.16 (S)-tert-butyl 2-(5-ethynyl-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (160 mg, 0.514 mmol) and J.7 (S)-tert-butyl 2-(4-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (171 mg, 0.437 mmol) containing Et_3N (0.2 mL) in dimethylformamide (3 mL) and the reaction mixture stirred at room temperature for 48 h. The volatile component was removed *in vacuo* and the residue was applied (dichloromethane) to 20 g Thomson

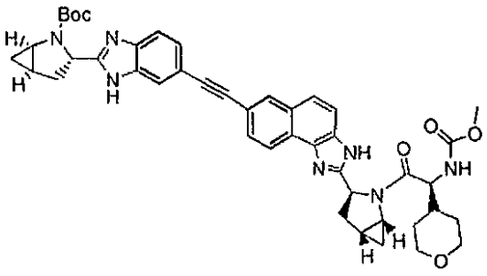
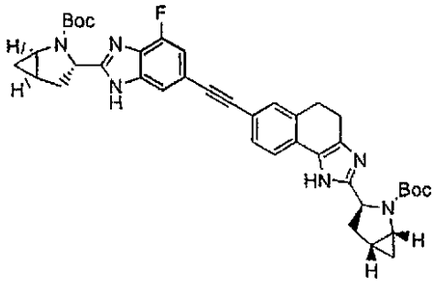
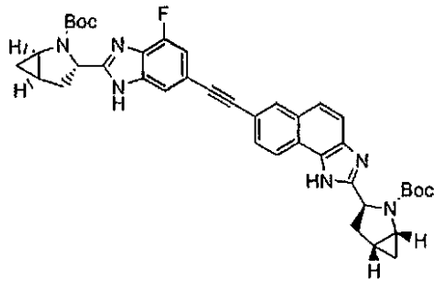
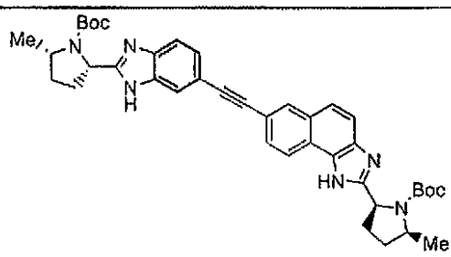
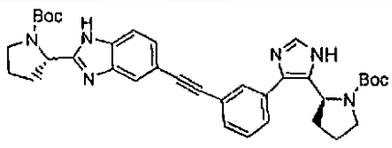
column and eluted with 50-100 % B over 500 mL (A/B dichloromethane /20%methanol in ethyl acetate) to provide J.18; 87 mg (26%). ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 10.97-10.51 (m, 2H), 7.9 (s, 0.41H), 7.75 (d, J = 8.2, 1.26H), 7.69-7.66 (m, 0.55H), 7.59 (s, 0.54H), 7.54-7.51 (m, 1.85H), 7.42-7.32 (m, 2H), 7.25 (s, 1H), 7.22 (br. s, 0.32) (br.s, 1H), 4.99-4.94 (m, 1H), 3.31 (br.s, 3H), 3.04/2.92 (br. s, 2H), 2.19-2.15 (m, 3H), 2.03-1.95 (m, 2H), 1.62/1.50 (br s, 20H). LC (Cond-J1): 1.6 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_6O_4$: 623.34; found: 623.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_6O_4$: 623.3340; found: 623.3344.

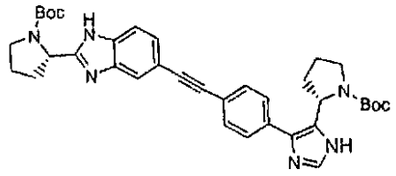
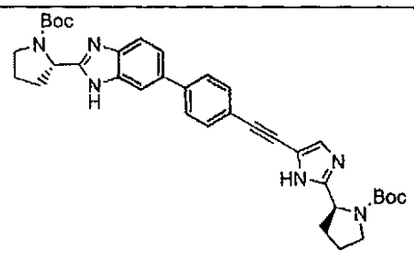
J.18.1	 From J.10 and J.16d	RT = 1.4 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_6O_4$ 651.36; found: 651.46.
J.18.2	 From J.16 and J.9e	RT = 1.34 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{44}N_7O_4$ 662.35; found: 662.35.
J.18a	 From J.16b and J.7b	RT = 1.6 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_6O_4$ 647.33; found:

		647.39.
J.18b	 From J.16c and J.7b	RT = 1.57 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}FN_6O_4$ 665.33; found: 665.49.
J.18c	 From J.16b and J.9c	RT = 1.42 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}FN_6O_4$ 665.33; found: 665.49.
J.18d	 From J.16 and J.9a	RT: 2.27 min, (Cond.-D2); Calcd for $C_{38}H_{45}N_6O_4$ $[M+H]^+$ 649.35; found: 649.49. HRMS: Calcd for $C_{38}H_{45}N_6O_4$ $[M+H]^+$ 649.3497; found: 649.3484.

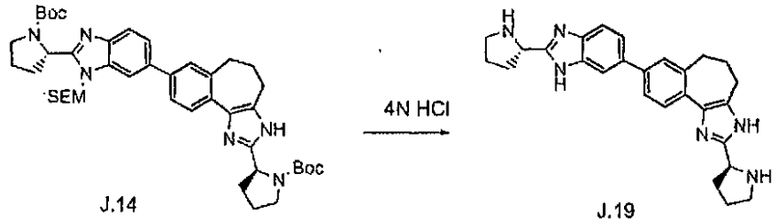
J.18e	 From J.18d according to the procedure described for J.14g.	RT: 2.31 min, (Cond.-D2); Calcd for $C_{38}H_{43}N_6O_4$ $[M+H]^+$ 647.33; found: 647.46. HRMS: Calcd for $C_{38}H_{43}N_6O_4$ $[M+H]^+$ 647.3340; found: 647.3328.
J.18f	 From J.16a and J.9a	RT: 1.61 min, (Cond.-J1); Calcd for $C_{38}H_{44}FN_6O_4$ $[M+H]^+$ 667.34; found: 667.46.
J.18g	 From J.18f according to the procedure described for J.14g.	RT: 1.64 min, (Cond.-J1); Calcd for $C_{38}H_{42}FN_6O_4$ $[M+H]^+$ 665.33; found: 665.49.

J.18h	 From J.16b and J.9b	RT: 1.44 min, (Cond.-J1); Calcd for $C_{40}H_{45}N_6O_4$ $[M+H]^+$ 673.35; found: 673.43.
J.18i	 From J.18h according to the procedure described for J.14g.	RT: 1.48 min, (Cond.-J1); Calcd for $C_{40}H_{43}N_6O_4$ $[M+H]^+$ 670.34; found: 670.46.
J.18i.1	 From J.16b and J.9f	RT: 2.03 min, (Cond.-D1); Calcd for $C_{43}H_{43}N_6O_4$ $[M+H]^+$ 707.34; found: 707.28.
J.18i.2	 From J.18i.1 according to the procedure described for J.14g.	RT: 2.10 min, (Cond.-D1); Calcd for $C_{43}H_{41}N_6O_4$ $[M+H]^+$ 705.32; found: 705.19.

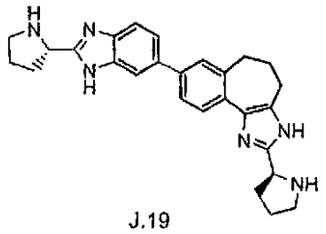
J.18i.3	 From J.16f and J.10b	RT = 1.92 min (Cond.-D1); LCMS: Calcd for $C_{44}H_{48}N_7O_6$ $(M+H)^+$ 770.37; found: 770.29.
J.18j	 From J.16c and J.9b	RT: 1.62 min, (Cond.-J1); Calcd for $C_{40}H_{44}FN_6O_4$ $[M+H]^+$ 691.34; found: 691.46.
J.18k	 From J.18j according to the procedure described for J.14g.	RT: 1.66 min, (Cond.-J1); Calcd for $C_{40}H_{42}FN_6O_4$ $[M+H]^+$ 689.33; found: 689.43.
J.18k.1	 From J.16d.1 and J.9g	RT: 3.44 min, (Cond.-J2); Calcd for $C_{40}H_{47}N_6O_4$ $[M+H]^+$ 675.37; found: 675.33
J.18l		RT = 1.67 min, (Cond.-J1); Calcd for $C_{36}H_{43}N_6O_4$

	From J.16 and J.17	$[M+H]^+$ 623.34; found: 623.46.
J.18m	 From J.16 and J.17a	RT = 1.67 min, (Cond.-J1); Calcd for $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623.34; found: 623.46.
JB.6	 From J.14e and JB.5	RT = 1.33 min, (Cond.-JB.1); Calcd for $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623.34; found: 623.24.

Synthetic Route 12



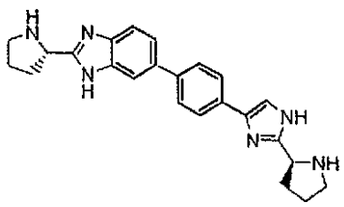
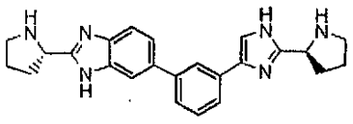
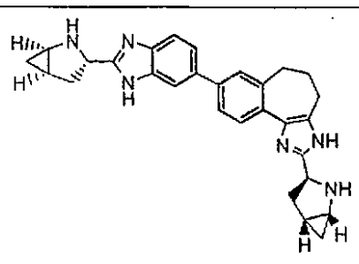
Examples J.19 – JB.7

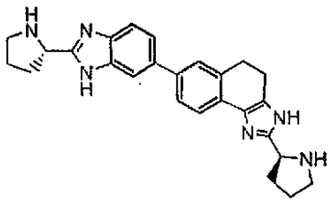
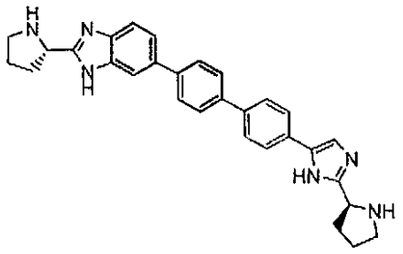
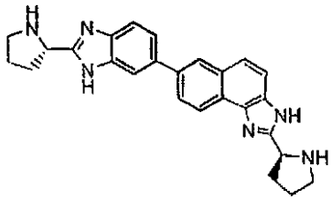
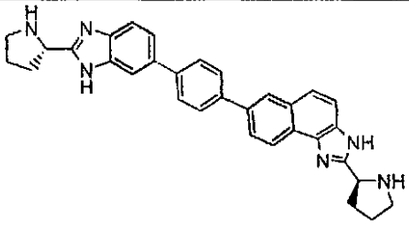


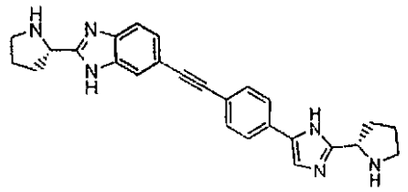
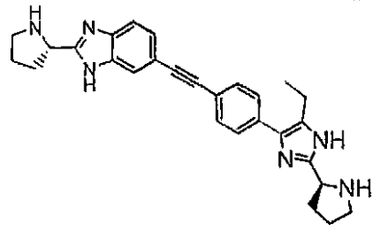
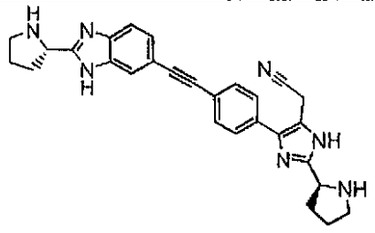
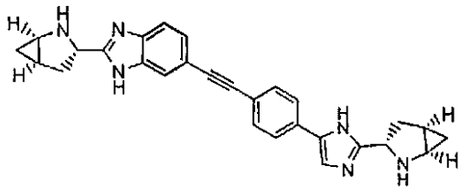
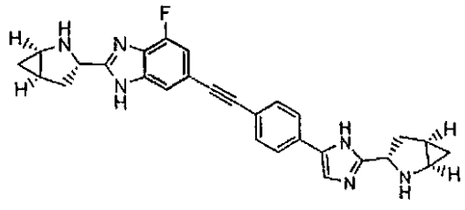
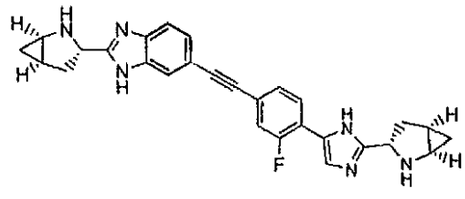
J.19

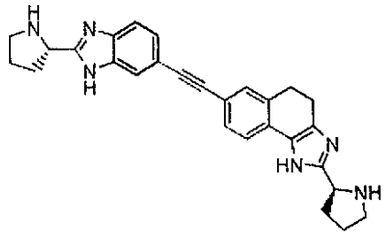
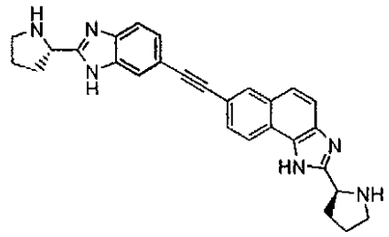
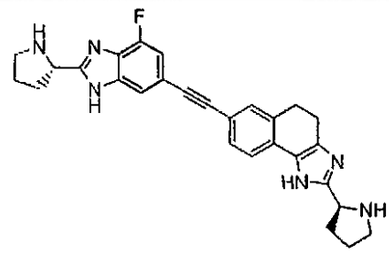
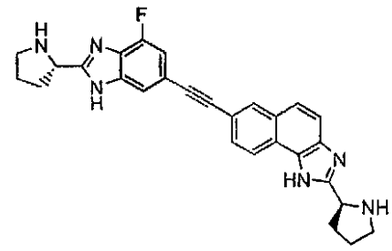
Example J.14 (85 mg, 0.11 mmol) was dissolved in methanol (1 mL) and 4N HCl/Dioxane (5 mL) was added and the reaction was stirred 16 hr. The solvents were removed in vacuo, and the tetra HCl salt J.19 was exposed to high vacuum for 18 h. LC (Cond-D2): 1.4 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{31}N_6$: 439.26;

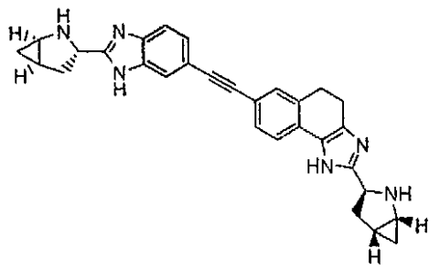
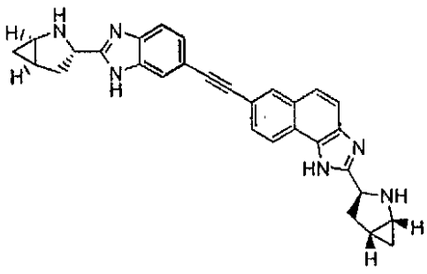
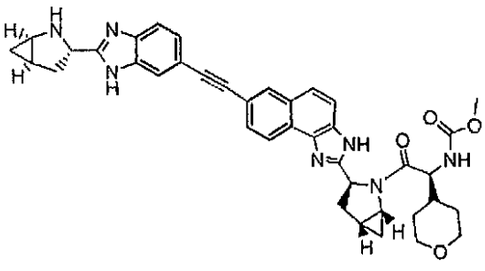
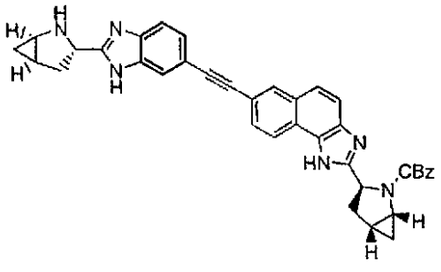
found: 439.29. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{31}N_6$: 439.2610; found 439.2593.

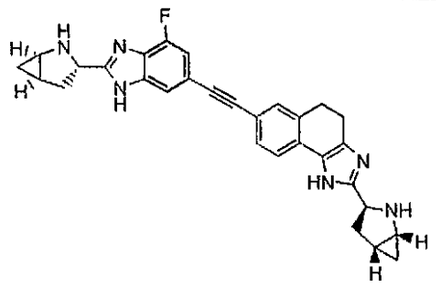
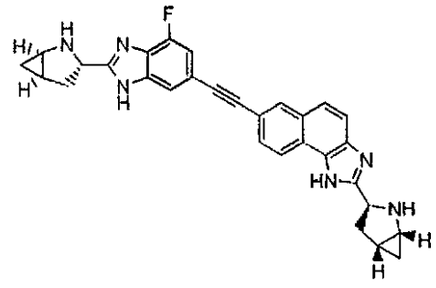
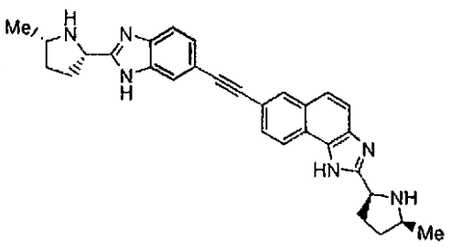
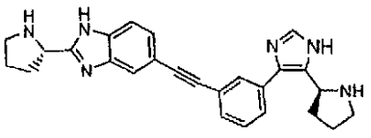
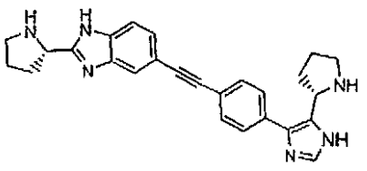
J.19a	 From J.14a	RT = 1.34 min (Cond.-D2) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_6$: 399.23; found: 399.24. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_6$: 399.2297; found: 399.2316.
J.19b	 From J.14b	RT = 1.46 min (Cond.-D2) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_6$: 399.23; found: 399.24. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_6$: 399.2297; found: 399.2298.
J.19c	 From J.14c	RT = 1.13 min (Cond.-J1) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{30}N_6$: 463.26; found: 463.38.

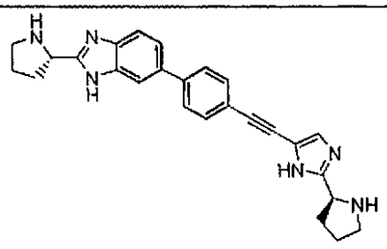
J.19d	 From J.14d	RT = 1.27 min, (Cond.-D2) LCMS: Calcd for $C_{26}H_{29}N_6$ $[M+H]^+$ 425.24; found:425.28. HRMS: Calcd for $C_{26}H_{29}N_6$ $[M+H]^+$ 425.2448; found: 425.2444.
J.19e	 From J.14f	RT = 1.30 min, (Cond.-J1) LCMS: Calcd for $C_{30}H_{31}N_6$ $[M+H]^+$ 475.26; found: 475.25.
J.19f	 From J.14g	RT = 1.46 min, (Cond.-D2) LCMS: Calcd for $C_{26}H_{27}N_6$ $[M+H]^+$ 423.23; found:423.31. HRMS: Calcd for $C_{26}H_{27}N_6$ $[M+H]^+$ 423.2292; found: 423.2287.
J.19f.1	 From J.14g.1	RT: 1.73 min, (Cond.-D1); Calcd for $C_{32}H_{31}N_6$ $[M+H]^+$ 499.26; found: 499.22.

J.20	 From J.18	RT = 1.18 min, (Cond.-J1) LCMS: Calcd for $C_{26}H_{27}N_6$ $[M+H]^+$ 423.23; found:423.24.
J.20.1	 From J.18.1	RT = 0.99 min (Cond.-J1); LCMS Calcd for $C_{28}H_{31}N_6$ $(M+H)^+$ 451.25; found: 451.28.
J.20.2	 From J.18.2	RT = 0.98 min (Cond.-J1); LCMS Calcd for $C_{28}H_{28}N_7$ $(M+H)^+$ 462.24; found: 462.24.
J.20a	 From J.18a	RT = 1.21 min, (Cond.-J1) LCMS: Calcd for $C_{28}H_{27}N_6$ $[M+H]^+$ 447.23; found: 447.18.
J.20b	 From J.18b	RT = 1.04 min, (Cond.-J1) LCMS: Calcd for $C_{28}H_{26}FN_6$ $[M+H]^+$ 465.21; found: 465.28.
J.20c		RT = 1.07 min, (Cond.-J1) LCMS: Calcd for $C_{28}H_{26}FN_6$ $[M+H]^+$ 465.21;

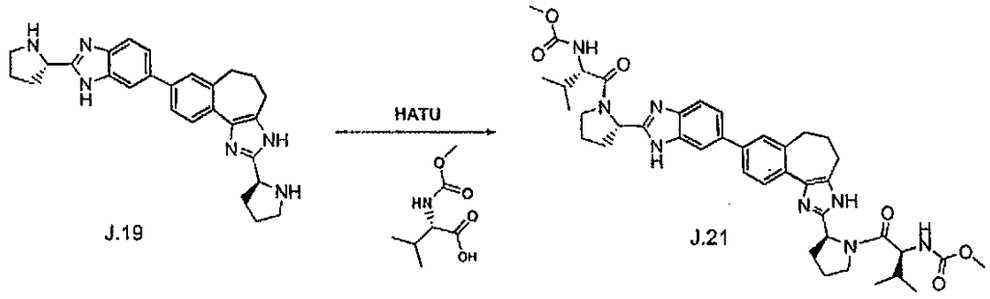
	From J.18c	found: 465.28.
J.20d	 From J.18d	RT = 1.60 min, (Cond.-D2) LCMS: Calcd for $C_{28}H_{29}N_6$ $[M+H]^+$ 449.24; found: 449.28.
J.20e	 From J.18e	RT = 1.78 min, (Cond.-D2) LCMS: Calcd for $C_{28}H_{27}N_6$ $[M+H]^+$ 447.23; found: 447.25.
J.20f	 From J.18f	RT = 1.07 min, (Cond.-J1) LCMS: Calcd for $C_{28}H_{28}FN_6$ $[M+H]^+$ 467.24; found: 467.25.
J.20g	 From J.18g	RT = 1.17 min, (Cond.-J1) LCMS: Calcd for $C_{28}H_{26}FN_6$ $[M+H]^+$ 465.22; found: 465.28.

J.20g.1	 From J.18h	RT = 1.43 min, (Cond.-D1) LCMS: Calcd for $C_{30}H_{29}N_6$ $[M+H]^+$ 473.25; found: 473.13.
J.20h	 From J.18i	RT = 1.09 min, (Cond.-J1) LCMS: Calcd for $C_{30}H_{27}N_6$ $[M+H]^+$ 471.23; found: 471.25.
J.20h.1	 From J.18i.3	RT: 1.60 min, (Cond.-D1); Calcd for $C_{39}H_{40}N_7O_4$ $[M+H]^+$ 670.32; found: 670.24.
J.20h.2	 From J.18i.2	RT: 1.77 min, (Cond.-D1); Calcd for $C_{38}H_{33}N_6O_2$ $[M+H]^+$ 605.27; found: 605.20.

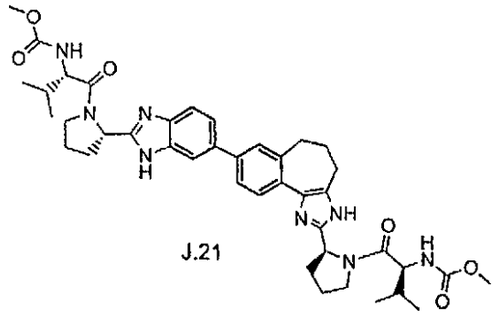
J.20i	 From J.18j	RT = 1.09 min, (Cond.-J1) LCMS: Calcd for $C_{30}H_{28}FN_6$ $[M+H]^+$ 491.24; found: 491.25.
J.20j	 From J.18k	RT = 1.17 min, (Cond.-J1) LCMS: Calcd for $C_{30}H_{26}FN_6$ $[M+H]^+$ 489.22; found: 489.22.
J.20j.1	 From J.18k.1	RT = 2.73 min, (Cond.-J2) LCMS: Calcd for $C_{30}H_{31}N_6$ $[M+H]^+$ 475.26; found: 475.17.
J.20k	 From J.18l	RT = 1.0 min (Cond.-J1) LCMS: Calcd for $C_{26}H_{27}N_6$ $[M+H]^+$ 423.23; found: 423.24.
J.20l		RT = 1.01 min (Cond.-J1) LCMS: Calcd for $C_{26}H_{27}N_6$ $[M+H]^+$

	From J.18m	423.23; found: 423.31.
JB.7	 From JB.6	RT = 1.0 min (Cond.-JB.1) LCMS: Calcd for $C_{26}H_{27}N_6$ $[M+H]^+$ 423.23; found: 423.17.

Synthetic Route 13.

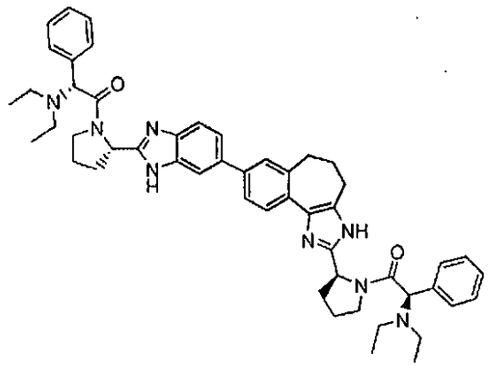
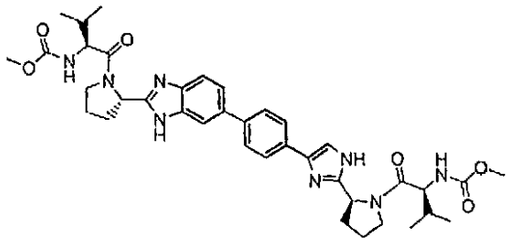


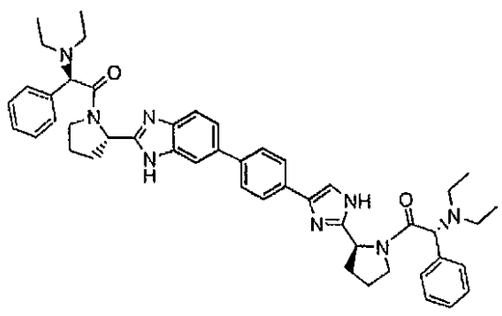
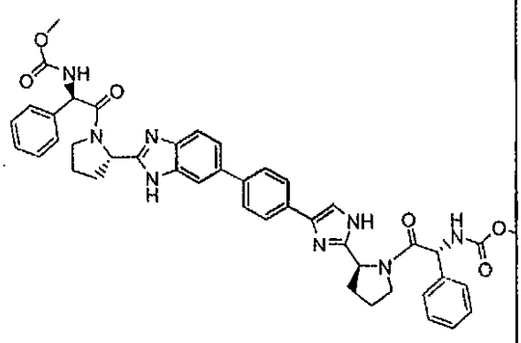
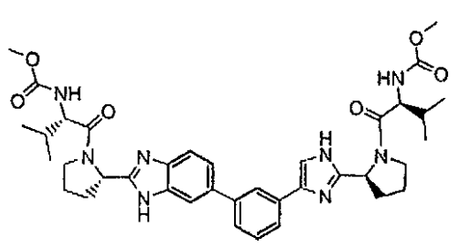
Examples J.21 - JB.12

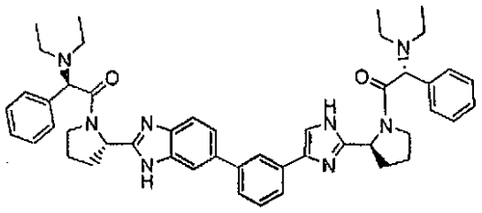
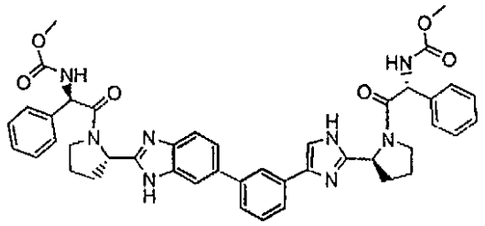


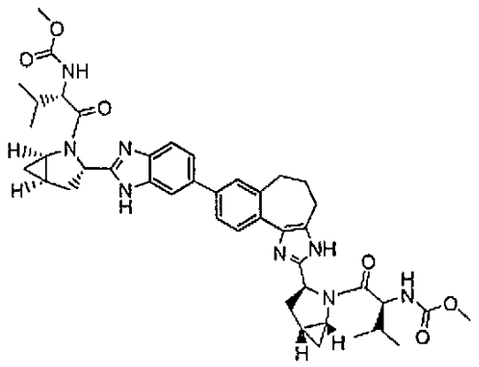
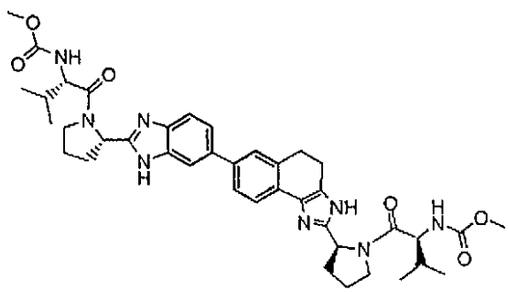
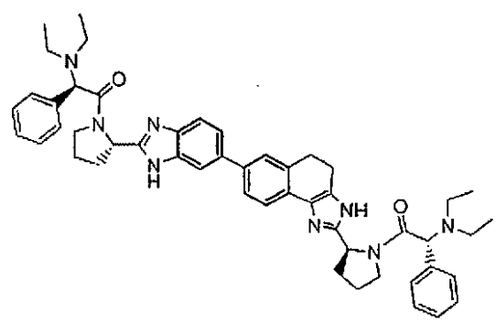
HATU (60 mg, 0.16 mmol) was added to a rapidly stirred solution of example J.19 (38.18 mg, 0.075 mmol), N-methoxycarbonyl-L-valine (26.2 mg, 0.15 mmol), and Hunig's base (0.095 mL, 0.54 mmol) in dimethylformamide (1.5 mL). The reaction mixture was stirred for 2 h and the solvent was removed under purge of nitrogen. The residue was diluted with methanol and subjected to prep. HPLC (Phenomenex LUNA C18 (30 x 100 mm); 5% - 100% B over 40 min; Flow Rate = 40 mL/min; Wavelength = 220 nm; Solvent A = 0.1% TFA in 10% methanol / 90% water; Solvent B = 0.1% TFA in 90% methanol /10% water) to give the bis TFA salt

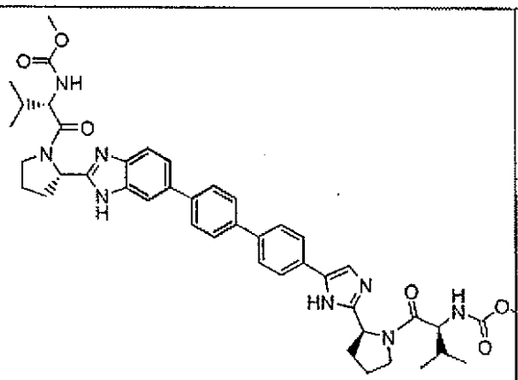
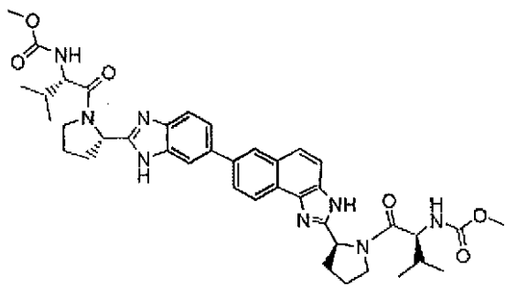
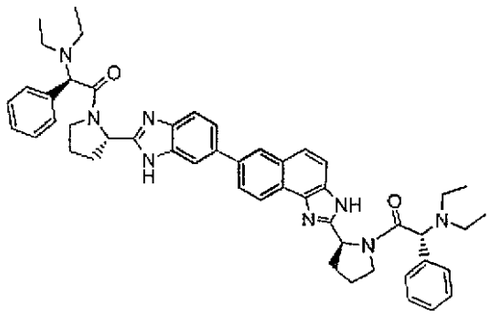
of J.21, 17.6 mg (24%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91-7.84 (m, 1H), 7.72-7.57 (series m, 5H), 7.30-6.8 (m, 2H), 5.50-5.17 (series m, 4H), 4.20 (m, 1H), 4.10 (br. s, 1H), 3.34-3.25 (m, 6H), 3.17 (s, 6H), 3.14-2.90 (series m, 4H), 2.23-2.20 (m, 2H), 2.13-1.93 (m, 8H), 1.32-1.03 (m, 12H). LC (Cond.-D2): 1.8 min; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_6$ 753.41; found: 753.55. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_6$ 753.4088; found: 753.4108.

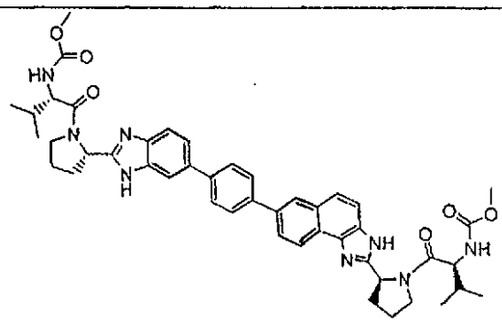
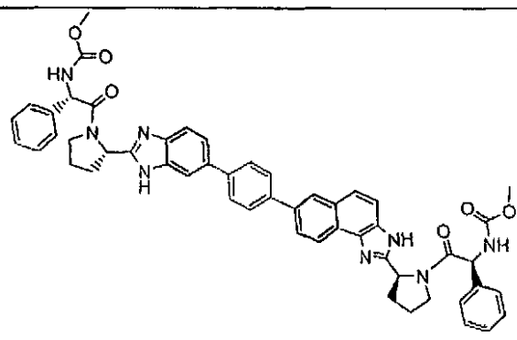
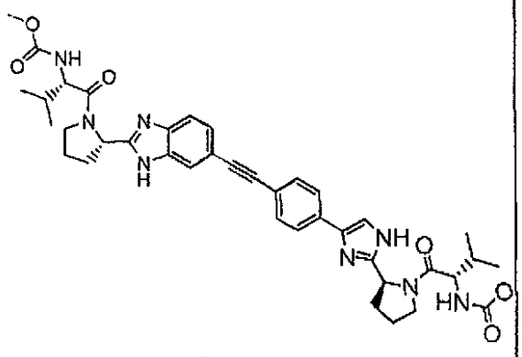
J.21a	 From J.19	RT= 2.1 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{61}N_8O_2$: 817.49; found: 817.63. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{61}N_8O_2$: 817.4917; found: 817.4927.
J.22	 From J.19a	RT = 1.88 min (Cond.-D2) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713.38; found: 713.31. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713.3775; found: 713.3804.

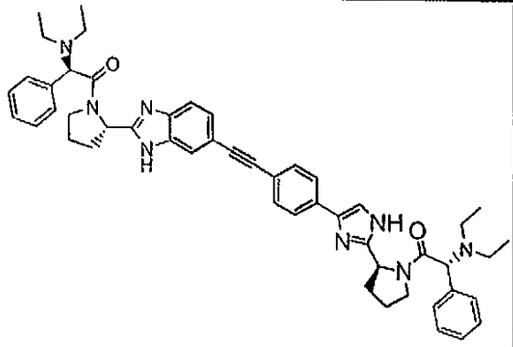
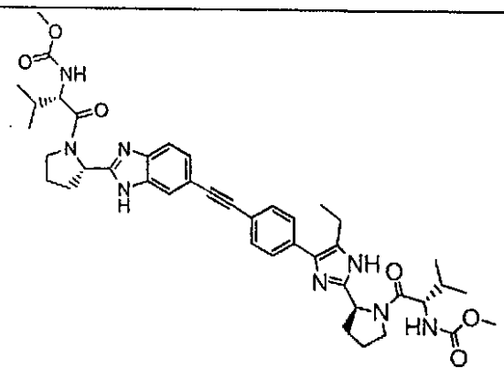
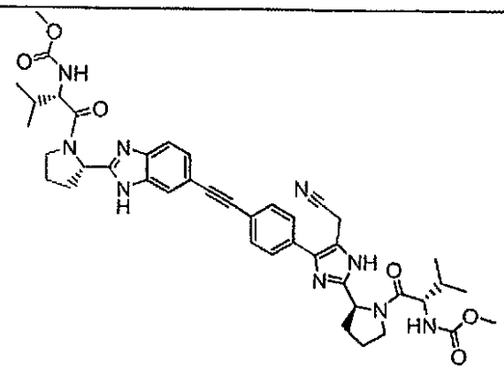
J.22a	 From J.19a	RT = 1.65 min (Cond.-D2) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777.46; found: 777.48. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777.4604; found: 777.4636.
J.22b	 From J.19a	RT = 1.99 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781.35; found: 781.37. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781.3462; found: 781.3483.
J.23	 From J.19b	RT = 1.92 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713.38; found: 713.40. HRMS: Anal. Calcd.

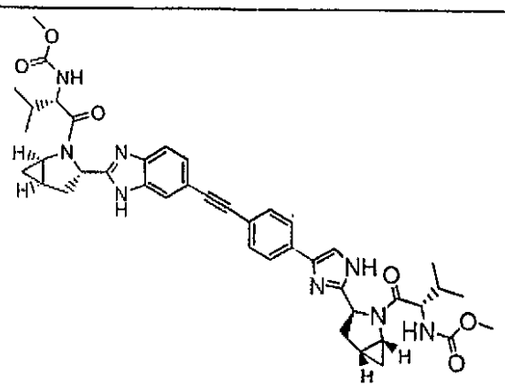
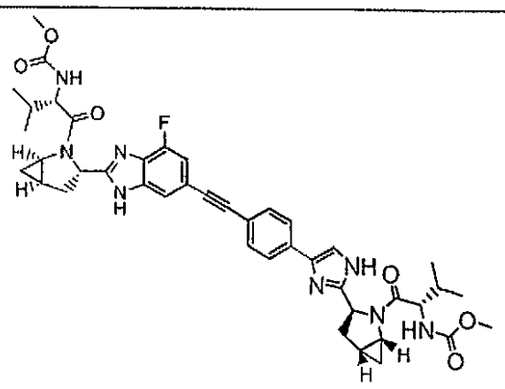
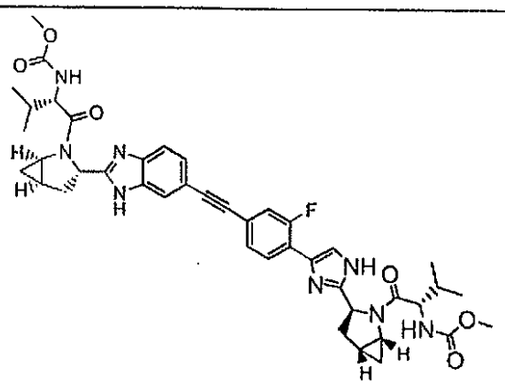
		for $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713.3804; found: 713.3798.
J.23a	 From J.19b	RT = 1.72 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777.46; found: 777.48. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777.4604; found: 777.4579.
J.23b	 From J.19b	RT = 2.02 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781.35; found: 781.37. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781.3462; found: 781.3497.

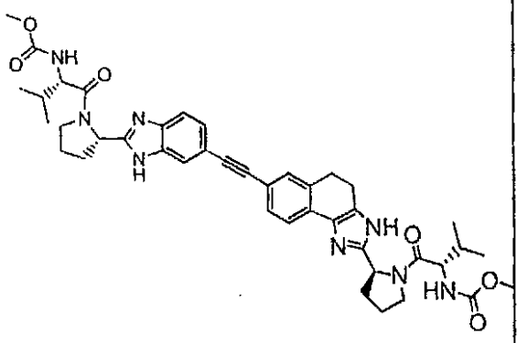
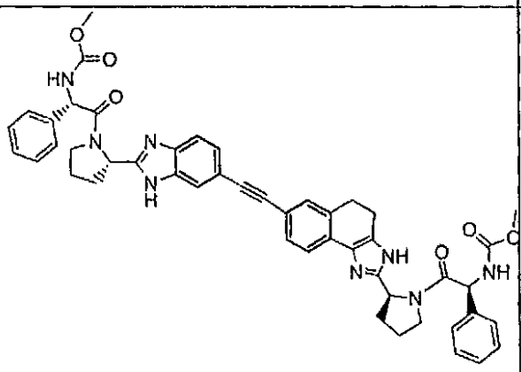
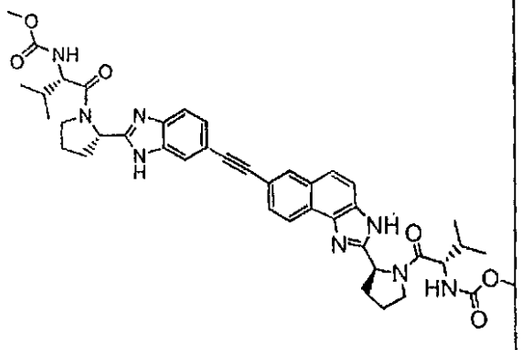
J.24	 From J.19c	RT = 1.5 min (Cond.-J1); 87%, LCMS: Calcd for $C_{43}H_{53}N_8O_6$ $(M+H)^+$ 777.41; found: 777.49. HRMS: Calcd for $C_{43}H_{53}N_8O_6$ $(M+H)^+$ 777.4083; found: 777.4088.
J.25	 From J.19d	RT = 1.83 min (Cond.-D2); LCMS: 95%, Calcd for $C_{40}H_{51}N_8O_6$ $(M+H)^+$ 739.39; found: 739.59. HRMS: Calcd for $C_{40}H_{51}N_8O_6$ $(M+H)^+$ 739.3926; found: 739.3916.
J.25.a	 From J.19d	RT = 1.58 min (Cond.-D2); LCMS: Calcd for $C_{50}H_{59}N_8O_2$ $(M+H)^+$ 803.47; found: 803.65. HRMS: Calcd for $C_{50}H_{59}N_8O_2$ $(M+H)^+$ 803.4755; found: 803.4749.

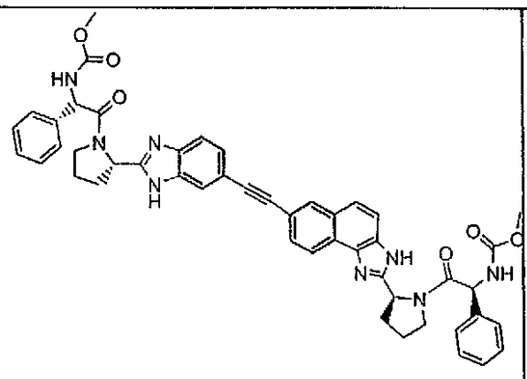
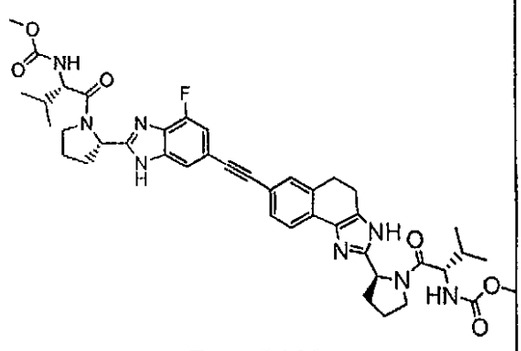
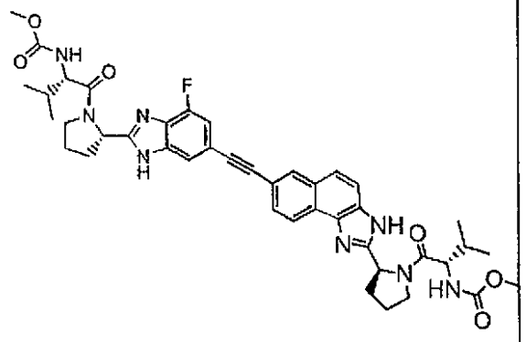
J.26	 From J.19e	RT = 1.51 min (Cond.-J1); LCMS Calcd for $C_{44}H_{53}N_8O_6$ $(M+H)^+$ 789.41; found: 789.55.
J.27	 From J.19f	RT = 1.94 min (Cond.-D2); LCMS: 95%, Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.38; found: 737.56. HRMS: Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.3770; found: 737.3756.
J.27a	 From J.19f	RT = 1.67 min (Cond.-D2); LCMS: Calcd for $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801.46; found: 801.68. HRMS: Calcd for $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801.4599; found: 801.4592.

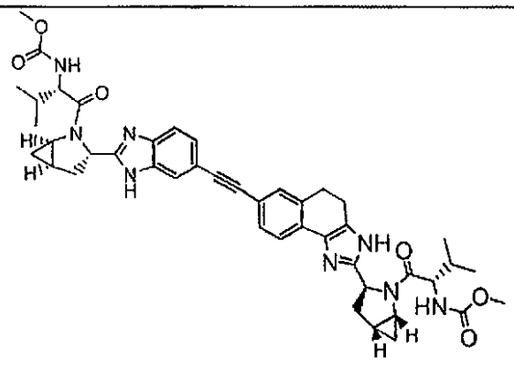
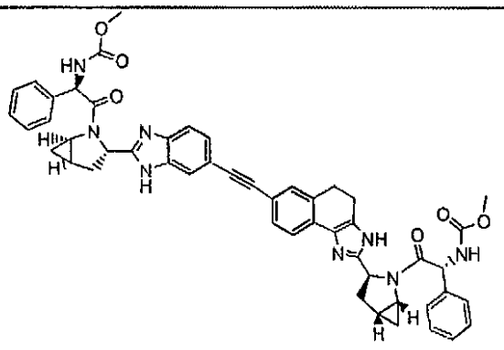
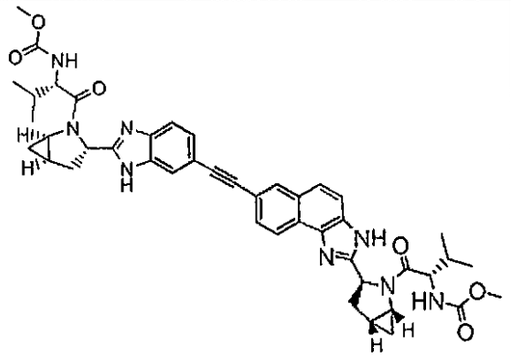
J.27b	 From J.19f.1	RT = 1.94 min (Cond.-D1); LCMS: Calcd for $C_{46}H_{53}N_8O_6$ $(M+H)^+$ 813.41; found: 813.46.
J.27c	 From J.19f.1	RT = 2.01 min (Cond.-D1); LCMS: Calcd for $C_{52}H_{49}N_8O_6$ $(M+H)^+$ 881.38; found: 881.37.
J.28	 From J.20	RT = 1.46 min (Cond.-J1); LCMS Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.38; found: 737.42. HRMS: Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.3770; found: 737.3774.
J.28a		RT = 1.30 min (Cond.-J1); LCMS Calcd for $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801.46; found: 801.62.

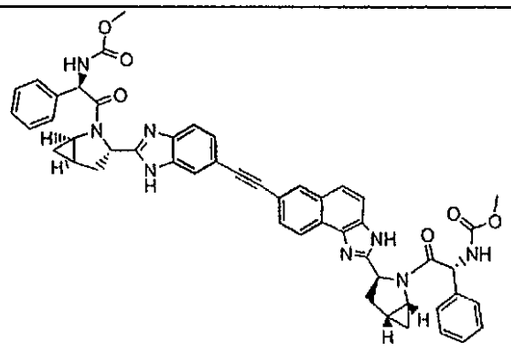
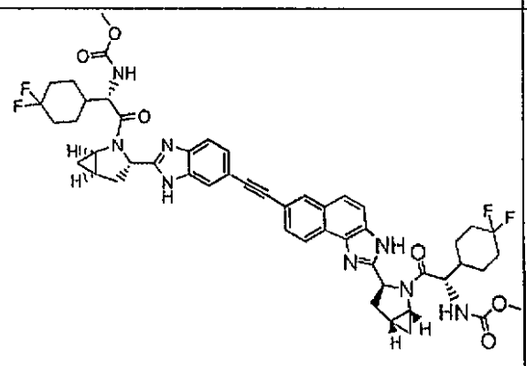
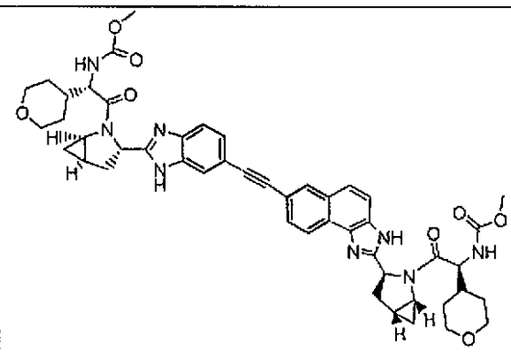
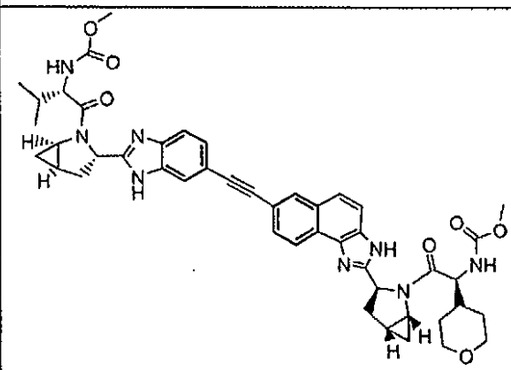
	 From J.20	HRMS: Calcd for $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801.4599; found: 801.4585.
J.28a.1	 From 20.1	RT = 1.29 min (Cond.-J1); LCMS Calcd for $C_{42}H_{53}N_8O_6$ $(M+H)^+$ 765.41; found: 765.49.
J.28a.2	 From 20.2	RT = 1.22 min (Cond.-J1); LCMS Calcd for $C_{42}H_{50}N_9O_6$ $(M+H)^+$ 776.39; found: 776.42.

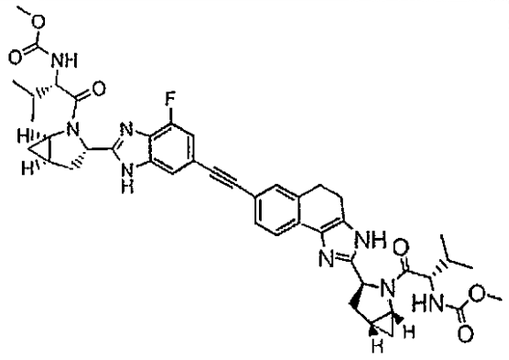
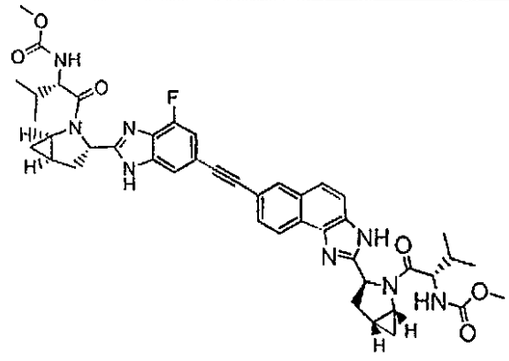
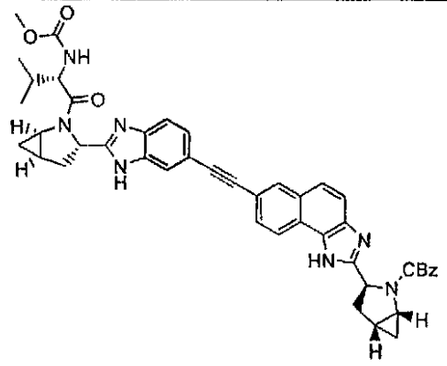
J.28b	 From J.20a	RT = 1.25 min (Cond.-J1); LCMS Calcd for $C_{42}H_{49}N_8O_6$ $(M+H)^+$ 761.38; found: 761.49.
J.28c	 From J.20b	RT = 1.44 min (Cond.-J1); LCMS Calcd for $C_{42}H_{48}FN_8O_6$ $(M+H)^+$ 779.37; found: 779.45.
J.28d	 J.20c	RT = 1.30 min (Cond.-J1); LCMS Calcd for $C_{42}H_{48}FN_8O_6$ $(M+H)^+$ 779.37; found: 779.45.

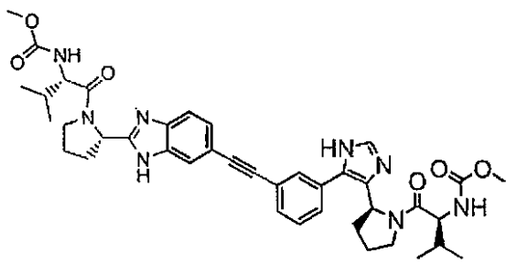
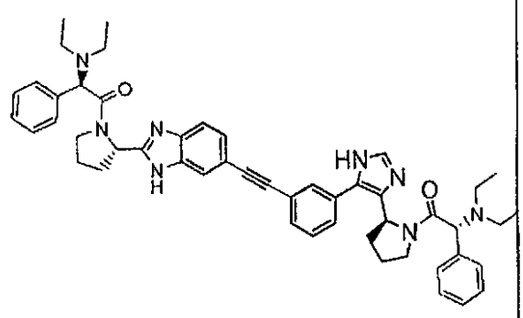
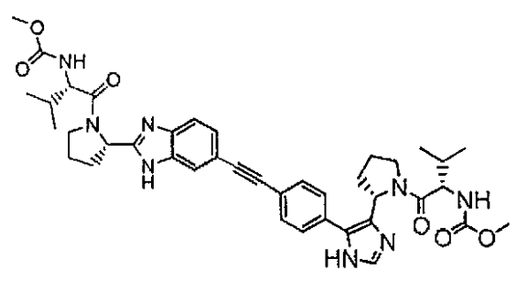
J.28e	 From J.20d	RT = 2.02 min (Cond.-D2); 95%, Calcd for $C_{42}H_{51}N_8O_6$ $(M+H)^+$ 763.39; found: 763.59. HRMS: Calcd for $C_{42}H_{51}N_8O_6$ $(M+H)^+$ 763.3926; found: 763.3918.
J.28e.1	 From J.20d	RT = 1.97 min (Cond.-D1); LCMS: Calcd for $C_{48}H_{47}N_8O_6$ $(M+H)^+$ 831.43; found: 831.36.
J.28f	 From J.20e	RT = 2.10 min (Cond.-D2); 95%, Calcd for $C_{42}H_{49}N_8O_6$ $(M+H)^+$ 761.38; found: 761.55. HRMS: Calcd for $C_{42}H_{49}N_8O_6$ $(M+H)^+$ 761.3770; found: 761.3765.

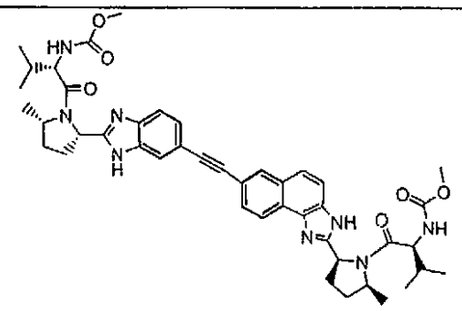
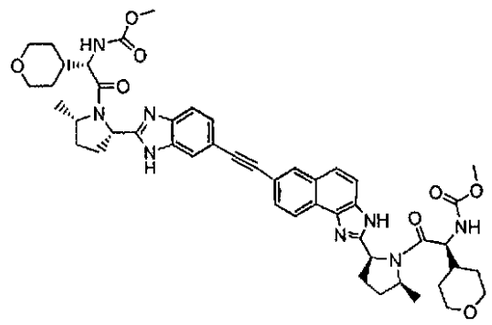
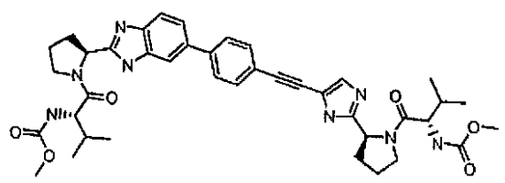
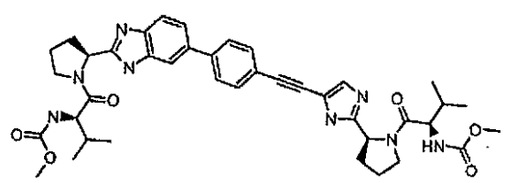
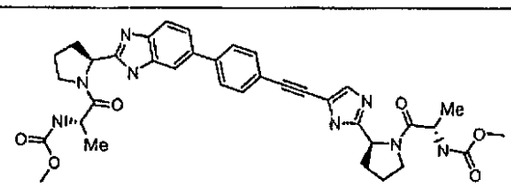
J.28f.1	 From J.20e	RT = 1.95 min (Cond.-D1); LCMS: Calcd for $C_{48}H_{45}N_8O_6$ $(M+H)^+$ 829.35; found: 829.45.
J.28g	 From J.20f	RT = 1.46 min (Cond.-J1); LCMS Calcd for $C_{42}H_{50}FN_8O_6$ $(M+H)^+$ 781.39; found: 781.49.
J.28h	 From J.20g	RT: 1.52 min, (Cond.-J1); Calcd for $C_{42}H_{48}FN_8O_6$ $[M+H]^+$ 779.37; found: 779.52.

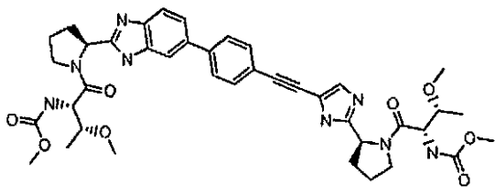
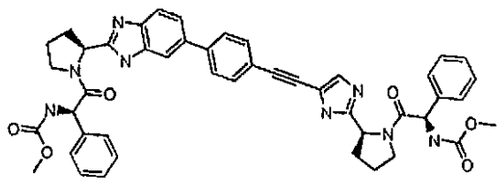
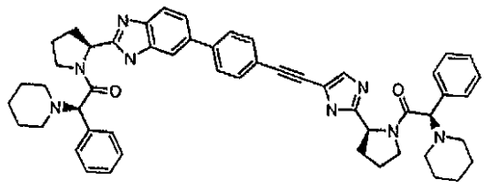
J.28h.1	 From J.20g.1	RT = 1.83 min (Cond.-D1); LCMS: Calcd for $C_{44}H_{51}N_8O_6$ $(M+H)^+$ 787.23; found: 787.40.
J.28h.2	 From J.20g.1	RT = 1.92 min (Cond.-D1); LCMS: Calcd for $C_{50}H_{47}N_8O_6$ $(M+H)^+$ 855.36; found: 855.21.
J.28i	 From J.20h	RT: 1.34 min, (Cond.-J1); Calcd for $C_{44}H_{49}N_8O_6$ $[M+H]^+$ 785.38; found: 785.55.

J.28i.1	 From J.20h	RT = 2.01 min (Cond.-D1); LCMS: Calcd for $C_{50}H_{45}N_8O_6$ $(M+H)^+$ 853.35; found: 853.25.
J.28i.2	 From J.20h	RT = 2.14 min (Cond.-D1); LCMS: Calcd for $C_{50}H_{55}F_2N_8O_6$ $(M+H)^+$ 937.40; found: 937.46.
J.28i.3	 From J.20h	RT = 2.83 min (Cond.-D1); LCMS: Calcd for $C_{48}H_{53}N_8O_8$ $(M+H)^+$ 869.40; found: 869.35.
J.28i.4		RT = 1.81 min (Cond.-D1); LCMS: Calcd for $C_{46}H_{51}N_8O_7$ $(M+H)^+$ 827.39; found: 827.26.

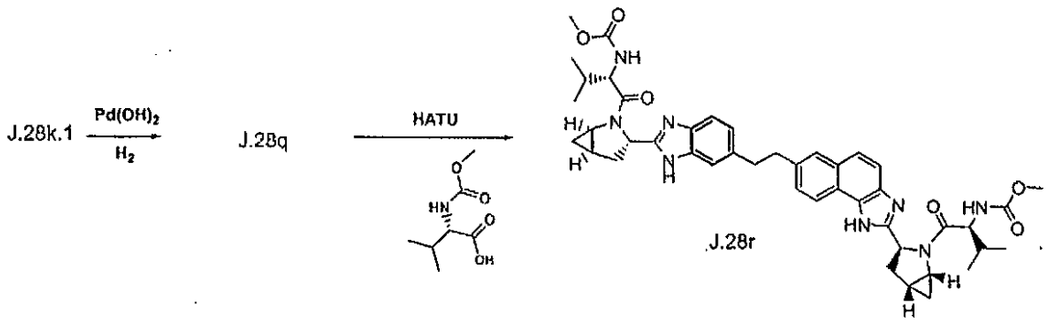
	From J.20h.1	
J.28j	 From J.20i	RT: 1.49 min, (Cond.-J1); Calcd for $C_{44}H_{50}FN_8O_6$ $[M+H]^+$ 805.39; found: 805.55.
J.28k	 From J.20j	RT: 1.54 min, (Cond.-J1); Calcd for $C_{44}H_{48}FN_8O_6$ $[M+H]^+$ 803.37; found: 803.58.
J.28k.1	 From J.20h.2	RT: 2.01 min, (Cond.-D1); Calcd for $C_{45}H_{44}N_7O_5$ $[M+H]^+$ 762.34; found: 762.16.

J.28l	 From J.20k	RT = 1.46 min (Cond.-J1); LCMS Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.38; found: 737.56. HRMS: Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.3770; found: 737.3760.
J.28m	 From J.20k	RT = 1.36 min (Cond.-J1); LCMS Calcd for $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801.46; found: 801.62. HRMS: Calcd for $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801.4599; found: 801.4597.
J.28n	 From J.20l	RT = 1.43 min (Cond.-J1); LCMS Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.38; found: not apparent. HRMS: Calcd for $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737.3770; found: 737.3759.

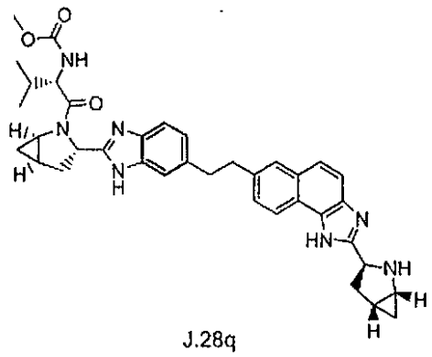
J.28o	 From J.20j.1	RT: 1.88 min, (Cond.-J2); Calcd for $C_{44}H_{53}N_8O_6$ $[M+H]^+$ 789.41; found: 789.36.
J.28p	 From J.20j.1	RT: 1.76 min, (Cond.-J2); Calcd for $C_{48}H_{57}N_8O_8$ $[M+H]^+$ 873.43; found: 873.43.
JB.8	 From JB.7	RT: 1.17 min, (Cond.-JB.1); Calcd for $C_{40}H_{49}N_8O_6$ $[M+H]^+$ 737.38; found: 737.31.
JB.8.1	 From JB.7	RT: 1.23 min, (Cond.-JB.1); Calcd for $C_{40}H_{49}N_8O_6$ $[M+H]^+$ 737.38; found: 737.33.
JB.9	 From JB.7	RT: 1.39 min, (Cond.-JB.1); Calcd for $C_{36}H_{41}N_8O_6$ $[M+H]^+$ 681.32; found: 681.21.

JB.10	 From JB.7	RT: 1.08 min, (Cond.-JB.1); Calcd for $C_{40}H_{49}N_8O_8$ $[M+H]^+$ 769.37; found: 769.31.
JB.11	 From JB.7	RT: 1.33 min, (Cond.-JB.1); Calcd for $C_{46}H_{45}N_8O_6$ $[M+H]^+$ 805.35; found: 805.27.
JB.12	 From JB.7	RT: 1.35 min, (Cond.-JB.1); Calcd for $C_{52}H_{56}N_8O_2$ $[M+H]^+$ 825.46; found: 825.34.

Synthetic Route 13a.

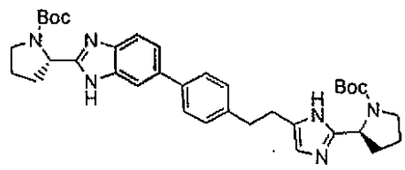


Examples J.28q – JB.13



J.28q

A solution of Example J.28k.1 (286.6 mg, 0.376 mmol) in MeOH (2 mL) was added to a stirred suspension of 20% palladium hydroxide on carbon (52.8 mg, 0.376 mmol) and potassium carbonate (104 mg, 0.752 mmol) in MeOH (4 mL) under an atmosphere of nitrogen. The flask was evacuated and charged with hydrogen (3x; balloon, 14 psi) and stirred for 3 h. Note: Significant amounts of N-methylated product form if allowed to go over 3h. The mixture was filtered over celite, and the celite pad washed with MeOH (100 mL), methylene chloride (50 mL), and MeOH (100 mL) again. The filtrate was concentrated and placed under high vacuum for 0.5 h before it was taken up in MeOH and passed through a nylon syringe frit (to remove traces of catalyst). Example, J.28q was obtained (202 mg, 85 % yield) as a yellow solid. RT: 1.62 min, (Cond.-D1); Calcd for $C_{37}H_{42}N_7O_2$ $[M+H]^+$ 632.34; found: 632.21.

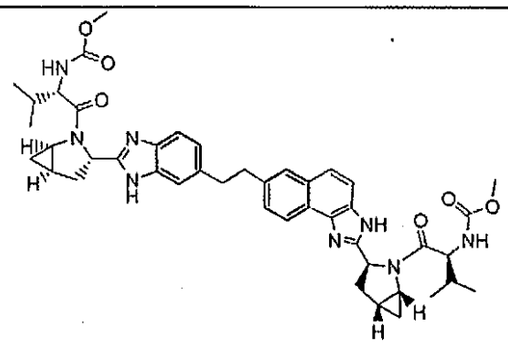
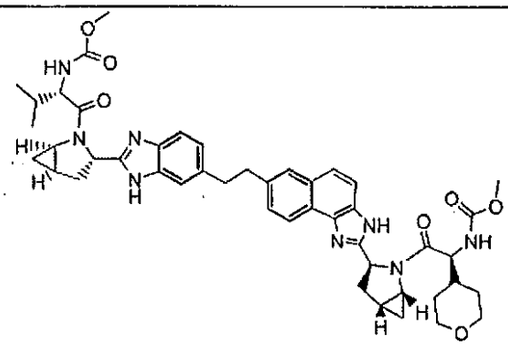
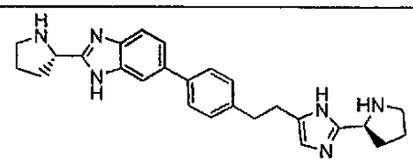


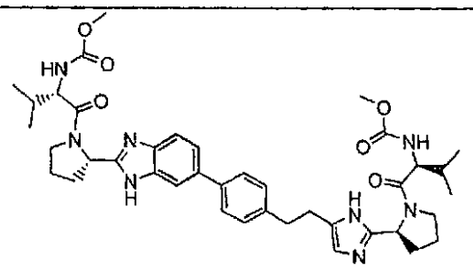
JB.13

10% Pd/C (50 mg, 0.470 mmol) was added in one portion to a suspension of a TFA salt of Example JB.6 (100 mg, 0.118 mmol) in MeOH (10 mL). The reaction mixture was purged with hydrogen and stirred under a balloon of hydrogen overnight at rt. The reaction mixture was filtered through Celite and concentrated. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 10 to 100 % ACN -Water + 0.1 % TFA) to yield a TFA salt of tert-butyl (2S)-2-(4-(2-(4-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate (70

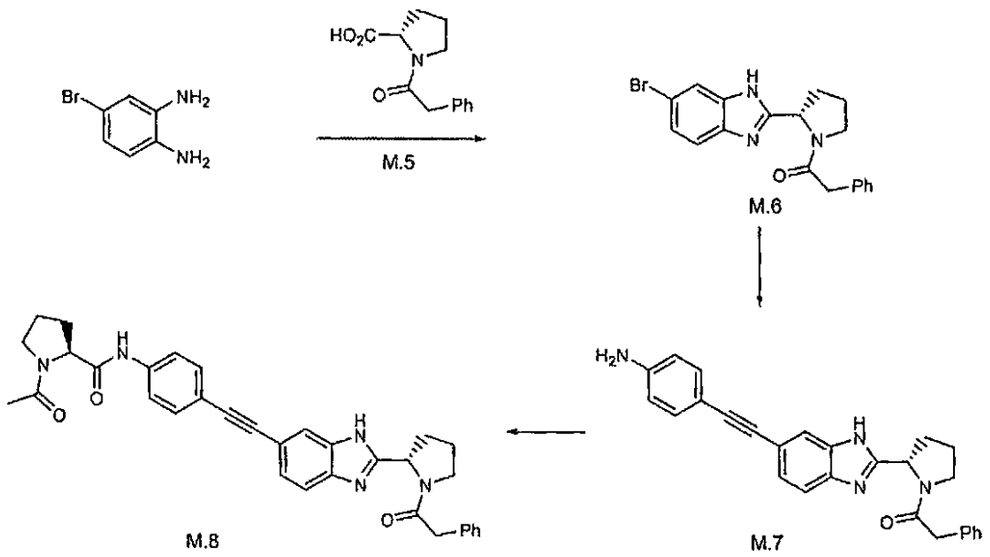
mg) as a white solid. ^{1}H NMR (500 MHz, MeOD) δppm 7.95 (d, *J*=9.5 Hz, 1H), 7.85 (d, *J*=9.2 Hz, 2H), 7.66 (br s, 2H), 7.31 - 7.44 (m, 2H), 7.26 (s, 0.5H), 7.14 (s, 0.5H), 5.29 (br s, 1H), 5.04 (br s, 1H), 3.73 - 3.82 (m, 1H), 3.64 (br s, 2H), 3.55 (br s, 1H), 3.02 - 3.15 (m, 4H), 2.56 - 2.70 (m, 1H), 2.41 - 2.55 (m, 1H), 2.24 (br s, 1H), 2.08 - 2.18 (m, 2H), 2.03 (br s, 3H), 1.49 (d, *J*=7.9 Hz, 9H), 1.26 (br s, 4.5H), 1.22 (br s, 4.5H). RT: 1.16 min, (Cond.-JB-1); Calcd for $C_{36}H_{46}N_6O_4$ $[M+H]^+$ 627.37; found: 627.31$[M+H]^+$.

Examples J.28r – JB.15

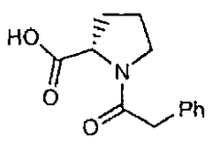
J.28r	 From J.28q according to the procedure described for J.21	RT = 1.78 min (Cond.-D1); LCMS: Calcd for $C_{44}H_{53}N_8O_6$ $(M+H)^+$ 789.41; found: 789.24.
J.28s	 From J.28q according to the procedure described for J.21	RT = 1.67 min (Cond.-D1); LCMS: Calcd for $C_{46}H_{55}N_8O_7$ $(M+H)^+$ 831.42; found: 831.26.
JB.14	 From JB.13 according to the procedure described for J.19	RT = 0.82 min (Cond.-JB-1); LC MS: Calcd for $C_{26}H_{31}N_6$ $(M+H)^+$ 427.26; found: 427.28.

JB.15	 From JB.14 according to the procedure described for J.21	RT = 1.06 min (Cond.-JB-1); LC MS: Calcd for $C_{40}H_{56}N_6O_6$ $(M+H)^+$ 741.41; found: 741.39.

Synthetic Route 14.

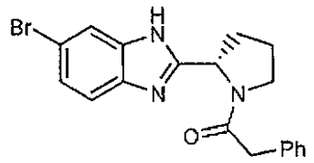


Examples M.5 – M.9



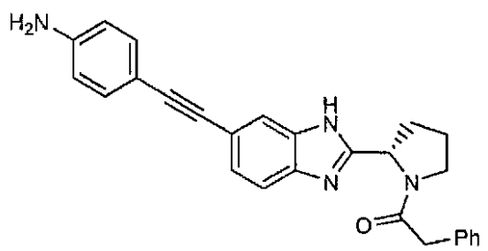
M.5

Example M.5 was prepared from L-proline according to the procedure described in Gudasheva, et al. Eur. J. Med. Chem. 1996, 31, 151.



M.6

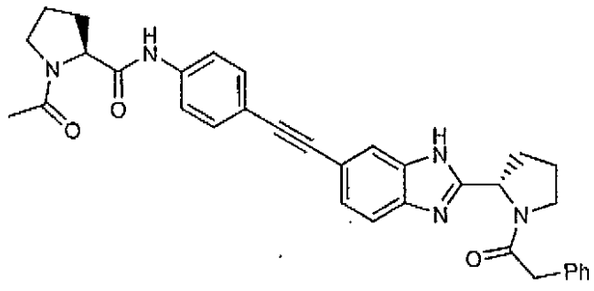
EDCI•HCl (1.76 g, 9.22 mmol) was added to a mixture of 4-bromobenzene-1,2-diamine (1.50 g, 8.03 mmol), M.5 (1.88 g, 8.06 mmol) and 1-hydroxybenzotriazole (1.31 g, 9.70 mmol) in dichloromethane (30 mL), and stirred at ambient conditions for 19 h. The mixture was then diluted with dichloromethane, washed with water (2x), dried (brine; $MgSO_4$), filtered, and concentrated in vacuo to provide a brown foam. Acetic acid (30 mL) was added to the foam, and the mixture was heated at 65 °C for 90 min. The volatile component was removed in vacuo, and the residue was dissolved in ethyl acetate and washed carefully with saturated $NaHCO_3$ solution (2x), and the organic phase was dried (brine; $MgSO_4$), filtered, and concentrated in vacuo. The resultant crude material was submitted to flash chromatography (silica gel; ethyl acetate) to provide Example M.6 as a tan foam (1.67 g). ^{1}H NMR ($CDCl_3$, δ= 7.24 ppm, 500 MHz): 10.71/10.68 (overlapping br s, 1H), 7.85 (s, 0.48H), 7.56 (d, J = 8.6, 0.52H), 7.50 (s, 0.52H), 7.35-7.22 (m, 6.48H), 5.38 (app br d, J = 8.1, 1H), 3.73 (d, J = 15.7, 1H), 3.67 (d, J = 15.6, 1H), 3.64-3.51 (m, 2H), 3.12-3.04 (m, 1H), 2.41-2.28 (m, 1H), 2.20-2.08 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{18}BrN_3O$: 386.07; found: 386.10.



M.7

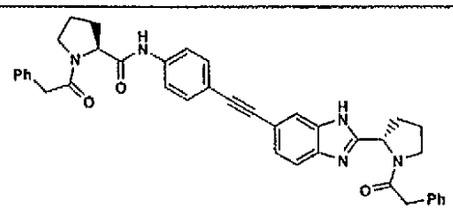
$Pd(Ph_3P)_2Cl_2$ (13.3 mg, 0.019 mmol) was added to a mixture of M.6 (152.9 mg, 0.40 mmol), 4-ethynylaniline (69.6 mg, 0.59 mmol), and Et_3N (2.20 mL) in dimethylformamide (2.0 mL) and the reaction was heated to 50 °C for 8.5 hr. The volatile component was removed *in vacuo* and the residue was submitted to flash chromatography (0-30% methanol/dichloromethane), then further purified on reverse

phase HPLC (methanol/water/TFA) to afford the TFA salt of M.7 (50 mg). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{25}N_4O$: 421.2; Found 421.21.

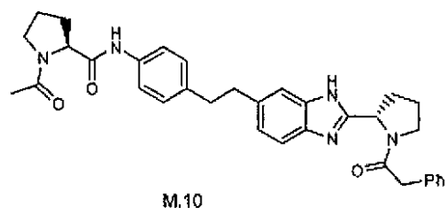


M.8

Dichloromethane (3.0 mL) was added to a mixture of M.7 (57.0 mg, 0.14 mmol), (S)-1-acetylpyrrolidine-2-carboxylic acid (23.3 mg, 0.15 mmol) and EEDQ (39.0 mg, 0.16 mmol) and stirred at ambient conditions for 16 hr. The volatile components were removed in vacuo, and the residue was dissolved in methanol and subjected to a reverse phase HPLC purification (methanol/water/TFA), followed by free-basing (SCX column; methanol wash; 2.0 M ammonia/methanol elution) and flash chromatography purification (5-15% methanol/ethyl acetate) to afford M.8 as a brown solid (38.0 mg). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{34}N_5O_3$: 560.27; found: 560.28.

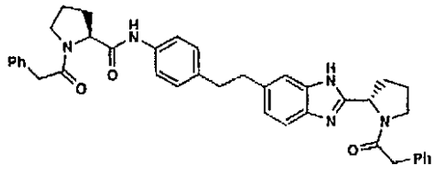
M.9	 From M.5 and M.7	LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{37}N_5O_3$: 636.30; found: 636.29.

Examples M.10 - M.11

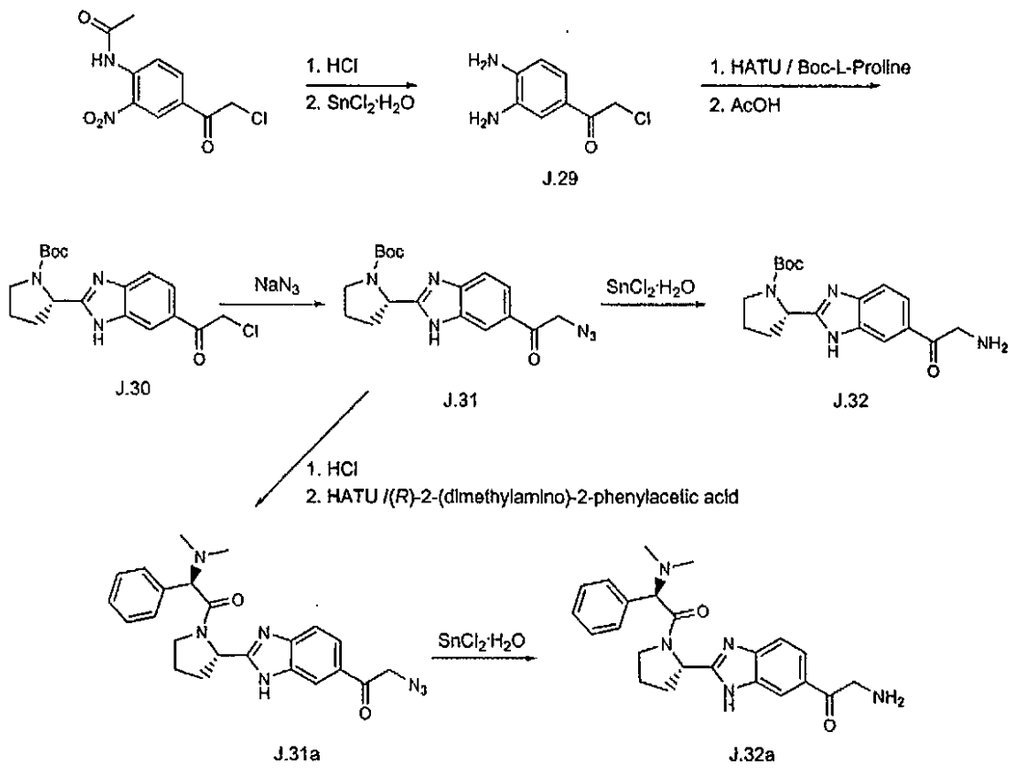


M.10

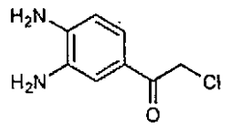
A mixture of M.8 (24.0 mg, 0.04 mmol) and Pd/C (10%, 14.1 mg) in methanol (3.0 mL) was stirred under a balloon of H_2 (1 atm) for 3 hr. The suspension was filtered through a pad of diatomaceous earth (Celite®) and concentrated in vacuo to afford M.10 as an off-white foam (22.0 mg). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{38}N_5O_3$: 564.30; found: 564.43.

M.11	 From M.9	LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_5O_3$: 640.33; found: 640.35.

Synthetic Route 15

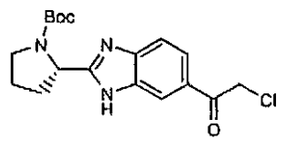


Examples J.29 -- J.32a



J.29

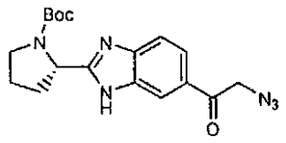
N-(4-(2-Chloroacetyl)-2-nitrophenyl)acetamide (25.7 g, 0.1 mol) was suspended in 250 mL of 3N HCl and heated at 80 °C in 1L pressure vessel for 20 h. After being cooled to room temperature, 1-(4-amino-3-nitrophenyl)-2-chloroethanone•HCl (23.2 g, 92%) was isolated by vacuum filtration as a bright yellow solid. The salt (23.2 g, 0.092 mol) was suspended in methanol (600 mL) and tin chloride dihydrate (65 g, 0.29 mol) was added in one portion. The mixture was heated at 70 °C for 14 h while being vigorously stirred. An additional 20 g of tin chloride dihydrate was added and the reaction stirred 8 h. The solvent was removed by rotory evaporation and the residue was taken up in ethyl acetate/$NaHCO_3$ soln (caution: much carbon dioxide evolution). The precipitated salts were removed by filtration and the organic layer was separated. The aqueous layer was extracted twice more (ethyl acetate) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to ¼ volume. 2-Chloro-1-(3,4-diaminophenyl) ethanone, J.29, 10.03 g (59%) was isolated by vacuum filtration as a brick red solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.17 (dd, J = 8.3, 2.3 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.57 (br. s, 2H), 4.85 (s, 2H), 4.78 (br. s, 2H). LC (Cond.-D2): 0.65 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{10}ClN_2O$: 185.05; found: 185.02. HRMS: Anal. Calcd. for $[M+H]^+$ $C_8H_{10}ClN_2O$: 185.0482; found: 185.0480. The reaction was repeated to supply more material.



J.30

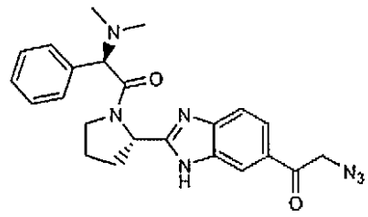
HATU (38.5 g, 101.3 mmol) was added portion wise to a vigorously stirred solution of J.29 (17.0 g, 92 mmol), N-Boc-L-proline (19.82 g, 92 mmol), and Hunig's base (17.6 mL, 101.3 mmol) in dimethylformamide (200 mL). After 6 h, the reaction mixture was concentrated in vacuo to remove solvent and the residue was

taken up in ethyl acetate, washed with saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Concentration yielded a viscous brown oil which was taken up in glacial acetic acid (100 mL) and heated at 60 °C for 20 h. The solvent was removed in vacuo and the residue was taken up in ethyl acetate, washed with saturated $NaHCO_3$ solution (adjust with 1N NaOH soln until pH = 9), brine, and dried (Na_2SO_4). The residue obtained upon concentration was pre-adsorbed onto SiO_2 (dichloromethane) and subjected to flash chromatography successively eluting with 50%, 75%, 100% ethyl acetate/hexanes to give J.30 (S)-*tert*-Butyl 2-(6-(2-chloroacetyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate 22.37 g (67%) was obtained as a yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.20 (s, 1H), 7.81 (dd, J = 8.3, 2.3 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 4.99/4.93 (s, 1H), 3.60 (br. s, 1H), 3.46-3.41 (m, 1H), 2.36-2.30 (m, 1H), 2.01-1.89 (m, 3H), 1.39/1.06 (s, 9H). LC (Cond.-D2): 1.85 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}ClN_3O_3$: 364.14; found: 364.20. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}ClN_3O_3$: 364.1428; found: 364.1427.



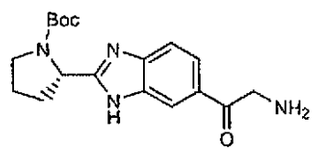
J.31

Sodium azide (1.79 g, 27.48 mmol) was added in one portion to a solution of J.30 (S)-*tert*-butyl 2-(6-(2-chloroacetyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (10.0 g, 27.48 mmol) in acetonitrile (200 mL) and stirred at 60 °C for 16 h. The reaction mixture was concentrated to 1/5 volume, diluted with ethyl acetate, and washed with water and brine prior to being dried (Na_2SO_4). Concentration gave J.31 (S)-tert-butyl 2-(6-(2-azidoacetyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate 6.8 g (48%) as a golden orange foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.22/8.03 (s, 1H), 7.80-7.75 (m, 1H), 7.65/7.56 (d, J = 8.5 Hz, 1H), 4.99-4.93 (m, 3H), 3.60 (br. s, 1H), 3.46-3.41 (m, 1H), 2.38-2.27 (m, 1H), 2.01-1.89 (m, 3H), 1.40/1.06 (s, 9H). LC (Cond.-D2): 1.97 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}N_6O_3$: 371.19; found: 371.32. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}N_6O_3$: 371.1832; found: 371.1825.



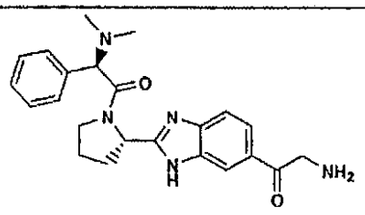
J.31a

To a solution of J.31 (1.8 g, 4.86 mmol) in ethyl acetate (5 mL) was added HCl/dioxane (10 mL of 4N), and the reaction was stirred 4 hr. The solvents were removed in vacuo, and the HCl salt was exposed to high vacuum for 18 h to give (S)-2-azido-1-(2-(pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethanone·2HCl a yellow solid. HATU (1.94 g, 5.10 mmol) was added to the HCl salt of (S)-2-azido-1-(2-(pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethanone (1.8 g, 4.86 mmol), (R)-2-(dimethylamino)-2-phenylacetic acid HCl salt (1.05 g, 4.86 mmol), and Hunig's base (3.4 mL, 19.4 mmol) in dimethylformamide (50 mL) while being rapidly stirred 6 h. The solvent was removed in vacuo and the reside was partitioned into two lots and separately pre-absorbed onto SiO_2 (dichloromethane), and subjected to flash chromatography on a 40 M Biotage silica gel column pre-equilibrated 2% B, and eluted with 2% B (150 mL); Segment 2: 2-40% B (1200 mL); Segment 3: 40 – 80% (600 mL). A = dichloromethane; B = 25% methanol/ dichloromethane to give J.31a (R)-1-((S)-2-(6-(2-azidoacetyl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-1-yl)-2-(dimethylamino)-2-phenylethanone (combined lots: 1.05 g (50%)) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.16 (s, 1H), 7.82 (dd, J = 8.8, 1.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.60-7.56 (m, 5H), 5.51 (s, 1H), 5.22 (dd, J = 8.2, 2.8, 1H), 4.95 (m, 2H), 4.09-4.05 (m, 1H), 3.17-3.12 (m, 1H), 2.90/2.84 (br. s, 6H), 2.23-2.19 (m, 1H), 2.21-1.89 (m, 3H). LC (D-Cond. 1): RT =1.5 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{26}N_7O_2$: 432.22; found: 431.93. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{26}N_7O_2$: 432.2148; found: 432.2127.

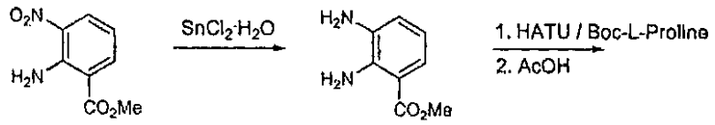


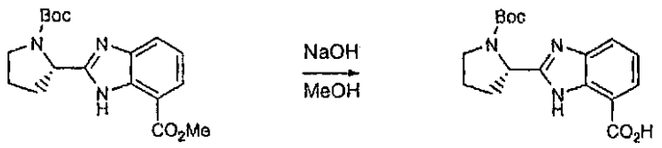
J.32

Tin(II)dichloride dehydrate (12.24 g, 54.26 mmol) was added to J.31 (6.8 g, 18.08 mmol) dissolved in methanol (200 mL). The reaction mixture was heated at 60 °C for 6 h and concentrated and dried under high vacuum to give the HCL salt of J.32 (S)-tert-butyl 2-(6-(2-aminoacetyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate, 16.6 g which contained tin salts. LC (Cond.-D2): 1.21 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{25}N_4O_3$: 345.18; found: 345. The material was used without purification.

J.32a		

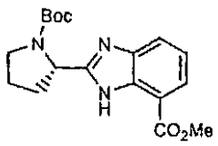
Synthetic Route 16





J.33 J.34

Examples J.33 –J.34a

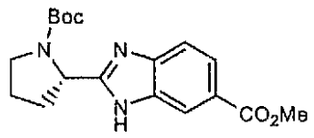


J.33

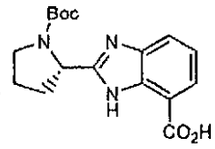
Tin(II)chloride dihydrate (17.25 g, 76.5 mmol) was added in one portion to methyl 2-amino-3-nitrobenzoate (5.0 g, 25.5 mmol) in methanol (100 mL) under nitrogen. The yellow mixture was vigorously stirred at 65 °C for 16 h, and the solvent was removed by rotory evaporation to near dryness. The residue was taken

up in ethyl acetate and the solution was poured into a large beaker containing 1:1 ethyl acetate/$NaHCO_3$ soln. (300 mL) and stirred 15 min. The precipitates were removed by filtration and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Concentration gave methyl 2,3-diaminobenzoate as a deep red viscous oil 4.1 g (97%).

HATU (10.66 g, 28.0 mmol) was added in one portion to a stirred solution of methyl 2,3-diaminobenzoate (4.1 g, 24.7 mmol), N-Boc-L-proline (5.49 g, 25.5 mmol), and Hunig's base (4.9 mL, 28.0 mmol) in dimethylformamide (50 mL). The reaction mixture was stirred 3 h and solvent removed in vacuo, and the residue was diluted with ethyl acetate, washed with 0.1N HCl, sat'd $NaHCO_3$, brine, and dried (Na_2SO_4). Concentration gave a reddish brown viscous oil which was taken up in glacial acetic acid (60 mL) and heated at 60 °C for 16 h. The solvent was removed in vacuo, and the residue was diluted with ethyl acetate, washed with sat'd $NaHCO_3$ soln., brine, and dried (Na_2SO_4). Concentration gave a residue that was divided into two lots, and each lot pre-adsorbed onto SiO_2 (dichloromethane), applied to a 40 M Biotage SiO_2 column, and eluted by gradient 10% - 100% B (1440 mL); A = hexanes; B = ethyl acetate to give J.33 (S)-methyl 2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-7-carboxylate 7.05 g (83%) as a reddish oil. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.86 (d, J = 7.9 Hz, 1H), 7.78 (t, J = 5 Hz, 1H), 7.28-7.24 (m, 1H), 5.20-5.11 (m, 1H), 3.95 (s, 3H), 3.60-3.52 (m, 1H), 3.43-3.38 (m, 1H), 2.33-2.22 (m, 1H), 2.15-2.0 (m, 2H), 1.91-1.86 (m, 1H), 1.40/1.05 (s, 9H). LC (Cond.-D2): RT =1.86 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{24}N_3O_4$: 346.18; found 346.26; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{24}N_3O_4$: 346.1767; found: 346.1776.

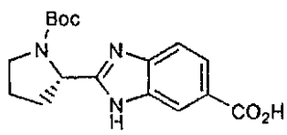
J.33a		RT = 0.72 min (Cond.-J3); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{24}N_3O_4$: 346.18; found: 346.

Example J.34

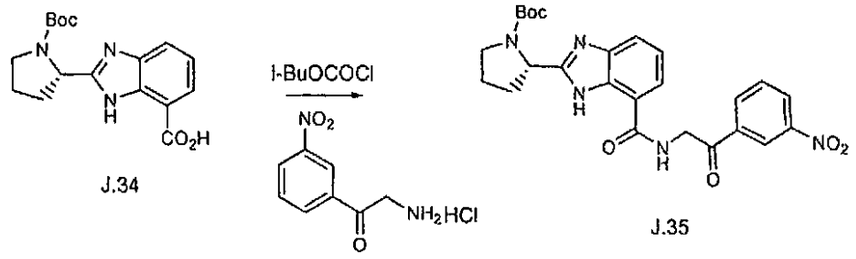


J.34

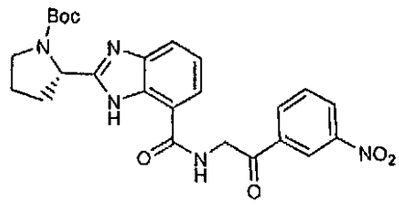
A solution of 5N sodium hydroxide (8 mL) was added to methyl ester J.33 (7.0 g, 20.3 mmol) in methanol (80 mL) and stirred 8 h. An additional 4 mL was added and stirring continued stirring for 18 h, at which time the reaction temperature was raised to 45 °C for a final 8 h to complete the hydrolysis. Most of the methanol was removed by rotory evaporation, and the basic aqueous solution was diluted with ethyl acetate. A precipitate formed and was isolated by filtration. The organic layer was separated and washed with brine. Additional lots of precipitate formed during partial concentration to ¼ vol, and the combined lots of J.34 (S)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-7-carboxylic acid totaled 5.49 g (82%) . ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.04-8.0 (m, 2H), 7.58 (br. s, 1H), 5.32 (s, 1H), 3.67-3.63 (m, 1H), 3.47-3.43 (m, 1H), 2.44-2.36 (m, 1H), 2.17-2.11 (m, 1H), 2.05-1.93 (m, 2H), 1.40/1.06 (s, 9H). LC (Cond.-D2): 1.68 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 332.16; found: 332.25. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 322.1610; found: 322.1625.

J.34a		RT = 1.64 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 332.16; found: 332.14. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 322.1605; found: 322.1603.

Synthetic Route 17.

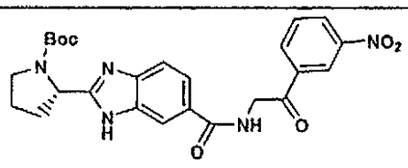


Examples J.35 – J.35a



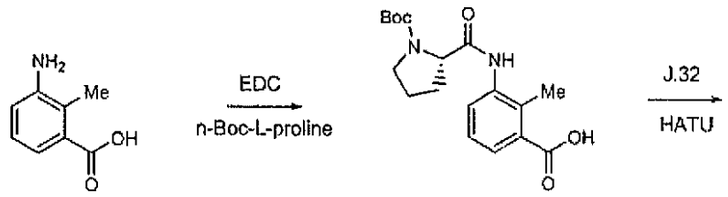
J.35

Iso-butyl chloroformate (0.45 mL, 3.4 mmol) was added dropwise to a solution of acid J.34 (1.0 g, 3.02 mmol) and N-methylmorpholine (1.2 mL, 10 mmol) in tetrahydrofuran (50 mL) cooled at 0 °C under nitrogen, and the ice bath was removed the reaction stirred 30 min. The solution was recooled and an additional 0.5 ml of base was added followed by of 2-nitrophenacylamine·HCl (700 mg, 3.2 mmol). The reaction mixture was stirred for 18 h at room temperature and diluted with ethyl acetate and sat'd $NaHCO_3$ soln. A precipitate was removed by filtration and the organic phase was concentrated. The residue was taken up in methanol and filtered to provide a second lot of precipitate. The combine lots of J.35, 796 mg (65%) were carried forward without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.5 (br. s, 1H), 8.73 (s, 1H), 8.52-8.49 (m, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 5.11-5.05 (m, 3H), 3.70-3.33 (m, 2H), 2.39-2.31 (m, 1H), 2.14-1.89 (m, 3H), 1.38/1.07 (s, 9H). LC (Cond.-J1): 1.64 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_5O_6$: 494.21; found: 494.17.

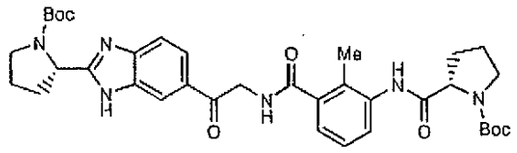
J.35a		RT = 1.5 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$

	From J.34a and 2-amino-1-(3-nitrophenyl)ethanone	$C_{25}H_{28}N_5O_6$: 494.20; found 494.

Synthetic Route 18

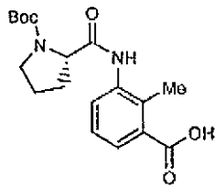


J.36



J.37

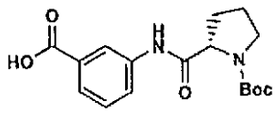
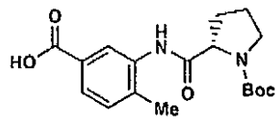
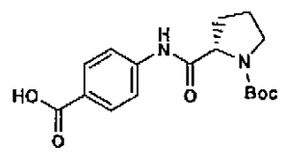
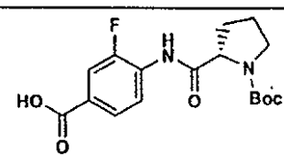
Examples J.36 –J.37e



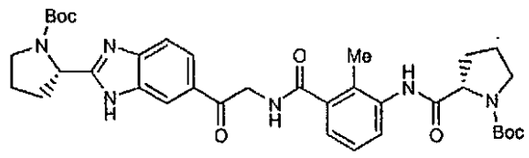
J.36

N-(3-Dimethylaminopropyl)-N-ethylcarbodimide·HCl salt (3.1 g, 16.6 mmol) was added to a suspension of 3-amino-2-methylbenzoic acid (2.5 g, 16.6 mmol) and N-Boc-L-proline (3.5 g, 16.6 mmol) in dichloromethane (40 mL). The reaction mixture was stirred under nitrogen for 18 h, diluted with solvent (1 vol) and washed with 1N HCl, brine, and dried ($MgSO_4$). Concentration gave a foam with was applied to a 40 M Biotage SiO_2 column, and eluted by gradient 20% - 60% B (1000 mL); A = 1% acetic acid / hexanes; B = 1% acetic acid / ethyl acetate to give J.36 (S)-3-(1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)-2-methylbenzoic acid 2.6 g (45%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.5 (br. s, 1H), 9.52/9.46 (s, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.44-7.40 (m, 1H), 7.29-7.24 (m, 1H), 4.32-4.28 (m, 1H), 3.47-3.48 (m, 1H), 3.34-3.29 (m, 1H), 2.33 (s, 3H), 1.93-1.80 (m, 4H), 1.41/1.36 (s, 9H).

LC (Cond.-J1): 1.55 min; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{25}N_2O_5$: 349.18; found 349.33.

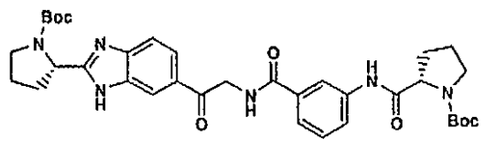
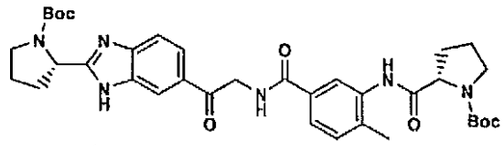
J.36a		RT = 2.12 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{23}N_2O_5$: 335.16; found 335.26. HRMS: Anal. Calcd. for $[M-H]^-$ $C_{17}H_{21}N_2O_5$: 333.1450; found: 333.1440.
J.36b		RT = 2.14 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{25}N_2O_5$: 349.18; found 349.25. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{25}N_2O_5$: 349.1763; found: 349.1748.
J.36c		RT = 2.09 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{23}N_2O_5$: 335.16; found 335.25. HRMS: Anal. Calcd. for $[M-H]^-$ $C_{17}H_{23}N_2O_5$: 333.1450; found: 333.1467.
J.36d	 (Obtain upon deprotection of the	RT = 2.24 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}FN_2O_5$: 353.15; found 353.22.

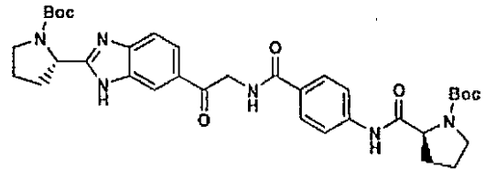
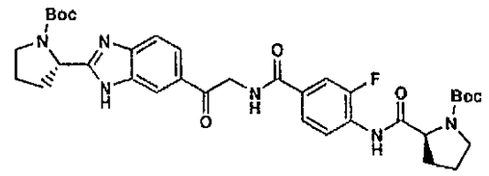
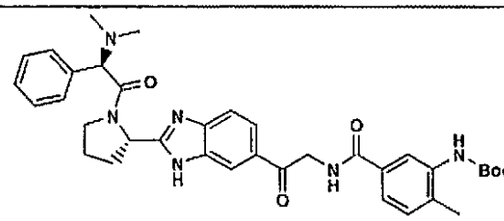
	allyl ester via $Pd(Ph_3)_4$).	HRMS: Anal. Calcd. for $[M-H]^-$ $C_{17}H_{20}FN_2O_5$: 351.1356; found: 351.1369.



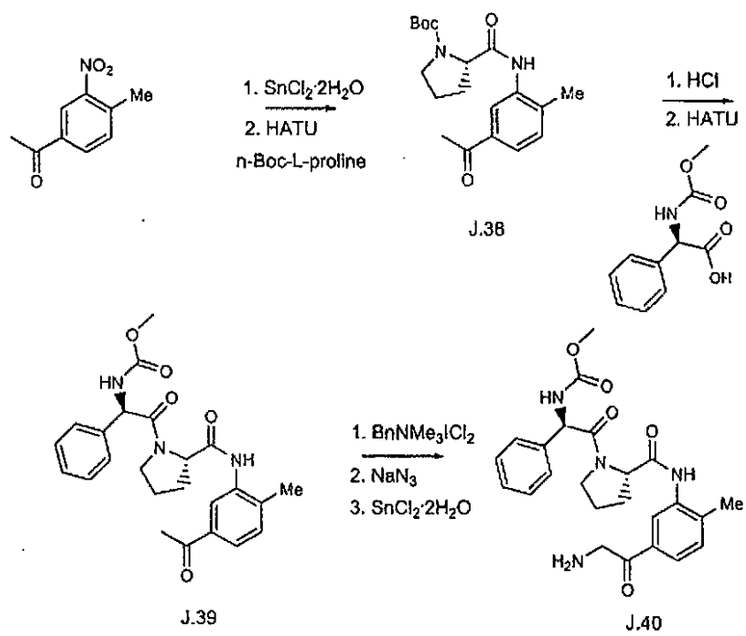
J.37

HATU (462 mg, 1.22 mmol) was added in one portion to a stirred solution of J.32 (450 mg, 1.22 mmol), J.36 (423 mg, 1.22 mmol), and Hunig's base (1.0 mL) in dimethylformamide (10 mL) and the reaction mixture was stirred 18 h. The solvent was removed in.vacuo and the residue was applied to a 25 M Biotage SiO_2 column, and eluted by gradient 5% - 60% B (500 mL); A = ethyl acetate; B = 10% methanol/ethyl acetate to give J.37, 439.6 mg (50%). ^1H NMR (300 MHz, DMSO-d_6) δ: 12.73-12.58 (m, 1H), 9.45/9.35 (s, 1H), 8.59 (br s, 1H), 8.33/8.12 (s, 1H) 7.86 (d, J = 8.4 Hz,.1H), 7.66/7.56 (d, J = 8.4 Hz, 1H), 7.40-7.36 (m, 1H), 7.25 (app br. s, 2H), 5.0-4.92 (m, 1H), 4.79 (d, J = 4.8 H, 2H), 4.33-4.30 (m, 1H), 3.60 (br. s, 1H), 3.47-3.41(m, 2H), 3.35-3.29 (m, 1H), 2.24 (s, 3H), 2.02-1.87 (m, 8H), 1.42-1.37/1.05 (m, 18H). LC (Cond.-J1): 1.65 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{47}N_6O_7$: 675.35; found 675.30.

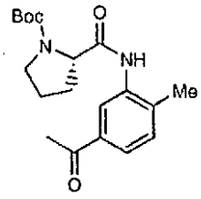
J.37a	 From J.32 and J.36a	RT = 2.29 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661.34; found 661.42.
J.37b	 From J.32 and J.36b	RT = 1.73 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{47}N_6O_7$: 675.37; found 675.31.

J.37c	 From J.32 and J.36c	RT = 2.25 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661.34; found 661.42.
J.37d	 From J.32 and J.36d	RT = 2.33 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}FN_6O_7$: 679.33; found 679.42.
J.37e	 From J.32a and 3-(t-butoxycarbonyl-amino)-4-methylbenzoic acid	RT = 2.08 min (Cond.-D2); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_6O_5$: 639.33; found 639.67.

Synthetic Route 19

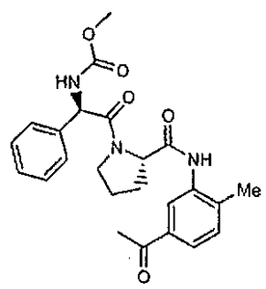


Examples J.38 – J.40



J.38

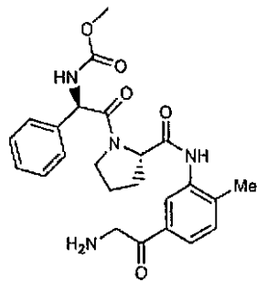
Tin(II)dichloride dihydrate (37 g, 168 mmol) was added to 4-methyl-3-nitroacetophenone (10 g, 56 mmol) dissolved in methanol (350 mL). The reaction mixture was heated at 60 °C for 18 h, concentrated, and dried under high vacuum to give to 1-(3-amino-4-methylphenyl)ethanone which contained tin salts. LC (Cond.-J1): 0.73 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{11}NO$: 150.08; found: 150. The material was used without purification. HATU (10.6 g, 28 mmol) was added in one portion to a stirred solution of 1-(3-amino-4-methylphenyl)ethanone (4.1 g, 28 mmol), N-Boc-L-proline (6 g, 28 mmol), and Hunig's base (25 mL) in DMF (225 mL) and the reaction mixture was stirred 18 h. The solvent was removed in vacuo and the residue was taken up in ethyl acetate/methanol (1:1) and applied to a flash SiO_2 column. A step elution by gradient 20%; 50%; 75%; 100% B (total elution vol 1500 mL); A = hexanes; B = ethyl acetate; and a final elution with;10% methanol/ethyl acetate was conducted to give J.38, 4.4 g (46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.51/9.45 (s, 1H), 7.95-7.92 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 4.33-4.29 (m, 1H), 3.48-3.29 (m, 2H), 2.50 (s, 3H), 2.26 (s, 3H), 1.98-1.80 (m, 4H), 1.41/1.36 (m, 9H). LC (Cond.-J1): 1.70 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{27}N_2O_4$: 347.20; found 347.41.



J.39

Example J.38 (3 g, 83 mmol) was dissolved in methanol (30 mL) and 4N HCl/dioxane (50 mL) was added and the reaction was stirred 18 hr. The solvents were removed in vacuo, and (S)-N-(5-acetyl-2-methylphenyl)pyrrolidine-2-carboxamide HCl salt was exposed to vacuum. LC (Cond-J1): 0.9 min. HATU (1.4 g, 3.5 mmol) was added in one portion to a stirred solution of (S)-N-(5-acetyl-2-methylphenyl)pyrrolidine-2-carboxamide·HCl (1.0 g, 3.5 mmol), (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (740 mg, 3.5 mmol), and Hunig's base (2.9 mL) in dimethylformamide (25 mL) and the reaction mixture was stirred 18 h. The solvent was removed in vacuo and the residue was applied to a 40 M Biotage SiO_2 column, and eluted by gradient 50% - 100% B (500 mL); A = hexanes; B = ethyl acetate to give J.39, methyl (R)-2-((S)-2-(5-acetyl-2-methylphenylcarbamoyl)pyrrolidin-1-yl)-2-oxo-1-phenylethylcarbamate 1.25 g (87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.42 (s, 1H), 7.95 (s, 1H), 7.75-7.69 (m, 2H), 7.43-7.19 (m, 6H), 5.50/5.40 (d, J = 7.7 Hz, 1H), 4.49-4.47 (m, 1H), 3.87-3.81 (m, 1H), 3.58-3.54 (m, 1H), 3.50 (s, 3H), 2.54 (s, 3H), 2.27 (s, 3H), 1.99-1.83 (m, 4H). LC (Cond.-J1): 1.65 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{28}N_3O_5$: 438.20; found 438.20.

Reference: Synthesis (1988) p 545. (Chlorination).

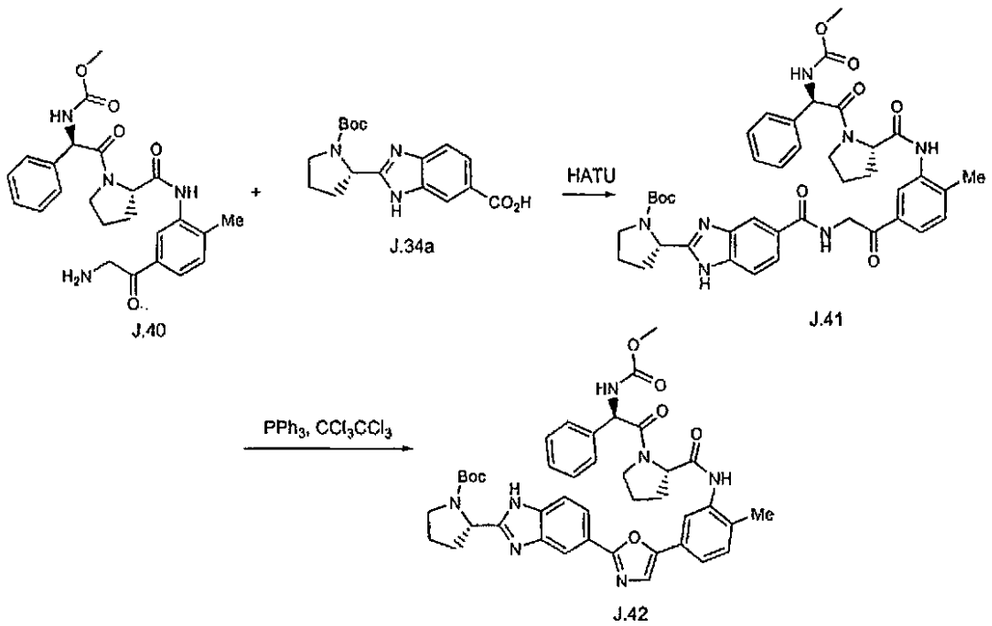


J.40

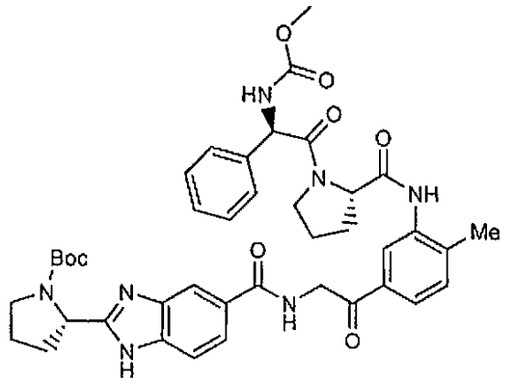
Benzyltrimethyldichloroiodate (2.0 g, 5.72 mmol) was added to a solution of J.39 (1.25 g, 2.86 mmol) in dichloromethane (65 mL) and methanol (20 mL). The reaction was heated for 3 h at 75 °C before being concentrated by rotory evaporation. The residue was taken up in ethyl acetate and washed with sodium thiosulfate soln, brine, and dried ($MgSO_4$) to afford an α-chloroketone. LC (Cond.-J1): 1.70 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}ClN_3O_5$: 471.16; found: 471.

The α-chloroketone was converted to the α-aminoketone J.40 as described in example J.31. [α-azidoketone: LC (Cond.-J1): 1.70 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_6O_5$: 479.20; found: 479.20.] J.26 LC (Cond.-J1): 1.70 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{29}N_4O_5$: 453.21; found: 453.

Synthetic Route 20.

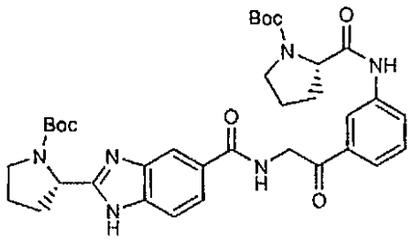
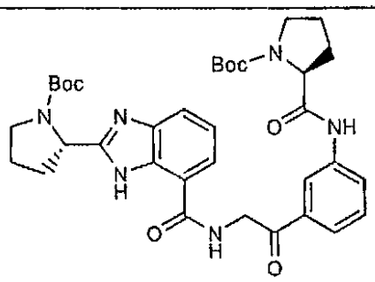


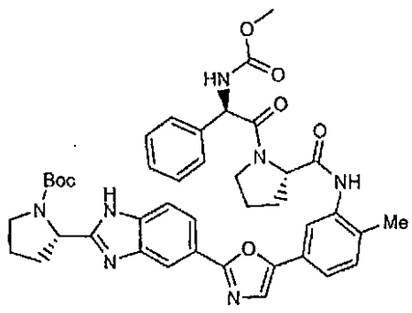
Example J.41 - J.42h



J.41

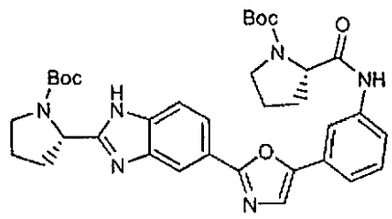
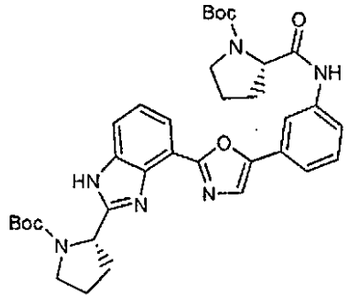
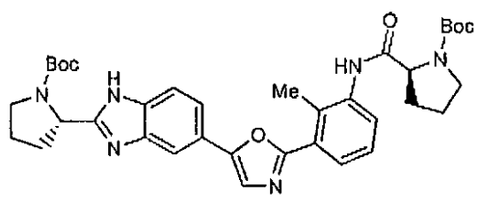
The α-aminoketone J.40 was coupled with J.34a as described in example J.37 to give J.41: LC (Cond.-J1): 1.90 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_8$: 766.36; found: 766.37.

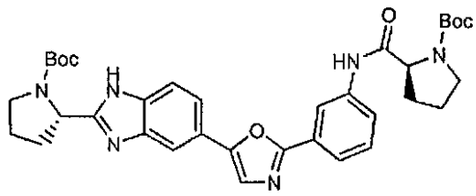
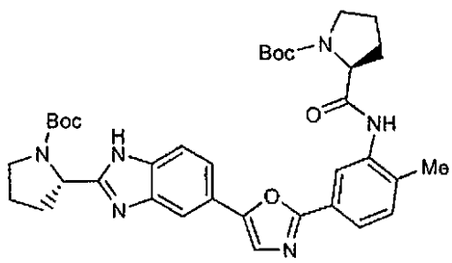
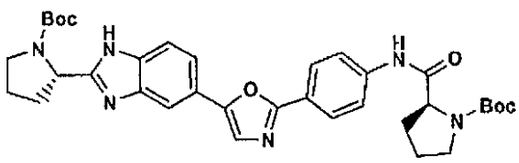
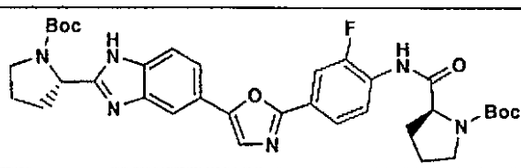
J.41a	 From J.35a and N-Boc-L-proline, prepared as described enroute to J.38.	RT = 1.64 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661.34; found 661.30.
J.41b	 From J.35 and N-Boc-L-proline, prepared as described enroute to J.38.	RT = 1.82 min (Cond.-J1); LCMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661.34; found 661.32.

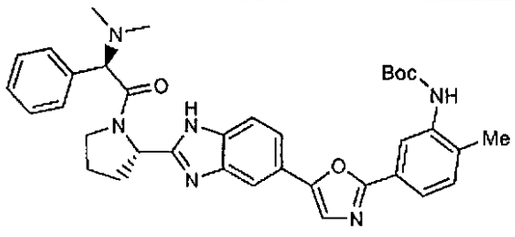


J.42

A solution of J.41 (237 mg, 0.31 mmol), triphenylphosphine (162 mg, 0.62 mmol), and triethylamine (0.2 mL, 1.74 mmol) in dichloromethane (3 mL) was stirred about 5 min under nitrogen atmosphere before addition of hexachloroethane (146 mg, 0.62 mmol) in one portion. The reaction mixture was stirred 18 h, partially concentrated, and applied to a 12 M Biotage silica gel column and eluted by gradient 40% - 100% B. A = hexanes; B = ethyl acetate to give J.42, 95 mg (41%). LC (Cond.-J1): 1.95 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_7$: 748.36; found: 748.29.

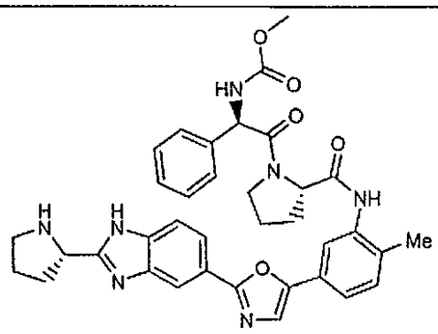
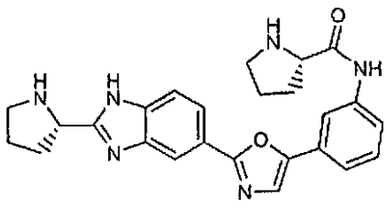
J.42a	 From J.41a	RT = 2.64 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643.32; found: 643.35. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643.3244; found 643.3242.
J.42b	 From J.41b	RT = 2.97 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643.32; found: 643.37. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643.3244; found 643.3265.
J.42c	 From J.37	RT = 2.51 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657.34; found: 657.36.

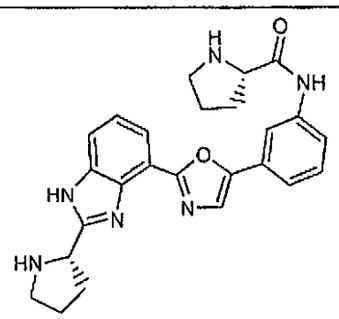
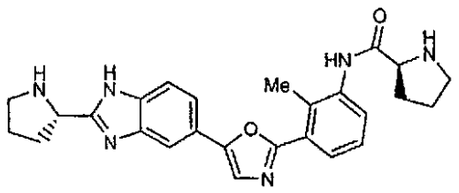
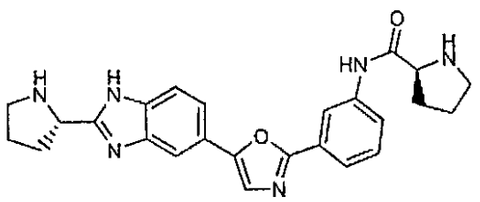
		HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657.3401; found 657.3407.
J.42d	 From J.37a	RT = 2.61 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643.32; found: 643.41.
J.42e	 From J.37b	RT = 2.63 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657.34; found: 657.73. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657.3401; found 657.3397.
J.42f	 From J.37c	RT = 1.59 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643.32; found: 643.41.
J.42g		RT = 2.64 min (D-Cond. 2); LC/MS: Anal. Calcd. for

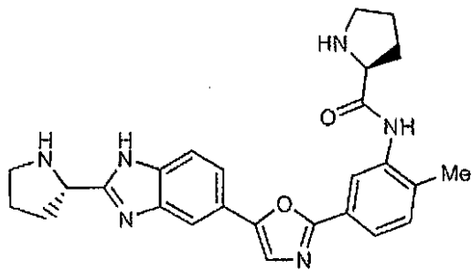
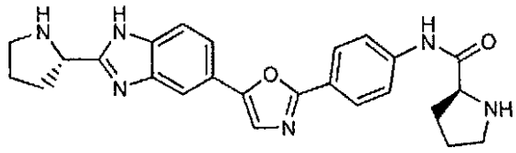
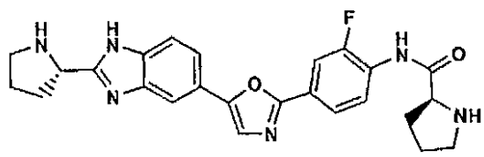
	From J.37d	$[M+H]^+$ $C_{35}H_{42}FN_6O_6$: 661.32; found: 661.40.
J.42h	 From J.37e	RT = 2.41 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621.32; found: 621.21.

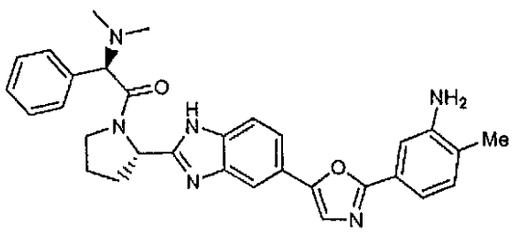
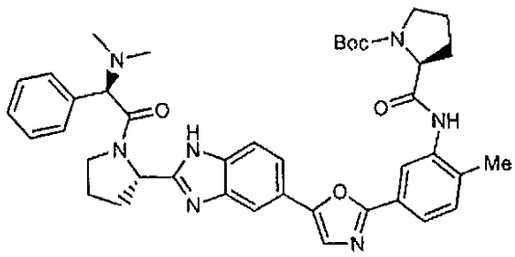
Examples J.43 – J.43j

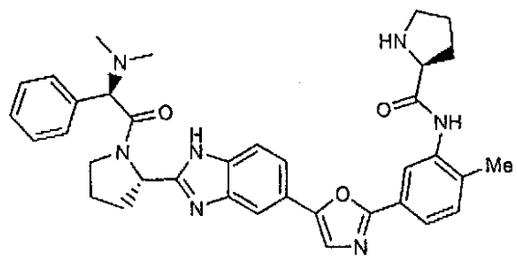
The pyrrolidines examples J.42 – J.42h were treated with HCl as described in example J.39 to give examples J.43 – J.43j as HCl salts.

J.43	 From J.42	RT = 1.80 min (Cond.-J1) LCMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{38}N_7O_5$: 648.29; found 648.
J.43a	 From J.42a	RT = 1.69 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.22; found: 443.23.
J.43b		RT = 1.86 min (D-Cond. 2); LC/MS:

	 From J.42b	Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.22; found: 443.07. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.2195; found 443.2213.
J.43c	 From J.42c	RT = 1.51 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6O_2$: 457.24; found: 457.19.
J.43d	 From J.42d	RT = 1.64 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.22; found: 443.31. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.2195; found 443.2205.

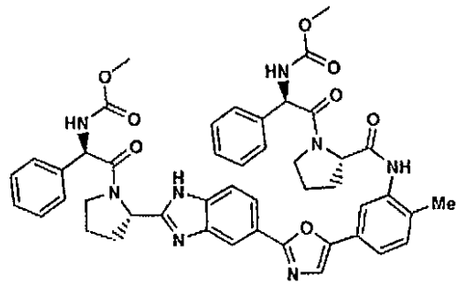
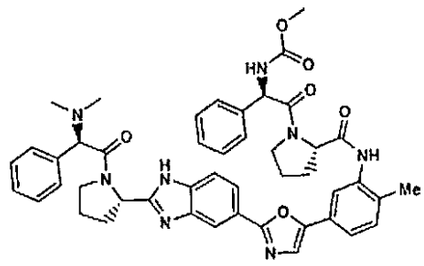
J.43e	 From J.42e	RT = 1.70 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6O_2$: 457.24; found: 457.29. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6O_2$: 457.2352; found 457.2332.
J.43f	 From J.42f	RT = 1.59 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.22; found: 443.31. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443.2195; found 443.2206.
J.43g	 From J.42g	RT = 1.61 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{26}FN_6O_2$: 461.21; found: 461.31. HRMS: Anal. Calcd.

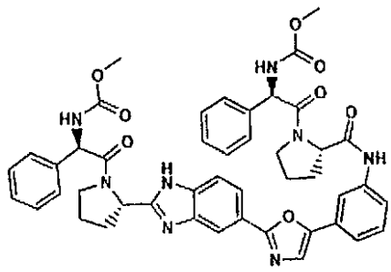
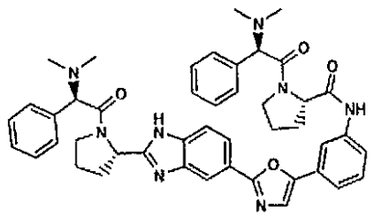
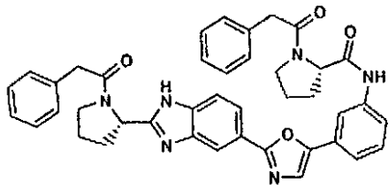
		for $[M+H]^+$ $C_{25}H_{26}FN_6O_2$: 461.2101; found 461.2101.
J.43h	 From J.42h	RT = 1.70 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{33}N_6O_2$: 521.27; found: 521.48. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{33}N_6O_2$: 521.2665; found 521.2673.
J.43i	 From J.43h and N-Boc-L-proline as described in example J.38.	RT = 2.33 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_5$: 718.37; found: 718.19. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_5$: 718.3717; found 718.3692.

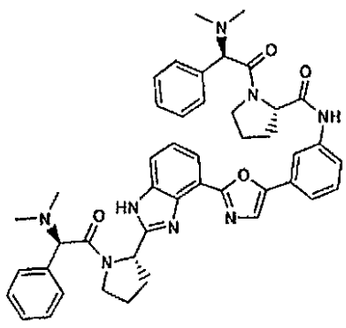
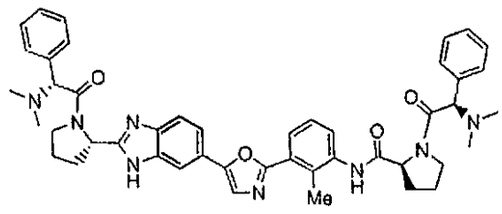
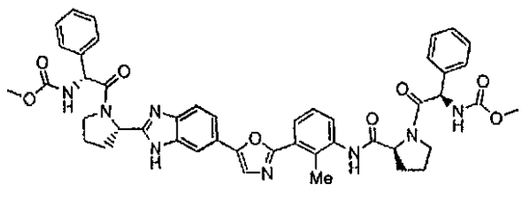
J.43j	 From J.43i as described in example J.39	RT = 1.69 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{40}N_7O_3$: 618.32; found: 618.38.

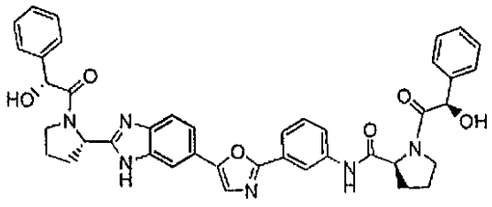
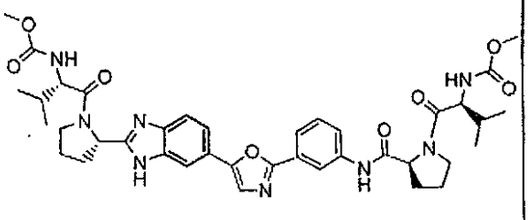
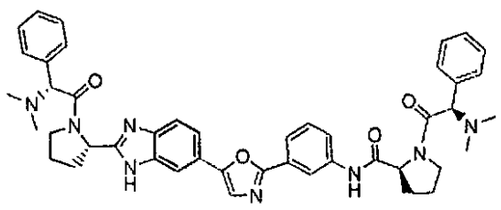
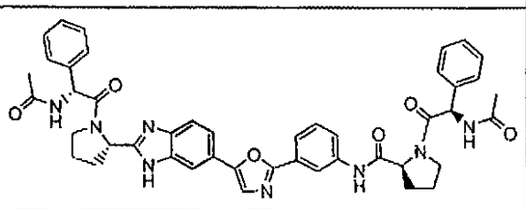
Examples J.44 – J.53a

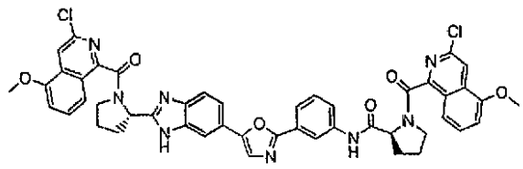
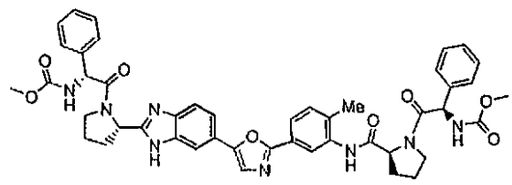
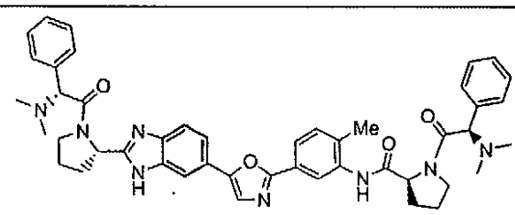
Examples J.44 – J.53a were prepared as described in example J.21.

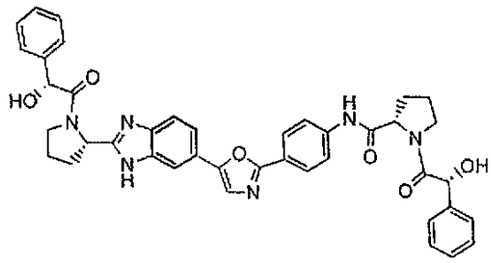
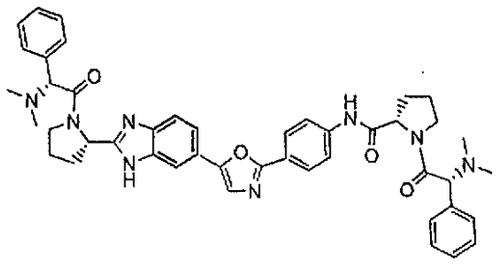
J.44	 From J.43	RT = 1.91 min (Cond.-J1) LRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839.35; found 839.29. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839.3517; found 839.3492.
J.44a	 From J.43	RT = 1.80 min (Cond.-J1) LRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_6$: 809.38; found 809.29. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_6$: 809.3775; found 809.3768.

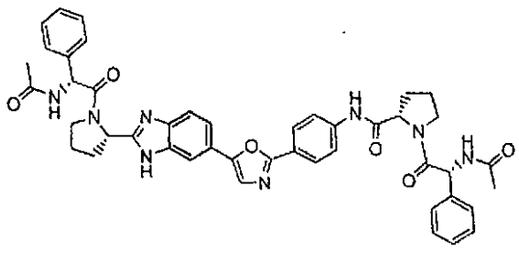
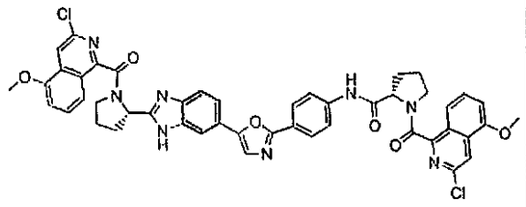
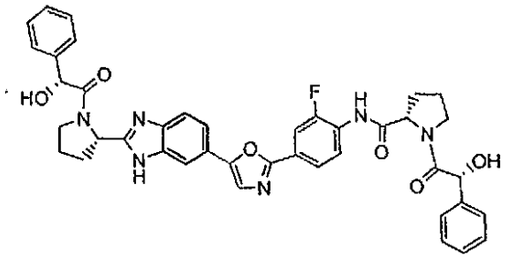
J.45	 From J.43a	RT = 2.42 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{45}N_8O_8$: 825.34; found: 825.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{45}N_8O_8$: 825.3360; found 825.3366.
J.45a	 From J.43a	RT = 2.27 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765.39; found: 765.36. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765.3877; found 765.3879.
J.45b	 From J.43a	RT = 2.48 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{39}N_6O_4$: 679.30; found: 679.37. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{39}N_6O_4$: 679.3033; found 679.3037.

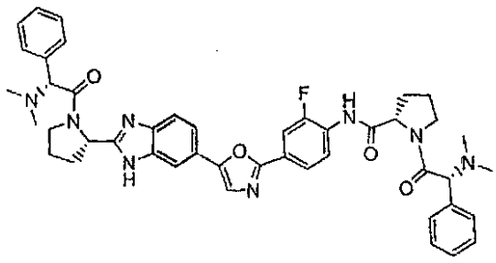
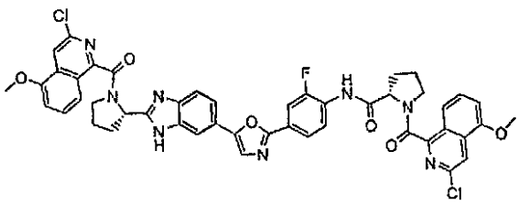
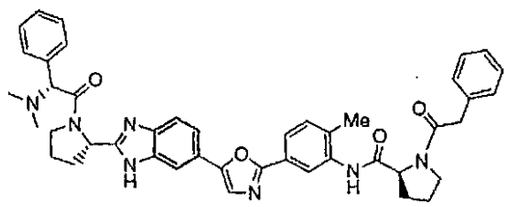
J.46	 From J.43b	RT = 2.10 min (D-Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765.39; found: 765.72. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765.3877; found 765.3899.
J.47	 From J.43c	RT = 1.77 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_4$: 779.40; found: 779.49. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_4$: 779.4033; found: 779.4042.
J.47a	 From J.43c	RT = 2.28 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839.35; found: 839.43. HRMS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839.3517; found: 839.3519.
J.48		RT = 2.21 min (Cond.-D2); LC/MS: Anal.

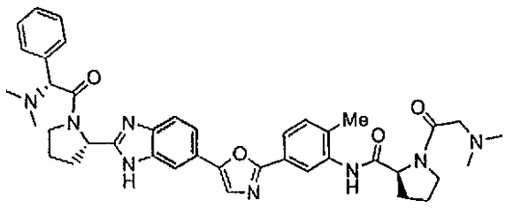
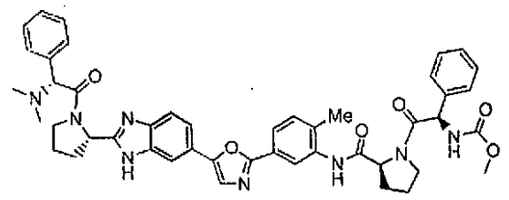
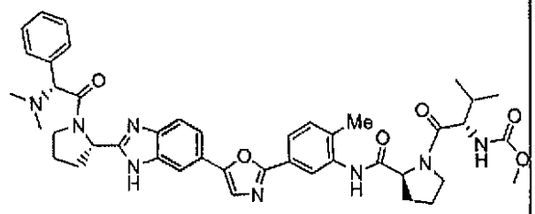
	 From J.43d	Calcd. for $[M+H]^+$ $C_{41}H_{39}N_6O_6$: 711.29; found: 711.46. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{39}N_6O_6$: 711.2931; found: 711.2942.
J.48a	 From J.43d	RT = 2.37 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_8$: 757.37; found: 757.37. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_8$: 757.3673; found: 757.3705.
J.48b	 From J.43d	RT = 1.92 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765.39; found: 765.59. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765.3877; found: 765.3841.
J.48c		RT = 2.26 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{45}N_8O_6$: 793.35;

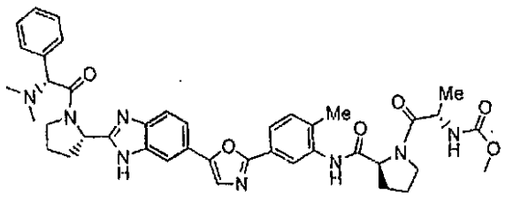
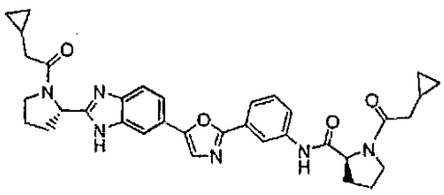
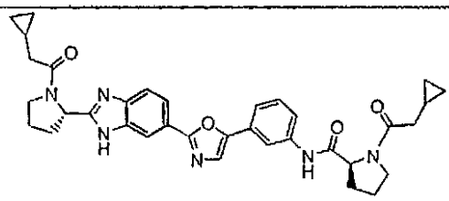
	From J.43d	found: 793.52. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{45}N_8O_6$: 793.3462; found: 793.3452.
J.48d	 From J.43d	RT = 2.88 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{39}Cl_2N_8O_6$: 881.24; found: 881.50. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{39}Cl_2N_8O_6$: 881.2370; found: 881.2347.
J.49	 From J.43e	RT = 2.41 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839.35; found: 839.27. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839.3517; found: 839.3535.
J.49a		RT = 2.07 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C46H51N8O4: 779.40; found: not apparent.

	From J.43e	HRMS: Anal. Calcd. for $[M+H]^+$ C46H51N8O4: 779.4033; found: 779.4014.
J.50	 From J.43f	RT = 2.26 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C41H39N6O6: 711.29; found: 711.39. HRMS: Anal. Calcd. for $[M+H]^+$ C41H39N6O6: 711.2931; found: 711.2958.
J.50a	 From J.43f	RT = 1.92 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C45H49N8O4: 765.39; found: 765.53. HRMS: Anal. Calcd. for $[M+H]^+$ C45H49N8O4: 765.3877; found: 765.3843.

J.50b	 From J.43f	RT = 2.29 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C45H45N8O6: 793.35; found: 793.49. HRMS: Anal. Calcd. for $[M+H]^+$ C45H45N8O6: 793.3462; found: 793.3442.
J.50c	 From J.43f	RT = 2.99 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C47H39Cl2N8O6: 881.24; found: 883.41. HRMS: Anal. Calcd. for $[M+H]^+$ C47H39Cl2N8O6: 881.2370; found: 881.2349.
J.51	 From J.43g	RT = 2.29 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C41H38FN6O6: 729.28; found: 729.36. HRMS: Anal. Calcd. for $[M+H]^+$ C41H38FN6O6: 729.2837; found:

		729.2847.
J.51a	 From J.43g	RT = 1.93 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C45H48FN8O4: 783.38; found: 783.52. HRMS: Anal. Calcd. for $[M+H]^+$ C45H48FN8O4: 783.3783; found: 783.3764.
J.51b	 From J.43g	RT = 2.89 min (Cond.-D2); LRMS: Anal. Calcd. for $[M+H]^+$ C47H38ClFN8O6: 899.23; found: 897.19. HRMS: Anal. Calcd. for $[M+H]^+$ C47H38ClFN8O6: 899.2275; found: 899.2287.
J.52	 From J.43j	RT = 2.23 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ C44H46N7O4: 736.36; found: 737.00. HRMS: Anal. Calcd. for $[M+H]^+$ C44H46N7O4:

		736.3611; found: 736.3622.
J.52a	 From J.43j	RT = 1.75 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_4$: 703.37; found: 703.81. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_4$: 703.3720; found: 703.3748.
J.52b	 From J.43j	RT = 2.22 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_6$: 809.38; found: 809.57. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_6$: 809.3775; found: 809.3803.
J.52c	 From J.43j	RT = 2.27 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_6$: 775.39; found: 775.39. HRMS: Anal. Calcd. for $[M+H]^+$

		C43H51N8O6: 775.3932; found: 775.3921.
J.52d	 From J.43j	RT = 2.09 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^{+}$ C41H47N8O6: 747.36; found: 747.34. HRMS: Anal. Calcd. for $[M+H]^{+}$ C41H47N8O6: 747.3619; found: 747.3610.
J.53	 From J.43d	RT = 2.22 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^{+}$ $C_{35}H_{39}N_6O_4$: 607.30; found: 607.71. HRMS: Anal. Calcd. for $[M+H]^{+}$ $C_{35}H_{39}N_6O_4$: 607.3033; found: 607.3015.
J.53a	 From J.43a	RT = 2.28 min (Cond.-D2); LC/MS: Anal. Calcd. for $[M+H]^{+}$ $C_{35}H_{39}N_6O_4$: 607.30; found: 607.34.

BIOLOGICAL ACTIVITY

An HCV Replicon assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned PCT/US2006/022197 and in O'Boyle et. al. *Antimicrob Agents Chemother.* **2005** Apr;49(4):1346-53. Assay methods incorporating luciferase reporters have also been used as described (Apath.com).

HCV-neo replicon cells and replicon cells containing mutations in the NS5A region were used to test the currently described family of compounds. The compounds were determined to have more than 10-fold less inhibitory activity on cells containing mutations than wild-type cells. Thus, the compounds of the present disclosure can be effective in inhibiting the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/O4014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype. It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC_{50} (Effective 50% inhibitory concentration) values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment, compounds of the present disclosure are inhibitory versus 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC_{50} values against HCV 1b are as follows A (1-10 μM); B (100-999 nM); C (4.57-99 nM); D (2pM-4.57 nM).

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

Table 2

Example	*EC50*	*Range*	*Name*
J.21		D	methyl ((1S)-1-(((2S)-2-(8-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

J.21a		D	(1R)-2-((2S)-2-(8-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.22		D	methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.22a		D	(1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.22b		D	methyl ((1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.23		D	methyl ((1S)-1-(((2S)-2-(5-(3-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.23a		D	(1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.23b		D	methyl ((1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.24	10 pM	D	methyl ((1S)-1-(((1R,3S,5R)-3-(8-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.25		D	methyl ((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-

			4,5-dihydro-3H-naphtho[1,2-d]imidazol-7-yl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.26	5 pM	D	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.27		D	methyl ((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-3H-naphtho[1,2-d]imidazol-7-yl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.27a		D	(1R)-2-((2R)-2-(7-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.27b		D	methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.27c	3.0 pM	D	methyl ((1R)-2-((2S)-2-(7-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.28		D	methyl ((1S)-1-(((2S)-2-(5-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28a		D	(1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.28a.1		D	methyl ((1S)-1-(((2S)-2-(5-((4-(4-ethyl-2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28a.2		D	methyl ((1S)-1-(((2S)-2-(4-(cyanomethyl)-5-(4-((2-((2S)-1-

			((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28b		D	methyl ((1S)-1-(((1R,3S,5R)-3-(5-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28c		D	methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-fluoro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28d		D	methyl ((1S)-1-(((1R,3S,5R)-3-(4-(2-fluoro-4-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28e		D	methyl ((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-3H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28e.1		D	methyl ((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.28f		D	methyl ((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-3H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28f.1		D	methyl ((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-

			pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.28g		D	methyl ((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28h	120 pM	D	methyl ((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28h.1		D	methyl ((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28h.2		D	methyl ((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate
J.28i		D	methyl ((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28i.1		D	methyl ((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate
J.28i.2	0.51 pM	D	methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate

J.28i.3		D	methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
J.28i.4		D	methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
J.28j		D	methyl ((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28k		D	methyl ((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28k.1		D	benzyl (1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-valyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate
J.28l	7 nM	C	methyl ((1S)-1-(((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-4-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28m	55.7 nM	C	(1R)-2-((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-4-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.28n		D	methyl ((1S)-1-(((2S)-2-(5-((4-(4-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-

			pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28o		D	methyl ((1S)-1-(((2S,5S)-2-(5-((2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28p		D	methyl ((1S)-2-((2S,5S)-2-(7-((2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
JB.8		D	methyl ((1S)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
JB.8.1		B	methyl ((1R)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
JB.9		D	methyl ((1S)-2-((2S)-2-(5-(4-((2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate
JB.10		D	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4-((2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate
JB.11		D	methyl ((1R)-2-((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
JB.12	65.2 pM	D	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-4-yl)ethynyl)phenyl)-1H-benzimidazole
J.28r	15.5 pM	D	methyl ((1S)-1-(((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28s		D	methyl ((1S)-2-((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
JB.15		D	methyl ((1S)-1-(((2S)-2-(4-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
M.8	46.4 nM	C	(S)-1-acetyl-N-(4-((2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethynyl)phenyl)pyrrolidine-2-carboxamide
M.9		C	(S)-1-(2-phenylacetyl)-N-(4-((2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethynyl)phenyl)pyrrolidine-2-carboxamide
M.10	202 nM	B	(S)-1-acetyl-N-(4-(2-(2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethyl)phenyl)pyrrolidine-2-carboxamide
M.11		C	(S)-1-(2-phenylacetyl)-N-(4-(2-(2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethyl)phenyl)pyrrolidine-2-carboxamide
J.44		D	methyl ((1R)-2-((2S)-2-((5-(2-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.44a		D	methyl (R)-2-((S)-2-(5-(2-(2-((S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)oxazol-

			5-yl)-2-methylphenylcarbamoyl)pyrrolidin-1-yl)-2-oxo-1-phenylethylcarbamate
J.45		D	methyl ((1R)-2-((2S)-2-((3-(2-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.45a		D	1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(3-(2-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)-L-prolinamide
J.45b		D	(S)-1-(2-phenylacetyl)-N-(3-(2-(2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)oxazol-5-yl)phenyl)pyrrolidine-2-carboxamide
J.46		D	(S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)-N-(3-(2-(2-((S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-4-yl)oxazol-5-yl)phenyl)pyrrolidine-2-carboxamide
J.47		D	1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide
J.47a		D	methyl ((1R)-2-((2S)-2-((3-(5-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.48		D	1-((2R)-2-hydroxy-2-phenylacetyl)-N-(3-(5-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.48a		D	methyl ((1S)-1-(((2S)-2-(5-(2-(3-((((2S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-1-pyrrolidinyl)carbonyl)amino)phenyl)-1,3-oxazol-5-yl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.48b		C	(2R)-2-(dimethylamino)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-

			benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-2-phenylacetamide
J.48c		D	1-((2R)-2-acetamido-2-phenylacetyl)-N-(3-(5-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.48d	147 nM	B	1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-N-(3-(5-(2-((2S)-1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.49		D	methyl ((1R)-2-((2S)-2-((5-(5-(2-(1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.49a		D	(S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)-N-(5-(5-(2-((S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)oxazol-2-yl)-2-methylphenyl)pyrrolidine-2-carboxamide
J.50		C	1-((2R)-2-hydroxy-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.50a		D	1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.50b		D	1-((2R)-2-acetamido-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.50c	>10 μM	A	1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-N-(4-(5-(2-((2S)-1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.51		C	N-(2-fluoro-4-(5-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-1-((2R)-2-hydroxy-2-phenylacetyl)-L-prolinamide
J.51a		D	1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-

			benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-fluorophenyl)-L-prolinamide
J.51b		B	1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-N-(4-(5-(2-((2S)-1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-fluorophenyl)-L-prolinamide
J.52		D	N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-1-(phenylacetyl)-L-prolinamide
J.52a		C	N,N-dimethylglycyl-N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide
J.52b		D	methyl ((1R)-2-((2S)-2-((5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.52c		D	N-(methoxycarbonyl)-L-valyl-N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide
J.52d		D	N-(methoxycarbonyl)-L-alanyl-N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide
J.53		B	1-(cyclopropylacetyl)-N-(3-(5-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.53a		A	1-(cyclopropylacetyl)-N-(3-(2-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)-L-prolinamide

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

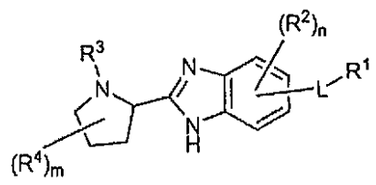
specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the 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 of Formula (I)

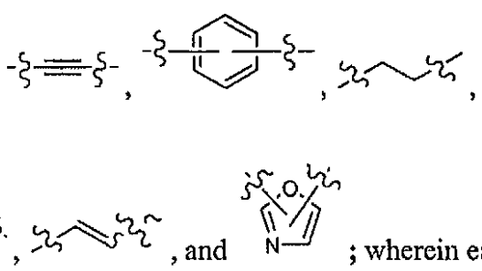


(I),

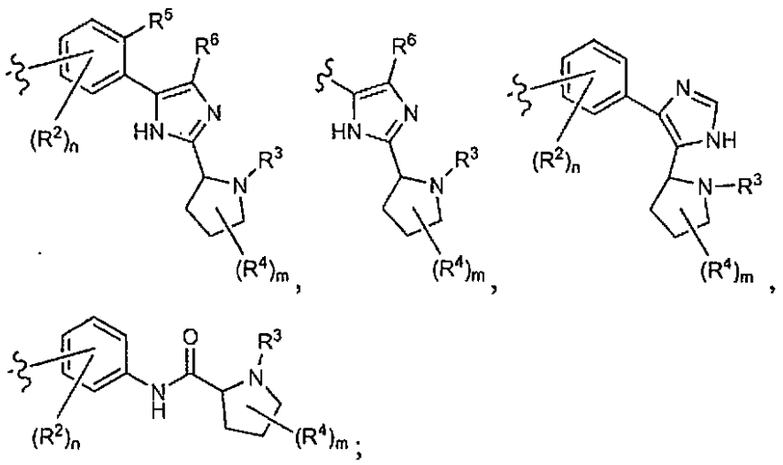
or a pharmaceutically acceptable salt thereof, wherein

each m is independently 0 or 1;

each n is independently 0 or 1;

L is a bond or is selected from  ; wherein each group is drawn with its left end attached to the benzimidazole and its right end attached to R^1;

R^1 is selected from



each R^2 is independently selected from alkyl and halo;

each R^3 is independently selected from hydrogen and $-C(O)R^7$;

R^4 is alkyl;

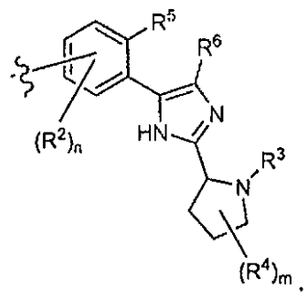
R^5 and R^6 are independently selected from hydrogen, alkyl, cyanoalkyl, and halo, or

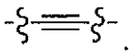
R^5 and R^6, together with the carbon atoms to which they are attached, form a six- or seven-membered ring optionally containing one heteroatom selected from nitrogen and oxygen and optionally containing an additional double bond; and

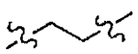
each R^7 is independently selected from alkoxy, alkyl, arylalkoxy, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

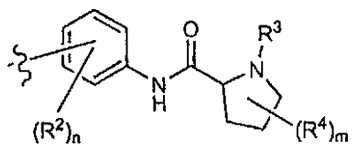
3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is

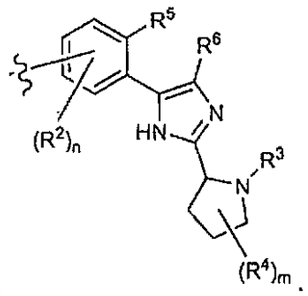


4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is  .

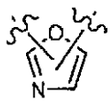
5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is  .

6. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from



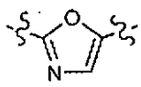
and


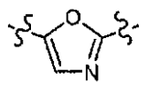
7. A compound of claim 1, or a pharmaceutically acceptable salt thereof,

wherein L is 

.

8. A compound of claim 7, or a pharmaceutically acceptable salt thereof,

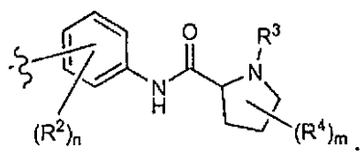
wherein L is selected from 

and 

.

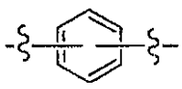
9. A compound of claim 8, or a pharmaceutically acceptable salt thereof,

wherein R^1 is



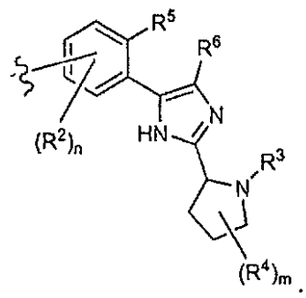
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10. A compound of claim 1, or a pharmaceutically acceptable salt thereof,

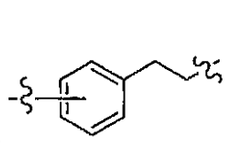
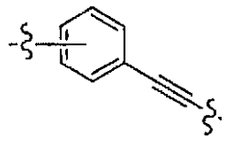
wherein L is 
.

11. A compound of claim 10, or a pharmaceutically acceptable salt thereof,

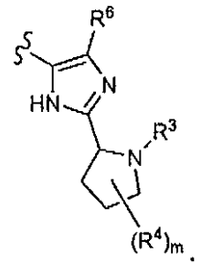
wherein R^1 is



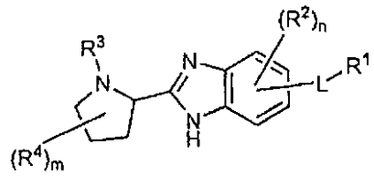
12. A compound of claim 1, or a pharmaceutically acceptable salt thereof,

wherein L is selected from  and  ; wherein each group is drawn with its left end attached to the benzimidazole and its right end attached to R^1.

13. A compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^1 is



14. A compound of Formula (II)



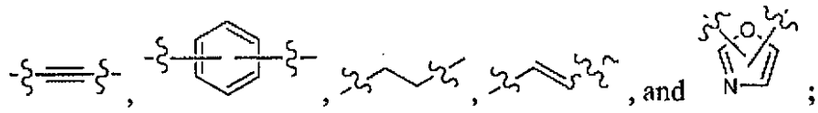
(II),

or a pharmaceutically acceptable salt thereof, wherein

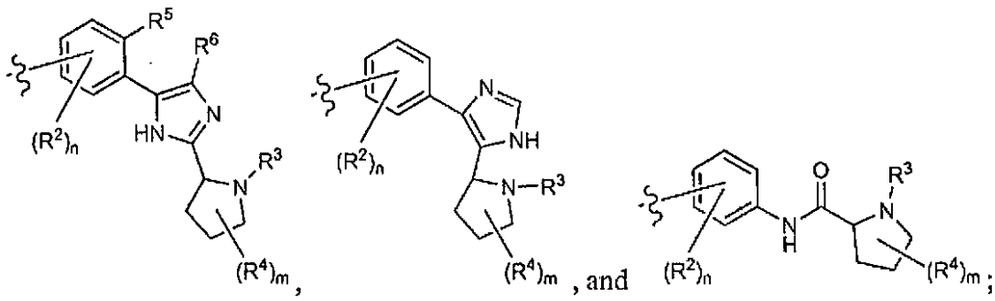
each m is independently 0 or 1;

each n is independently 0 or 1;

L is a bond or is selected from



R^1 is selected from



each R^2 is independently selected from alkyl and halo;

each R^3 is independently selected from hydrogen and $-C(O)R^7$;

R^4 is alkyl;

R^5 and R^6 are independently hydrogen or halo, or

R^5 and R^6, together with the carbon atoms to which they are attached, form a six- or seven-membered ring optionally containing one heteroatom selected from nitrogen and oxygen and optionally containing an additional double bond; and

each R^7 is independently selected from alkoxy, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl.

15. A compound selected from

methyl ((1S)-1-(((2S)-2-(8-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(8-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

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

(1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

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

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

(1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(8-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-1,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-3H-naphtho[1,2-d]imidazol-7-yl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

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

methyl ((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-3H-naphtho[1,2-d]imidazol-7-yl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2R)-2-(7-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(7-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(5-((4-(4-ethyl-2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(cyanomethyl)-5-(4-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(5-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-fluoro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(2-fluoro-4-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-3H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-3H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

benzyl (1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-valyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate;

methyl ((1S)-1-(((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-4-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-4-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(5-((4-(4-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,5S)-2-(5-((2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S,5S)-2-(7-((2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

(S)-1-acetyl-N-(4-((2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethynyl)phenyl)pyrrolidine-2-carboxamide;

(S)-1-(2-phenylacetyl)-N-(4-((2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethynyl)phenyl)pyrrolidine-2-carboxamide;

(S)-1-acetyl-N-(4-(2-(2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethyl)phenyl)pyrrolidine-2-carboxamide;

(S)-1-(2-phenylacetyl)-N-(4-(2-(2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)ethyl)phenyl)pyrrolidine-2-carboxamide;

methyl ((1R)-2-((2S)-2-((5-(2-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl (R)-2-((S)-2-(5-(2-(2-((S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)oxazol-5-yl)-2-methylphenylcarbamoyl)pyrrolidin-1-yl)-2-oxo-1-phenylethylcarbamate;

methyl ((1R)-2-((2S)-2-((3-(2-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(3-(2-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)-L-prolinamide;

(S)-1-(2-phenylacetyl)-N-(3-(2-(2-((S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)oxazol-5-yl)phenyl)pyrrolidine-2-carboxamide;

(S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)-N-(3-(2-(2-((S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-4-yl)oxazol-5-yl)phenyl)pyrrolidine-2-carboxamide;

1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide;

methyl ((1R)-2-((2S)-2-((3-(5-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

1-((2R)-2-hydroxy-2-phenylacetyl)-N-(3-(5-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

methyl ((1S)-1-(((2S)-2-(5-(2-(3-((((2S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-1-pyrrolidinyl)carbonyl)amino)phenyl)-1,3-oxazol-5-yl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(2R)-2-(dimethylamino)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-2-phenylacetamide;

1-((2R)-2-acetamido-2-phenylacetyl)-N-(3-(5-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-N-(3-(5-(2-((2S)-1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

methyl ((1R)-2-((2S)-2-((5-(5-(2-(1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)-N-(5-(5-(2-((S)-1-((R)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)oxazol-2-yl)-2-methylphenyl)pyrrolidine-2-carboxamide;

1-((2R)-2-hydroxy-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

1-((2R)-2-acetamido-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-N-(4-(5-(2-((2S)-1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide;

N-(2-fluoro-4-(5-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-1-((2R)-2-hydroxy-2-phenylacetyl)-L-prolinamide;

1-((2R)-2-(dimethylamino)-2-phenylacetyl)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-fluorophenyl)-L-prolinamide;

1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-N-(4-(5-(2-((2S)-1-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-fluorophenyl)-L-prolinamide;

N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-1-(phenylacetyl)-L-prolinamide;

N,N-dimethylglycyl-N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide;

methyl ((1R)-2-((2S)-2-((5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)carbamoyl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

N-(methoxycarbonyl)-L-valyl-N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide;

N-(methoxycarbonyl)-L-alanyl-N-(5-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)-2-methylphenyl)-L-prolinamide;

methyl ((1S)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(4-((2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

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

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

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-4-yl)ethynyl)phenyl)-1H-benzimidazole;

methyl ((1S)-1-(((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

1-(cyclopropylacetyl)-N-(3-(5-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide; and

1-(cyclopropylacetyl)-N-(3-(2-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)-L-prolinamide;

or a pharmaceutically acceptable salt thereof.

16. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. The composition of claim 16 further comprising one or two additional compounds having anti-HCV activity.

18. The composition of claim 17 wherein at least one of the additional compounds is an interferon or a ribavirin.

19. The composition of claim 18 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

20. The composition of claim 17 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.

21. The composition of claim 17 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.

22. 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.

23. The method of claim 22 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.

24. The method of claim 23 wherein at least one of the additional compounds is an interferon or a ribavirin.

25. The method of claim 24 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

26. The method of claim 23 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.

27. The method of claim 23 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/023582

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/4184 A61K31/4178 A61P31/12 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/36554 A1 (VIROPHARMA INC [US]) 9 October 1997 (1997-10-09) claim 1	1-27
A	WO 02/04425 A2 (BOEHRINGER INGELHEIM CA LTD [CA]; BEAULIEU PIERRE LOUIS [CA]; FAZAL GU) 17 January 2002 (2002-01-17) claim 1	1-27

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2010	13/04/2010

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/023582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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TRADUCCIÓN SOLICITUD

INHIBIDORES DEL VIRUS DE LA HEPATITIS C

REFERENCIA A SOLICITUDES RELACIONADAS

Esta solicitud reinvindica el beneficio de la solicitud provisional de Estados Unidos número de serie 61/153.186 presentada el 17 de febrero de 2009.

La presente exposición se refiere de forma general a compuestos antivirales y, más específicamente, se refiere a compuestos que pueden inhibir la función de la proteína NS5A codificada por el virus de la hepatitis C (VHC), a composiciones que comprenden dichos compuestos y a procedimientos para inhibir la función de la proteína NS5A.

El VHC es un importante patógeno humano que infecta a unos 170 millones de personas en todo el mundo - aproximadamente cinco veces el número de infectados por el virus de la inmunodeficiencia humana tipo 1. Una fracción sustancial de estos individuos infectados con el VHC desarrolla enfermedad hepática progresiva grave, incluyendo cirrosis y carcinoma hepatocelular.

La norma actual para el tratamiento contra el VHC que emplea una combinación de interferón pegilado y ribavirina, tiene una tasa de éxitos inadecuada a la hora de conseguir una respuesta viral sostenida y causa numerosos efectos secundarios. Así, existe una clara y antigua necesidad de desarrollar terapias eficaces para solucionar esta necesidad médica no satisfecha

El VHC es un virus ARN de cadena positiva. En base a la comparación de la secuencia de aminoácidos deducida y a la extensa similitud en la región sin traducir 5', el VHC se ha clasificado como un género separado en la familia

de Flaviviridae. Todos los miembros de la familia Flaviviridae tienen viriones encapsulados que contienen un genoma de ARN de cadena positiva que codifica todas las proteínas específicas de virus conocidas mediante traducción de un marco de lectura abierto no interrumpido único.

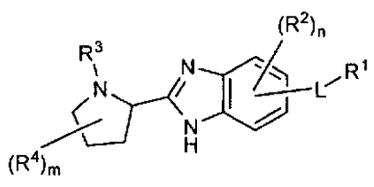
Dentro de la secuencia de nucleótidos y aminoácidos codificados en todo el genoma del VHC se encuentra una considerable heterogeneidad debido a la alta tasa de errores de la ARN polimerasa codificada por ARN que conduce a una baja capacidad de lectura. Se han caracterizado al menos seis genotipos principales y se han descrito más de 50 subtipos con distribución en todo el mundo. La significación clínica de la heterogeneidad genética del VHC ha demostrado propensión a derivar en mutaciones durante el tratamiento de monoterapia, así, se desean otras opciones de tratamiento para uso. El posible efecto modulador de genotipos sobre la patogénesis y tratamiento sigue mostrándose difícil de alcanzar.

El genoma del ARN del VHC es de aproximadamente 9500 nucleótidos y tiene un marco de lectura abierto (ORF) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En células infectadas, esta poliproteína se corta en múltiples sitios por proteasas celulares y virales para producir las proteínas estructurales y no estructurales (NS). En el caso del VHC, la generación de proteínas estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A y NS5B) se efectúa por dos proteasas virales. Se cree que la primera es una metaloproteasa y corta la unión NS2-NS3; la segunda es una serina proteasa contenida en la región N-terminal de NS3 (también denominada en la presente memoria proteasa NS3) y media todas los cortes posteriores cadena abajo de NS3, ambos en cis, en el sitio de corte NS3-NS4A,

y en trans, para los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B restantes. La proteína NS4A parece servir para múltiples funciones, actuando tanto como cofactor para la NS3 proteasa como ayudando en la localización de membrana de NS3 y otros componentes de replicasa viral. La formación de un complejo de NS3 con NS4A es necesaria para que la correcta actividad de proteasa de lugar a una mayor eficacia proteolítica de los sucesos de ruptura. La proteína NS3 también presenta actividades nucleósido trifosfatasa y ARN helicasa. NS5B (también denominada en la presente memoria polimerasa del VHC) es una ARN polimerasa dependiente de ARN que está implicada en la replicación del VHC con otras proteínas de VCH, incluyendo NS5A, un complejo de replicasa.

Se desean compuestos útiles para tratar pacientes infectados por VHC que inhiban de forma selectiva la replicación viral del VHC. En particular, se desean compuestos que sean eficaces para inhibir la función de la proteína NS5A. La proteína NS5A del VHC se describe, por ejemplo, en las siguientes referencias: S. L. Tan, et al., *Virology*, 284:1-12 (2001); K.-J. Park, et al., *J. Biol. Chem.*, 30711-30718 (2003); T. L. Tellinghuisen, et al., *Nature*, **435**, 374 (2005); R. A. Love, et al., *J. Virol*, **83**, 4395 (2009); N. Appel, et al., *J. Biol. Chem.*, **281**, 9833 (2006); L. Huang, *J. Biol. Chem.*, **280**, 36417 (2005); C. Rice, et al., WO2006093867.

En un primer aspecto, la presente exposición proporciona un compuesto de Fórmula (I)

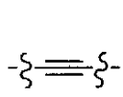
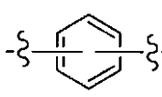
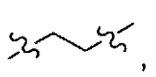
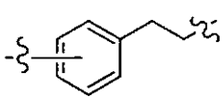
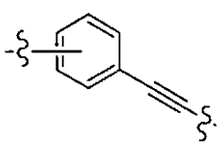
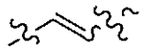
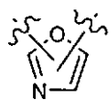


(I),

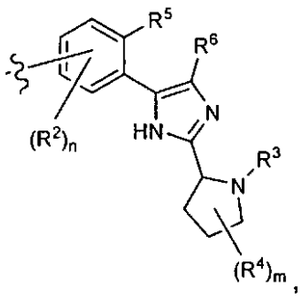
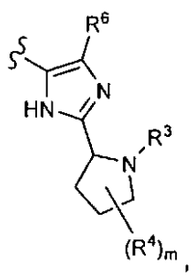
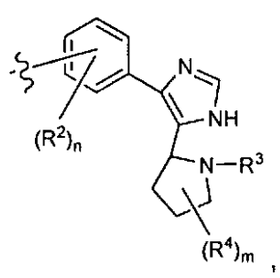
o una de sus sales farmacéuticamente aceptables, en la que

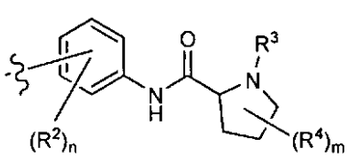
cada m es independientemente 0 ó 1;

cada n es independientemente 0 ó 1;

L es un enlace o se selecciona de  ,  ,  ,  ,  ,  , y  ; en los que cada grupo está representado con su extremo izquierdo unido al bencimidazol y su extremo derecho unido a R^1;

R^1 se selecciona de

 ,  ,  ,



cada R^2 se selecciona independientemente de alquilo y halo;

cada R^3 se selecciona independientemente de hidrógeno y $-C(O)R^7$;

R^4 es alquilo;

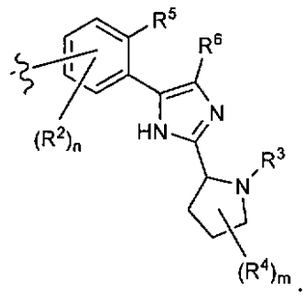
R^5 y R^6 se seleccionan independientemente de hidrógeno, alquilo, cianoalquilo y halo, o

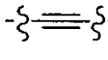
R^5 y R^6, junto con los átomos de carbono a los que están unidos, forman un anillo de seis o siete miembros que opcionalmente contiene un heteroátomo seleccionado de nitrógeno y oxígeno y opcionalmente un doble enlace adicional; y

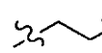
cada R^7 se selecciona independientemente de alcoxi, alquilo, arilalcoxi, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo.

En una primera realización del primer aspecto, la presente exposición proporciona un compuesto de Fórmula (I) o una de sus sales farmacéuticamente aceptables, en la que L es un enlace.

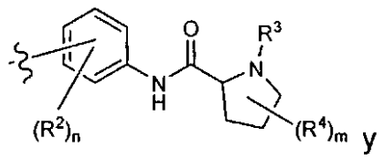
En una segunda realización del primer aspecto R^1 es

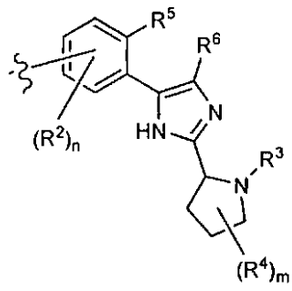


En una tercera realización del primer aspecto, la presente exposición proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que L es  .

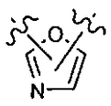
En una cuarta realización del primer aspecto, la presente exposición proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que L es  .

En una quinta realización R^1 se selecciona de

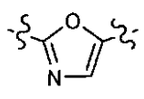


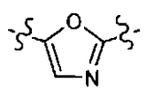
y


En una sexta realización del primer aspecto, la presente exposición proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que L es



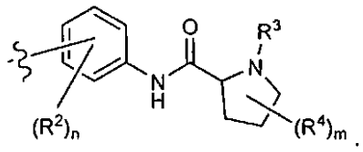
.

En una séptima realización, L se selecciona de 

y 

.

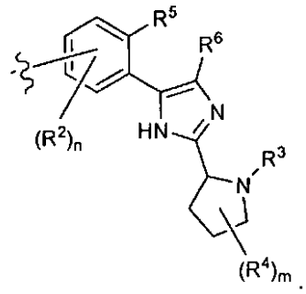
En una octava realización R^1 es

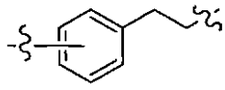
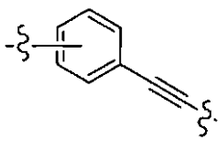


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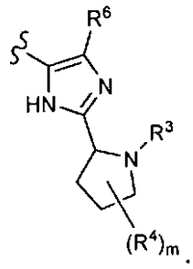
En una novena realización del primer aspecto, la presente exposición proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que L es 
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En una décima realización R^1 es

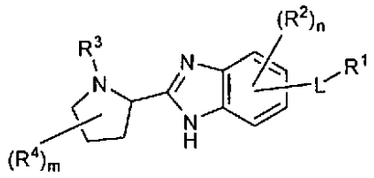


En una undécima realización del primer aspecto, la presente exposición propociona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que L se selecciona de  y  ; estando cada grupo representado con su extremo izquierdo unido al bencimidazol y con su extremo derecho unido a R^1.

En una duocécima realización R^1 es



En un segundo aspecto, la presente exposición proporciona un compuesto de Fórmula (II)



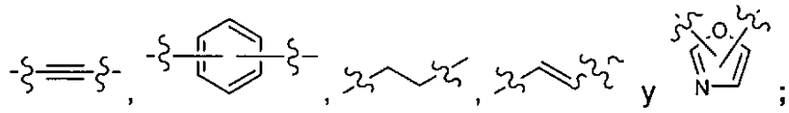
(II),

o una de sus sales farmacéuticamente aceptable, en la que

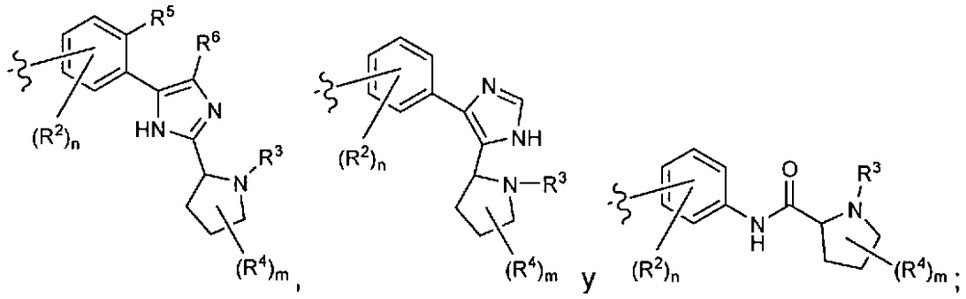
cada m es independientemente 0 ó 1;

cada n es independientemente 0 ó 1;

L es un enlace o se selecciona de



R^1 se selecciona de



cada R^2 se selecciona independientemente de alquilo y halo;

cada R^3 se selecciona independientemente de hidrógeno y -C(O)R^7;

R^4 es alquilo;

R^5 y R^6 son independientemente hidrógeno o halo, o

R^5 y R^6, junto con los átomos de carbono a los que están unidos, forman un anillo de seis o siete miembros que opcionalmente contiene un heteroátomo seleccionado de nitrógeno y oxígeno y que opcionalmente contiene un doble enlace adicional; y

cada R^7 se selecciona independientemente de alcoxi, alquilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo.

En un tercer aspecto la presente exposición proporciona una composición que comprende un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, y un vehículo farmacéuticamente aceptable. En una primera realización del tercer aspecto la composición comprende además uno o dos compuestos adicionales que tienen actividad contra el VHC. En una segunda realización del tercer aspecto, al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera realización el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

En una cuarta realización del tercer aspecto la presente exposición proporciona una composición que comprende un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, un vehículo farmacéuticamente aceptable y uno o dos compuestos adicionales que tienen actividad contra el VHC, seleccionándose al menos uno de los compuestos adicionales de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T colaborador de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta realización del tercer aspecto la presente exposición proporciona una composición que comprende un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, un vehículo farmacéuticamente aceptable y uno o dos compuestos adicionales que tienen

actividad contra el VHC, siendo al menos uno de los compuestos adicionales eficaz para inhibir la función de una diana seleccionada de metaloproteinasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, salida de VHC, proteína NS5A de VHC y IMPDH para el tratamiento de una infección por VHC.

En un cuarto aspecto la presente exposición proporciona un procedimiento para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables. En una primera realización del cuarto aspecto el procedimiento comprende además administrar uno o dos compuestos adicionales que tienen actividad contra el VHC antes, después o de forma simultánea con el compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables. En una segunda realización del cuarto aspecto al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera realización del cuarto aspecto el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

En una cuarta realización del cuarto aspecto la presente exposición proporciona un procedimiento para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables y uno o dos compuestos adicionales que tienen actividad contra el VHC antes, después o de forma simultánea con el compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables,

seleccionándose al menos uno de los compuestos adicionales de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T colaboradores de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta realización del cuarto aspecto la presente exposición proporciona un procedimiento para tratar una infección por VHC en un paciente que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables y uno o dos compuestos adicionales que tienen actividad contra el VHC antes, después o de forma simultánea con el compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, siendo al menos uno de los compuestos adicionales eficaz para inhibir la función de una diana seleccionada de metaloproteinasa de VHC, serina proteasa de VHC, polimerasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, salida de VHC, proteína NS5A de VHC y IMPDH para el tratamiento de una infección por VHC.

Otras realizaciones de la presente exposición pueden comprender combinaciones adecuadas de dos o más de las realizaciones y/o aspectos expuestos en la presente memoria.

Otras realizaciones y aspectos de la exposición serán evidentes de acuerdo con la descripción proporcionada a continuación.

Los compuestos de la presente exposición también existen como tautómeros; por tanto la presente exposición también incluye formas tautoméricas.

La descripción de la presente exposición en el presente documento se interpretará en consonancia con las leyes y principios de los enlaces químicos.

Se sobreentiende que los compuestos incluidos en la presente exposición son aquellos que son adecuados para uso como agentes farmacéuticos.

Se pretende que la definición de cualquier sustituyente o variable (por ejemplo, R^2 y R^4) en una posición particular en una molécula sea independiente de sus definiciones en cualquier otra parte de dicha molécula. Por ejemplo, cuando n es 2, cada uno de los dos grupos R^2 puede ser igual o diferente.

Todas las patentes, solicitudes de patente y referencias bibliográficas citadas en esta memoria descriptiva se incorporan a la presente por referencia en su totalidad. En el caso de inconsistencias, prevalecerá la presente exposición, que incluye las definiciones.

Tal como se usa en la presente memoria descriptiva, los siguientes términos tienen los significados indicados:

Tal como se usa en la presente, las formas singulares "un", "uno" y "el/la" incluyen la referencia en plural a no ser que el contexto dictamine claramente lo contrario.

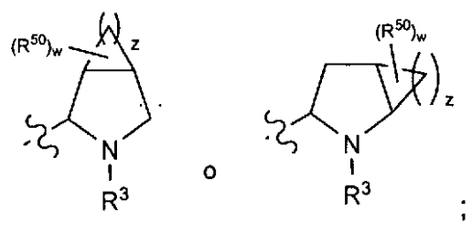
A no ser que se indique de otro modo, todos los grupos arilo, cicloalquilo y heterociclilo de la presente exposición pueden estar sustituidos como se describe en cada una de sus respectivas definiciones. Por ejemplo, la parte arilo de un grupo arilalquilo puede estar sustituida como se describe en la definición del término "arilo".

El término "alcoxi," tal como se usa en la presente memoria, se refiere a un grupo alquilo unido al resto molecular principal a través de un átomo de

oxígeno.

El término "alcoxicarbonilo," tal como se usa en la presente memoria, se refiere a un grupo alcoxi unido al resto molecular principal a través de un grupo carbonilo.

El término "alquilo," tal como se usa en la presente memoria, se refiere a un grupo derivado de un grupo hidrocarbonado saturado de cadena lineal o ramificada que contiene de uno a seis átomos de carbono. En los compuestos de la presente exposición, cuando m es 1 y R^4 es alquilo, el alquilo puede formar opcionalmente un anillo condensado de tres o cuatro miembros con un átomo de carbono adyacente proporcionando una de las estructuras mostradas a continuación:



en las que z es 1 ó 2, w es 0, 1 ó 2, y R^{50} es alquilo. Cuando w es 2, los dos grupos alquilo R^{50} pueden ser iguales o distintos.

El término "arilo," tal como se usa en la presente memoria, se refiere a un grupo fenilo o un sistema de anillo bicíclico condensado en el que uno o ambos de los anillos es un grupo fenilo. Los sistemas de anillo bicíclico condensado están constituidos por un grupo fenilo condensado con un anillo carbocíclico aromático o no aromático de cuatro a seis miembros. Los grupos arilo de la presente exposición pueden estar unidos al resto molecular principal a través de cualquier átomo de carbono sustituible en el grupo. Ejemplos representativos de grupos arilo incluyen, aunque sin quedar limitados a los

mismos, indanilo, indenilo, naftilo, fenilo y tetrahidronaftilo. Los grupos arilo de la presente exposición están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, un segundo grupo arilo, arilalcoxi, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo, oxo y $-P(O)OR_2$, donde cada R se selecciona independientemente de hidrógeno y alquilo; y donde la parte alquilo del arilalquilo y el heterociclilalquilo está no sustituida y 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 están además opcionalmente sustituidas con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "arilalcoxi", tal y como se usa en la presente memoria, se refiere a un grupo arilalquilo unido al resto molecular principal a través de un átomo de oxígeno.

El término "arilalquilo," tal como se usa en la presente memoria, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos arilo. La parte alquilo del arilalquilo está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados independientemente de alcoxi, alquilcarboniloxi, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi y $-NR^cR^d$, estando el heterociclilo además opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo no sustituido, arilalcoxi no sustituido, arilalcoxicarbonilo no sustituido, halo,

haloalcoxi, haloalquilo, hidroxi, -NR^xR^y y oxo.

El término "carbonilo," tal como se usa en la presente memoria, se refiere a -C(O)-.

El término "cianoalquilo", tal y como se usa en la presente memoria, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos ciano.

El término "cicloalquilo," tal como se usa en la presente memoria, se refiere a un sistema de anillo hidrocarbonado saturado monocíclico que tiene de tres a siete átomos y ningún heteroátomo. Ejemplos representativos de grupos cicloalquilo incluyen, pero no están limitados a, ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Los grupos cicloalquilo de la presente exposición están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi, hidroxialquilo, nitro y -NR^xR^y, estando el arilo y el heterociclilo además opcionalmente sustituidos con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, hidroxi y nitro.

El término "(cicloalquil)alquilo", tal y como se usa en la presente memoria, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos cicloalquilo.

El término "cicloalquiloxi," tal como se usa en la presente memoria, se refiere a un grupo cicloalquilo unido al resto molecular principal a través de un átomo de oxígeno.

El término "cicloalquiloxicarbonilo," tal como se usa en la presente memoria, se refiere a un grupo cicloalquiloxi unido al resto molecular principal a través de un grupo carbonilo.

Los términos "halo" y "halógeno," tal como se usan en la presente memoria, se refieren a F, Br, Cl o I.

El término "heterociclilo", tal como se usa en la presente memoria, se refiere a un anillo de cuatro, cinco, seis o siete miembros que contiene uno, dos, tres o cuatro heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre. El anillo de cuatro miembros no tiene ningún doble enlace, el anillo de cinco miembros tiene de ninguno a dos dobles enlaces y los anillos se seis y siete miembros tienen de ninguno a tres dobles enlaces. El término "heterociclilo" también incluye grupos bicíclicos en los que el anillo heterociclilo está condensado con otro grupo heterociclilo monocíclico o un anillo carbocíclico aromático o no aromático de cuatro a seis miembros; así como grupos bicíclicos con puente tales como 7-azabiciclo[2.2.1]hept-7-ilo, 2-azabiciclo[2.2.2]oct-2-ilo y 2-azabiciclo[2.2.2]oct-3-ilo. Los grupos heterociclilo de la presente exposición pueden estar unidos al resto molecular principal a través de cualquier átomo de carbono o átomo de nitrógeno en el grupo. Ejemplos de grupos heterociclilo incluyen, aunque sin quedar limitados a los mismos, benzotienilo, furilo, imidazolilo, indolinilo, indolilo, isoquinolinilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, piperazinilo, piperidinilo, pirazolilo, piridinilo, pirrolidinilo, pirrolopiridinilo, pirrolilo, quinolinilo, tiazolilo, tienilo y tiomorfolinilo. Los grupos heterociclilo de la presente exposición están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, un segundo grupo heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo y oxo,

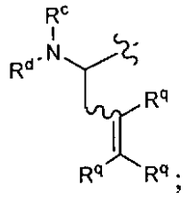
donde la parte alquilo del arilalquilo y el heterociclilalquilo está no sustituida y donde el arilo, la parte arilo del arilalquilo, la parte arilo del arilcarbonilo, el segundo grupo heterociclilo, y la parte heterociclilo del heterociclilalquilo y el heterociclilcarbonilo están además opcionalmente sustituidas con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "heterociclilalquilo," tal como se usa en la presente memoria, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos heterociclilo. La parte alquilo del heterociclilalquilo está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados independientemente de alcoxi, alquilcarboniloxi, arilo, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^cR^d$, estando el arilo además opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo no sustituido, arilalcoxi no sustituido, arilalcoxicarbonilo no sustituido, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^xR^y$.

El término "$-NR^cR^d$," tal como se usa en la presente memoria, se refiere a dos grupos, R^c y R^d, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^c y R^d se seleccionan independientemente de hidrógeno, alqueniloxicarbonilo, alcoxialquilcarbonilo, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilalquilcarbonilo, arilcarbonilo, ariloxicarbonilo, arilsulfonilo, cicloalquilo, cicloalquiloxicarbonilo, 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, donde R' se selecciona de alquilo y fenilo no sustituido y donde la parte alquilo del arilalquilo, el arilalquilcarbonilo, el heterociclilalquilo y el heterociclilalquilcarbonilo están además opcionalmente sustituidos con un grupo $-NR^eR^f$; y donde el arilo, la parte arilo del arilalcoxicarbonilo, el arilalquilo, el arilalquilcarbonilo, el arilcarbonilo, el ariloxicarbonilo y el arilsulfonilo, el heterociclilo y la parte heterociclilo del heterociclilalcoxicarbonilo, el heterociclilalquilo, el heterociclilalquilcarbonilo, el heterociclilcarbonilo y el heterocicliloxicarbonilo están además opcionalmente sustituidas con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "(NR^cR^d)alquenilo, tal como se usa en la presente memoria, se refiere a



en la que R^c y R^d son como se definen en la presente memoria y cada uno de R^q es independientemente hidrógeno o alquilo C_{1-3}.

El término "(NR^cR^d)alquilo," tal como se usa en la presente memoria, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^cR^d$. La parte alquilo del (NR^cR^d)alquilo está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados de alcoxi, alcoxialquilcarbonilo, alcoxicarbonilo, alquilsulfanilo, arilalcoxicarbonilo, carboxi, cicloalquilo, heterociclilo, heterociclilcarbonilo, hidroxi y (NR^eR^f)carbonilo; estando el heterociclilo además opcionalmente sustituido con uno, dos, tres, cuatro o cinco

sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "-NR^eR^f," tal como se usa en la presente memoria, se refiere a dos grupos, R^e y R^f, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^e y R^f se seleccionan independientemente de hidrógeno, alquilo, arilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, (cicloalquil)alquilo no sustituido, heterociclilo no sustituido, heterociclilalquilo no sustituido, (NR^xR^y)alquilo y (NR^xR^y)carbonilo.

El término "-NR^xR^y," tal como se usa en la presente memoria, se refiere a dos grupos, R^x y R^y, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^x y R^y se seleccionan independientemente de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo no sustituido, arilalcoxicarbonilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, heterociclilo no sustituido y ($NR^{x'}R^{y'}$)carbonilo, seleccionándose $R^{x'}$ y $R^{y'}$ independientemente de hidrógeno y alquilo.

En los compuestos de la presente exposición existen centros asimétricos. Estos centros están designados por los símbolos "R" o "S", dependiendo de la configuración de sustituyentes alrededor del átomo de carbono quiral. Se sobreentiende que la descripción incluye todas las formas de isómeros estereoquímicos, o sus mezclas, que poseen la capacidad de inhibir NS5A. Se pueden preparar estereoisómeros individuales de compuestos por medio de síntesis a partir de materiales de partida disponibles de forma comercial que contienen centros quirales o preparando mezclas de productos enantioméricos seguido por separación tal como conversión a una mezcla de diastereoisómeros seguida por separación o recristalización,

técnicas cromatográficas o separación directa de enantiómeros en columnas cromatográficas quirales. Los compuestos de partida de estereoquímica particular están disponibles de forma comercial o se pueden preparar o resolver por procesos conocidos en la técnica.

Ciertos compuestos de la presente exposición también pueden existir en diferentes formas conformacionales estables que pueden separarse. La asimetría de torsión debida a la rotación restringida alrededor de un enlace sencillo asimétrico, por ejemplo, debida a impedimento estérico o tensión en el anillo, puede permitir la separación de diferentes confórmeros. La presente exposición incluye cada uno de los isómeros conformacionales de estos compuestos y sus mezclas.

La expresión "compuestos de la presente exposición" y expresiones equivalentes, pretenden incluir compuestos de Fórmula (I), y sus enantiómeros, diastereoisómeros y sales farmacéuticamente aceptables. Igualmente, las referencias a intermedios pretenden incluir sus sales cuando el contexto así lo permita.

La presente exposición pretende incluir todos los isótopos de átomos que estén presentes en los compuestos de la presente invención. Isótopos incluyen los átomos que tienen el mismo número atómico pero diferentes números másicos. A modo de ejemplo general y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen ^{13}C y ^{14}C. Compuestos marcados con isótopos de la invención se pueden preparar de forma general por técnicas convencionales conocidas por los expertos en la técnica o por procedimientos análogos a los descritos en el presente documento, usando un reaccionante apropiado marcado con isótopos en luga

de los reaccionantes no marcados con isótopos. Tales compuestos pueden tener una diversidad de usos potenciales, por ejemplo como patrones y reaccionantes en la determinación de la actividad biológica. En el caso de isótopos estables, tales compuestos pueden tener el potencial de modificar favorablemente las propiedades biológicas, farmacológicas o farmacocinéticas.

Los compuestos de la presente exposición pueden existir como sales farmacéuticamente aceptables. La expresión "sal farmacéuticamente aceptable," tal como se usa en la presente memoria, representa sales o formas híbridas de los compuestos de la presente exposición que son solubles o dispersables en agua o en aceite, que son, dentro del alcance del criterio médico habitual, adecuados para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica u otro problema o complicación proporcionado con la relación beneficio/riesgo razonable y que son eficaces para su uso deseado. Las sales se pueden preparar durante el aislamiento final y purificación de los compuestos o por separado haciendo reaccionar un átomo de nitrógeno adecuado con un ácido adecuado. Sales de adición de ácidos representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, canforato, canfosulfonato; digluconato, dihidrobromuro, dihidrocloruro, dihidroyoduro, glicerofosfato, hemisulfato, heptanoato, hexanoato, formiato, fumarato, hidrocloruro, hidrobromuro, hidroyoduro, 2-hidroxietanosulfonato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, 2-naftalenosulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluenosulfonato y undecanoato.

Ejemplos de ácidos que se pueden emplear para formar sales de adición farmacéuticamente aceptables incluyen ácidos orgánicos tales como clorhídrico, bromhídrico, sulfúrico y fosfórico y ácidos orgánicos tales como oxálico, maleico, succínico y cítrico.

Sales de adición de bases se pueden preparar durante el aislamiento y purificación finales de los compuestos haciendo reaccionar un grupo carboxi con una base adecuada tal como el hidróxido, carbonato o bicarbonato de un catión metálico o con amoníaco o una amina orgánica primaria, secundaria o terciaria. Los cationes de sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio y aluminio, así como cationes de amina cuaternario no tóxicos tales como amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piridina, N,N-dimetilanilina, N-metilpiperidina, N-metilmorfolina, diciclohexilamina, procaína, dibencilamina, N,N-dibencilfenetilamina y N,N'-dibenciletilendiamina. Otras aminas orgánicas representativas útiles para la formación de sales de adición de bases incluyen etilendiamina, etanolamina, dietanolamina, piperidina y piperazina.

Cuando es posible que, para uso en terapia, se puedan administrar cantidades terapéuticamente eficaces de un compuesto de fórmula (I), así como sus sales farmacéuticamente aceptables, en forma del compuesto químico en bruto, es posible presentar el ingrediente activo como una composición farmacéutica. Por consiguiente, la exposición proporciona además composiciones farmacéuticas que incluyen cantidades terapéuticamente eficaces de compuestos de fórmula (I) o sus sales farmacéuticamente aceptables, y uno o más vehículos, diluyentes o excipientes

farmacéuticamente aceptables. La expresión "cantidad terapéuticamente eficaz," tal como se usa en la presente memoria, se refiere a la cantidad total de cada ingrediente activo que es suficiente para mostrar un beneficio significativo al paciente, por ejemplo, una reducción de la carga viral. Cuando se aplica a un ingrediente activo particular, administrado solo, la expresión se refiere a dicho ingrediente solo. Cuando se aplica a una combinación, la expresión se refiere a cantidades combinadas de los ingredientes que dan lugar a un efecto terapéutico, cuando se administran en combinación, en serie o de forma simultánea. Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables, son como se han descrito antes. El(los) vehículo(s), diluyente(s) o excipiente(s) deben ser aceptables en el sentido de que sean compatibles con el resto de ingredientes de la formulación y no sean perjudiciales a su receptor. De acuerdo con otro aspecto de la presente exposición se proporciona también un procedimiento para la preparación de una formulación farmacéutica que incluye mezclar un compuesto de fórmula (I), o una de sus sales farmacéuticamente aceptables, con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables. El término "farmacéuticamente aceptable", tal como se usa en la presente memoria, se refiere a los compuestos, materiales, composiciones y/o formas farmacéuticas que son, dentro del alcance del criterio médico habitual, adecuados para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica u otro problema o complicación proporcionado con una relación beneficio/riesgo razonable, y son eficaces para su uso deseado.

Las formulaciones farmacéuticas pueden presentarse en formas de monodosis que contienen una cantidad predeterminada de ingrediente activo

por monodosis. En una monoterapia para la prevención y tratamiento de enfermedad mediada por VHC son típicos niveles de dosis que varían de aproximadamente 0,01 a aproximadamente 250 miligramos por kilogramo ("mg/kg") de peso corporal por día, con preferencia de aproximadamente 0,05 a aproximadamente 100 mg/kg de peso corporal por día de los compuestos de la presente exposición. De forma típica, las composiciones farmacéuticas de esta exposición se administrarán de aproximadamente 1 a aproximadamente 5 veces por día o, como alternativa, como una infusión continua. Dicha administración se puede usar como una terapia crónica o aguda. La cantidad de ingrediente activo que se puede combinar con los materiales vehículo para producir una forma farmacéutica única variará dependiendo del trastorno que se esté tratando, la intensidad del trastorno, el tiempo de administración, la vía de administración, la velocidad de excreción del compuesto empleado, la duración del tratamiento y la edad, género, peso y estado del paciente. Las formulaciones de monodosis preferidas son aquellas que contienen una dosis diaria o subdosis, tal como se ha explicado en la presente memoria, o una fracción apropiada de las mismas, del ingrediente activo. El tratamiento se puede iniciar con pequeñas dosis sustancialmente menores que la dosis óptima del compuesto. A continuación, se incrementa la dosis en pequeños incrementos hasta que se alcanza el efecto óptimo en las circunstancias dadas. En general, el compuesto se administra de la forma más deseable en un nivel de concentración que por lo general proporcionará resultados antivirales eficaces sin causar ningún efecto secundario lesivo o perjudicial.

Cuando las composiciones de esta exposición comprenden una combinación de un compuesto de la presente exposición y uno o más agentes

terapéuticos o profilácticos adicionales, ambos, el compuesto y el agente adicional están presentes normalmente en niveles de dosis de aproximadamente 10 a 150% y, más preferentemente de aproximadamente 10 a 80% de la dosis normalmente administrada en una pauta de monoterapia.

Las formulaciones farmacéuticas se pueden adaptar para administración por cualquier vía adecuada, por ejemplo, por vía oral (incluyendo bucal y sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual o transdérmica), vaginal o parenteral (incluyendo inyección subcutánea, intracutánea, intramuscular, intraarticular, intrasinovial, intraesternal, intratecal, intralesional, intravenosa o intradérmica o infusiones). Tales formulaciones se pueden preparar por cualquier procedimiento conocido en la técnica farmacéutica, por ejemplo, poniendo en contacto el ingrediente activo con el/los vehículo(s) o excipiente(s). Se prefieren la administración oral o la administración por inyección.

Las formulaciones farmacéuticas adaptadas para administración oral pueden presentarse en forma de unidades discretas tales como cápsulas o comprimidos; polvos o granulados; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; o emulsiones aceite en agua o emulsiones agua en aceite.

Por ejemplo, para administración oral en la forma de un comprimido o cápsula, el componente farmacológico activo puede combinarse con un vehículo inerte farmacéuticamente aceptable oral no tóxico tal como etanol, glicerol, agua y similares. Los polvos se preparan triturando el compuesto hasta un tamaño fino adecuado y mezclando con un vehículo farmacéutico triturado de igual modo tal como un carbohidrato comestible como por ejemplo

almidón o manitol. También pueden estar presentes aromatizantes, conservantes, dispersantes y colorantes.

Las cápsulas se elaboran preparando una mezcla de polvo, como se ha descrito antes y llenando vainas de gelatina preformadas. Antes de la operación de llenado se pueden añadir a la mezcla de polvo deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilenglicol sólido. También se puede añadir para mejorar la disponibilidad del medicamento cuando se ingiera la cápsula un agente disgregante o solubilizante tal como agar-agar, carbonato de calcio o carbonato de sodio.

Por otro lado, cuando se desee o sea necesario, también se pueden incorporar en la mezcla ligantes, lubricantes, disgregantes y colorantes adecuados. Ligantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas sintéticas y naturales, tales como goma arábica, tragacanto o alginato sódico, carboximetilcelulosa, polietilenglicol y similares. Los lubricantes usados en estas formas farmacéuticas incluyen oleato sódico, cloruro sódico y similares Los disgregantes incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantana y similares. Los comprimidos se formulan por ejemplo, preparando una mezcla de polvo, granulando o peletizando, añadiendo un lubricante y disgregante y prensando en comprimidos. Una mezcla de polvo se prepara mezclando el compuesto triturado adecuado con un diluyente o base como se ha descrito antes y, opcionalmente, con un ligante tal como carboximetilcelulosa, un alginato, gelatina o polivinilpirrolidona, una solución retardante como parafina, un acelerador de la reabsorción como sal

cuaternaria y/o un agente de absorción como bentonita, caolín o fosfato dicálcico. La mezcla de polvo se puede granular humectando con un ligante tal como sirope, pasta de almidón, goma arábiga, mucílago o soluciones de materiales celulósicos o poliméricos y forzando a través e un tamiz. Como una alternativa a la granulación, la mezcla de polvo se puede hacer pasar a través de la máquina de comprimidos y el resultado es pellas imperfectas que se rompen en gránulos. Los gránulos se pueden lubricar para prevenir que se peguen a los troqueles formadores de comprimidos por medio de la adición de ácido esteárico, una sal estearato, talco o aceite mineral. La mezcla lubricante se comprime luego en comprimidos. Los compuestos de la presente exposición también se pueden combinar con un vehículo inerte fluido y comprimirse en comprimidos directamente sin llevarlos a las etapas de granulación o peletizado. Se puede disponer un revestimiento protector opaco o transparente consistente en una capa de goma laca, una capa de azúcar o material polimérico y un revestimiento final de cera. Se pueden añadir colorantes a estos revestimientos para distinguir las diferentes monodosis.

Los fluidos orales tales como soluciones, jarabes o elixires se pueden preparar en forma de monodosis de modo que una cantidad dada contenga una cantidad predeterminada del compuesto. Los jarabes se pueden preparar disolviendo el compuesto en una solución acuosa adecuadamente aromatizada, mientras que los elixires se preparan usando un vehículo no tóxico. También se pueden añadir solubilizantes y emulsionantes tales como alcoholes isostearílicos etoxilados y éteres de polioxietilen sorbitol, conservantes, aditivos aromatizantes como esencia de menta piperita o edulcorantes naturales, o sacarina u otros edulcorantes artificiales.

Cuando sea apropiado, las formulaciones de monodosis para administración oral se pueden microencapsular. La formulación también se puede preparar para prolongar o retrasar la liberación como por ejemplo recubriendo o embebiendo un material en forma de partículas en polímeros, cera o similares.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables, se pueden administrar también en forma de sistemas de liberación de liposomas, tales como vesículas unilaminares pequeñas, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas se pueden formar a partir de una diversidad de fosfolópidos tales como colesterol, estearilamina o fosfatidilcolinas.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables también se pueden liberar mediante el uso de anticuerpos monoclonales como vehículos individuales a los que se acoplan las moléculas de compuesto. Los compuestos también se pueden acoplar con polímeros solubles como portadores de fármaco diana. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol o polietilenoxidepolilisina sustituida con restos palitoílo. Además, los compuestos se pueden acoplar a una clase de polímeros biodegradables útiles para conseguir una liberación controlada de un fármaco, por ejemplo, poli(ácido láctico), polepsilon caprolactona, poli(ácido hidroxi butírico), poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de bloque de hidrogeles reticulados o anfifilos.

Las formulaciones farmacéuticas adaptadas para administración transdérmica se pueden presentar como parches discretos destinados a

permanecer en contacto íntimo con la epidermis del receptor durante un período prolongado de tiempo. Por ejemplo, el ingrediente activo puede liberarse del parche por iontoforesis como se describe de forma general en *Pharmaceutical Research* 1986, *3*(6), 318.

Las formulaciones farmacéuticas adaptadas para administración tópica se pueden formular como pomadas, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, pulverizaciones, aerosoles o aceites.

Las formulaciones farmacéuticas adaptadas para administración rectal pueden presentarse como supositorios o enemas.

Las formulaciones farmacéuticas adaptadas para administración nasal en las que el vehículo es un sólido incluyen un polvo grueso que tiene un tamaño de partículas de por ejemplo en el intervalo de 20 a 500 micrómetros que se administra en la forma en que se toma rape, es decir, por inhalación rápida a través de la vía nasal desde un recipiente de polvo mantenido próximo a la nariz. Formulaciones adecuadas en las que el vehículo es un líquido, para administración como una pulverización nasal o como gotas nasales incluyen soluciones acuosas u oleosas del ingrediente activo.

Formulaciones farmacéuticas adaptadas para administración por inhalación incluyen polvos o vaporizaciones de partículas finas, que se pueden generar por diversos tipos de aerosoles a presión, nebulizadores o insufladores dosificadores.

Las formulaciones farmacéuticas adaptadas para administración vaginal se pueden preparar como formulaciones de pesarios, tampones, cremas, geles, pastas, espumas o pulverizaciones.

Las formulaciones farmacéuticas adaptadas para administración

parenteral incluyen soluciones para inyección estériles acuosas y no acuosas que pueden contener antioxidantes, tampones, bacteriostáticos y otros que hacen la formulación isotónica con la sangre del receptor deseado; y suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes espesantes. Las formulaciones se pueden presentar en recipientes de monodosis o multidosis, por ejemplo, ampollas y viales sellados, y pueden almacenarse en estado secado por congelación (liofilizado) que únicamente requiere la adición del vehículo líquido estéril, por ejemplo agua para inyección, inmediatamente antes de usar. Las soluciones y suspensiones para inyección extemporánea se pueden preparar a partir de polvos, gránulos y comprimidos estériles.

Se sobreentiende que además de los ingredientes citados de forma particular antes, las formulaciones pueden incluir otros agentes convencionales en la técnica relacionados con el tipo de formulación en cuestión, por ejemplo los adecuados para administración oral pueden incluir agentes aromatizantes.

El término "paciente" incluye seres humanos y otros animales.

El término "tratamiento" se refiere a: (i) prevenir la aparición de una enfermedad, trastorno o estado patológico en un paciente que puede estar predispuesto a la enfermedad, trastorno y/o estado patológico pero al que todavía no se le ha diagnosticado que lo tiene; (ii) inhibir la enfermedad, trastorno o estado patológico, es decir, detener su desarrollo; y (iii) aliviar la enfermedad, trastorno o estado patológico, es decir, causando la regresión de la enfermedad, trastorno y/o estado patológico.

Los compuestos de la presente exposición también se pueden administrar con una ciclosporina, por ejemplo, ciclosporina A. Ciclosporina A ha

demostrado ser activa contra el VHC en ensayos clínicos (*Hepatology* 2003, *38*, 1282; *Biochem. Biophys. Res. Commun.* 2004, *313*, 42; *J. Gastroenterol.* 2003, *38*, 567).

La Tabla 1 siguiente enumera algunos ejemplos ilustrativos de compuestos que se pueden administrar con los compuestos de esta exposición. Los compuestos de la exposición se pueden administrar con otros compuestos con actividad contra el VHC en terapia de combinación, bien conjuntamente o por separado, o combinando los compuestos en una composición.

Tabla 1

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
NIM811 Debio-025		Inhibidores de ciclofilina	Novartis Debiopharma
Zadaxin		Immunomodulador	SciClone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista del TLR9	Coley
Batabulina (T67)	Anticancerígeno	Inhibidor de β-Tubulina	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	Antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
GS-9132 (ACH-806)	Antiviral	Inhibidor del VHC	Achillion / Gilead
Compuestos y sales de pirazolopirimidina Del documento WO-2005/047288 26 de mayo de 2005	Antiviral	Inhibidores del VHC	Arrow Therapeutics Ltd.
Levovirina	Antiviral	Inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	Inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	Anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	Inhibidor de la serina proteasa NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly y Co. Inc., Indianapolis, IN
HCV-796	Antiviral	Inhibidor de la replicasa NS5B	Wyeth / Viropharma
NM-283	Antiviral	Inhibidor de la replicasa NS5B	Idenix / Novartis
GL-59728	Antiviral	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
GL-60667	Antiviral	Inhibidor de la replicasa NS5B	Gene Labs / Novartis

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
2'C MeA	Antiviral	Inhibidor de la replicasa NS5B	Gilead
PSI 6130	Antiviral	Inhibidor de la replicasa NS5B	Roche
R1626	Antiviral	Inhibidor de la replicasa NS5B	Roche
2'C Metil adenosina	Antiviral	Inhibidor de la replicasa NS5B	Merck
JTK-003	Antiviral	Inhibidor de RdRp	Japan Tobacco Inc., Tokyo, Japan
Levovirina	Antiviral	Ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirina	Antiviral	Ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Viramidina	Antiviral	Profármaco de ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazima	Antiviral	Ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	Inhibidor de la serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
SCH 503034	Antiviral	Inhibidor de la serina proteasa	Schering Plough
Zadazim	Inmunomodulador	Inmunomodulador	SciClone Pharmaceuticals Inc., San Mateo, CA

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
Ceplene	Immunomodulador	Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
CELLCEPT®	Inmunosupresor	Inmunosupresor de IgG de VHCV	F. Hoffmann-La Roche LTD, Basilea, Suiza
Civacir	Inmunosupresor	Inmunosupresor de IgG de VHCV	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferón	IFN-α2b de albúmina	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, Canada
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

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
Intron A y Zadaxin	Interferón	IFN-α2b/α1-timosina	RegeneRx Biopharma. 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
Interferón-β	Interferón	Interferón-β-1a	Serono
Multiferon	Interferón	IFN de larga duración	Viragen/ Valentis
Wellferon	Interferón	IFN-αn1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, UK
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 Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys y Ribavirin	Interferón	IFN-α2a pegilado/ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza
PEG-Intron	Interferón	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
PEG-Intron / Ribavirina	Interferón	IFN-α2b PEGilado/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Hepatoprotector	Antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Hepatoprotector	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Inhibidor de la serina proteasa	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	Inhibidor de la replicasa NS5B	Genelabs
ANA-971	Antiviral	Agonista de TLR-7	Anadys
Boceprevir	Antiviral	Inhibidor de la serina proteasa	Schering Plough
TMS-435	Antiviral	Inhibidor de la serina proteasa	Tibotec BVBA, Mechelen, Bélgica
BI-201335	Antiviral	Inhibidor de la serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
MK-7009	Antiviral	Inhibidor de la serina proteasa	Merck
PF-00868554	Antiviral	inhibidor de replicasa	Pfizer
ANA598	Antiviral	Inhibidor de NS5B polimerasa no nucleósido	Anadys Pharmaceuticals, Inc., San Diego, CA, USA

Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
IDX375	Antiviral	Inhibidor de replicasa no nucleótido	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	Inhibidor de NS5B polimerasa	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada
PSI -7851	Antiviral	Inhibidor de polimerasa nucleósido	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	Inhibidor de NS5B polimerasa	ViroChem Pharma
VCH-916	Antiviral	Inhibidor de NS5B polimerasa	ViroChem Pharma
GS-9190	Antiviral	Inhibidor de NS5B polimerasa	Gilead
Interferon Peg lamda	Antiviral	Interferón	ZymoGenetics/Bristol-Myers Squibb

Los compuestos de la presente exposición también se pueden usar como reactivos de laboratorio. Los compuestos pueden ser instrumentos a la hora de proporcionar herramientas de investigación para diseñar ensayos de replicación viral, validación de sistemas de ensayos animales y estudios de biología estructural para mejorar aun más el conocimiento de los mecanismos de enfermedad del VHC. Además, los compuestos de la presente exposición son útiles para establecer o determinar el sitio de unión de otros compuestos antivíricos, por ejemplo, por inhibición competitiva.

Los compuestos de esta exposición también pueden ser útiles para tratar o prevenir contaminación viral de materiales y por tanto reducir el riesgo

de infección viral de laboratorio o personal médico o pacientes que entren en contacto con tales materiales, por ejemplo, sangre, tejidos, instrumental y prendas quirúrgicas, instrumental y prendas de laboratorio, y aparatos y materiales para la extracción o transfusión de sangre.

Esta exposición pretende incluir compuestos que tienen la fórmula (I) cuando se preparan por procedimientos de síntesis o por procedimientos metabólicos que incluyen los que se producen en el cuerpo humano o animal (*en vivo*) o procedimientos que se producen *en vitro*.

Las abreviaturas usadas en la presente solicitud, incluyendo en particular en los esquemas ilustrativos y ejemplos siguientes, son bien conocidas por los expertos en la técnica. Algunas de las abreviaturas usadas son las siguientes: TA para temperatura ambiente; T_R para tiempo de retención; min para minutos; TFA para ácido trifluoroacético; DMSO para dimetilsulfóxido; Ph para fenilo; THF para tetrahidrofurano; Et_2O para éter dietílico; Boc o BOC para terc-butoxicarbonilo; MeOH para metanol; Et para etilo; DMF para dimetilformamida; h o hr para horas; TBDPS para terc-butildifenilsililo; DMAP para N,N-dimetilaminopiridina; TBAF para fluoruro de tetrabutilamonio; Et_3N o TEA para trietilamina; HATU para hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio; Ac para acetato o acetilo; SEM para 2-trimetilsililetoximetoxi; EDC o EDCI para 1-etil-3-(3-dimetilaminopropil)carbodiimida; EEDQ para N-etoxicarbonil-2-etoxi-1,2-dihidroquinolina; MeOH para metanol; i-Bu para isobutilo; Bn para bencilo; y Me para metilo.

Los compuestos y procedimientos de la presente exposición se comprenderán mejor en relación con los siguientes esquemas de síntesis que

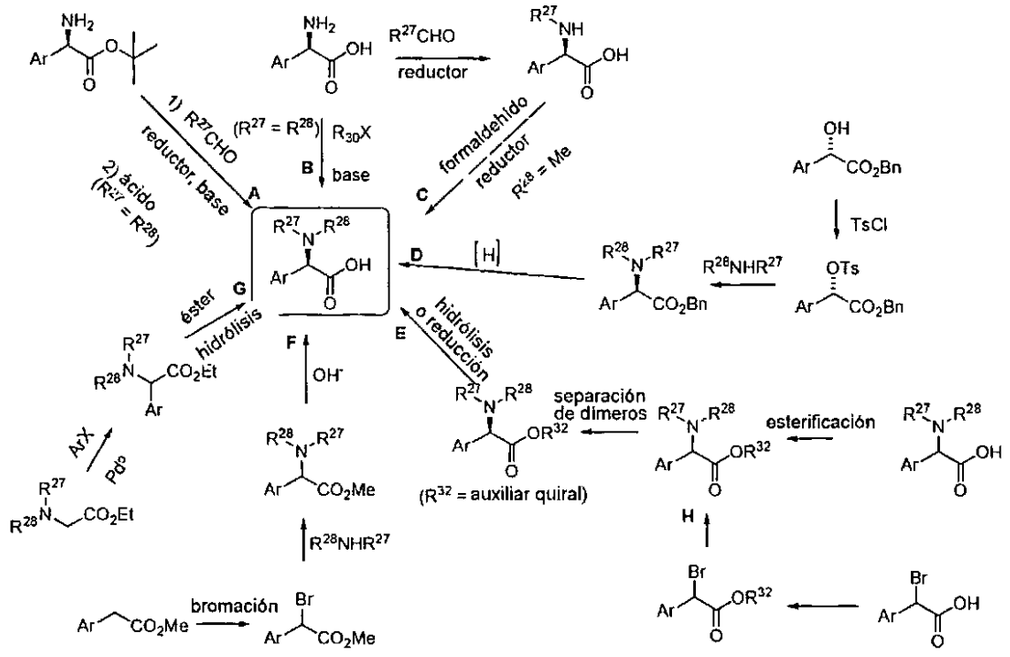
ilustran los procedimientos por medio de los cuales se pueden preparar los compuestos de la presente exposición. Los materiales de partida se pueden obtener de suministradores comerciales o prepararse por procedimientos de la bibliografía bien conocidos por los expertos en la técnica. Será fácilmente evidente para un experto en la técnica que los compuestos definidos antes se pueden sintetizar por sustitución de los reaccionantes y agentes apropiados en las síntesis mostradas a continuación. También será evidente para un experto en la técnica que las etapas de protección y desprotección selectiva, además del orden de las propias etapas, se pueden llevar a cabo en un orden variable, dependiendo de la naturaleza de las variables para completar con éxito las síntesis siguientes. Las variables son como se han definido antes a no ser que de indique de otro modo más adelante.

Esquema 1: Derivados de fenilglicina sustituidos

Los derivados de fenilglicina sustituidos se pueden preparar por una serie de procedimientos mostrados a continuación. Se puede alquilar de forma reductora (ruta A) éster t-butílico de fenilglicina con un aldehído apropiado y un reductor tal como cianoborohidruro sódico en medio ácido. La hidrólisis del éster t-butílico se puede llevar a cabo con un ácido fuerte tal como HCl o ácido trifluoroacético. De forma alternativa, se puede alquilar fenilglicina con un haluro de alquilo tal como yoduro de etilo y una base como bicarbonato sódico o carbonato potásico (ruta B). La ruta C ilustra la alquilación reductora de fenilglicina como en la ruta A seguida por una segunda alquilación reductora con un aldehído alternativo como formaldehído en presencia de un agente reductor y ácido. La ruta D ilustra la síntesis de fenilglicinas sustituidas a través

de los análogos de ácido mandélico correspondientes. La conversión del alcohol secundario a un grupo saliente competente se puede llevar a cabo con cloruro de p-toluenosulfonilo. El desplazamiento del grupo tosilato con una amina apropiada seguida por retirada reductora del éster bencílico puede proporcionar derivados de fenilglicina sustituidos. En la ruta E se resuelve un derivado de fenilglicina sustituido racémico por esterificación con un compuesto auxiliar quiral enantioméricamente puro tal como, aunque sin quedar limitados a los mismos, (+)-1-feniletanol, (-)-1-feniletanol, una oxazolidinona de Evan, o pantolactona enantioméricamente pura. La separación de diastereoisómeros se lleva a cabo por cromatografía (gel de sílice, HPLC, cristalización y similares) seguida por la retirada del compuesto auxiliar quiral proporcionando derivados de fenilglicina enantioméricamente puros. La ruta H ilustra una secuencia de síntesis que interseccíona con la ruta E en la que se instala el compuesto auxiliar quiral citado antes de la adición de la amina. De forma alternativa, se puede bromar un éster de un ácido arilacético con una fuente de ion bromonio tal como bromo, N-bromosuccinimida o CBr_4. El bromuro de bencilo resultante se puede desplazar con una diversidad de aminas mono o disustituidas en presencia de una base de amina terciaria tal como trietilamina o base de Hunig. La hidrólisis del éster metílico por tratamiento con hidróxido de litio a baja temperatura o HCl 6N a temperatura elevada proporciona los derivados de fenilglicina sustituidos. Otro procedimiento se muestra en la ruta G. Los análogos de glicina se pueden obtener con una diversidad de haluros de arilo en presencia de una fuente de paladio(0) tal como bis(tributilfosfina) paladio y base como fosfato potásico. El éster resultante se puede hidrolizar entonces por tratamiento con base o ácido. Se sobreentiende que en la técnica

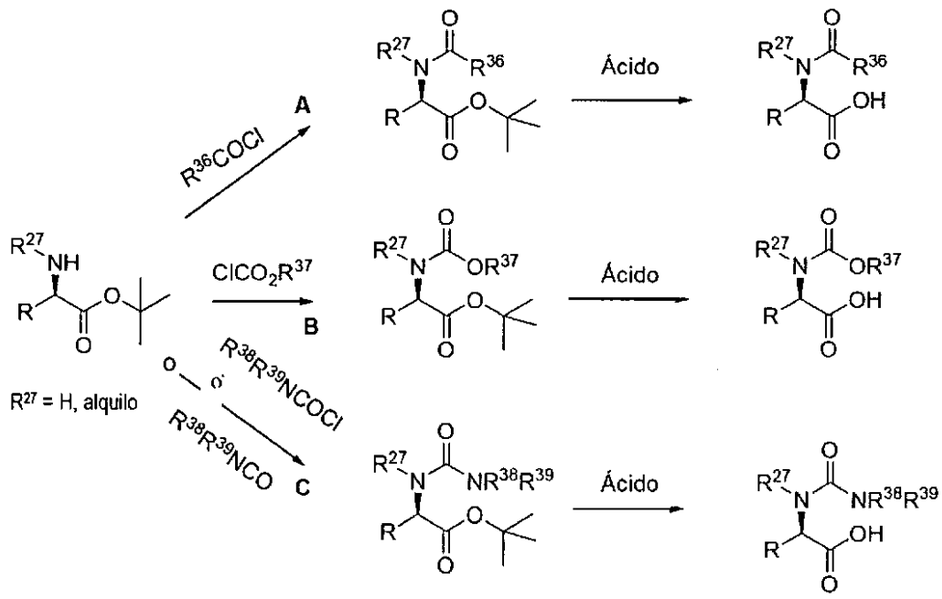
existen otros procedimientos bien conocidos para preparar derivados de fenilglicina y se pueden modificar para proporcionar los compuestos deseados en esta descripción. Se sobreentiende que los derivados de fenilglicina finales se pueden purificar hasta una pureza enantiomérica mayor que 98% de ee por HPLC preparativa.



Esquema 2: Derivados de aminoácido acilados

En otra realización de la presente exposición, se pueden preparar derivados de fenilglicina acilados como se ilustra a continuación. Los derivados de fenilglicina en los que se protege el ácido carboxílico como un éster que se retira fácilmente se pueden acilar con un cloruro de ácido en presencia de una base tal como trietilamina para proporcionar las amidas correspondientes (ruta A). La ruta B ilustra la acilación del derivado de fenilglicina de partida con un cloroformiato apropiado mientras que la ruta C muestra la reacción con un

isocianato o cloruro de carbamoílo apropiado. Cada uno de los intermedios mostrados en las rutas A – C se pueden desproteger por procedimientos conocidos por los expertos en la técnica (es decir; tratamiento del éster t-butílico con base fuerte tal como HCl o ácido trifluoroacético).



Esquema 3

Los ácidos fenilacéticos sustituidos con amino se pueden preparar por tratamiento de un ácido clorometilfenilacético con un exceso de una amina.

Síntesis de caps comunes

Condiciones de ensayo de los compuestos

La valoración de la pureza y el análisis de masas de baja resolución se llevaron a cabo en un sistema de CL Shimadzu CL acoplado con un sistema de EM Waters Micromass ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. Condiciones adicionales de CL aplicables a

la presente sección, a no ser que se indique de otro modo.

Condiciones de EM-W1

Columna = XTERRA 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones de EM-W2

Columna = XTERRA 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones de EM-W5

Columna = XTERRA 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 30

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones-D1

Columna = XTERRA C18 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones-D2

Columna = Phenomenex-Luna 4,6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones-MD1

Columna = XTERRA 4.6 X 50 mm S5

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones-M3

Columna = XTERRA C18 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 40

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones-OL1

Columna = Phenomenex-Luna 3,0 x 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Tiempo de parada = 5 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condiciones-OL2

Columna = Phenomenex-Luna 50 x 2 mm 3 u

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Tiempo de parada = 5 min

Caudal = 0,8 ml/min

Temperatura del horno = 40ºC

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en acetonitrilo al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en acetonitrilo al 90%/H_2O al 10%

Condición I

Columna = Phenomenex-Luna 3,0X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condición II

Columna = Phenomenex-Luna 4,6X50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condición III

Columna = HPLC XTERRA C18 3,0 x 50mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

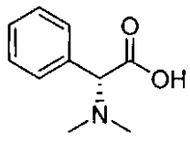
Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/H_2O al 90%

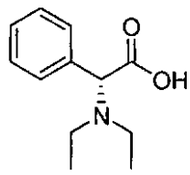
Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Cap-1



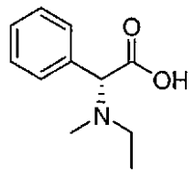
Se añadió una suspensión de Pd al 10%/C (2,0 g) en metanol (10 ml) a una mezcla de (R)-2-fenilglicina (10 g, 66,2 mmol), formaldehído (33 ml de 37% en peso en agua), HCl 1N (30 ml) y metanol (30 ml) y se expuso a H_2 (413,57 kPa) durante 3 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de *Cap*-1 como agujas blancas (4,0 g). Rotación óptica: -117,1° [c = 9,95 mg/ml en H_2O; λ = 589 nm]. RMN de ^1H (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): T_R = 0,25; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180,10; encontrado 180,17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180,1025; encontrado 180,1017.

Cap-2



Se añadió $NaBH_3CN$ (6,22 g, 94 mmol) en porciones durante unos pocos minutos a una mezcla enfriada (hielo/agua) de (R)-2-fenilglicina (6,02 g, 39,8 mmol) y MeOH (100 ml), y se agitó durante 5 min. Se añadió acetaldehído (10 ml) gota a gota durante 10 minutos y se continuó agitando a la misma temperatura fría durante 45 minutos y a temperatura ambiente durante ~6,5 hr. La mezcla de reacción se volvió a enfriar con baño de hielo-agua, se trató con agua (3 ml) y luego se inactivó con una adición gota a gota de HCl concentrado durante ~ 45 min hasta que el pH de la mezcla fue ~ 1,5 – 2,0. El baño de enfriamiento se retiró y se continuó agitando mientras se añadía HCl concentrado con el fin de mantener el pH de la mezcla aproximadamente a 1,5-2,0. La mezcla de reacción se agitó durante una noche, se filtró para separar la suspensión blanca y el filtrado se concentró a vacío. El material bruto se recristalizó en etanol proporcionando la sal HCl de *Cap*-2 como un sólido blanco brillante en dos tandas (tanda-1: 4,16 g; tanda-2: 2,19 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): 10,44 (1,00, s ancho, 1H), 7,66 (m, 2H), 7,51 (m, 3H), 5,30 (s, 1H), 3,15 (m ancho, 2H), 2,98 (m ancho, 2H), 1,20 (s ancho aparente, 6H). Tanda-1: $[\alpha]^{25}$ -102,21° (c = 0,357, H_2O); canda-2: $[\alpha]^{25}$ -99,7° (c = 0,357, H_2O). CL (Cond. I): T_R = 0,43 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208,13; encontrado 208,26

Cap-3

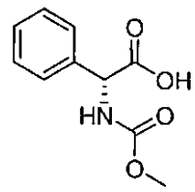


Se añadió secuencialmente acetaldehído (5,0 ml, 89,1 mmol) y una suspensión de Pd al 10%/C (720 mg) en metanol/H_2O (4 ml/1 ml) a una mezcla enfriada (~ 15 °C) de (R)-2-fenilglicina (3,096g, 20,48 mmol), HCl 1N (30 ml) y metanol (40 ml). Se retiró el baño de enfriamiento y la mezcla de reacción se agitó bajo un globo de H_2 durante 17 horas. Se añadió más acetaldehído (10 ml, 178,2 mmol) y se continuó agitando en atmósfera de H_2 durante 24 horas [Nota: el suministro de H_2 se reponía cuando era necesario a través de la reacción]. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de ácido (R)-2-(etilamino)-2-fenilacético como un sólido blanco brillante (2,846 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 14,15 (s ancho, 1H), 9,55 (s ancho, 2H), 7,55-7,48 (m, 5H), 2,88 (m ancho, 1H), 2,73 (m ancho, 1H), 1,20 (t aparente, J = 7,2, 3H). CL (Cond. I): T_R = 0,39 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$: 180,10; encontrado 180,18.

Se añadió una suspensión de Pd al 10%/C (536 mg) en metanol/H_2O (3 ml/1 ml) a una mezcla de ácido (R)-2-(etilamino)-2-fenilacético/HCl (1,492 g, 6,918 mmol), formaldehído (20 ml de 37% en peso en agua), HCl 1N (20 ml) y metanol (23 ml). La mezcla de reacción se agitó bajo un globo de H_2 durante ~72 horas, en el que se el suministro de H_2 se reanudaba según se necesitaba. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el

filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol (50 ml) proporcionando la sal HCl de *Cap*-3 como un sólido blanco (985 mg). RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 10,48 (s ancho, 1H), 7,59-7,51 (m, 5H), 5,26 (s, 1H), 3,08 (s ancho aparente, 2H), 2,65 (s ancho, 3H), 1,24 (m ancho, 3H). CL (Cond. I): T_R = 0,39 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,12; encontrado 194,18; EMAR: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,1180; encontrado 194,1181.

Cap-4

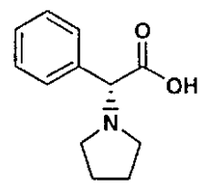


Se añadió $ClCO_2Me$ (3,2 ml, 41,4 mmol) gota a gota a una semisolución en THF enfriada (hielo/agua) (410 ml) de 2-amino-2-fenilacetato de (R)-terc-butilo/HCl (9,877 g, 40,52 mmol) y diisopropiletilamina (14,2 ml, 81,52 mmol) durante 6 min, y se agitó a una temperatura similar durante 5,5 horas. El componente volátil se eliminó a vacío, y el residuo se repartió entre agua (100 ml) y acetato de etilo (200 ml). La fase orgánica se lavó con HCl 1N (25 ml) y solución saturada de $NaHCO_3$ (30 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío. El aceite resultante incoloro se trituró en hexanos, se filtró y se lavó con hexanos (100 ml) proporcionando 2-(metoxicarbonilamino)-2-fenilacetato de (R)-terc-butilo como un sólido blanco (7,7 g). RMN de ^{1}H (DMSO-d_6, 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. I): T_R = 1,53 min; índice

de homogeneidad ~90 %; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288,12; encontrado 288,15.

Se añadió TFA (16 ml) gota a gota a una solución enfriada (hielo/agua) en CH_2Cl_2 (160 ml) del producto anterior durante 7 minutos y se retiró el baño de enfriamiento y la mezcla de reacción se agitó durante 20 horas. Puesto que la desprotección todavía no fue completa, se añadió más TFA (1,0 ml) y se continuó agitando durante otras 2 horas más. El componente volátil se eliminó a vacío, y el residuo oleoso resultante se trató con éter dietílico (15 ml) y hexanos (12 ml) proporcionando un precipitado. El precipitado se filtró y se lavó con éter dietílico/hexanos (relación ~1:3; 30 ml) y se secó a vacío proporcionando *Cap*-4 como un sólido blanco apelusado (5,57 g). Rotación óptica: -176,9° [c = 3,7 mg/ml en H_2O; λ = 589 nm]. RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,84 (s ancho, 1H), 7,96 (d, *J* = 8,3, 1H), 7,41-7,29 (m, 5H), 5,14 (d, *J* = 8,3, 1H), 3,55 (s, 3H). CL (Cond. I): T_R = 1,01 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210,08; encontrado 210,17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210,0766; encontrado 210,0756.

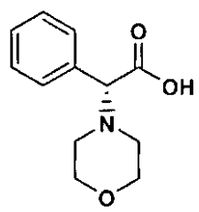
Cap-5



Se calentó a 100°C durante 21 horas una mezcla de (R)- 2-fenilglicina (1,0 g, 6,62 mmol), 1,4-dibromobutano (1,57 g, 7,27 mmol) y Na_2CO_3 (2,10 g, 19,8 mmol) en etanol (40 ml). La mezcla de reacción se enfrió hasta

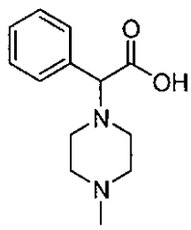
temperatura ambiente y se filtró, y el filtrado se concentró a vacío. El residuo se disolvió en etanol y se acidificó con HCl 1N hasta pH 3-4, y el componente volátil se eliminó a vacío. El material bruto resultante se purificó por una HPLC de fase inversa (agua/metanol/TFA) proporcionando la sal TFA de *Cap*-5 como una espuma blanca semiviscosa (1,0 g). RMN de ^{1}H (DMSO-d_6, δ = 2,5, 500 MHz) δ 10,68 (s ancho, 1H), 7,51 (m, 5H), 5,23 (s, 1H), 3,34 (s ancho aparente, 2H), 3,05 (s ancho aparente, 2H), 1,95 (s ancho aparente, 4H); T_R = 0,30 min (Cond. I); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206,12; encontrado 206,25.

Cap-6



La sal TFA de *Cap*-6 se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el procedimiento de preparación de *Cap*-5. RMN de ^{1}H (DMSO-d_6, δ = 2,5, 500 MHz) δ 12,20 (s ancho, 1H), 7,50 (m, 5H), 4,92 (s, 1H), 3,78 (s ancho aparente, 4H), 3,08 (s ancho aparente, 2H), 2,81 (s ancho aparente, 2H); T_R = 0,32 min (Cond. I); >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222,11; encontrado 222,20; EMAR: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222,1130; encontrado 222,1121.

Cap-7



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

Se añadió gota a gota una solución en CH_2Cl_2 (200 ml) de cloruro de p-toluenosulfonilo (8,65 g, 45,4 mmol) a una solución (-5 °C) en CH_2Cl_2 (200 ml) de 2-hidroxi-2-fenilacetato de (S)-bencilo (10,0 g, 41,3 mmol), trietilamina (5,75 ml, 41,3 mmol) y 4-dimetilaminopiridina (0,504 g, 4,13 mmol), mientras se mantenía la temperatura de -5 °C a 0 °C. La reacción se agitó a 0 °C durante 9 horas, y luego se almacenó en un congelador (-25 °C) durante 14 horas. Se dejó descongelar hasta temperatura ambiente y se lavó con agua (200 ml), HCl 1N (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 2-fenil-2-(tosiloxi)acetato de bencilo como un aceite viscoso que solidificó en reposo (16,5 g). La integridad quiral del producto no se verificó y dicho producto se usó en la etapa siguiente sin purificación adicional. RMN de ^1H (DMSO-d_6, 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). T_R = 3,00 (Cond. III); índice de homogeneidad >90%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419,09; encontrado 419,04.

Se calentó a 65°C durante 7 horas una solución en THF (75 ml) de 2-fenil-2-(tosiloxi)acetato de bencilo (6,0 g, 15,1 mmol), 1-metilpiperazina (3,36 ml, 30,3 mmol) y N,N-diisopropiletilamina (13,2 ml, 75,8 mmol). Se dejó enfriar la reacción hasta temperatura ambiente y el componente volátil se eliminó a vacío. El residuo se repartió entre etilacetato y agua, y la fase orgánica se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El

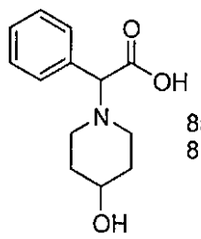
material bruto resultante se purificó por cromatografía ultrarrápida (gel de sílice, etilo acetato) proporcionando 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo como un aceite viscoso anaranjado-pardo (4,56 g). El análisis HPLC quiral (Chiralcel OD-H) indicó que la muestra es una mezcla de enantiómeros en una relación 38,2 a 58,7. La separación de los enantiómeros se realizó como sigue: se disolvió el producto en 120 ml de etanol/heptano (1:1) y se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluyendo con 85:15 Heptano/etanol a 75 ml/min, y se controló a 220 nm. El enantiómero-1(1,474 g) y el enantiómero-2 (2,2149 g) se recuperaron como aceite viscoso. RMN de ^{1}H ($CDCl_3$, δ = 7,26, 500 MHz) 7,44-7,40 (m, 2H), 7,33-7,24 (m, 6H), 7,21-7,16 (m, 2H), 5,13 (d, *J* = 12,5, 1H), 5,08 (d, *J* = 12,5, 1H), 4,02 (s, 1H), 2,65-2,38 (s ancho aparente, 8H), 2,25 (s, 3H). T_R = 2,10 (Cond. III); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325,19; encontrado 325,20.

Se añadió una solución en metanol (10 ml) de cualquiera de los enantiómeros de 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo (1,0 g, 3,1 mmol) a una suspensión de Pd al 10%/C (120 mg) en metanol (5,0 ml). La mezcla de reacción se expuso a un globo de hidrógeno con un control cuidadoso durante <50 min. Inmediatamente después de completarse la reacción, se filtró el catalizador a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío proporcionando *Cap*-7, contaminado con ácido fenilacético como una espuma color castaño (867,6 mg; la masa es superior al rendimiento teórico). El producto se usó en la etapa siguiente sin purificación adicional. RMN de ^{1}H (DMSO-d_6, δ = 2,5, 500 MHz) δ 7,44-7,37 (m, 2H), 7,37-7,24 (m, 3H), 3,92 (s, 1H), 2,63-2,48 (s ancho ap., 2H), 2,48-2,32 (m, 6H), 2,19

(s, 3H); T_R = 0,31 (Cond. II); índice de homogeneidad >90%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235,14; encontrado 235,15; EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235,1447; encontrado 235,1440.

La síntesis de *Cap*-8 y *Cap*-9 se llevó a cabo de acuerdo con la síntesis de *Cap*-7 usando aminas apropiadas para la etapa de desplazamiento de SN_2 (es decir, 4-hidroxipiperidina para *Cap*-8 y (S)-3-fluoropirrolidina para *Cap*-9) y condiciones modificadas para la separación de los intermedios estereoisoméricos respectivos, como se describe más adelante.

Cap-8

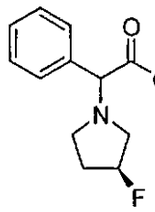


8a: enantiómero 1
8b: enantiómero 2

La separación enantiomérica del intermedio 2-(4-hidroxipiperidin-1-il)-2-fenil acetato de bencilo se efectuó empleando las siguientes condiciones: se disolvió el compuesto (500 mg) en etanol/heptano (5 ml/45 ml). La solución resultante se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 2 cm ID x 25 cm de longitud, 10 μm) eluyendo con 80:20 de heptano/etanol a 10 ml/min, controlada a 220 nm, proporcionando 186,3 mg de enantiómero-1 y 209,1 mg de enantiómero-2 como aceites viscosos amarillo claro. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de *Cap*-7 proporcionando *Cap*-8: RMN de ^1H (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). T_R = 0,28 (Cond. II); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236,13; encontrado 236,07; EMAR: Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236,1287; encontrado 236,1283.

Cap-9

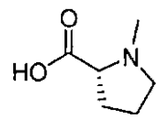


9a: diastereómero 1
9b: diastereómero 2

La separación enantiomérica del intermedio 2-((S)-3-fluoropirrolidin-1-il)-2-fenilacetato de bencilo se efectuó empleando las siguientes condiciones: se separó el éster (220 mg) en una columna HPLC quiral (Chiracel OJ-H, 0,46 cm ID x 25 cm L, 5 μm) eluyendo con 95% de CO_2 / 5% de metanol con 0,1% de TFA, a una presión de $10x10^5$ Pa, 70 ml/min de Caudal, y una temperatura de 35 °C. Se concentró el eluato de HPLC para los estereoisómeros respectivos y el residuo se disolvió en CH_2Cl_2 (20 ml) y se lavó con un medio acuoso (10 ml agua + 1 ml de solución saturada de $NaHCO_3$). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 92,5 mg de fracción-1 y 59,6 mg de fracción-2. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de *Cap*-7 para preparar Caps 9a y 9b. *Cap*-9a (diastereómero-1; la muestra es una sal TFA como resultado de la purificación en una HPLC de fase inversa usando H_2O/metanol/TFA como disolvente): RMN de ^1H (DMSO-d_6, δ = 2,5, 400 MHz) 7,55-7,48 (m, 5H), 5,38 (d de m, *J* = 53,7, 1H), 5,09 (s ancho, 1H), 3,84-2,82 (m ancho, 4H), 2,31-2,09

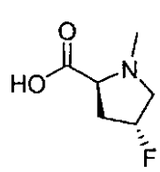
(m, 2H). T_R = 0,42 (Cond. I); índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224,11; encontrado 224,14; *Cap*-9b (diastereómero-2): RMN de ^1H (DMSO-d_6, δ = 2,5, 400 MHz) 7,43-7,21 (m, 5H), 5,19 (d de m, J = 55,9, 1H), 3,97 (s, 1H), 2,95-2,43 (m, 4H), 2,19-1,78 (m, 2H). T_R = 0,44 (Cond. I); CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224,11; encontrado 224,14.

Cap-10



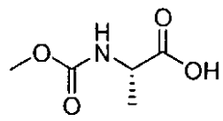
A una solución de D-prolina (2,0 g, 17 mmol) y formaldehído (2,0 ml de 37% en peso en H_2O) en metanol (15 ml) se añadió una suspensión de Pd al 10%/C (500 mg) en metanol (5 ml). La mezcla se agitó bajo un globo de hidrógeno durante 23 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío proporcionando *Cap*-10 como un sólido blanquecino (2,15 g). RMN de ^1H (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). T_R = 0,28 (Cond. II); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130,09; encontrado 129,96.

Cap-11



Una mezcla de ácido (2S,4R)-4-fluoropirrolidin-2-carboxílico (0,50 g, 3,8 mmol), formaldehído (0,5 ml de 37% en peso en H_2O), HCl 12 N (0,25 ml) y Pd al 10%/C (50 mg) en metanol (20 ml) se agitó bajo un globo de hidrógeno durante 19 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El residuo se recristalizó en isopropanol proporcionando la sal HCl de *Cap*-11 como un sólido blanco (337,7 mg). RMN de ^{1}H (DMSO-d_6, 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). T_R = 0,28 (Cond. II); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 148,08; encontrado 148,06.

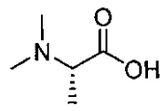
Cap-12 (igual que Cap 52)



Se disolvió L-alanina (2,0 g, 22,5 mmol) en solución acuosa al 10% de carbonato sódico (50 ml), y se añadió a la misma una solución en THF (50 ml) de cloroformiato de metilo (4,0 ml). La mezcla de reacción se agitó en condiciones ambientales durante 4,5 horas y se concentró a vacío. El sólido blanco resultante se disolvió en agua y se acidificó con HCl 1N hasta un pH ~ 2-3. Las soluciones resultantes se extrajeron con acetato de etilo (3 x 100 ml), y la fase orgánica reunida se secó (Na_2SO_4), se filtró y se concentró a vacío proporcionando un aceite incoloro (2,58 g). Se purificaron 500 mg de este material por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando 150 mg de *Cap*-12 como un aceite incoloro. RMN de ^{1}H (DMSO-d_6, δ = 2,5, 500

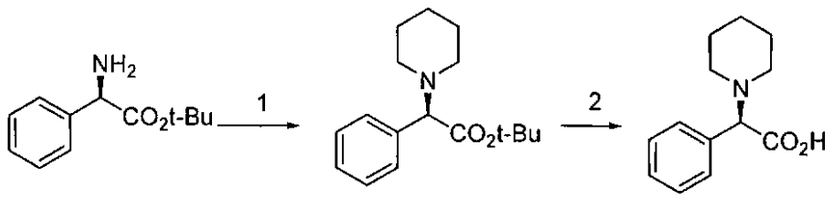
MHz) 7,44 (d, *J* = 7,3, 0,8H), 7,10 (s ancho, 0,2H), 3,97 (m, 1H), 3,53 (s, 3H), 1,25 (d, *J* = 7,3, 3H).

Cap-13



Se agitó una mezcla de L-alanina (2,5 g, 28 mmol), formaldehído (8,4 g, 37% en peso), HCl 1N (30 ml) y Pd al 10%/C (500 mg) en metanol (30 ml) en una atmósfera de hidrógeno (344,64 kPa) durante 5 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío proporcionando la sal HCl de *Cap*-13 como un aceite que solidificó en reposo a vacío (4,4 g; la masa es superior al rendimiento teórico). El producto se usó sin purificación adicional. RMN de ^{1}H (DMSO-d_6, δ = 2,5, 500 MHz) δ 12,1 (s ancho, 1H), 4,06 (q, *J* = 7,4, 1H), 2,76 (s, 6H), 1,46 (d, *J* = 7,3, 3H).

Cap-14



Cap-14

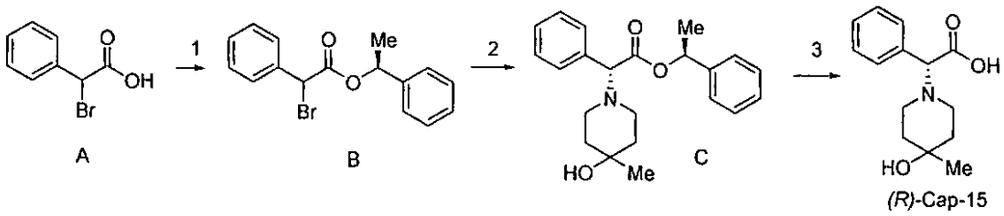
Etapa 1: Una mezcla éster terc-butílico de (R)-(-)-D-fenilglicina (3,00 g, 12,3 mmol), $NaBH_3CN$ (0,773 g, 12,3 mmol), KOH (0,690 g, 12,3 mmol) y ácido acético (0,352 ml, 6,15 mmol) se agitó en metanol a 0 °C. A esta mezcla se

añadió dialdehído glutárico (2,23 ml, 12,3 mmol) gota a gota durante 5 minutos. La mezcla de reacción se agitó calentando hasta temperatura ambiente y se continuó agitando a la misma temperatura durante 16 horas. El disolvente se eliminó seguidamente y el residuo se repartió con NaOH acuoso al 10% y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta sequedad proporcionando un aceite transparente. Este material se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0,1%) dando el éster intermedio (2,70 g, 56%) como un aceite transparente. RMN de ^1H (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). CL/EM: Anal. Calculado para $C_{17}H_{25}NO_2$: 275; encontrado: 276 $(M+H)^+$.

Etapa 2: A una solución agitada del éster intermedio (1,12 g, 2,88 mmol) en diclorometano (10 ml) se añadió TFA (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se concentró hasta sequedad dando un aceite amarillo claro. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0,1%). Las fracciones apropiadas se reunieron y se concentraron hasta sequedad a vacío. El residuo se disolvió entonces en una cantidad mínima de metanol y se aplicó en cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos se aclararon con metanol (40 ml) y luego eluyó el compuesto deseado usando amoníaco 2M en metanol (50 ml). Las fracciones que contenían producto se reunieron y concentraron y el residuo se suspendió en agua. La liofilización de esta solución proporcionó el compuesto del epígrafe (0,492 g, 78%) como un sólido

amarillo claro. RMN de ^{1}H (DMSO-d_6) δ 7,50 (s, 5H), 5,13 (s, 1H), 3,09 (s ancho, 2H), 2,92-2,89 (m, 2H), 1,74 (m, 4H), 1,48 (s ancho, 2H). CL/EM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

Cap-15



Etapa 1: 2-Bromo-2-fenilacetato de (S)-1-feniletilo: A una mezcla de ácido 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 añadió EDCI sólido (12,46 g, 0,065 mol) todo de una vez. La solución resultante se agitó a temperatura ambiente en Ar durante 18 horas y luego se diluyó con acetato de etilo, se lavó (H_2O x 2, salmuera), se secó (Na_2SO_4), se filtró y se concentró dando un aceite amarillo pálido. La cromatografía ultrarrápida (SiO_2/ hexano-etilo acetato, 4:1) de este aceite proporcionó el compuesto del epígrafe (11,64 g, 73%) como un sólido blanco. RMN de ^{1}H (400 MHz, $CDCl_3$) δ 7,53-7,17 (m, 10H), 5,95 (q, *J* = 6,6 Hz, 0,5H), 5,94 (q, *J* = 6,6 Hz, 0,5H), 5,41 (s, 0,5H), 5,39 (s, 0,5H), 1,58 (d, *J* = 6,6 Hz, 1,5H), 1,51 (d, *J* = 6,6 Hz, 1,5H).

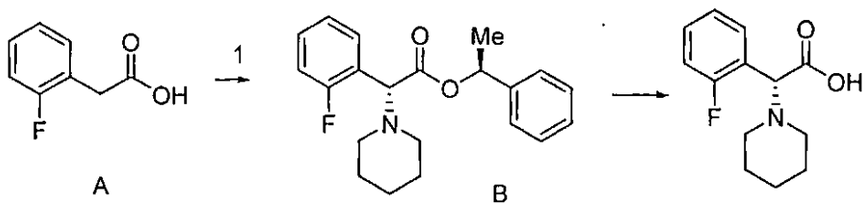
Etapa 2: (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (0,464 g, 1,45 mmol) en THF (8 ml) se añadió trietilamina (0,61 ml, 4,35 mmol), seguido por yoduro de tetrabutilamonio (0,215 g, 0,58 mmol). La mezcla de reacción se

agitó a temperatura ambiente durante 5 minutos y luego se añadió una solución de 4-metil-4-hidroxipiperidina (0,251 g, 2,18 mmol) en THF (2 ml). La mezcla se agitó durante 1 hora a temperatura ambiente y luego se calentó a 55-60 °C (temperatura de baño de aceite) durante 4 horas. La mezcla de reacción enfriada se diluyó entonces con acetato de etilo (30 ml), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (0-60% de etilo acetato-hexano) proporcionando primero el isómero (S,R) del compuesto del epígrafe (0,306 g, 60%) como un sólido blanco y luego el correspondiente isómero (S,S)(0,120 g, 23%), también como un sólido blanco. Isómero (S,R): RMN de ^1H (CD_3OD) δ 7,51-7,45 (m, 2H), 7,41-7,25 (m, 8H), 5,85 (q, *J* = 6,6 Hz, 1H), 4,05 (s, 1H), 2,56-2,45 (m, 2H), 2,41-2,29 (m, 2H), 1,71-1,49 (m, 4H), 1,38 (d, *J* = 6,6 Hz, 3H), 1,18 (s, 3H). CLEM: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$. Isómero (S,S): RMN de ^1H (CD_3OD) δ 7,41-7,30 (m, 5H), 7,20-7,14 (m, 3H), 7,06-7,00 (m, 2H), 5,85 (q, *J* = 6,6 Hz, 1H), 4,06 (s, 1H), 2,70-2,60 (m, 1H), 2,51 (dt, *J* = 6,6, 3,3 Hz, 1H), 2,44-2,31 (m, 2H), 1,75-1,65 (m, 1H), 1,65-1,54 (m, 3H), 1,50 (d, *J* = 6,8 Hz, 3H), 1,20 (s, 3H). CLEM: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$.

Etapa 3: ácido (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0,185 g, 0,52 mmol) en diclorometano (3 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-TFA al 0,1%) dando el compuesto del epígrafe (como sal TFA)

como un sólido azulado pálido (0,128 g, 98%). CLEM: Anal. Calculado para $C_{14}H_{19}NO_3$: 249; encontrado: 250 $(M+H)^+$.

Cap-16



(R)-Cap-16

Etapa 1: 2-(2-fluorofenil)acetato de (S)-1-feniletilo: Una mezcla de ácido 2-fluorofenilacético (5,45 g, 35,4 mmol), (S)-1-feniletanol (5,62 g, 46,0 mmol), EDCI (8,82 g, 46,0 mmol) y DMAP (0,561 g, 4,60 mmol) en CH_2Cl_2 (100 ml) se agitó a temperatura ambiente durante 12 horas. El disolvente se concentró a continuación y el residuo se repartió con H_2O-acetato de etilo. Se separaron las fases y la fase acuosa se volvió a extraer con acetato de etilo (2x). Las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-20% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe como un aceite incoloro (8,38 g, 92%). RMN de ^1H (400 MHz, CD_3OD) δ 7,32 - 7,23 (m, 7H), 7,10-7,04 (m, 2), 5,85 (q, J = 6,5 Hz, 1H), 3,71 (s, 2H), 1,48 (d, J = 6,5 Hz, 3H).

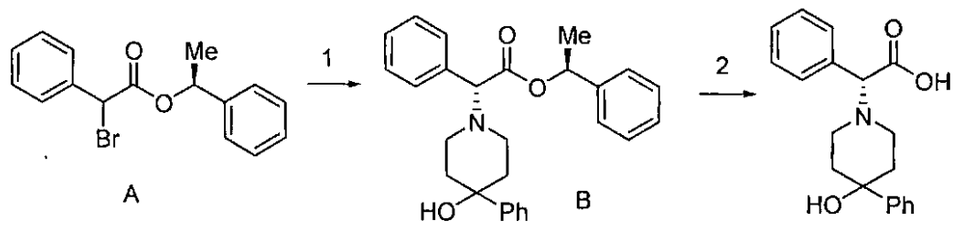
Etapa 2: 2-(2-Fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo): A una solución de 2-(2-fluorofenil)acetato de (S)-1-feniletilo (5,00 g, 19,4 mmol) en THF (1200 ml) a 0°C se añadió DBU (6,19 g, 40,7 mmol) y la solución se dejó calentar hasta temperatura ambiente mientras se agitaba durante 30

minutos. La solución se enfrió entonces hasta -78 °C y se añadió una solución de CBr_4 (13,5 g, 40,7 mmol) en THF (100 ml) y la mezcla se dejó calentar hasta -10 °C y se agitó a esta temperatura durante 2 horas. La mezcla de reacción se inactivó con NH_4Cl acuoso saturado y se separaron las fases. La fase acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. Al residuo se añadió piperidina (5,73 ml, 58,1 mmol) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles se concentraron entonces a vacío y el residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-30% de éter dietílico-hexano) proporcionando una mezcla pura de diastereoisómeros (relación 2:1 por RMN de ^1H) como un aceite amarillo (2,07 g, 31%), junto con material de partida sin reaccionar (2,53 g, 51%). Otra cromatografía de la mezcla diastereomérica (Biotage/ 0-10% éter dietílico-tolueno) proporcionó el compuesto del epígrafe como un aceite incoloro (0,737 g, 11%). RMN de ^1H (400 MHz, CD_3OD) 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). CLEM: Anal. Calculado para $C_{21}H_{24}FNO_2$: 341; encontrado: 342 $(M+H)^+$.

Etapa 3: ácido (R)-2-(2-fluorofenil)-2-(piperidin-1-il)acético: Una mezcla de 2-(2-fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo) (0,737 g, 2,16 mmol) y $Pd(OH)_2$ al 20%/C (0,070 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de H_2) durante 2 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Esto proporcionó el

compuesto del epígrafe como un sólido incoloro (0,503 g, 98%). RMN de ^{1}H (400 MHz, CD_3OD) 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 (s ancho, 4H), 1,62 (s ancho, 2H). CLEM: Anal. Calculado para $C_{13}H_{16}FNO_2$: 237; encontrado: 238 $(M+H)^+$.

Cap-17

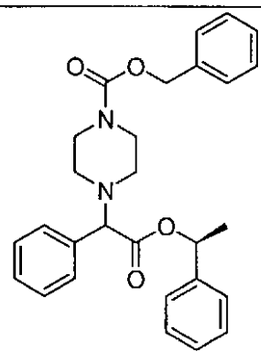


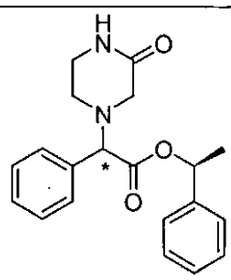
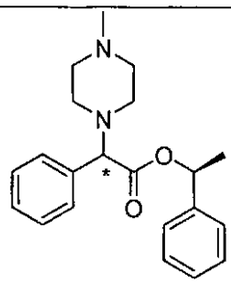
(R)-Cap-17

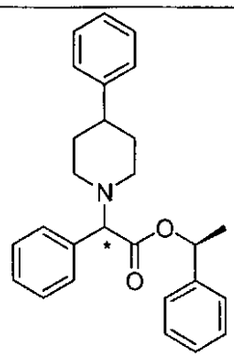
Etapa 1: (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1,50 g, 4,70 mmol) en THF (25 ml) se añadió trietilamina (1,31 ml, 9,42 mmol), seguido por yoduro de tetrabutilamonio (0,347 g, 0,94 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego se añadió una solución de 4-fenil-4-hidroxipiperidina (1,00 g, 5,64 mmol) en THF (5 ml). La mezcla se agitó durante 16 horas y luego se diluyó con acetato de etilo (100 ml), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó en una columna de gel de sílice (acetato de etilo 0-60%-hexano) proporcionando una mezcla aproximadamente 2:1 de diastereoisómeros, como se juzgó por RMN de ^{1}H. La separación de esos isómeros se llevó a cabo usando cromatografía de fluido supercrítico (Chiralcel OJ-H, 30 x 250mm; 20% etanol en CO_2 a 35 °C), dando primero el isómero (R) del compuesto del epígrafe (0,534 g, 27%) como un aceite amarillo y luego el isómero (S)

correspondiente (0,271 g, 14%), también como un aceite amarillo. Isómero (S,R): RMN de ^{1}H (400 MHz, CD_3OD) δ 7,55-7,47 (m, 4H), 7,44-7,25 (m, 10H), 7,25-7,17 (m, 1H), 5,88 (q, *J* = 6,6 Hz, 1H), 4,12 (s, 1H), 2,82-2,72 (m, 1H), 2,64 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,58-2,52 (m, 1H), 2,40 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,20 (dt, *J* = 12,1, 4,6 Hz, 1H), 2,10 (dt, *J* = 12,1, 4,6 Hz, 1H), 1,72-1,57 (m, 2H), 1,53 (d, *J* = 6,5 Hz, 3H). CLEM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$; Isómero (S,S): RMN de ^{1}H (400 MHz, CD_3OD) δ 7,55-7,48 (m, 2H), 7,45-7,39 (m, 2H), 7,38-7,30 (m, 5H), 7,25-7,13 (m, 4H), 7,08-7,00 (m, 2H), 5,88 (q, *J* = 6,6 Hz, 1H), 4,12 (s, 1H), 2,95-2,85 (m, 1H), 2,68 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,57-2,52 (m, 1H), 2,42 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,25 (dt, *J* = 12,1, 4,6 Hz, 1H), 2,12 (dt, *J* = 12,1, 4,6 Hz, 1H), 1,73 (dd, *J* = 13,6, 3,0 Hz, 1H), 1,64 (dd, *J* = 13,6, 3,0 Hz, 1H), 1,40 (d, *J* = 6,6 Hz, 3H). CLEM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$.

Los ésteres siguientes se prepararon de una forma similar.

Intermedio-17a		Diastereómero 1: RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 1,36 (d, *J*=6,41 Hz, 3H) 2,23 - 2,51 (m, 4H) 3,35 (s, 4H) 4,25 (s, 1H) 5,05 (s, 2H) 5,82 (d, *J*=6,71 Hz, 1H) 7,15 - 7,52 (m, 15H). CLEM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458,22; Encontrado: 459,44 $(M+H)^+$. Diastereómero 2: RMN de ^{1}H (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). CLEM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458,22; Encontrado: 459,44 $(M+H)^+$.
Intermedio -17b		Diastereómero 1: T_R = 11,76 min (Condición II); CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338,16 Encontrado: 339,39 $(M+H)^+$; Diastereómero 2: T_R = 10,05 min (Condición II); CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338,16; Encontrado: 339,39 $(M+H)^+$.
Intermedio -17c		Diastereómero 1: T_R = 4,55 min (Condición I); CLEM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338,20 Encontrado: 339,45 $(M+H)^+$; Diastereómero 2: T_R = 6,00 min (Condición I); CLEM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338,20 Encontrado: 339,45 $(M+H)^+$.

Intermedio -17d		Diastereómero 1: T_R = 7,19 min (Condición I); CLEM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399,22 Encontrado: 400,48 $(M+H)^+$; Diastereómero 2: T_R = 9,76 min (Condición I); CLEM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399,22 Encontrado: 400,48 $(M+H)^+$.

Condiciones de SFC quiral para determinar el tiempo de retención

Condición I

Columna: Columna Chiralpak AD-H, 4,62X250 mm, 5µm

Disolventes: 90% de CO_2 - metanol al 10% con DEA al 0,1%

Temp: 35 °C

Presión: 15 MPa

Caudal: 2,0 ml/min.

UV controlado a 220 nm

Inyección: 1,0 mg/3 ml de metanol

Condición II

Columna: Columna Chiralcel OD-H, 4,62X250 mm, 5µm

Disolventes: 90% de CO_2 - metanol al 10% con DEA al 0,1%

Temp: 35 °C

Presión: 15 MPa

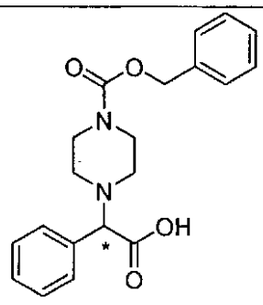
Caudal: 2,0 ml/min.

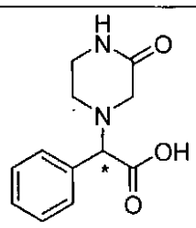
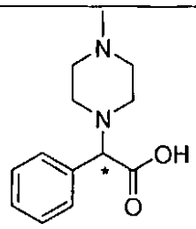
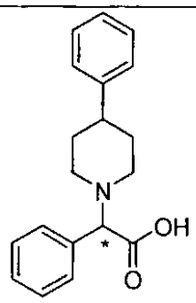
UV controlado a 220 nm

Inyección: 1,0 mg/ml de metanol

Cap-17, Etapa 2: ácido (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0,350 g, 0,84 mmol) en diclorometano (5 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-TFA al 0,1%) dando el compuesto del epígrafe (como sal TFA) como un sólido blanco (0,230 g, 88%). CLEM: Anal. Calculado para $C_{19}H_{21}NO_3$: 311,15; encontrado: 312 $(M+H)^+$.

Los siguientes ácidos carboxílicos se prepararon en forma ópticamente pura de una forma similar:

Cap-17a		T_R = 2,21 (Condición II); RMN de ^1H (500 MHz, DMSO-d_6) 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). CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_4$ 354,16; Encontrado: 355,38 $(M+H)^+$.

Cap-17b		T_R = 0,27 (Condición III); CLEM: Análisis calculado para: $C_{12}H_{14}N_2O_3$ 234,10; Encontrado: 235,22 $(M+H)^+$.
Cap-17c		T_R = 0,48 (Condición II); CLEM: Análisis calculado para: $C_{13}H_{18}N_2O_2$ 234,14; Encontrado: 235,31 $(M+H)^+$.
Cap-17d		T_R = 2,21 (Condición I); CLEM: Análisis calculado para: $C_{19}H_{21}NO_2$ 295,16; Encontrado: 296,33 $(M+H)^+$.

Condiciones de CLEM para determinar el tiempo de retención

Condición I

Columna: Phenomenex-Luna 4,6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = metanol al 10% - H_2O al 90% - TFA al 0,1%

Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0,1%

Condición II

Columna: Waters-Sunfire 4,6 X 50 mm S5

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = metanol al 10% - H_2O al 90% - TFA al 0,1%

Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0,1%

Condición III

Columna: Phenomenex 10μ 3,0 X 50 mm

% Inicial de B = 0

% Final de B = 100

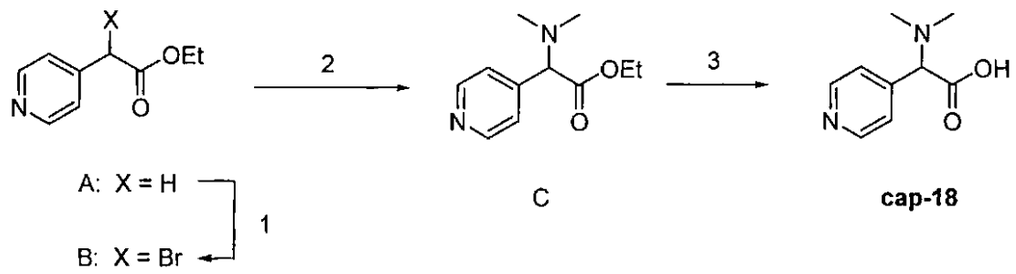
Tiempo de gradiente = 2 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = metanol al 10% - H_2O al 90% - TFA al 0,1%

Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0,1%



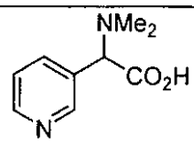
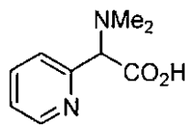
Etapa 1: 2-(4-piridil)-2-bromoacetato de (R,S)-etilo: A una solución de 4-piridilacetato de etilo (1,00 g, 6,05 mmol) en THF seco (150 ml) a 0 °C en argón se añadió DBU (0,99 ml, 6,66 mmol). La mezcla de reacción se dejó calentar hasta temperatura ambiente durante 30 minutos y luego se enfrió hasta -78 °C. A esta mezcla se añadió CBr_4 (2,21 g, 6,66 mmol) y se continuó agitando a -78 °C durante 2 horas. Seguidamente la mezcla de reacción se inactivó con NH_4Cl acuoso saturado y se separaron las fases. La fase orgánica se lavó (salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío. El aceite amarillo resultante se purificó inmediatamente por cromatografía ultrarrápida (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (1,40 g, 95%) como un aceite amarillo algo estable. RMN de ^1H (400 MHz, $CDCl_3$) 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). CLEM: Anal. Calculado para $C_9H_{10}BrNO_2$: 242, 244; encontrado: 243, 245 $(M+H)^+$.

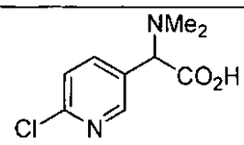
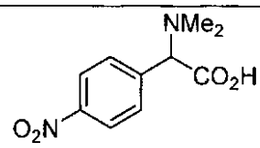
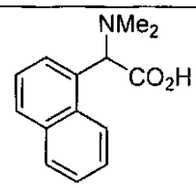
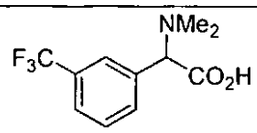
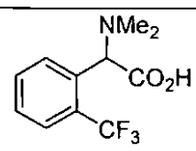
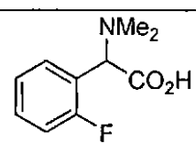
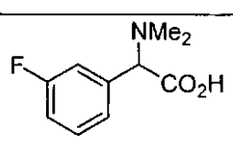
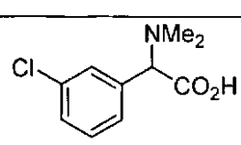
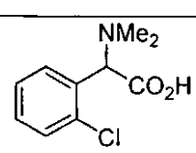
Etapa 2: 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo: A una solución de 2-(4-piridil)-2-bromoacetato de (R,S)-etilo (1,40 g, 8,48 mmol) en DMF (10 ml) a temperatura ambiente se añadió dimetilamina (2M en THF, 8,5 ml, 17,0 mmol). Después de completarse la reacción (que se juzgó por cromatografía en capa fina) los volátiles se eliminaron a vacío y el residuo se purificó por cromatografía ultrarrápida (columna Biotage, 40+M SiO_2; 50%-

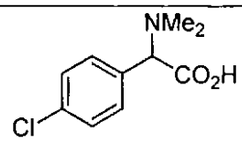
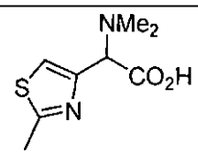
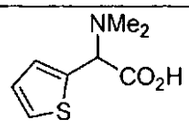
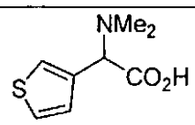
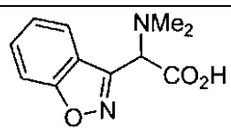
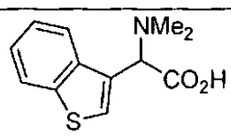
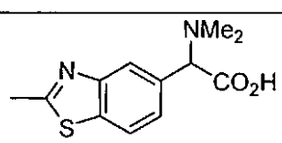
100% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe (0,539 g, 31%) como un aceite amarillo claro. RMN de ^{1}H (400 MHz, $CDCl_3$) δ 8,58 (d, *J* = 6,0 Hz, 2H), 7,36 (d, *J* = 6,0 Hz, 2H), 4,17 (m, 2H), 3,92 (s, 1H), 2,27 (s, 6H), 1,22 (t, *J* = 7,0 Hz). CLEM: Anal. Calculado para $C_{11}H_{16}N_2O_2$: 208; encontrado: 209 $(M+H)^+$.

Etapa 3: ácido (R,S)-2-(4-piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0,200 g, 0,960 mmol) en una mezcla de THF-metanol-H_2O (1:1:1, 6 ml) se añadió LiOH en polvo (0,120 g, 4,99 mmol) a temperatura ambiente. La solución se agitó durante 3 horas y luego se acidificó hasta pH 6 usando HCl 1N. La fase acuosa se lavó con acetato de etilo y luego se liofilizó dando el diclorhidrato del compuesto del epígrafe como un sólido amarillo (que contenía LiCl). El producto se usó como tal en las posteriores etapas. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 8,49 (d, *J* = 5,7 Hz, 2H), 7,34 (d, *J* = 5,7 Hz, 2H), 3,56 (s, 1H), 2,21 (s, 6H).

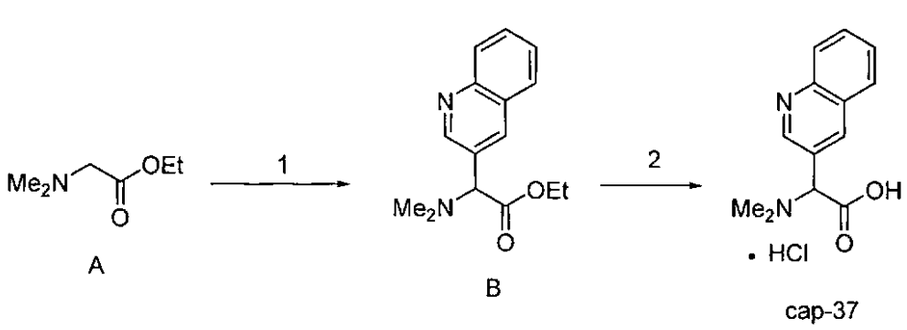
Los siguientes ejemplos se prepararon de una forma similar usando el procedimiento descrito antes;

Cap-19		CLEM: Anal. Calculado para $C_9H_{12}N_2O_2$: 180; encontrado: 181 $(M+H)^+$.
Cap-20		CLEM: sin ionización. RMN de ^{1}H (400 MHz, CD_3OD) δ 8,55 (d, *J* = 4,3 Hz, 1H), 7,84 (t aparente, *J* = 5,3 Hz, 1H), 7,61 (d, *J* = 7,8 Hz, 1H), 7,37 (t aparente, *J* = 5,3 Hz, 1H), 4,35 (s, 1H), 2,60 (s, 6H).

Cap-21		CLEM: Anal. Calculado para $C_9H_{11Cl}N_2O_2$: 214, 216; encontrado: 215, 217 $(M+H)^+$.
Cap-22		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-23		CLEM: Anal. Calculado para $C_{14}H_{15}NO_2$: 229; encontrado: 230 $(M+H)^+$.
Cap-24		CLEM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-25		CLEM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-26		CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.
Cap-27		CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-28		CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-29		CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.

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

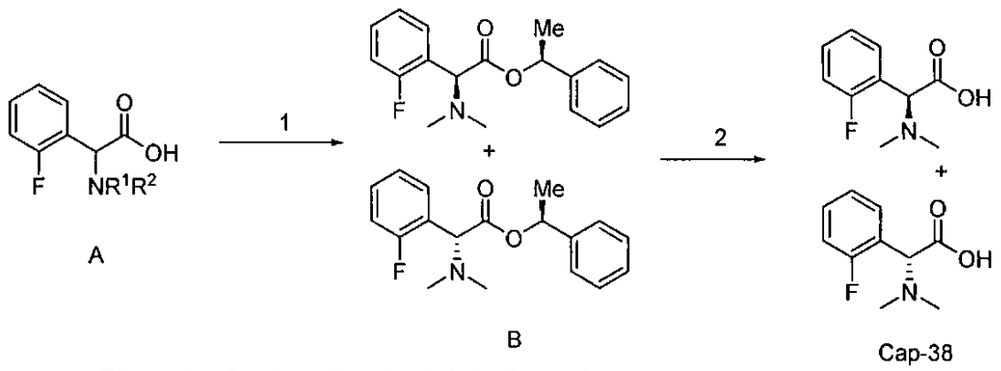
Cap-37



Etapa 1: 2-(quinolin-3-il)-2-(N,N-dimetilamino)-acetato de (R,S)-etilo: Una

mezcla de N,N-dimetilaminoacetato de etilo (0,462 g, 3,54 mmol), K_3PO_4 (1,90 g, 8,95 mmol), Pd(t-$Bu_3P)_2$ (0,090 g, 0,176 mmol) y tolueno (10 ml) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. La mezcla de reacción se calentó entonces a 100 °C durante 12 horas, después de lo cual se enfrió hasta temperatura ambiente y se vertió en H_2O. La mezcla se extrajo con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó primero por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) y luego por cromatografía ultrarrápida (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (0,128 g, 17%) como un aceite naranja. RMN de ^1H (400 MHz, $CDCl_3$) 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). CLEM: Anal. Calculado para $C_{15}H_{18}N_2O_2$: 258; encontrado: 259 $(M+H)^+$.

Etapa 2: Ácido (R,S) 2-(quinolin-3-il)-2-(N,N-dimetilamino)acético: Se calentó una mezcla de 2-(quinolin-3-il)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0,122 g, 0,472 mmol) y HCl 6M (3 ml) a 100 °C durante 12 horas. El disolvente se eliminó a vacío proporcionando el diclorhidrato del compuesto del epígrafe (0,169 g, >100%) como una espuma amarillo claro. El material sin purificar se usó en las etapas siguientes sin purificación adicional. CLEM: Anal. Calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.



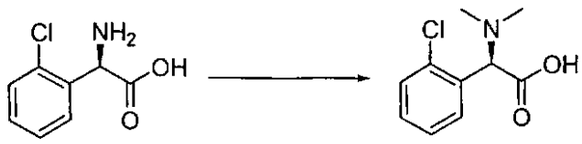
Etapa 1: 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo) y 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletil): A una mezcla de ácido (RS)-2-(dimetilamino)-2-(2-fluorofenil)acético (2,60 g, 13,19 mmol), DMAP (0,209 g, 1,71 mmol) y (S)-1-feniletanol (2,09 g, 17,15 mmol) en CH_2Cl_2 (40 ml) se añadió EDCI (3,29 g, 17,15 mmol) y la mezcla se dejó agitando a temperatura ambiente durante 12 horas. El disolvente se eliminó entonces a vacío y el residuo se repartió con acetato de etilo-H_2O. Se separaron las fases, la fase acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-50% de éter dietílico-hexano). La mezcla diastereomérica pura resultante se separó entonces por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0,1%) dando primero (R)-2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-1-fenetilo (0,501 g, 13%) y luego (S)-2-(dimetilamino)-2-(2-fluorofenil)-acetato de (S)-1-fenetilo (0,727 g. 18%), ambas como sus sales TFA. isómero (S,R): RMN de ^1H (400 MHz, CD_3OD) δ 7,65 - 7,70 (m, 1H), 7,55-7,60 (ddd, J = 9,4, 8,1, 1,5 Hz, 1H), 7,36-7,41 (m, 2H), 7,28-7,34 (m, 5H), 6,04 (q, J = 6,5 Hz, 1H), 5,60 (s, 1H), 2,84 (s, 6H), 1,43 (d, J = 6,5 Hz, 3H). CLEM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302

$(M+H)^+$; isómero (S,S): RMN de ^1H (400 MHz, CD_3OD) δ 7,58-7,63 (m, 1H), 7,18-7,31 (m, 6H), 7,00 (dd, *J* = 8,5, 1,5 Hz, 2H), 6,02 (q, *J* = 6,5 Hz, 1H), 5,60 (s, 1H), 2,88 (s, 6H), 1,54 (d, *J* = 6,5 Hz, 3H). CLEM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$.

Etapa 2: ácido (R)-2-(dimetilamino)-2-(2-fluorofenil)acético: Una mezcla de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo), sal TFA (1,25 g, 3,01 mmol) y 20% de $Pd(OH)_2/C$ (0,125 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de H_2) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Esto dio el compuesto del epígrafe como un sólido incoloro (0,503 g, 98%). RMN de ^1H (400 MHz, CD_3OD) δ 7,53-7,63 (m, 2H), 7,33-7,38 (m, 2H), 5,36 (s, 1H), 2,86 (s, 6H). CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.

El isómero S se podía obtener a partir de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletilo), sal TFA de una forma similar.

Cap-39

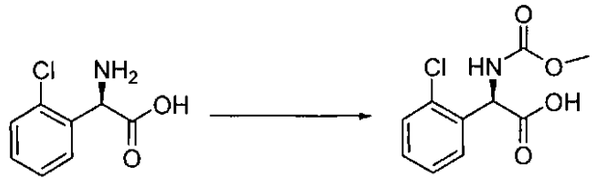


cap-39

Una mezcla de (R)-(2-clorofenil)glicina (0,300 g, 1,62 mmol), formaldehído (solución acuosa al 35%, 0,80 ml, 3,23 mmol) y 20% de $Pd(OH)_2/C$ (0,050 g) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de H_2) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se

concentró a vacío. El residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0,1%) dando la sal TFA del compuesto del epígrafe ácido (R)-2-(dimetilamino)-2-(2-clorofenil)acético como un aceite incoloro (0,290 g, 55%). RMN de ^1H (400 MHz, CD_3OD) δ 7,59-7,65 (m, 2H), 7,45-7,53 (m, 2H), 5,40 (s, 1H), 2,87 (s, 6H). CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.

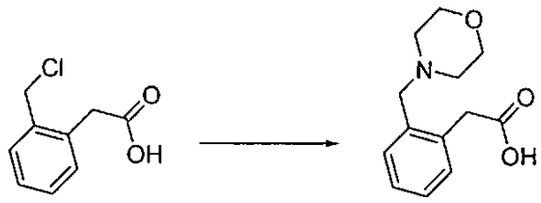
Cap-40



cap-40

A una solución enfriada en hielo de (R)-(2-clorofenil)glicina (1,00 g, 5,38 mmol) y NaOH (0,862 g, 21,6 mmol) en H_2O (5,5 ml) se añadió cloroformiato de metilo (1,00 ml, 13,5 mmol) gota a gota. La mezcla se dejó agitando a 0 °C durante 1 hora y luego se acidificó mediante la adición de HCl concentrado (2,5 ml). La mezcla se extrajo con acetato de etilo (2x) y la fase orgánica reunida se lavó (H_2O, salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío dando el compuesto del epígrafe ácido (R)-2-(metoxicarbonilamino)-2-(2-clorofenil)acético como una espuma amarillo-naranja (1,31 g, 96%). RMN de ^1H (400 MHz, CD_3OD) δ 7,39 – 7,43 (m, 2H), 7,29 – 7,31 (m, 2H), 5,69 (s, 1H), 3,65 (s, 3H). CLEM: Anal. Calculado para $C_{10}H_{10}ClNO_4$: 243; encontrado: 244 $(M+H)^+$.

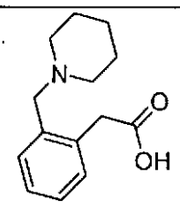
Cap-41

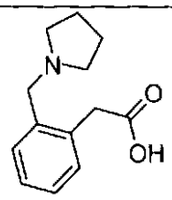
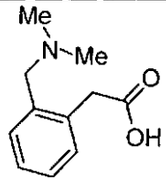
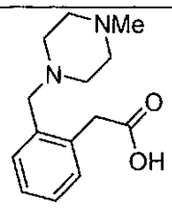


cap-41

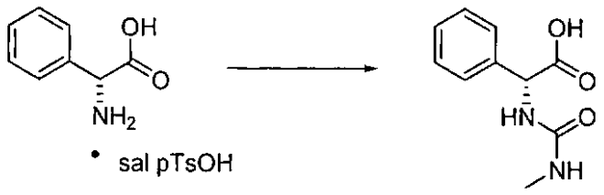
A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2,00 g, 10,8 mmol) en THF (20 ml) se añadió morfolina (1,89 g, 21,7 mmol) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó entonces con acetato de etilo y se extrajo con H_2O (2x). La fase acuosa se liofilizó y el residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-10% de metanol-CH_2Cl_2) dando el compuesto del epígrafe ácido 2-(2-(morfolinometil)fenil)acético como un sólido incoloro (2,22 g, 87%). RMN de ^1H (400 MHz, CD_3OD) δ 7,37-7,44 (m, 3H), 7,29-7,33 (m, 1H), 4,24 (s, 2H), 3,83 (s ancho, 4H), 3,68 (s, 2H), 3,14 (s ancho, 4H). CLEM: Anal. Calculado para $C_{13}H_{17}NO_3$: 235; encontrado: 236 $(M+H)^+$.

Los siguientes ejemplos se prepararon de igual modo usando el procedimiento descrito para Cap-41:

Cap-42		CLEM: Anal. Calculado para $C_{14}H_{19}NO_2$: 233; encontrado: 234 $(M+H)^+$.

Cap-43		CLEM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.
Cap-44		CLEM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 194 $(M+H)^+$.
Cap-45		CLEM: Anal. Calculado para $C_{14}H_{20}N_2O_2$: 248; encontrado: 249 $(M+H)^+$.

Cap-45a



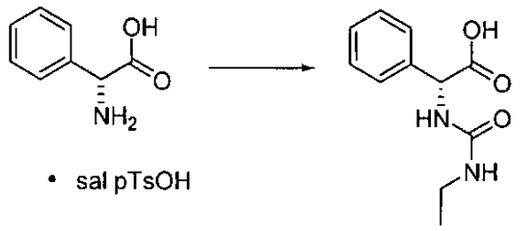
• sal pTsOH

Cap-45a

Se añadió HMDS (1,85 ml, 8,77 mmol) a una suspensión de p-toluenosulfonato del ácido (R)-2-amino-2-fenilacético (2,83 g, 8,77 mmol) en CH_2Cl_2 (10 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió isocianato de metilo (0,5 g, 8,77 mmol) en una porción continuando la agitación durante 30 minutos. La reacción se inactivó mediante adición de H_2O (5 ml) y se filtró el precipitado resultante, se lavó con H_2O y n-hexanos, y se secó a vacío. Se recuperó ácido (R)-2-(3-metilureido)-2-

fenilacético (1,5 g; 82 %) como un sólido blanco y se usó sin purificación adicional. RMN de ^{1}H (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). CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_3$ 208,08 encontrado 209,121 $(M+H)^+$; HPLC Phenomenex C-18 3,0 × 46 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, T_R = 1,38 min, índice de homogeneidad 90 %.

Cap-46

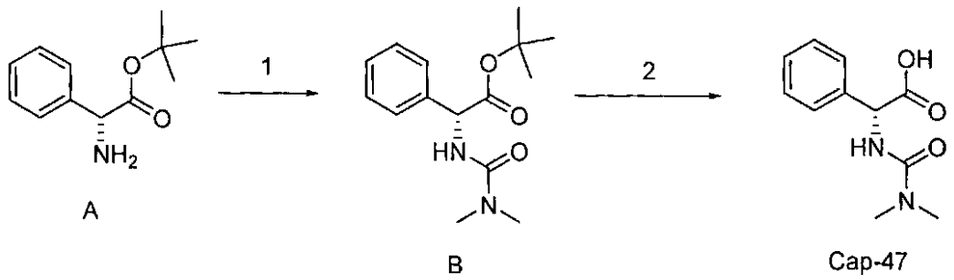


cap-46

El producto deseado se preparó de acuerdo con el procedimiento descrito para *Cap*-45a. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0,96 (t, *J*=7,17 Hz, 3H) 2,94 - 3,05 (m, 2H) 5,17 (d, *J*=7,93 Hz, 1H) 6,05 (t, *J*=5,19 Hz, 1H) 6,60 (d, *J*=7,63 Hz, 1H) 7,26 - 7,38 (m, 5H) 12,68 (s, 1H). CLEM: Anal. Calculado para $C_{11}H_{14}N_2O_3$ 222,10 encontrado 223,15 $(M+H)^+$.

HPLC XTERRA C-18 3,0 × 506 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,2% H_3PO_4, B = 10% de agua, 90% de metanol, 0,2% H_3PO_4, T_R = 0,87 min, índice de homogeneidad 90 %.

Cap-47



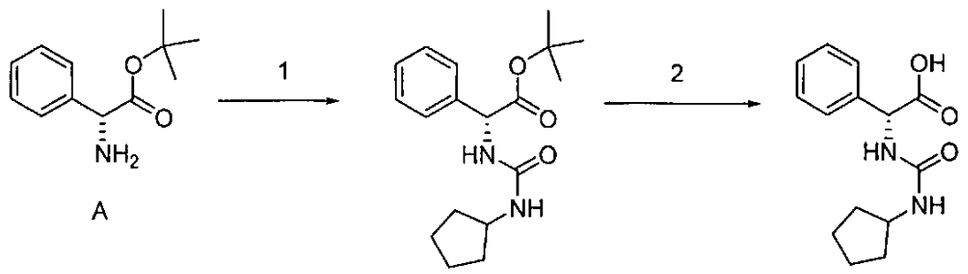
A B Cap-47

Etapa 1: 2-(3,3-dimetilureido)-2-fenilacetato de (R)-terc-butilo: A una solución agitada de (R)-terc–butil-2-amino-2-fenilacetato (1,0 g, 4,10 mmol) y base de Hunig (1,79 ml, 10,25 mmol) en DMF (40 ml) se añadió cloruro de dimetilcarbamoílo (0,38 ml, 4,18 mmol) gota a gota durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se disolvió en acetato de etilo. La fase orgánica se lavó con H_2O, HCl ac. 1N y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3,3-dimetilureido)-2-fenilacetato de (R)-terc-butilo como un sólido blanco (0,86 g; 75%) y se usó sin purificación posterior. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 1,33 (s, 9H) 2,82 (s, 6H) 5,17 (d, *J*=7,63 Hz, 1H) 6,55 (d, *J*=7,32 Hz, 1H) 7,24 - 7,41 (m, 5H). CLEM: Anal. Calculado para $C_{15}H_{22}N_2O_3$ 278,16 encontrado 279,23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4,6 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, T_R = 2,26 min, índice de homogeneidad 97%.

Etapa 2: ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-terc-butilo (0,86 g, 3,10 mmol) en CH_2Cl_2 (250 ml) se añadió TFA (15 ml) gota a gota y la solución

resultante se agitó a ta durante 3 horas. El compuesto deseado precipitó entonces en solución con una mezcla de EtOAC:Hexanos (5:20), se separó por filtración y se secó a presión reducida. Se aisló ácido (R)-2-(3,3-dimetilureido)-2-fenilacético como un sólido blanco (0,59g, 86%) y se usó sin purificación posterior. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 2,82 (s, 6H) 5,22 (d, *J*=7,32 Hz, 1H) 6,58 (d, *J*=7,32 Hz, 1H) 7,28 (t, *J*=7,17 Hz, 1H) 7,33 (t, *J*=7,32 Hz, 2H) 7,38 - 7,43 (m, 2H) 12,65 (s, 1H). CLEM: Anal. Calculado para $C_{11}H_{14}N_2O_3$: 222,24; encontrado: 223,21 $(M+H)^+$. HPLC XTERRA C-18 3,0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,2% H_3PO_4, B = 10% de agua, 90% de metanol, 0,2% H_3PO_4, T_R = 0,75 min, índice de homogeneidad 93%.

Cap-48



A B Cap-48

Etapa 1: 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo: A una solución agitada de clorhidrato del ácido (R)-2-amino-2-fenilacético (1,0 g, 4,10 mmol) y base de Hunig (1,0 ml, 6,15 mmol) en DMF (15 ml) se añadió isocianato de ciclopentilo (0,46 ml, 4,10 mmol) gota a gota y durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se suspendió

en acetato de etilo. La fase orgánica se lavó con H_2O y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo como un aceite opaco (1,32 g; 100 %) y se usó sin purificación posterior. RMN de ^1H (500 MHz, CD_3Cl-D) δ ppm 1,50 - 1,57 (m, 2H) 1,58 - 1,66 (m, 2H) 1,87 - 1,97 (m, 2H) 3,89 - 3,98 (m, 1H) 5,37 (s, 1H) 7,26 - 7,38 (m, 5H). CLEM: Anal. Calculado para $C_{18}H_{26}N_2O_3$ 318,19 encontrado 319,21 $(M+H)^+$; HPLC XTERRA C-18 3,0 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, T_R = 2,82 min, índice de homogeneidad 96%.

Etapa 2: Ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo (1,31 g, 4,10 mmol) en CH_2Cl_2 (25 ml) se añadió TFA (4 ml) y trietilsilano (1,64 ml; 10,3 mmol) gota a gota, y la solución resultante se agitó a temperatura ambiente durante 6 horas. Los componentes volátiles se eliminaron a presión reducida y el producto bruto se recristalizó en acetato de etilo/pentanos proporcionando ácido (R)-2-(3-ciclopentilureido)-2-fenilacético como un sólido blanco (0,69 g, 64%). RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 1,17 - 1,35 (m, 2H) 1,42 - 1,52 (m, 2H) 1,53 - 1,64 (m, 2H) 1,67 - 1,80 (m, 2H) 3,75 - 3,89 (m, 1H) 5,17 (d, *J*=7,93 Hz, 1H) 6,12 (d, *J*=7,32 Hz, 1H) 6,48 (d, *J*=7,93 Hz, 1H) 7,24 - 7,40 (m, 5H) 12,73 (s, 1H). CLEM: Anal. Calculado para $C_{14}H_{18}N_2O_3$: 262,31; encontrado: 263,15 $(M+H)^+$. HPLC XTERRA C-18 3,0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,2% H_3PO_4, B = 10% de agua, 90% de metanol, 0,2% H_3PO_4, T_R = 1,24 min, índice de homogeneidad 100%.

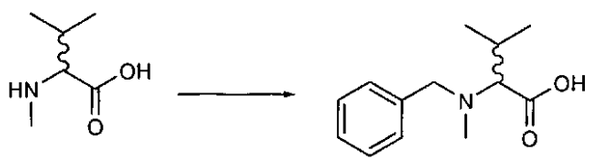
Cap-49



cap-49

A una solución agitada de ácido 2-(bencilamino)acético (2,0 g, 12,1 mmol) en ácido fórmico (91 ml) se añadió formaldehído (6,94 ml, 93,2 mmol). Después de cinco horas a 70 °C, la mezcla de reacción se concentró a presión reducida hasta 20 ml y precipitó un sólido blanco. Después de filtrar, las aguas madres se recogieron y se concentró además a presión reducida proporcionando el producto bruto. La purificación por HPLC preparativa de fase inversa (Xterra 30 X 100 mm, detección a 220 nm, Caudal 35 ml/min, 0 a 35% de B durante 8 min; A = 90% de agua, 10 % de metanol, 0,1% de TFA, B = 10% de agua, 90 % de metanol, 0,1% de TFA) proporcionó el compuesto del epígrafe ácido 2-(bencil(metil)-amino)acético como su sal TFA (723 mg, 33%) como una cera incolora. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 2,75 (s, 3H) 4,04 (s, 2H) 4,34 (s, 2H) 7,29 - 7,68 (m, 5H). CLEM: Análisis calculado para: $C_{10}H_{13}NO_2$ 179,09; Encontrado: 180,20 $(M+H)^+$.

Cap-50

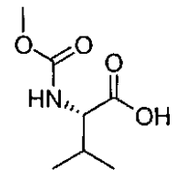


Cap-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico(0,50 g,

3,81 mmol) en agua (30 ml) se añadió K_2CO_3 (2,63 g, 19,1 mmol) y cloruro de bencilo (1,32 g, 11,4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se extrajo con acetato de etilo (30 ml x 2) y la fase acuosa se concentró a presión reducida proporcionando el producto bruto que se purificó por HPLC preparativa de fase inversa (Xterra 30 x 100mm, detección a 220 nm, Caudal 40 ml/min, 20 a 80% de B durante 6 min; A = 90% de agua, 10 % de metanol, 0,1% de TFA, B = 10% de agua, 90 % de metanol, 0,1% de TFA) proporcionando ácido 2-(bencil(metil)amino)-3-metilbutanoico, sal TFA (126 mg, 19%) como una cera incolora. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 0,98 (d, 3H) 1,07 (d, 3H) 2,33 - 2,48 (m, 1H) 2,54 - 2,78 (m, 3H) 3,69 (s, 1H) 4,24 (s, 2H) 7,29 - 7,65 (m, 5H). CLEM: Análisis calculado para: $C_{13}H_{19}NO_2$ 221,14; Encontrado: 222,28 $(M+H)^+$.

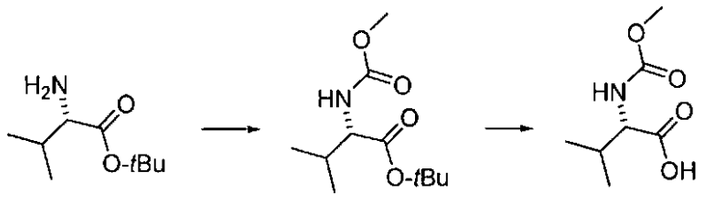
Cap-51



Se añadió Na_2CO_3 (1,83g, 17,2 mmol) a una solución de NaOH (33 ml de 1M/H_2O, 33 mmol) de L-valina (3,9 g, 33,29 mmol) y la solución resultante se enfrió con baño de hielo-agua. Se añadió gota a gota durante 15 minutos cloroformiato de metilo (2,8 ml, 36,1 mmol), se retiró el baño de enfriamiento y la mezcla de reacción se agitó a temperatura ambiente durante 3,25 horas. La mezcla de reacción se lavó con éter (50 ml, 3x), y la fase acuosa se enfrió con un baño de hielo-agua y se acidificó con HCl concentrado hasta un pH de 1-2, y se extrajo con CH_2Cl_2 (50 ml, 3x). La fase orgánica se secó ($MgSO_4$) y se

evaporó a vacío proporcionando *Cap*-51 como un sólido blanco (6 g). RMN de ^{1}H para el rotámero dominante (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 12,54 (s, 1H), 7,33 (d, J = 8,6, 1H), 3,84 (dd, J = 8,4, 6,0, 1H), 3,54 (s, 3H), 2,03 (m, 1H), 0,87 (m, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176,0923; encontrado 176,0922.

Cap 51 (ruta alternativa)



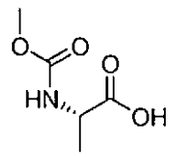
Se añadió DIEA (137,5 ml, 0,766 mol) a una suspensión de clorhidrato de 2-amino-3-metilbutanoato de (*S*)-*terc*-butilo (75,0 g, 0,357 mol) en THF (900 ml), y la mezcla se enfrió hasta 0 °C (baño de hielo/agua). Se añadió gota a gota durante 45 minutos cloroformiato de metilo (29,0 ml, 0,375 mol), se retiró el baño de enfriamiento y la mezcla heterogénea se agitó a temperatura ambiente durante 3 h. El disolvente se eliminó a presión reducida y el residuo se repartió entre EtOAc y agua (1 litro de cada uno). La fase orgánica se lavó con H_2O (1 l) y salmuera (1 l), se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El material bruto se hizo pasar a través de un lecho corto de gel de sílice (1 kg), eluyendo con hexanos (4 l) y EtOAc:hexanos 15:85 (4 l) proporcionando 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-terc-butilo como un aceite transparente (82,0 g, 99% de rendimiento). RMN de ^{1}H (500 MHz, DMSO-d_6, δ = 2,5 ppm) 7,34 (d, J = 8,6, 1 H), 3,77 (dd, J = 8,6, 6,1, 1 H), 3,53 (s, 3 H), 1,94 - 2,05 (m, 1 H), 1,39 (s, 9 H), 0,83 - 0,92 (m, 6 H). RMN de ^{13}C (126 MHz, DMSO-d_6, δ = 39,2 ppm) 170,92, 156,84, 80,38, 60,00, 51,34,

29,76, 27,62, 18,92, 17,95. CL/EM: $[M+Na]^+$ 254,17.

Se añadieron ácido trifluoroacético (343 ml, 4,62 mol) y Et_3SiH (142 ml, 0,887 mol) secuencialmente a una solución de 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-terc-butilo (82,0 g, 0,355 mol) en CH_2Cl_2 (675 ml), y la mezcla se agitó a temperatura ambiente durante 4 h. El componente volátil se eliminó a presión reducida y el aceite resultante se trituró con éter de petróleo (600 ml) proporcionando un sólido blanco, que se filtró y se lavó con hexanos (500 ml) y éter de petróleo (500 ml). La recristalización en EtOAc/éter de petróleo proporcionó *Cap-51* como cristales a modo de escamas blancos (54,8 g, 88 % de rendimiento). PF = 108,5-109,5 °C. RMN de ^1H (500 MHz, DMSO-d_6, δ = 2,5 ppm) 12,52 (s, 1 H), 7,31 (d, J = 8,6, 1 H), 3,83 (dd, J = 8,6, 6,1, 1 H), 3,53 (s, 3 H), 1,94 - 2,07 (m, 1 H), 0,86 (dd, J = 8,9, 7,0, 6 H). RMN de ^{13}C (126 MHz, DMSO-d_6, δ = 39,2 ppm) 173,30, 156,94, 59,48, 51,37, 29,52, 19,15, 17,98. CL/EM: $[M+H]^+$ = 176,11. Análisis calculado para $C_7H_{13}NO_4$: C, 47,99; H, 7,48; N, 7,99. Encontrado: C, 48,17; H, 7,55; N, 7,99. Rotación óptica: $[\alpha]_D$ = -4,16 (12,02 mg/ml; MeOH). Pureza óptica: >99,5 % ee. Nota: la valoración de la pureza óptica se realizó en el derivado éster metílico de *Cap-51*, que se preparó según un protocolo de esterificación normalizado en $TMSCHN_2$ (benceno/MeOH). Condiciones del análisis de HPLC: columna, ChiralPak AD-H (4,6 x 250mm, 5µm); disolvente, heptano al 95% / IPA al 5% (isocrático); caudal, 1 ml/min; temperatura, 35 °C; UV controlado a 205 nm.

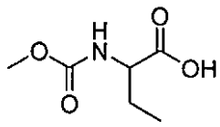
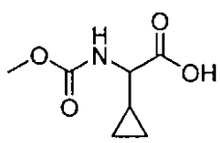
[Nota: Cap 51 también se podía adquirir de Flamm.]

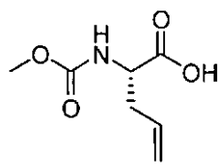
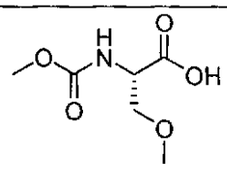
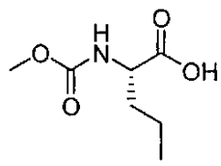
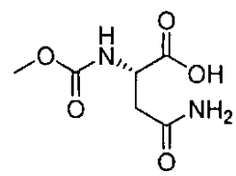
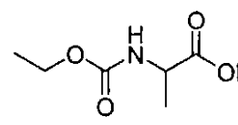
Cap-52 (Igual que Cap-12)

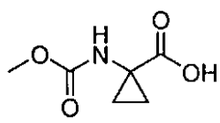
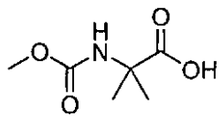
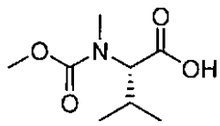
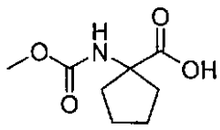
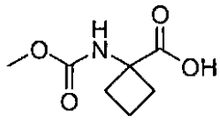


Cap-52 se sintetizó a partir de L-alanina de acuerdo con el procedimiento descrito para la síntesis de *Cap*-51. Con fines caracterizadores, se purificó una porción del material bruto por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando *Cap*-52 como un aceite incoloro viscoso. RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 12,49 (s ancho, 1H), 7,43 (d, *J* = 7,3, 0,88H), 7,09 (s ancho aparente, 0,12H), 3,97 (m, 1H), 3,53 (s, 3H), 1,25 (d, *J* = 7,3, 3H).

Cap-53 a -64 se prepararon a partir de materiales partida apropiados de acuerdo con el procedimiento descrito para la síntesis de *Cap*-51, con las modificaciones indicadas si las hubiera.

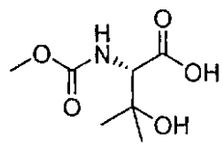
Cap	Estructura	Datos
Cap-53a: (R) *Cap-53b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,51 (s ancho, 1H), 7,4 (d, *J* = 7,9, 0,9H), 7,06 (s ap., 0,1H), 3,86-3,82 (m, 1H), 3,53 (s, 3H), 1,75-1,67 (m, 1H), 1,62-1,54 (m, 1H), 0,88 (d, *J* = 7,3, 3H). T_R = 0,77 minutos (Cond. II); CL/EM: Anal. Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184,06; encontrado 184,07. EMAR Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184,0586; encontrado 184,0592.
Cap-54a: (R) *Cap-54b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,48 (s, 1H), 7,58 (d, *J* = 7,6, 0,9H), 7,25 (s ap., 0,1H), 3,52 (s, 3H), 3,36-3,33 (m, 1H), 1,10-1,01 (m, 1H), 0,54-0,49 (m, 1H), 0,46-0,40 (m, 1H), 0,39-0,35 (m,

		1H), 0,31-0,21 (m, 1H). EMAR Calculado para $[M+H]^+$ $C_7H_{12}NO_4$: 174,0766; encontrado 174,0771
Cap-55		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,62 (s, 1H), 7,42 (d, *J* = 8,2, 0,9H), 7,07 (s ap., 0,1H), 5,80-5,72 (m, 1H), 5,10 (d, *J* = 17,1, 1H), 5,04 (d, *J* = 10,4, 1H), 4,01-3,96 (m, 1H), 3,53 (s, 3H), 2,47-2,42 (m, 1H), 2,35-2,29 (m, 1H).
Cap-56		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,75 (s, 1H), 7,38 (d, *J* = 8,3, 0,9H), 6,96 (s ap., 0,1H), 4,20-4,16 (m, 1H), 3,60-3,55 (m, 2H), 3,54 (s, 3H), 3,24 (s, 3H).
Cap-57		RMN de ^1H (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. II): T_R = 1,39 CL/EM: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176,09; encontrado 176,06.
Cap-58		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,63 (s ancho, 1H), 7,35 (s,1H), 7,31 (d, *J* = 8,2, 1H), 6,92 (s, 1H), 4,33-4,29 (m, 1H), 3,54 (s, 3H), 2,54(dd, *J* = 15,5, 5,4, 1H), 2,43 (dd, *J* = 15,6, 8,0, 1H). T_R = 0,16 min (Cond. II); CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}N_2O_5$: 191,07; encontrado 191,14.
Cap-59a: (R) *Cap-59b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,49 (s ancho, 1H), 7,40 (d, *J* = 7,3, 0,89H), 7,04 (s ancho, 0,11H), 4,00-3,95 (m, 3H), 1,24 (d, *J* = 7,3, 3H), 1,15 (t, *J* = 7,2, 3H). EMAR: Anal. Calculado para

		$[M+H]^+$ $C_6H_{12}NO_4$: 162,0766; encontrado 162,0771.
Cap-60		El material bruto se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando un aceite viscoso incoloro que cristalizó en un sólido blanco al exponerse a alto vacío. RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,38 (s ancho, 1H), 7,74 (s, 0,82H), 7,48 (s, 0,18H), 3,54/3,51 (dos s, 3H), 1,30 (m, 2H), 0,98 (m, 2H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{10}NO_4$: 160,0610; encontrado 160,0604.
Cap-61		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,27 (s ancho, 1H), 7,40 (s ancho, 1H), 3,50 (s, 3H), 1,32 (s, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162,0766; encontrado 162,0765.
Cap-62		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,74 (s ancho, 1H), 4,21 (d, *J* = 10,3, 0,6H), 4,05 (d, *J* = 10,0, 0,4H), 3,62/3,60 (dos singletes, 3H), 3,0 (s, 3H), 2,14-2,05 (m, 1H), 0,95 (d, *J* = 6,3, 3H), 0,81 (d, *J* = 6,6, 3H). CL/EM: Anal. Calculado para $[M-H]^-$ $C_8H_{14}NO_4$: 188,09; encontrado 188,05.
Cap-63		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para el procedimiento general.] RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): 12,21 (s ancho, 1H), 7,42 (s ancho, 1H), 3,50 (s, 3H), 2,02-1,85 (m, 4H), 1,66-1,58 (m, 4H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{14}NO_4$: 188,09; encontrado 188,19.
Cap-64		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para el procedimiento general.] RMN de ^1H (DMSO-

		d_6, δ = 2,5 ppm, 400 MHz): 12,35 (s ancho, 1H), 7,77 (s, 0,82H), 7,56/7,52 (s ancho solapante, 0,18H), 3,50 (s, 3H), 2,47-2,40 (m, 2H), 2,14-2,07 (m, 2H), 1,93-1,82 (m, 2H).

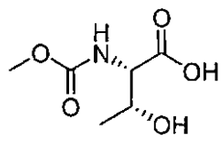
Cap-65



Se añadió cloroformiato de metilo (0,65 ml, 8,39 mmol) gota a gota durante 5 minutos a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0,449 g, 4,23 mmol), NaOH (8,2 ml de 1M/H_2O, 8,2 mmol) y ácido (*S*)-2-amino-3-hidroxi-3-metilbutanoico (1,04 g, 7,81 mmol). La mezcla de reacción se agitó durante 45 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 3,75 hr. La mezcla de reacción se lavó con CH_2Cl_2, y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta una región de pH de 1-2. El componente volátil se eliminó a vacío y el residuo se suspendió en una mezcla 2:1 de MeOH/CH_2Cl_2 (15 ml) y se filtró, y el filtrado se sometió a evaporación rotativa proporcionando *Cap*-65 como una espuma semiviscosa blanca (1,236 g). RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 6,94 (d, *J* = 8,5, 0,9 H), 6,53 (s ancho, 0,1H), 3,89 (d, *J* = 8,8, 1H), 2,94 (s, 3H), 1,15 (s, 3H), 1,13 (s, 3H).

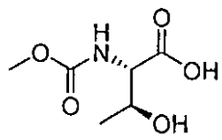
Cap-66 y -67 se prepararon a partir de materiales de partida disponibles comercialmente empleando el procedimiento descrito para la síntesis de *Cap*-65.

Cap-66



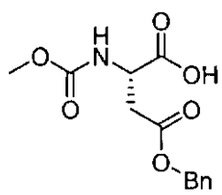
RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,58 (s ancho, 1H), 7,07 (d, *J* = 8,3, 0,13H), 6,81 (d, *J* = 8,8, 0,67H), 4,10-4,02 (m, 1,15H), 3,91 (dd, *J* = 9,1, 3,5, 0,85H), 3,56 (s, 3H), 1,09 (d, *J* = 6,2, 3H). [Nota: solo se indican las señales dominantes de NH]

Cap-67



RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): 12,51 (s ancho, 1H), 7,25 (d, *J* = 8,4, 0,75H), 7,12 (d ancho, *J* = 0,4, 0,05H), 6,86 (s ancho, 0,08H), 3,95-3,85 (m, 2H), 3,54 (s, 3H), 1,08 (d, *J* = 6,3, 3H). [Nota: solo se indican las señales dominantes de NH]

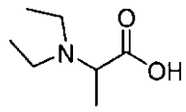
Cap-68



Se añadió cloroformiato de metilo (0,38 ml, 4,9 mmol) gota a gota a una mezcla de NaOH 1N (ac) (9,0 ml, 9,0 mmol), $NaHCO_3$ 1M (ac) (9,0 ml, 9,0 mol), éster β-bencílico del ácido L-aspártico (1,0 g, 4,5 mmol) y dioxano (9 ml). La mezcla de reacción se agitó en condiciones ambientales durante 3 hr, y luego

se lavó con acetato de etilo (50 ml, 3x). La fase acuosa se acidificó con HCl 12N hasta un pH ~ 1-2, y se extrajo con acetato de etilo (3 x 50 ml). Las fases orgánicas reunidas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron a vacío proporcionando *Cap*-68 como un aceite amarillo claro (1,37g; la masa es superior al rendimiento teórico, y el producto se usó sin purificación adicional). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,88 (s ancho, 1H), 7,55 (d, *J* = 8,5, 1H), 7,40-7,32 (m, 5H), 5,13 (d, *J* = 12,8, 1H), 5,10 (d, *J* = 12,9, 1H), 4,42-4,38 (m, 1H), 3,55 (s, 3H), 2,87 (dd, *J* = 16,2, 5,5, 1H), 2,71 (dd, *J* =16,2, 8,3, 1H). CL (Cond. II): T_R = 1,90 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282,10; encontrado 282,12.

Cap-69a y -69b

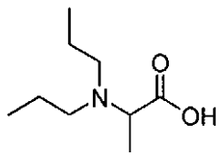
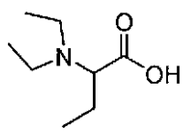
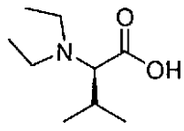
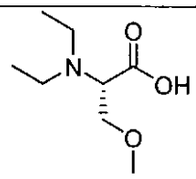


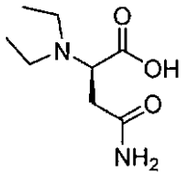
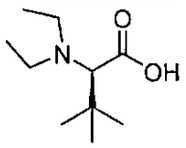
Cap-69a: enantiómero (R)
Cap-69b: enantiómero (S)

Se añadió $NaCNBH_3$ (2,416 g, 36,5 mmol) en lotes a una solución acuosa enfriada (~15 °C) (17 ml)/MeOH (10 ml) de alanina (1,338 g, 15,0 mmol). Unos pocos minutos después se añadió gota a gota durante 4 minutos acetaldehído (4,0 ml, 71,3 mmol), se retiró entonces el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 6 hr. Se añadió más acetaldehído (4,0 ml) y la reacción se agitó durante 2 hr. Se añadió HCl concentrado lentamente a la mezcla de reacción hasta que el pH alcanzó ~ 1,5, y la mezcla resultante se calentó durante 1 hora a 40°C. La mayoría del componente volátil se eliminó a vacío y el residuo se purificó con una resina de intercambio iónico Dowex ® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado mezclando 18 ml de

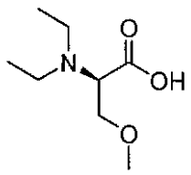
NH_4OH y 282 ml de agua) proporcionando *Cap*-69 (2,0 g) como un sólido higroscópico blando blanquecino. RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 3,44 (q, *J* = 7,1, 1H), 2,99-2,90 (m, 2H), 2,89-2,80 (m, 2H), 1,23 (d, *J* = 7,1, 3H), 1,13 (t, *J* = 7,3, 6H).

Cap-70 a *-74x* se prepararon de acuerdo con el procedimiento descrito para la síntesis de *Cap*-69 empleando materiales de partida apropiados.

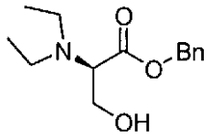
Cap-70a: (R) *Cap-70b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 3,42 (q, *J* = 7,1, 1H), 2,68-2,60 (m, 4H), 1,53-1,44 (m, 4H), 1,19 (d, *J* = 7,3, 3H), 0,85 (t, *J* = 7,5, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174,15; encontrado 174,13.
Cap-71a: (R) *Cap-71b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 3,18-3,14 (m, 1H), 2,84-2,77 (m, 2H), 2,76-2,68 (m, 2H), 1,69-1,54 (m, 2H), 1,05 (t, *J* = 7,2, 6H), 0,91 (t, *J* = 7,3, 3H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{18}NO_2$: 160,13; encontrado 160,06.
Cap-72		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 2,77-2,66 (m, 3H), 2,39-2,31 (m, 2H), 1,94-1,85 (m, 1H), 0,98 (t, *J* = 7,1, 6H), 0,91 (d, *J* = 6,5, 3H), 0,85 (d, *J* = 6,5, 3H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174,15; encontrado 174,15.
Cap-73		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 9,5 (s ancho, 1H), 3,77 (dd, *J* = 10,8, 4,1,1H), 3,69-3,61 (m, 2H), 3,26 (s, 3H), 2,99-2,88 (m, 4H), 1,13 (t, *J* = 7,2, 6H).

Cap-74		RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 7,54 (s, 1H), 6,89 (s, 1H), 3,81 (t, *J* = 6,6, k,1H), 2,82-2,71 (m, 4H), 2,63 (dd, *J* = 15,6, 7,0, 1H), 2,36 (dd, *J* = 15,4, 6,3, 1H), 1,09 (t, *J* = 7,2, 6H). T_R = 0,125 minutos (Cond. II); CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189,12; encontrado 189,13.
Cap-74x		CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{22}NO_2$: 188,17; encontrado 188,21

Cap-75



Cap-75, etapa a



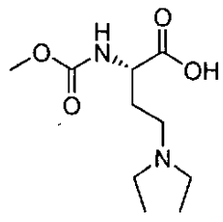
Se añadió $NaBH_3CN$ (1,6 g, 25,5 mmol) a una solución enfriada (baño de hielo/agua) en agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2,0 g, 8,6 mmol). Se añadió acetaldehído (1,5 ml, 12,5 mmol) gota a gota durante 5 min, se retiró el baño de enfriamiento, y la mezcla de reacción se agitó en condiciones ambientales durante 2 hr. La reacción se inactivó cuidadosamente con HCl 12N y se concentró a vacío. El residuo se disolvió en agua y se purificó con una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de

2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo como un aceite incoloro viscoso (1,9 g). RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 9,73 (s ancho, 1H), 7,52-7,36 (m, 5H), 5,32 (d, *J* = 12,2, 1H), 5,27 (d, *J* = 12,5, 1H), 4,54-4,32 (m, 1H), 4,05-3,97 (m, 2H), 3,43-3,21 (m, 4H), 1,23 (t, *J* = 7,2, 6H). CL/EM (Cond. II): T_R = 1,38 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{22}NO_3$: 252,16; encontrado 252,19.

Cap-75

Se añadió NaH (0,0727 g, 1,82 mmol, 60%) a una solución enfriada (hielo-agua) en THF (3,0 ml) de la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo (0,3019 g, 0,8264 mmol) preparada antes, y la mezcla se agitó durante 15 min. Se añadió yoduro de metilo (56 µl, 0,90 mmol) y se continuó agitando durante 18 hr dejando que el baño se descongelara hasta condiciones ambiente. La reacción se inactivó con agua y se cargó en un cartucho MCX preacondicionado con MeOH (6 g) y se lavó con metanol seguido por elución del compuesto con NH_3 2N/Metanol. La eliminación del componente volátil a vacío proporcionó *Cap*-75, contaminado con ácido (R)-2-(dietilamino)-3-hidroxipropanoico, como un semisólido amarillo (100 mg). El producto se usó como tal sin purificación adicional.

Cap-76

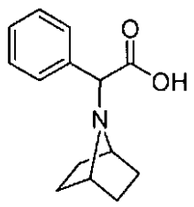


Se añadió $NaCNBH_3$ (1,60 g, 24,2 mmol) en cargas a una solución enfriada (~15 °C) en agua/MeOH (12 ml cada uno) de ácido (*S*)-4-amino-2-(terc-butoxicarbonilamino) butanoico (2,17 g, 9,94 mmol). Unos pocos minutos después se añadió acetaldehído (2,7 ml, 48,1 mmol) gota a gota durante 2 min, se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 3,5 hr. Se añadió más acetaldehído (2,7 ml, 48,1 mmol) y la reacción se agitó durante 20,5 hr. Se eliminó a vacío la mayoría del componente MeOH, y la mezcla restante se trató con HCl concentrado hasta que su pH llegó a ~ 1,0 y luego se calentó durante 2 horas a 40 °C. El componente volátil se eliminó a vacío, y el residuo se trató con HCl 4 M/dioxano (20 ml) y se agitó en condiciones ambientales durante 7,5 hr. El componente volátil se eliminó a vacío y el residuo se purificó con resina de intercambio iónico Dowex ® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado a partir de 18 ml de NH_4OH y 282 ml de agua) proporcionando el intermedio ácido (S)-2-amino-4-(dietilamino)butanoico como un sólido blanquecino (1,73 g).

Se añadió cloroformiato de metilo (0,36 ml, 4,65 mmol) gota a gota durante 11 min a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0,243 g, 2,29 mmol), NaOH (4,6 ml de 1M/H_2O, 4,6 mmol) y el producto anterior (802,4 mg). La mezcla de reacción se agitó durante 55 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 5,25 hr. La mezcla de reacción se diluyó con un volumen igual de agua y se lavó con CH_2Cl_2 (30 ml, 2x), y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta un pH en torno a 2. El componente volátil se eliminó a vacío y el material bruto se desbasificó con resina MCX (6,0g; la columna se lavó con

agua, y la muestra se eluyó con NH_3 2,0 M/MeOH) proporcionando *Cap*-76 impuro como un sólido blanquecino (704 mg). RMN de ^1H (MeOH-d_4, 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). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233,15; encontrado 233,24.

Cap-77a y -77b

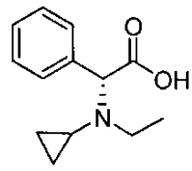


Cap-77a: enantiómero 1
Cap-77b: enantiómero 2

La síntesis de *Cap*-77 se llevó a cabo de acuerdo con el procedimiento descrito para *Cap*-7 usando 7-azabiciclo[2.2.1]heptano para la etapa de desplazamiento SN_2, y efectuando la separación enantiomérica del intermedio 2-(7-azabiciclo[2.2.1]heptan-7-il)-2-fenilacetato de bencilo usando las siguientes condiciones: el intermedio (303,7 mg) se disolvió en etanol, y la solución resultante se inyectó en una columna HPLC quiral (columna Chiracel AD-H, 30 x 250 mm, 5 um) eluyendo con 90% de CO_2-10% de EtOH a 70 ml/min, y una temperatura de 35 °C proporcionando 124,5 mg de enantiómero-1 y 133,8 mg de enantiómero-2. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de *Cap*-7 proporcionando *Cap*-77: RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 7,55 (m, 2H), 7,38-7,30 (m, 3H), 4,16 (s, 1H), 3,54 (s ancho aparente, 2H), 2,08-1,88 (m, 4 H), 1,57-1,46 (m, 4H). CL (Cond. I): T_R = 0,67 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232,13; encontrado 232,18. EMAR: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$:

232,1338; encontrado 232,1340.

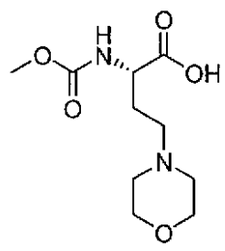
Cap-78



Se añadió $NaCNBH_3$ (0,5828 g, 9,27 mmol) a una mezcla de la sal HCl de ácido (*R*)-2-(etilamino)-2-fenilacético (un intermedio en la síntesis de *Cap*-3; 0,9923 mg, 4,60 mmol) y (1-etoxiciclopropoxi)trimetilsilano (1,640 g, 9,40 mmol) en MeOH (10 ml), y se calentó la mezcla semiheterogénea a 50 °C con un baño de aceite durante 20 hr. Se añadieron más (1-etoxiciclopropoxi)trimetilsilano (150 mg, 0,86 mmol) y $NaCNBH_3$ (52 mg, 0,827 mmol) y la mezcla de reacción se calentó otras 3,5 hr. Se dejó enfriar hasta temperatura ambiente y se acidificó ~ pH entorno a 2 con HCl concentrado, y la mezcla se filtró y el filtrado se evaporó en un rotavapor. El material bruto resultante se suspendió en *i*-PrOH (6 ml) y se calentó para efectuar la disolución y la parte no disuelta se separó por filtración y el filtrado se concentró a vacío. Se purificó aproximadamente 1/3 del material bruto resultante con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando la sal TFA de *Cap*-78 como un aceite incoloro viscoso (353 mg). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz; después de intercambio de D_2O): δ 7,56-7,49 (m, 5H), 5,35 (S, 1H), 3,35 (m, 1H), 3,06 (s ancho aparente, 1H), 2,66 (m, 1H), 1,26 (t, *J* = 7,3, 3H), 0,92 (m, 1H), 0,83-0,44 (m, 3H). CL (Cond. I): T_R = 0,64 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220,13; encontrado 220,21. EMAR: Anal. Calculado

para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220,1338; encontrado 220,1343.

Cap-79



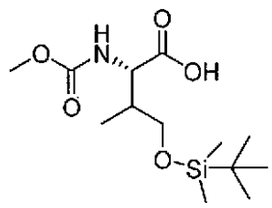
Se burbujeó ozono a través de una solución enfriada (-78 °C) en CH_2Cl_2 (5,0 ml) de *Cap*-55 (369 mg, 2,13 mmol) durante aproximadamente 50 min hasta que la mezcla de reacción alcanzó un tinte de color azul. Se añadió Me_2S (10 gotas de pipeta) y la mezcla de reacción se agitó durante 35 min. Se reemplazó el baño de -78 °C con un baño a -10 °C y se continuó agitando durante otros 30 min, y luego se eliminó el componente volátil a vacío proporcionando un aceite viscoso incoloro.

Se añadió $NaBH_3CN$ (149 mg, 2,25 mmol) a una solución en MeOH (5,0 ml) del material bruto anterior y morfolina (500 µl, 5,72 mmol) y la mezcla se agitó en condiciones ambientales durante 4 hr. Se enfrió hasta temperatura de hielo-agua y se trató con HCl concentrado para llevar el pH a ~2,0, y luego se agitó durante 2,5 hr. El componente volátil se eliminó a vacío, y el residuo se purificó con una combinación de resina MCX (lavado con MeOH; elución con NH_3 2,0 N/MeOH) y una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando *Cap*-79 que contenía una cantidad desconocida de morfolina.

Con el fin de consumir la morfolina contaminante, se disolvió el material anterior en CH_2Cl_2 (1,5 ml) y se trató con Et_3N (0,27 ml, 1,94 mmol) seguido por anhídrido acético (0,10 ml, 1,06 mmol) y se agitó en condiciones ambientales

durante 18 hr. Se añadieron THF (1,0 ml) y H_2O (0,5 ml) y se continuó agitando durante 1,5 hr. El componente volátil se eliminó a vacío, y el residuo resultante se hizo pasar a través de resina MCX (lavado con MeOH; elución con NH_3 2,0 N/MeOH) proporcionando *Cap*-79 impuro como un aceite viscoso marrón, que se usó para la etapa siguiente sin purificación adicional.

Cap-80a y -80b



Cap-80a: diastereómero S/S
Cap-80b: diastereómero S/R

Se añadió $SOCl_2$ (6,60 ml, 90,5 mmol) gota a gota durante 15 min a una mezcla enfriada (hielo-agua) de ácido (S)-3-amino-4-(benciloxi)-4-oxobutanoico (10,04g, 44,98 mmol) y MeOH (300 ml), se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 29 hr. Se eliminó la mayor parte del componente volátil a vacío y el residuo se repartió cuidadosamente entre EtOAc (150 ml) y solución saturada de $NaHCO_3$. La fase acuosa se extrajo con EtOAc (150 ml, 2x), y la fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 4-metil-2-aminosuccinato de (S)-1-bencilo como un aceite incoloro (9,706g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 7,40-7,32 (m, 5H), 5,11 (s, 2H), 3,72 (t aparente, J = 6,6, 1H), 3,55 (s, 3H), 2,68 (dd, J = 15,9, 6,3, 1H), 2,58 (dd, J = 15,9, 6,8, 1H), 1,96 (s, 2H). CL (Cond. I): T_R = 0,90 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_4$: 238,11; encontrado 238,22.

Se añadió $Pb(NO_3)_2$ (6,06 g, 18,3 mmol) durante 1 minuto a una solución

en CH_2Cl_2 (80 ml) de 4-metil-2-aminosuccinato de (S)-1-bencilo (4,50 g, 19,0 mmol), 9-bromo-9-fenil-9*H*-fluoreno (6,44 g, 20,0 mmol) y Et_3N (3,0 ml, 21,5 mmol) y la mezcla heterogénea se agitó en condiciones ambientales durante 48 hr. La mezcla se filtró y el filtrado se trató con $MgSO_4$ y se filtró de nuevo y el filtrado final se concentró. El material bruto resultante se sometió a una purificación en Biotage (350 g gel de sílice, elución con CH_2Cl_2) proporcionando 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo como aceite incoloro muy viscoso (7,93 g). RMN de ^1H (DMSO-d_6, 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 solapado con disolvente). CL (Cond. I): T_R = 2,16 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{28}NO_4$: 478,20; encontrado 478,19.

Se añadió LiHMDS (9,2 ml de 1,0 M/THF, 9,2 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) THF (50 ml) de 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo (3,907 g, 8,18 mmol) y se agitó durante ~1 hr. Se añadió MeI (0,57 ml, 9,2 mmol) gota a gota durante 8 min a la mezcla y se continuó agitando durante 16,5 hr dejando que el baño de enfriamiento se descongelara hasta temperatura ambiente. Después de inactivar con solución saturada de NH_4Cl (5 ml), se eliminó a vacío la mayor parte del componente orgánico y el residuo se repartió entre CH_2Cl_2 (100 ml) y agua (40 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se purificó con un Biotage (350 g gel de sílice; 25% de EtOAc/hexanos) proporcionando 3,65 g de una mezcla de diastereoisómeros 2S/3S y 2S/3R de 4-metil 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de 1-bencilo en una relación ~1,0:0,65 (RMN de ^1H). La

estereoquímica del isómero dominante no se determinó en este paso y la mezcla se sometió a la etapa siguiente sin separación. Datos parciales de RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): Diastereómero mayoritario, δ 4,39 (d, J = 12,3, 1H de CH_2), 3,33 (s, 3H, solapado con señal de H_2O), 3,50 (d, J = 10,9, NH), 1,13 (d, J = 7,1, 3H); Diastereómero minoritario, 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. I): T_R = 2,19 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{32}H_{30}NO_4$: 492,22; encontrado 492,15.

Se añadió hidruro de diisobutilaluminio (20,57 ml de 1,0 M en hexanos, 20,57 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) en THF (120 ml) de 4-metil-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de (2S)-1-bencilo (3,37 g, 6,86 mmol) preparado antes y se agitó a -78 °C durante 20 hr. La mezcla de reacción se separó del baño de enfriamiento y se vertió rápidamente en H_3PO_4 ~1M/H_2O (250 ml) con agitación y la mezcla se extrajo con éter (100 ml, 2x). La fase orgánica reunida se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. Se preparó una malla de gel de sílice del material bruto y se sometió a cromatografía (25% de EtOAc/hexanos; elución por gravedad) proporcionando 1,1 g de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con alcohol bencílico, como un aceite incoloro viscoso y 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo que contenía el estereoisómero (2S,3R) como una impureza. La muestra anterior se volvió a someter a las mismas condiciones de purificación de cromatografía en columna proporcionando 750 mg de material purificado como una espuma blanca. [Nota: el isómero (2S, 3S) eluye antes que el isómero (2S,3R) en las condiciones

anteriores]. Isómero (2S, 3S): RMN de ^{1}H (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 (t aparente, *J* = 5,2, OH), 3,22 (d, *J* = 10,1, NH), 3,17 (m, 1H), 3,08 (m, 1H), ~2,5 (m, 1H, solapado con la señal del disolvente), 1,58 (m, 1H), 0,88 (d, *J* = 6,8, 3H). CL (Cond. I): T_R = 2,00 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464,45; encontrado 464,22. Isómero (2S, 3R): RMN de ^{1}H (DMSO-d_6, 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 (t aparente, *J* = 4,9, 1H), 4,32 (d, *J* = 12,1, 1H), 3,59-3,53 (m, 2H), 3,23 (m, 1H), 2,44 (dd, *J* = 9,0, 8,3, 1H), 1,70 (m, 1H), 0,57 (d, *J* = 6,8, 3H). CL (Cond. I): T_R = 1,92 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464,45; encontrado 464,52.

Las asignaciones estereoquímicas relativas de los productos de reducción con DIBAL se hicieron basándose en estudios NOE llevados a cabo en derivados lactona preparados a partir de cada isómero empleando el siguiente protocolo: Se añadió LiHMDS (50 µl de 1,0 M/THF, 0,05 mmol) a una solución enfriada (hielo-agua) en THF (2,0 ml) de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (62,7 mg, 0,135 mmol), y la mezcla de reacción se agitó a temperatura similar durante ~2 hr. El componente volátil se eliminó a vacío y el residuo se repartió entre CH_2Cl_2 (30 ml), agua (20 ml) y solución acuosa saturada de NH_4Cl (1 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se sometió a una purificación Biotage (40 g gel de sílice; 10-15% de EtOAc/hexanos) proporcionando (3S,4S)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona como una película incolora de sólido (28,1 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de

(2S,3R)-bencilo de forma similar a (3S,4R)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona. Isómero (3S,4S)-lactona: RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 400 MHz), 7,83 (d, *J* = 7,5, 2H), 7,46-7,17 (m, 11H), 4,14 (t aparente, *J* = 8,3, 1H), 3,60 (d, *J* = 5,8, NH), 3,45 (t aparente, *J* = 9,2, 1H), ~2,47 (m, 1H, parcialmente solapado con la señal del disolvente), 2,16 (m, 1H), 0,27 (d, *J* = 6,6, 3H). CL (Cond. I): T_R = 1,98 min; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378,15; encontrado 378,42. Isómero (3S,4R)-lactona: RMN de ^{1}H (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. I): T_R = 2,03 min; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378,15; encontrado 378,49.

Se añadieron TBDEM-Cl (48 mg, 0,312 mmol) seguido por imidazol (28,8 mg, 0,423 mmol) a una solución en CH_2Cl_2 (3 ml) de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (119,5 mg, 0,258 mmol), y la mezcla se agitó en condiciones ambientales durante 14,25 hr. La mezcla de reacción se diluyó entonces con CH_2Cl_2 (30 ml) y se lavó con agua (15 ml), y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó con una Biotage (40 g gel de sílice; 5% de EtOAc/hexanos) proporcionando 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con impurezas con base de TBDMS, como un aceite incoloro viscoso (124,4 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo. Isómero (2S,3S)-silil éter: RMN de ^{1}H

(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 ejecución de prolongó hasta 4 min): T_R = 3,26 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578,31; encontrado 578,40. Isómero (2S,3R)-silil éter: RMN de ^1H (DMSO-d_6, 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).

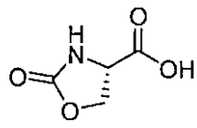
Se unió un globo de hidrógeno a una mezcla de 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (836 mg, 1,447 mmol) y Pd al 10%/C (213 mg) en EtOAc (16 ml) y la mezcla se agitó a temperatura ambiente durante ~ 21 hr, recargándose el globo con H_2 cuando fue necesario. La mezcla de reacción se diluyó con CH_2Cl_2 y se filtró a través de un lecho de tierra de diatomeas (Celite-545®), y se lavó el lecho con EtOAc (200 ml), EtOAc/MeOH (mezcla 1:1, 200 ml) y MeOH (750 ml). La fase orgánica combinada se concentró y se preparó una malla de gel de sílice a partir del material bruto resultante y se sometió a una cromatografía ultrarrápida (mezcla 8:2:1 de EtOAc/i-PrOH/H_2O) proporcionando ácido (2S,3S)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico como un sólido apelusado blanco (325 mg). Se elaboró 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a ácido (2S,3R)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico. (Isómero

2S,3S)-amino ácido: RMN de ^1H (Metanol-d_4, 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). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248,17; encontrado 248,44. Isómero (2S,3R)-amino ácido: RMN de ^1H (Metanol-d_4, 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. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248,17; encontrado 248,44.

Se añadieron agua (1 ml) y NaOH (0,18 ml de 1,0 M/H_2O, 0,18 mmol) a una mezcla de ácido (2S,3S)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico (41,9 mg, 0,169 mmol) y Na_2CO_3 (11,9 mg, 0,112 mmol), y se sometió a ultrasonidos durante aproximadamente 1 minuto para efectuar la disolución de los reaccionantes. La mezcla se enfrió entonces con un baño de hielo-agua, se añadió cloroformiato de metilo (0,02 ml, 0,259 mmol) se durante 30 s y se continuó con agitación vigorosa a temperatura similar durante 40 minutos y luego a temperatura ambiente durante 2,7 hr. La mezcla de reacción se diluyó con agua (5 ml), se enfrió con baño de hielo-agua y se trató gota a gota con solución acuosa de HCl 1,0 N HCl (~0,23 ml). La mezcla se diluyó adicionalmente con agua (10 ml) y se extrajo con CH_2Cl_2 (15 ml, 2x). La fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando *Cap*-80a como un sólido blanquecino. Se elaboró ácido (2S,3R)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico de forma similar a *Cap*-80b. *Cap*-80a: RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz), 12,57 (s ancho, 1H), 7,64 (d, *J* = 8,3, 0,3H), 7,19 (d, *J* = 8,8, 0,7H), 4,44 (dd, *J* = 8,1, 4,6, 0,3H), 4,23 (dd, *J* = 8,7, 4,4, 0,7H), 3,56/3,53 (dos singletes, 3H), 3,48-3,40 (m,

2H), 2,22-2,10 (m, 1H), 0,85 (s, 9H), ~0,84 (d, 0,9H, solapado con la señal de t-Bu), 0,79 (d, *J* = 7, 2,1H), 0,02/0,01/0,00 (tres singletes solapados, 6H). CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328,16; encontrado 328,46. *Cap*-80b: RMN de ^1H ($CDCl_3$, δ = 7,24 ppm, 400 MHz), 6,00 (d ancho, *J* = 6,8, 1H), 4,36 (dd, *J* = 7,1, 3,1, 1H), 3,87 (dd, *J* = 10,5, 3,0, 1H), 3,67 (s, 3H), 3,58 (dd, *J* = 10,6, 4,8, 1H), 2,35 (m, 1H), 1,03 (d, *J* = 7,1, 3H), 0,90 (s, 9H), 0,08 (s, 6H). CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328,16; encontrado 328,53. Los productos brutos se utilizaron sin purificación adicional.

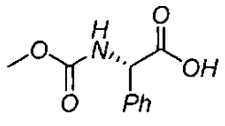
Cap-81



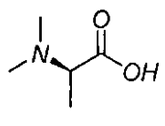
Se preparó de acuerdo con el protocolo descrito por Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 a Cap-85

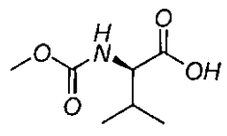
Cap-82 a *Cap*-85 se sintetizaron a partir de los materiales de partida apropiados de acuerdo con el procedimiento descrito para *Cap*-51 o *Cap*-13. Las muestras presentaron perfiles espectrales similares a los de sus enantiómeros (es decir, *Cap*-4, *Cap*-13, *Cap*-51 y *Cap*-52, respectivamente).



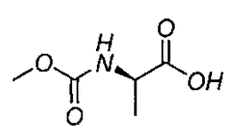
Cap-82



Cap-83

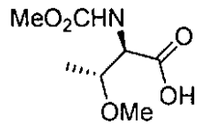


Cap-84



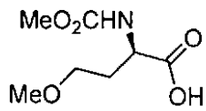
Cap-85

Cap-86



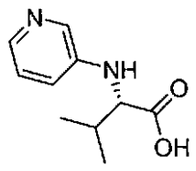
A una mezcla de O-metil-L-treonina (3,0 g, 22,55 mmol), NaOH (0,902 g, 22,55 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (1,74 ml, 22,55 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 12 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2x250 ml) y MeOH al 10% en CH_2Cl_2 (250 ml) y las fases orgánicas reunidas se concentraron a vacío proporcionando un aceite incoloro (4,18 g, 97%) que era de pureza suficiente para usar en las etapas siguientes. RMN de ^1H (400 MHz, $CDCl_3$) δ 4,19 (s, 1H), 3,92-3,97 (m, 1H), 3,66 (s, 3H), 1,17 (d, *J* = 7,7 Hz, 3H). CLEM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 190 $(M-H)^-$.

Cap-87



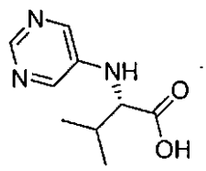
A una mezcla de L-homoserina (2,0 g, 9,79 mmol), Na_2CO_3 (2,08 g, 19,59 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (0,76 ml, 9,79 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 48 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2X250 ml) y las fases orgánicas reunidas se concentraron a vacío proporcionando un sólido incoloro (0,719 g, 28%) que era de pureza suficiente para usar en las etapas siguientes. RMN de ^1H (400 MHz, $CDCl_3$) δ 4,23 (dd, *J* = 4,5, 9,1 Hz, 1H), 3,66 (s, 3H), 3,43-3,49 (m, 2H), 2,08 – 2,14 (m, 1H), 1,82 – 1,89 (m, 1H). CLEM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 192 $(M+H)^+$.

Cap-88



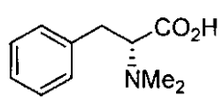
Se calentó una mezcla de L-valina (1,0 g, 8,54 mmol), 3-bromopiridina (1,8 ml, 18,7 mmol), K_2CO_3 (2,45 g, 17,7 mmol) y CuI (169 mg, 0,887 mmol) en DMSO (10 ml) a 100°C durante 12h. La mezcla de reacción se enfrió hasta ta, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio iónico (Strata). La suspensión se dejó reposar durante 20 min y se cargó en un lecho de resina de intercambio catiónico (Strata) (aproximadamente 25 g). Se lavó el lecho con H_2O (200 ml), MeOH (200 ml) y luego NH_3 (3M en MeOH, 2X200 ml). Se concentraron las fracciones apropiadas a vacío y el residuo (aproximadamente 1,1 g) se disolvió en H_2O, se congeló y liofilizó. El compuesto del epígrafe se obtuvo como una espuma (1,02 g, 62%). RMN de ^1H (400 MHz, DMSO-d_6) δ 8,00 (s ancho, 1H), 7,68 – 7,71 (m, 1H), 7,01 (s ancho, 1H), 6,88 (d, J = 7,5 Hz, 1H), 5,75 (s ancho, 1H), 3,54 (s, 1H), 2,04 – 2,06 (m, 1H), 0,95 (d, J = 6,0 Hz, 3H), 0,91 (d, J = 6,6 Hz, 3H). CLEM: Anal. Calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

Cap-89



Se calentó a 100ºC durante 12 horas una mezcla de L-valina (1,0 g, 8,54 mmol), 5-bromopirimidina (4,03 g, 17,0 mmol), K_2CO_3 (2,40 g, 17,4 mmol) y CuI (179 mg, 0,94 mmol) en DMSO (10 ml). La mezcla de reacción se enfrió hasta TA, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio catiónico (Strata). La suspensión se dejó reposar durante 20 minutos y se cargó en un lecho de resina de intercambio catiónico (Strata) (aproximadamente 25g). El lecho se lavó con H_2O (200 ml), MeOH (200 ml) y luego NH_3 (3M en MeOH, 2x200 ml). Se concentraron las fracciones apropiadas a vacío y se disolvió el residuo (aproximadamente 1,1 g) en H_2O, se congeló y liofilizó. El compuesto del epígrafe se obtuvo como una espuma (1,02 g, 62%). La RMN de ^1H (400 MHz, CD_3OD) mostró que la mezcla contenía valina y no se pudo estimar la pureza. El material se usó como tal en las posteriores reacciones. CLEM: Anal. Calculado para $C_9H_{13}N_3O_2$: 195; encontrado: 196 $(M+H)^+$.

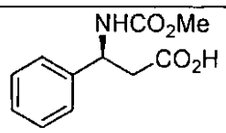
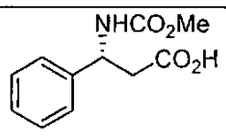
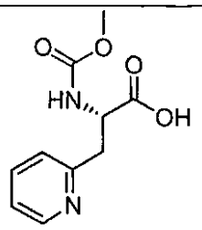
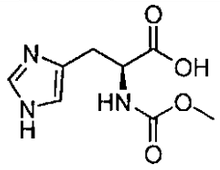
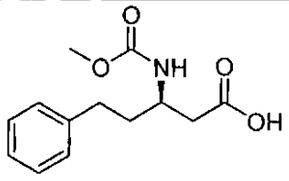
Cap–90

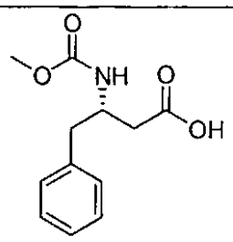
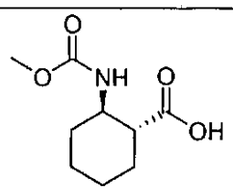
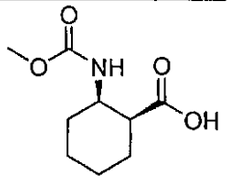
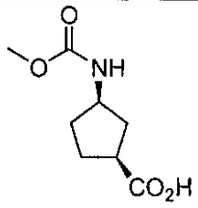
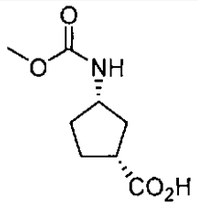
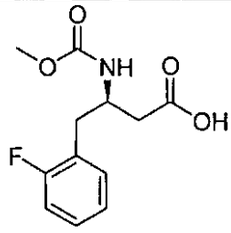


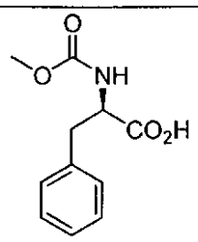
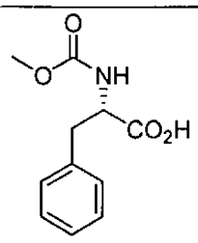
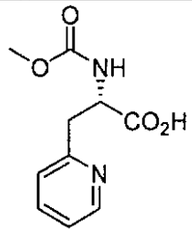
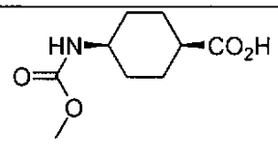
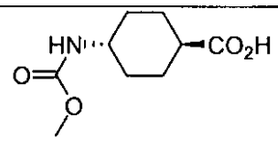
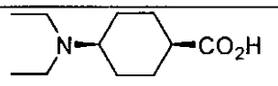
Se preparó *Cap*-90 de acuerdo con el procedimiento descrito para la

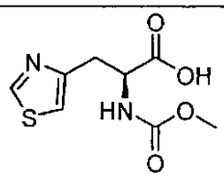
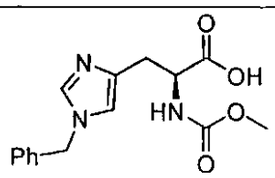
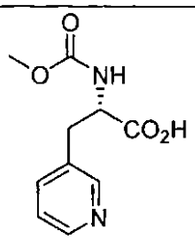
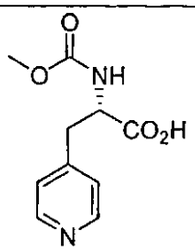
preparación de *Cap*-1. El material bruto se usó como tal en las etapas posteriores. CLEM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

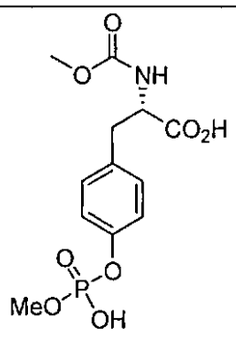
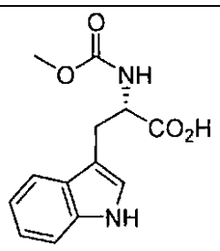
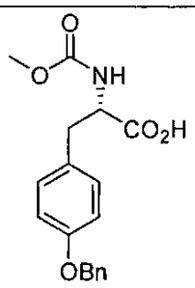
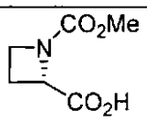
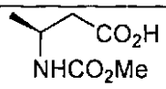
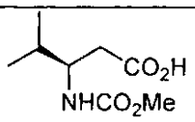
Los siguientes caps se prepararon de acuerdo con el procedimiento del usado para la preparación del cap 51, a menos que se indique de otro modo:

Cap	Estructura	CLEM
Cap-91		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-92		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-93		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-94		CLEM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.
Cap-95		CLEM: Anal. Calculado para $C_{13}H_{17}NO_4$: 251; encontrado: 250 $(M-H)^-$.

Cap-96		CLEM: Anal. Calculado para $C_{12}H_{15}NO_4$: 237; encontrado: 236 $(M-H)^-$.
Cap-97		CLEM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 200 $(M-H)^-$.
Cap-98		CLEM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 202 $(M+H)^+$.
Cap-99		RMN de ^1H (400 MHz, CD_3OD) 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		RMN de ^1H (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		CLEM: Anal. Calculado para $C_{12}H_{14}NO_4F$: 255; encontrado: 256 $(M+H)^+$.

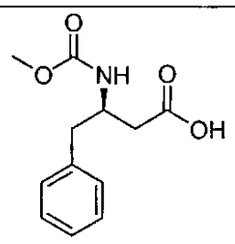
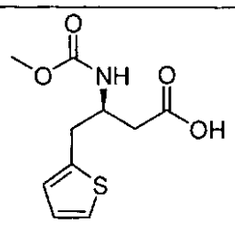
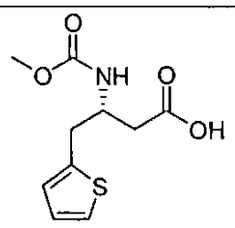
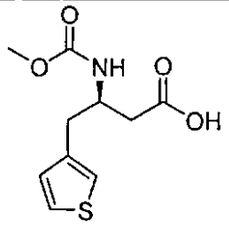
Cap-101		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-102		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$
Cap-103		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-104		RMN de ^1H (400 MHz, CD_3OD) 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).
Cap-105		RMN de ^1H (400 MHz, CD_3OD) δ 3,60 (s, 3H), 3,33 – 3,35 (m, 1H, parcialmente oscurecido por disolvente), 2,37 – 2,41 y 2,16 – 2,23 (m, 1H), 1,94 – 2,01 (m, 4H), 1,43 – 1,53 (m, 2H), 1,17 – 1,29 (m, 2H).
Cap-106	 Se preparó a partir de ácido cis-4-aminociclohexanocarboxílico y acetaldehído empleando u procedimiento similar descrito	RMN de ^1H (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 (dt aparente J = 4,0, 12,9 Hz, 2H), 1,26

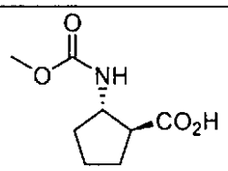
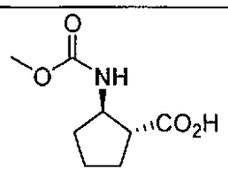
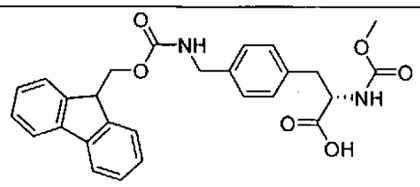
	para la síntesis de Cap-2. La sal HCl bruta se hizo pasar a través de MCX (lavado con $MeOH/H_2O/CH_2Cl_2$; elución con NH_3 2N /MeOH) proporcionando un aceite que se disolvió en CH_3CN/H_2O y se liofilizó proporcionando un sólido color castaño.	(t, J = 7,3 Hz, 6H).
Cap-107		CLEM: Anal. Calculado para $C_8H_{10}N_2O_4S$: 230; encontrado: 231 $(M+H)^+$.
Cap-108		CLEM: Anal. Calculado para $C_{15}H_{17}N_3O_4$: 303; encontrado: 304 $(M+H)^+$.
Cap-109		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-110		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.

Cap-111		CLEM: Anal. Calculado para $C_{12}H_{16}NO_8P$: 333; encontrado: 334 $(M+H)^+$.
Cap-112		CLEM: Anal. Calculado para $C_{13}H_{14}N_2O_4$: 262; encontrado: 263 $(M+H)^+$.
Cap-113		CLEM: Anal. Calculado para $C_{18}H_{19}NO_5$: 329; encontrado: 330 $(M+H)^+$.
Cap-114		RMN de ^1H (400 MHz, $CDCl_3$) δ 4,82 – 4,84 (m, 1H), 4,00 – 4,05 (m, 2H), 3,77 (s, 3H), 2,56 (s ancho, 2H)
Cap-115		RMN de ^1H (400 MHz, $CDCl_3$) δ 5,13 (s ancho, 1H), 4,13 (s ancho, 1H), 3,69 (s, 3H), 2,61 (d, J = 5,0 Hz, 2H), 1,28 (d, J = 9,1 Hz, 3H).
Cap-116		RMN de ^1H (400 MHz, $CDCl_3$) δ 5,10 (d, J = 8,6 Hz, 1H), 3,74 – 3,83 (m, 1H), 3,69 (s, 3H), 2,54 – 2,61 (m, 2H), 1,88 (sept, J = 7,0 Hz, 1H), 0,95 (d, J = 7,0 Hz, 6H).

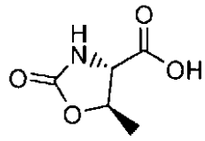
Cap-117 a Cap-123

Para la preparación de *Cap*-117 a *Cap*-123 los Boc aminoácidos se obtuvieron de suministradores comerciales y se desprotegieron por tratamiento con TFA al 25% en CH_2Cl_2. Después de completarse la reacción que se juzgó por CLEM se eliminaron los disolventes a vacío y se carbamoiló la sal TFA correspondiente del aminoácido con cloroformiato de metilo de acuerdo con el procedimiento descrito para el *Cap*-51.

Cap	Estructura	CLEM
Cap-117		CLEM: Anal. Calculado para $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$.
Cap-118		CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-119		CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-120		CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.

Cap-121		RMN de ^1H (400 MHz, $CDCl_3$) δ 4,06 – 4,16 (m, 1H), 3,63 (s, 3H), 3,43 (s, 1H), 2,82 y 2,66 (s ancho, 1H), 1,86 – 2,10 (m, 3H), 1,64 – 1,76 (m, 2H), 1,44 – 1,53 (m, 1H).
Cap-122		El perfil de RMN de ^1H es similar al de su enantiómero, Cap-121.
Cap-123		CLEM: Anal. Calculado para $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$.

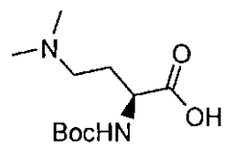
Cap-124



Se carbamoiló la sal clorhidrato de éster terc-butílico de L-treonina de acuerdo con el procedimiento para *Cap*-51. La mezcla de reacción bruta se acidificó con HCl 1N hasta pH~1 y la mezcla se extrajo con EtOAc (2X50 ml). Las fases orgánicas reunidas se concentraron a vacío dando un aceite incoloro que solidificó en reposo. La capa acuosa se concentró a vacío y la mezcla resultante de producto y sales inorgánicas del producto y sales inorgánicas se trituró con EtOAc-CH_2Cl_2-MeOH (1:1:0,1) y luego se concentró la fase orgánica a vacío dando un aceite incoloro que por CLEM se mostró que era el producto

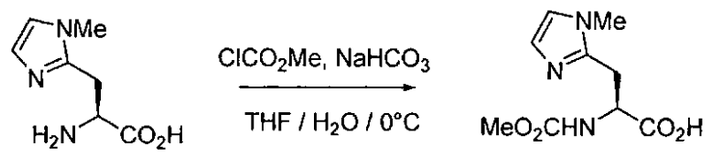
deseado. Ambas tandas se reunieron dando 0,52 g de un sólido. RMN de ^1H (400 MHz, CD_3OD) δ 4,60 (m, 1H), 4,04 (d, *J* = 5,0 Hz, 1H), 1,49 (d, *J* = 6,3 Hz, 3H). CLEM: Anal. Calculado para $C_5H_7NO_4$: 145; encontrado: 146 $(M+H)^+$.

Cap-125



A una suspensión de $Pd(OH)_2$ (20%, 100 mg), formaldehído acuoso (37% en peso, 4 ml), ácido acético (0, 5 ml) en metanol (15 ml) se añadió ácido (S)-4-amino-2-(terc-butoxicarbonilamino)butanoico (1 g, 4,48 mmol). La reacción se purgó varias veces con hidrógeno y se agitó durante la noche bajo un globo de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se eliminó el compuesto volátil a vacío. El material resultante bruto se usó como tal para la etapa siguiente. CLEM: Anal. Calculado para $C_{11}H_{22}N_2O_4$: 246; encontrado: 247 $(M+H)^+$.

Cap-126



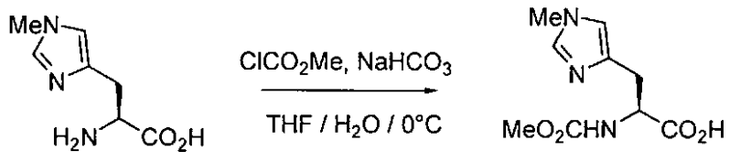
cj-25 *cap-126*

Este procedimiento es una modificación del que se usó para preparar *Cap*-51. A una suspensión de 3-metil-L-histidina (0,80 g, 4,70 mmol) en THF

(10mL) y H_2O (10 ml) a 0°C se añadió $NaHCO_3$ (0,88 g, 10,5 mmol). La mezcla resultante se trató con $ClCO_2Me$ (0,40 ml, 5,20 mmol) y se dejó agitar la mezcla a 0°C. Después de agitar durante aproximadamente. 2h la CLEM no mostró material de partida. La reacción se acidificó hasta pH 2 con HCl 6 N.

Los disolventes se eliminaron a vacío y el residuo se suspendió en 20 ml de MeOH al 20% en CH_2Cl_2. La mezcla se filtró y se concentró dando una espuma amarillo claro (1,21 g,). La CLEM y RMN de ^1H mostraron que el material era una mezcla 9:1 del éster metílico y el producto deseado. Este material se suspendió en THF (10 ml) y H_2O (10 ml), se enfrió hasta 0°C y se añadió LiOH (249,1 mg, 10,4 mmol). Después de agitar aproximadamente 1h la CLEM mostró que no quedaba éster. Seguidamente la mezcla se acidificó con HCl 6N y los disolventes se eliminaron a vacío. La CLEM y RMN de ^1H confirmaron la ausencia del éster. El compuesto del epígrafe se obtuvo como su sal HCl contaminada con sales inorgánicas (1,91 g, >100%). El compuesto se usó como tal en posteriores etapas sin purificación adicional. RMN de ^1H (400 MHz, CD_3OD) δ 8,84, (s, 1H), 7,35 (s, 1H), 4,52 (dd, J = 5,0, 9,1 Hz, 1H), 3,89 (s, 3H), 3,62 (s, 3H), 3,35 (dd, J = 4,5, 15,6 Hz, 1H, parcialmente oscurecido por disolvente), 3,12 (dd, J = 9,0, 15,6 Hz, 1H). CLEM: Análisis calculado para $C_9H_{13}N_3O_4$: 227,09; encontrado: 228,09 $(M+H)^+$.

Cap-127

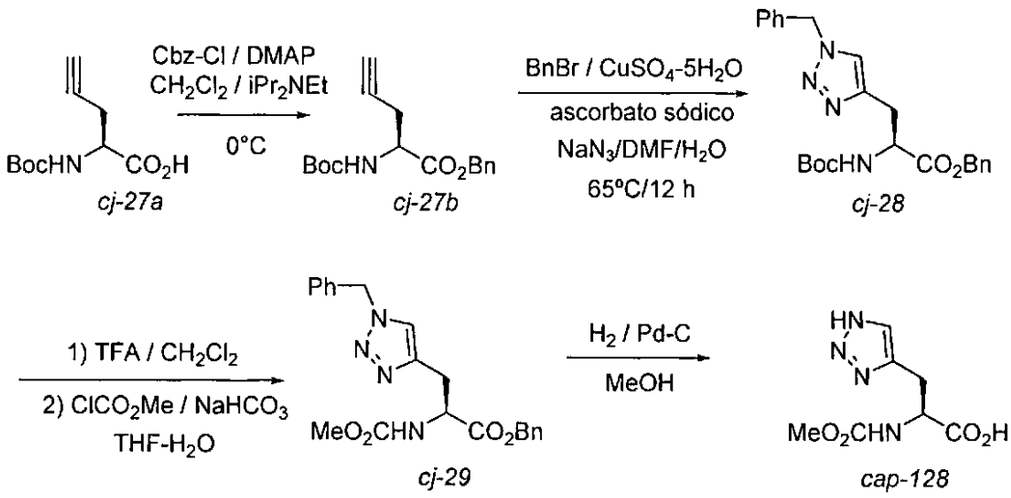


cj-26 *cap-127*

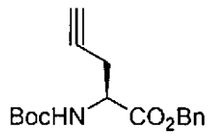
Cap-127 se preparó de acuerdo con el procedimiento para *Cap*-126 anterior partiendo de ácido (S)-2-amino-3-(1-metil-1H-imidazol-4-il)propanoico (1,11 g, 6,56 mmol), $NaHCO_3$ (1,21 g, 14,4 mmol) y $ClCO_2Me$ (0,56 ml, 7,28 mmol). El compuesto del epígrafe se obtuvo como su sal HCl (1,79 g, >100%) contaminado con sales inorgánicas. La CLEM y RMN de ^1H mostraron la presencia de aproximadamente 5% del éster metílico. La mezcla bruta se usó como tal sin purificación adicional. RMN de ^1H (400 MHz, CD_3OD) δ 8,90 (s, 1H), 7,35 (s, 1H), 4,48 (dd, J = 5,0, 8,6 Hz, 1H), 3,89 (s, 3H), 3,62 (s, 3H), 3,35 (m, 1H), 3,08 (m, 1H).

CLEM: Anal. Calculado para $C_9H_{13}N_3O_4$: 227,09; encontrado: 228 $(M+H)^+$.

Preparación de Cap-128



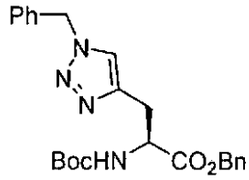
Etapa 1. Preparación de 2-(terc-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b).



cj-27b

A una solución de *cj-27a* (1,01 g, 4,74 mmol), DMAP (58 mg, 0,475 mmol) y iPr_2NEt (1,7 ml, 9,8 mmol) en CH_2Cl_2 (100 ml) a 0°C se añadió Cbz-Cl (0,68 ml, 4,83 mmol). La solución se dejó agitando durante 4 h a 0°C, se lavó ($KHSO_4$ 1N, salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío. El residuo se purificó por cromatografía en columna ultrarrápida (TLC 6:1 hex:EtOAc) dando el compuesto del epígrafe (1,30 g, 91%) como un aceite incoloro. RMN de ^1H (400 MHz, $CDCl_3$) δ 7,35 (s, 5H), 5,35 (d ancho, J = 8,1 Hz, 1H), 5,23 (d, J = 12,2 Hz, 1H), 5,17 (d, J = 12,2 Hz, 1H), 4,48 – 4,53 (m, 1H), 2,68 – 2,81 (m, 2H), 2,00 (t, J = 2,5 Hz, 1H), 1,44 (s, 9H). CLEM: Anal. Calculado para $C_{17}H_{21}NO_4$: 303; encontrado: 304 $(M+H)^+$.

Etapa 2. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(terc-butoxicarbonilamino)propanoato de (S)-bencilo (cj-28).



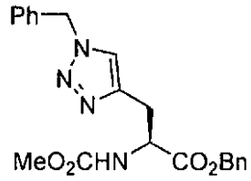
cj-28

A una mezcla de 2-(terc-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (0,50 g, 1,65 mmol), ascorbato sódico (0,036 g, 0,18 mmol), $CuSO_4$-$5H_2O$ (0,022 g, 0,09 mmol) y NaN_3 (0,13 g, 2,1 mmol) en DMF-H_2O (5 ml, 4:1) a ta se añadió BnBr (0,24 ml, 2,02 mmol) y la mezcla se calentó hasta 65°C. Después de 5 horas, la CLEM indicó baja conversión. Se añadió una porción adicional de

NaN_3 (100 mg) y se continuó calentando durante 12 horas. La reacción se vertió en EtOAc y H_2O y se agitó. Las fases se separaron y la fase acuosa se extrajo tres veces con EtOAc y las fases orgánicas reunidas se lavaron (H_2O x3, salmuera), se secaron (Na_2SO_4), se filtraron y concentraron. El residuo se purificó por cromatografía ultrarrápida (Biotage, 40+M 0-5% de MeOH en CH_2Cl_2; TLC 3% de MeOH en CH_2Cl_2) proporcionando un aceite amarillo claro que solidificó en reposo (748,3 mg, 104%). La RMN fue consistente con el producto deseado pero sugirió la presencia de DMF. El material se usó como tal sin purificación adicional. RMN de ^1H (400 MHz, DMSO-d_6) 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).

CLEM: Anal. Calculado para $C_{24}H_{28}N_4O_4$: 436; encontrado: 437 $(M+H)^+$.

Etapa 3. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (cj-29).

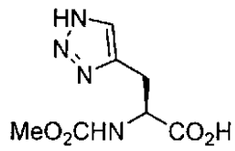


cj-29

Se añadió TFA (4 ml) a una solución de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(terc-butoxicarbonilamino)propanoato de (S)-bencilo (0,52 g, 1,15 mmol) en CH_2Cl_2. La mezcla se dejó agitando a temperatura ambiente durante 2h. La mezcla se concentró a vacío dando un aceite incoloro que solidificó en reposo. Este material se disolvió en THF-H_2O y se enfrió hasta 0°C. Se añadió $NaHCO_3$

sólido (0,25 g, 3,00 mmol) seguido por $ClCO_2Me$ (0,25 ml, 3,25 mmol). Después de agitar durante 1,5h la mezcla se acidificó hasta pH~2 con HCl 6N y luego se vertió en H_2O-EtOAc. Las capas orgánicas se separaron y se extrajo la capa acuosa 2x con EtOAc. Las capas orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío dando un aceite incoloro (505,8 mg, 111%, la RMN sugirió la presencia de una impureza no identificada) que solidificó en reposo en la bomba. El material se usó como tal sin purificación posterior. RMN de ^1H (400 MHz, DMSO-d_6) 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). CLEM: Anal. Calculado para $C_{21}H_{22}N_4O_4$: 394; encontrado: 395 $(M+H)^+$.

Etapa 4. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (*Cap*-128).

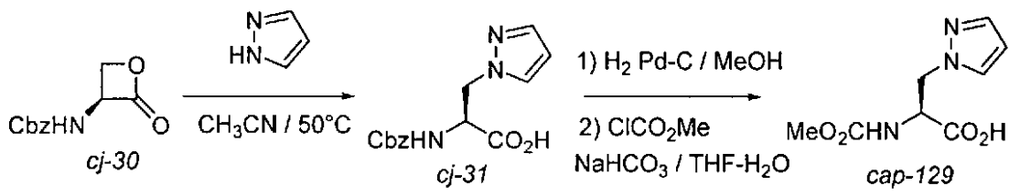


Cap-128

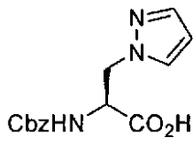
Se sometió 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (502 mg, 1,11 mmol) a hidrogenación en presencia de Pd-C (82 mg) en MeOH (5 ml) a presión atmosférica durante 12h. La mezcla se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Se obtuvo ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico como una goma incolora (266 mg, 111%) que estaba contaminada con aproximadamente 10% del éster metílico. El material se usó sin purificación adicional.

RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12,78 (s ancho, 1H), 7,59 9s, 1H), 7,50 (d, *J* = 8,0 Hz, 1H), 4,19 – 4,24 (m, 1H), 3,49 (s, 3H), 3,12 (dd, *J* = 4,8 Hz, 14,9 Hz, 1H), 2,96 (dd, *J* = 9,9, 15,0 Hz, 1H). CLEM: Anal. Calculado para $C_7H_{10}N_4O_4$: 214; encontrado: 215 $(M+H)^+$.

Preparación de Cap-129



Etapa 1. Preparación de ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico(cj-31).



cj-31

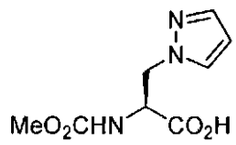
Se calentó una suspensión de 2-oxooxetan-3-ilcarbamato de (S)-bencilo (0,67 g, 3,03 mmol) y pirazol (0,22 g, 3,29 mmol) en CH_3CN (12 ml) a 50°C durante 24h. La mezcla se enfrió hasta TA durante la noche y el sólido se filtró proporcionando ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (330,1 mg). El filtrado se concentró a vacío y luego se trituró con una pequeña cantidad de CH_3CN (aproximadamente 4 ml) proporcionando una segunda tanda (43,5 mg). Rendimiento total 370,4 mg (44%).

p.f. 165,5 – 168°C. p.f. lit 168,5 – 169,5 Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105.

RMN de ^{1}H (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). CLEM: Anal. Calculado para $C_{14}H_{15}N_3O_4$: 289; encontrado: 290 $(M+H)^+$.

Etapa 2. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (*Cap*-129).

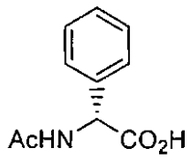


cap-129

Se sometió ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (0,20 g, 0,70 mmol) a hidrogenación en presencia de Pd-C (45 mg) en MeOH (5 ml) a presión atmosférica durante 2h. El producto parecía ser insoluble en MeOH, por tanto se diluyó la mezcla rxn con 5 ml de H_2O y unas pocas gotas de HCl 6N. La solución homogénea se filtró a través de tierra de diatomeas (Celite®), y el MeOH se eliminó a vacío. La solución restante se congeló y se liofilizó dando una espuma amarilla (188,9 mg). Este material se suspendió en THF-H_2O (1:1, 10 ml) y luego se enfrió hasta 0°C. A la mezcla fría se añadió $NaHCO_3$ (146,0 mg, 1,74 mmol) cuidadosamente (generación de CO_2). Después de cesar la generación de gas (aproximadamente 15 min) se añadió $ClCO_2Me$ (0,06 ml, 0,78 mmol) gota a gota. La mezcla se dejó agitando durante 2 horas y se acidificó hasta pH~2 con HCl 6N y se vertió en EtOAc. Las fases se separaron y la fase acuosa se extrajo con EtOAC (x5). Las fases orgánicas reunidas se lavaron (salmuera), se secaron (Na_2SO_4), se filtraron y concentraron dando el compuesto del epígrafe como un sólido incoloro (117,8 mg, 79%).

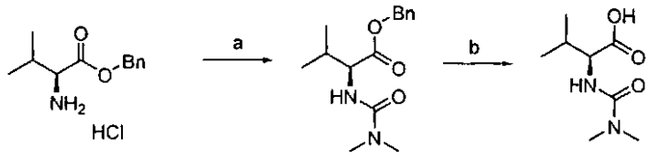
RMN de ^{1}H (400 MHz, DMSO-d_6) δ 13,04 (s, 1H), 7,63 (d, J = 2,6 Hz, 1H), 7,48 (d, J = 8,1 Hz, 1H), 7,44 (d, J = 1,5 Hz, 1H), 6,19 (t aparente, J = 2,0 Hz, 1H), 4,47 (dd, J = 3,0, 12,9 Hz, 1H), 4,29 – 4,41 (m, 2H), 3,48 (s, 3H). CLEM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.

Cap-130



Cap-130 se preparó por acilación de (R)-fenilglicina disponible comercialmente de forma análoga al procedimiento dado en: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

Cap-131

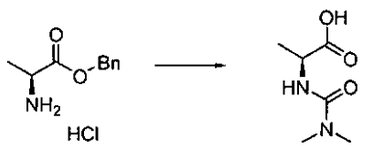


Etapa a: Se añadió cloruro de dimetilcarbamoílo (0,92 ml, 10 mmol) lentamente a una solución de clorhidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2,44 g; 10 mmol) y base de Hunig (3,67 ml, 21 mmol) en THF (50 ml). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16 horas) y se concentró a presión reducida. El residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El aceite amarillo resultante se purificó por cromatografía ultrarrápida, eluyendo con acetato de

etilo:hexanos (1:1). Las fracciones recogidas se concentraron a vacío proporcionando 2,35 g (85%) de aceite transparente. RMN de. ^{1}H (300 MHz, DMSO-d_6) δ ppm 0,84 (d, *J*=6,95 Hz, 3H), 0,89 (d, *J*=6,59 Hz, 3H), 1,98-2,15 (m, 1H), 2,80 (s, 6H), 5,01-5,09 (m, *J*=12,44 Hz, 1H), 5,13 (d, *J*=12,44 Hz, 1H), 6,22 (d, *J*=8,05 Hz, 1H), 7,26-7,42 (m, 5H). CL (Cond. 1): T_R = 1,76 min; EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279,17; encontrado 279,03.

Etapa b: A una solución en MeOH (50 ml) del intermedio preparado antes (2,35 g; 8,45 mmol) se añadió Pd/C (10%; 200 mg) y la suspensión negra resultante se llenó con N_2 (3x) y se colocó en 1 atm de H_2. La mezcla se agitó a temperatura ambiente durante la noche y se filtró a través de un filtro de microfibra para separar el catalizador. La solución transparente resultante se concentró entonces a presión reducida obteniendo 1,43 g (89%) de *Cap-131* como espuma blanca, que se usó sin purificación posterior. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0,87 (d, *J*=4,27 Hz, 3H), 0,88 (d, *J*=3,97 Hz, 3H), 1,93-2,11 (m, 1H), 2,80 (s, 6H), 3,90 (dd, *J*=8,39, 6,87 Hz, 1H), 5,93 (d, *J*=8,54 Hz, 1H), 12,36 (s, 1H). CL (Cond. 1): T_R = 0,33 min; EM: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189,12; encontrado 189,04.

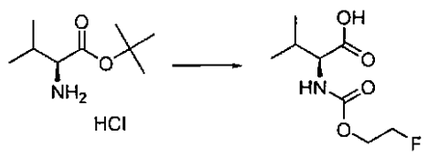
Cap-132



Cap-132 se preparó a partir de clorhidrato de 2-aminopropanoato de (S)-bencilo de acuerdo con el procedimiento descrito para *Cap-131*. RMN de ^{1}H

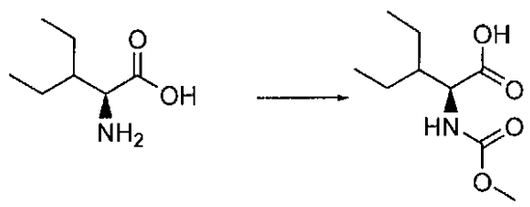
(500 MHz, DMSO-d_6) δ ppm 1,27 (d, *J*=7,32 Hz, 3H), 2,80 (s, 6H), 4,06 (ct, 1H), 6,36 (d, *J*=7,32 Hz, 1H), 12,27 (s, 1H). CL (Cond. 1): T_R = 0,15 min; EM: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161,09; encontrado 161,00.

Cap-133



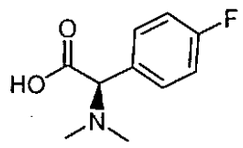
Cap-133 se preparó a partir de clorhidrato de 2-amino-3-metilbutanoato de (S)-terc-butilo y cloroformiato de 2-fluoroetilo de acuerdo con el procedimiento descrito para *Cap-47*. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0,87 (t, *J* = 6,71 Hz, 6H), 1,97-2,10 (m, 1H), 3,83 (dd, *J*=8,39, 5,95 Hz, 1H), 4,14-4,18 (m, 1H), 4,20-4,25 (m, 1H), 4,50-4,54 (m, 1H), 4,59-4,65 (m, 1H), 7,51 (d, *J* = 8,54 Hz, 1H), 12,54 (s, 1H).

Cap-134



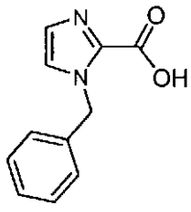
Cap-134 se preparó a partir de (S)-dietil alanina y cloroformiato de metilo de acuerdo con el procedimiento descrito para *Cap-51*. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0,72-0,89 (m, 6H), 1,15-1,38 (m, 4H), 1,54-1,66 (m, 1H), 3,46-3,63 (m, 3H), 4,09 (dd, *J* = 8,85, 5,19 Hz, 1H), 7,24 (d, *J* = 8,85 Hz, 1H), 12,55 (s, 1H). CL (Cond. 2): T_R = 0,66 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$: 204,12; encontrado 204,02.

Cap-135



Una solución de ácido D-2-amino-(4-fluorofenil)acético (338 mg, 2,00 mmol), HCl 1*N* en éter dietílico (2,0 ml, 2,0 mmol) y formalina (37%, 1 ml) en metanol (5 ml) se sometió a hidrogenación bajo un globo en paladio al 10% sobre carbón (60 mg) durante 16 h a 25ºC. La mezcla se filtró a través de Celite proporcionando la sal HCl de *Cap-135* como una espuma blanca (316 mg, 80%). RMN de ^{1}H (300 MHz, MeOH-d_4) δ 7,59 (dd, J = 8,80, 5,10 Hz, 2H), 7,29 (t, J = 8,6 Hz, 2H), 5,17 (s, 1H), 3,05 (s muy ancho, 3H), 2,63 (s muy ancho, 3H); T_R = 0,19 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198,09; encontrado: 198,10.

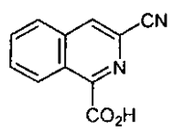
Cap-136



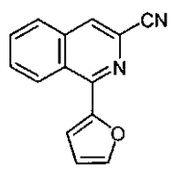
A una suspensión enfriada (-50 ºC) de 1-bencil-1*H*-imidazol (1,58 g, 10,0 mmol) en éter dietílico anhidro (50 ml) en nitrógeno se añadió n-butil litio (2,5 M en hexanos, 4,0 ml, 10,0 mmol) gota a gota. Después de agitar durante 20

minutos a -50 °C, se hizo burbujear dióxido de carbono (pasado a través de Drierite) en la mezcla de reacción durante 10 minutos antes de dejar calentar hasta 25°C. El precipitado pesado que se formó al añadir dióxido de carbono a la mezcla de reacción se filtró proporcionando un sólido blanco higroscópico que se recogió en agua (7 ml), se acidificó hasta pH = 3, se enfrió y se indujo a cristalizar con raspado. La filtración de este precipitado dio un sólido blanco que se suspendió en metanol, se trató con HCl 1*N*/éter dietílico (4 ml) y se concentró a vacío. La liofilización del residuo en agua (5 ml) proporcionó la sal HCl de *Cap-136, (230 mg, 105%)* como un sólido blanco (40%). RMN de ^{1}H (300 MHz, DMSO-d_6) δ 7,94 (d, *J* = 1,5 Hz, 1H), 7,71 (d, *J* = 1,5 Hz, 1H), 7,50-7,31 (m, 5H), 5,77 (s, 2H); T_R = 0,51 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203,08; encontrado: 203,11.

Cap-137



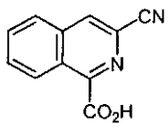
Cap-137, etapa a



Una suspensión de 1-cloro-3-cianoisoquinolina (188 mg, 1,00 mmol; preparada de acuerdo con el procedimiento del documento WO 2003/ 099274) (188 mg, 1,00 mmol), fluoruro de cesio (303,8 mg, 2,00 mmol), dicloruro de

bis(tri-*terc*-butilfosfina)paladio (10 mg, 0,02 mmol) y 2-(tributilestannil)furano (378 µl, 1,20 mmol) en dioxano anhidro (10 ml) en nitrógeno se calentó a 80 °C durante 16 horas de enfriar hasta 25°C y se trató con solución acuosa saturada de fluoruro potásico con agitación vigorosa durante 1 h. La mezcla se repartió entre acetato de etilo y la fase orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación del residuo sobre gel de sílice (elución con acetato de etilo de 0% a 30%/hexanos) proporcionó *Cap-137, etapa a* (230 mg, 105%) como un sólido blanco que se usó directamente a continuación. T_R = 1,95 min (Condiciones de EM-W2); índice de homogeneidad del 90%; EMBR: Análisis calculado para $[M+H]^+$ $C_{14}H_8N_2O$: 221,07; encontrado: 221,12.

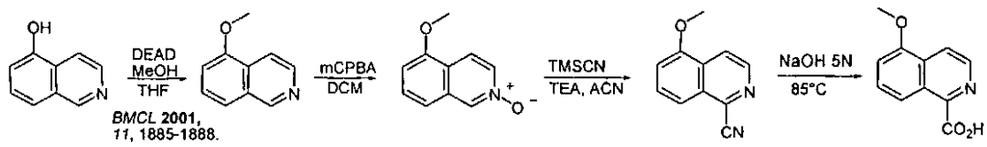
Cap-137



A una suspensión de *Cap 137, etapa a*, (110 mg, 0,50 mmol) y peryodato sódico (438 mg, 2,05 mmol) en tetracloruro de carbono (1 ml), acetonitrilo (1 ml) y agua (1,5 ml) se añadió tricloruro de rutenio hidratado (2 mg, 0,011 mmol). La mezcla se agitó a 25 °C durante 2 h y luego se repartió entre diclorometano y agua. La fase acuosa se separó, se extrajo dos veces más con diclorometano y se secaron los extractos reunidos sobre Na_2SO_4, se filtraron y concentraron. La trituración del residuo con hexanos proporcionó *Cap-137* (55 mg, 55%) como un sólido de color grisáceo. T_R = 1,10 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_8N_2O_2$: 200,08; encontrado: 200,08.

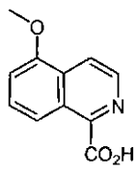
Caps 138 a 158

Estrategia de síntesis. Procedimiento A.

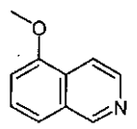


BMCL **2001**, *11*, 1885-1888.

Cap-138



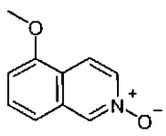
Cap-138, etapa a



A una suspensión agitada de 5-hidroxiisoquinolina (preparada de acuerdo con el procedimiento del documento WO 2003/ 099274) (2,0 g, 13,8 mmol) y trifenilfosfina (4,3 g, 16,5 mmol) en tetrahidrofurano seco (20 ml) se añadió metanol seco (0,8 ml) y azodicarboxilato de dietilo (3,0 ml, 16,5 mmol) en varias porciones. La mezcla se agitó a temperatura ambiente durante 20 h antes de diluir con acetato de etilo y se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se preabsorbió sobre gel de sílice y se sometió a cromatografía (elución con acetato de etilo al 40%/hexanos) proporcionando *Cap-138, etapa a* (1,00 g, 45%) como un sólido amarillo claro. RMN de ^1H ($CDCl_3$, 500 MHz) δ 9,19 (s, 1H), 8,51 (d, J = 6,0 Hz, 1H), 7,99 (d, J = 6,0 Hz, 1H), 7,52-7,50 (m, 2H), 7,00-6,99 (m, 1H), 4,01 (s, 3H); T_R = 0,66 min

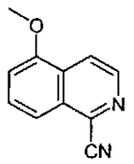
(Cond. D2); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO$: 160,08; encontrado 160,10.

Cap-138, etapa b



A una solución agitada de *Cap 138, etapa a* (2,34 g, 14,7 mmol) en diclorometano anhidro (50 ml) a temperatura ambiente se añadió ácido *meta*-cloroperbenzoico (77%, 3,42 g, 19,8 mmol) en una porción. Después de agitar durante 20 horas, se añadió carbonato potásico en polvo (2,0 g) y la mezcla se agitó durante 1 hora a temperatura ambiente antes de que se filtrara y concentrara a vacío proporcionando *Cap-138, etapa b* (2,15 g, 83,3%) como un sólido amarillo pálido que era suficientemente puro para usarse posteriormente directamente. RMN de ^1H ($CDCl_3$, 400 MHz) δ 8,73 (d, J = 1,5 Hz, 1H), 8,11 (dd, J = 7,3, 1,7 Hz, 1H), 8,04 (d, J=7,1 Hz, 1H), 7,52 (t, J = 8,1 Hz, 1H), 7,28 (d, J = 8,3 Hz, 1H), 6,91 (d, J = 7,8 Hz, 1H), 4,00 (s, 3H); T_R = 0,92 min, (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO_2$: 176,07; encontrado: 176,0.

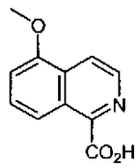
Cap-138, etapa c



A una solución agitada de *Cap 138, etapa b* (0,70 g, 4,00 mmol) y trietilamina (1,1 ml, 8,00 mmol) en acetonitrilo seco (20 ml) a temperatura

ambiente en nitrógeno se añadió cianuro de trimetilsililo (1,60 ml, 12,00 mmol). La mezcla se calentó a 75 °C durante 20 h antes de enfriar hasta temperatura ambiente, se diluyó con acetato de etilo y se lavó con solución saturada de bicarbonato sódico y salmuera antes de secar sobre Na_2SO_4 y concentrar el disolvente. El residuo se sometió a cromatografía ultrarrápida sobre gel de sílice (elución con gradiente de acetato de etilo al 5%/en hexanos) hasta acetato de etilo al 25%/en hexanos) proporcionando *Cap-138, etapa c* (498,7 mg, 68%) como un sólido blanco cristalino junto con 223 mg (30%) de más *Cap-138, etapa c* recuperado del filtrado. RMN de ^1H ($CDCl_3$, 500 MHz) δ 8,63 (d, *J* = 5,5 Hz, 1H), 8,26 (d, *J* = 5,5 Hz, 1H), 7,88 (d, *J* = 8,5 Hz, 1H), 7,69 (t, *J* = 8,0 Hz, 1H), 7,08 (d, *J* = 7,5 Hz, 1H), 4,04 (s, 3H); T_R = 1,75 min, (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185,07; encontrado: 185,10.

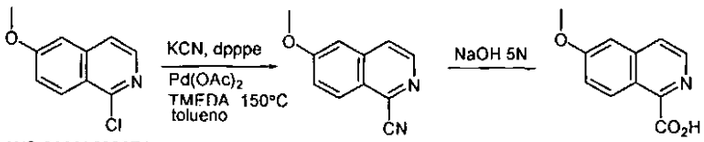
Cap-138



Se trató *Cap-138, etapa c* (0,45 g, 2,44 mmol) con solución de hidróxido sódico 5*N* (10 ml) y la suspensión resultante se calentó a 85°C durante 4 h, se enfrió hasta 25 °C, se diluyó con diclorometano y se acidificó con ácido clorhídrico 1*N*. La fase orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, se concentró hasta ¼ del volumen y se filtró proporcionando *Cap-138* (0,44 g, 88,9%) como un sólido amarillo. RMN de ^1H (DMSO-d_6, 400 MHz) δ 13,6 (s ancho, 1H), 8,56 (d, *J* = 6,0 Hz, 1H), 8,16 (d, *J* = 6,0 Hz, 1H),

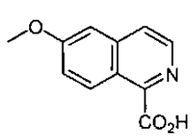
8,06 (d, *J* = 8,8 Hz, 1H), 7,71-7,67 (m, 1H), 7,30 (d, *J* = 8,0 Hz, 1H), 4,02 (s, 3H); T_R = 0,70 min (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

Estrategia de síntesis. Procedimiento B (derivado de *Tetrahedron Letters*, **2001**, *42*, 6707).

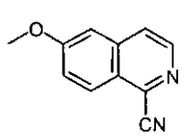


WO 2003/ 099274

Cap-139



Cap-139, etapa a



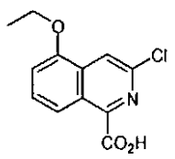
A un vial a rosca de pared gruesa que contenía una suspensión desgasificada en argón de 1-cloro-6-metoxiisoquinolina (1,2 g, 6,2 mmol; preparado de acuerdo con el procedimiento del documento WO 2003/ 099274), cianuro potásico (0,40 g, 6,2 mmol), 1,5-bis(difenilfosfino)pentano (0,27 g, 0,62 mmol) y acetato de paladio (II) (70 mg, 0,31 mmol) en tolueno anhidro (6 ml) se añadió *N,N,N',N'*-tetrametiletilendiamina (0,29 ml, 2,48 mmol). El vial se selló, se calentó hasta 150 ºC durante 22 h y luego se dejó enfriar hasta 25 ºC. La

mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice (elución con gradiente de acetato de etilo al 5%/hexanos hasta acetato de etilo al 25%/hexanos proporcionando *Cap-139, etapa a* (669,7 mg, 59%) como un sólido blanco. RMN de ^1H ($CDCl_3$, 500 MHz) δ 8,54 (d, *J* = 6,0 Hz, 1H), 8,22 (d, *J* = 9,0 Hz, 1H), 7,76 (d, *J* = 5,5 Hz, 1H), 7,41-7,39 (m, 1H), 7,13 (d, *J* = 2,0 Hz, 1H), 3,98 (s, 3H); T_R = 1,66 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185,07; encontrado: 185,2.

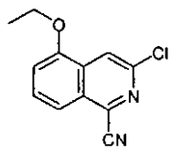
Cap-139

Cap-139 se preparó a partir de la hidrólisis básica de *Cap-139, etapa a* con NaOH 5*N* de acuerdo con el procedimiento descrito para *Cap 138*. RMN de ^1H (400 MHz, DMSO-d_6) δ 13,63 s muy ancho, 1H), 8,60 (d, *J* = 9,3 Hz, 1H), 8,45 (d, *J* = 5,6 Hz, 1H), 7,95 (d, *J* = 5,9 Hz, 1H), 7,49 (d, *J* = 2,2 Hz, 1H), 7,44 (dd, *J* = 9,3, 2,5 Hz, 1H), 3,95 (s, 3H); T_R = 0,64 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

Cap-140

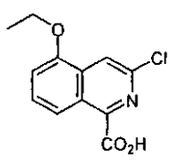


Cap-140, etapa a



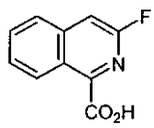
A una mezcla agitada vigorosamente de 1,3-dicloro-5-etoxiisoquinolina (482 mg, 2,00 mmol; preparada de acuerdo con el procedimiento del documento WO 2005/ 051410), acetato de paladio (II) (9 mg, 0,04 mmol), carbonato sódico (223 mg, 2,10 mmol) y 1,5-bis(difenilfosfino)pentano (35 mg, 0,08 mmol) en dimetilacetamida seca (2 ml) a 25 °C en nitrógeno se añadió N,N,N',N'-tetrametiletilendiamina (60 ml, 0,40 mmol). Después de 10 min, la mezcla se calentó hasta 150 °C, y luego se añadió una solución patrón de acetona cianohidrina (preparada a partir de 457 µl de acetona cianohidrina en 4,34 ml de DMA) en porciones de 1 ml durante 18 h usando una bomba de jeringa. La mezcla se repartió entonces entre acetato de etilo y agua y se separó la fase orgánica, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice (elución con gradiente de acetato de etilo al 10% en hexanos hasta acetato de etilo al 40% en hexanos) proporcionando *Cap-140, etapa a* (160 mg, 34%) como un sólido amarillo. T_R = 2,46 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_9ClN_2O$: 233,05; encontrado: 233,08.

Cap-140

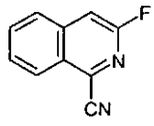


Cap-140 se preparó por la hidrólisis ácida de *Cap-140, etapa a* con HCl 12*N* como se describe en el procedimiento para la preparación de *Cap 141*, descrito más adelante. T_R = 2,24 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252,04; encontrado: 252,02.

Cap-141

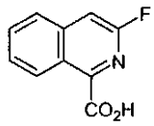


Cap-141, etapa a



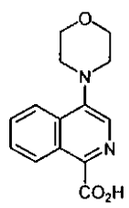
Cap-141, etapa a se preparó a partir de 1-bromo-3-fluoroisoquinolina (preparada a partir de 3-amino-1-bromoisoquinolina usando el procedimiento esbozado en *J. Med. Chem.* **1970**, *13*, 613) como se describe en el procedimiento para la preparación de *Cap-140, etapa a* (*vide supra*). RMN de ^1H (500 MHz, $CDCl_3$) δ 8,35 (d, *J* = 8,5 Hz, 1H), 7,93 (d, *J* = 8,5 Hz, 1H), 7,83 (t, *J* = 7,63 Hz, 1H), 7,77-7,73 (m, 1H), 7,55 (s, 1H); T_R = 1,60 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_6FN_2$: 173,05; encontrado: 172,99.

Cap-141

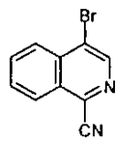


Se trató *Cap-141, etapa a* (83 mg, 0,48 mmol) con HCl 12*N* (3 ml) y la suspensión resultante se calentó a 80 °C durante 16 h antes de enfriar hasta temperatura ambiente y se diluyó con agua (3 ml). La mezcla se agitó durante 10 min y luego se filtró proporcionando *Cap-141* (44,1 mg, 47,8%) como un sólido blanquecino. El filtrado se diluyó con diclorometano y se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró proporcionando más *Cap-141* (29,30 mg, 32%) que era suficientemente puro para usarlo posteriormente. RMN de ^1H (DMSO-d_6, 500 MHz) δ 14,0 (s ancho, 1H), 8,59-8,57 (m, 1H), 8,10 (d, J = 8,5 Hz, 1H), 7,88-7,85 (m, 2H), 7,74-7,71 (m, 1H); T_R = 1,33 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 191,97.

Cap-142



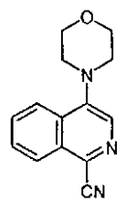
Cap-142, etapa a



Cap-142, etapa a se preparó a partir de N-óxido de 4-bromoisoquinolina como se describe en el procedimiento en dos etapas para la preparación de

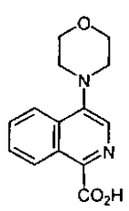
Cap-138, etapas b y c. T_R = 1,45 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_6BrN_2$: 232,97; encontrado: 233,00.

Cap-142, etapa b



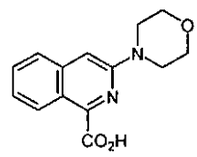
A una suspensión desgasificada en argón de *Cap-142, etapa a* (116 mg, 0,50 mmol), fosfato potásico tribásico (170 mg, 0,80 mmol), acetato de paladio (II) (3,4 mg, 0,015 mmol) y 2-(diciclohexilfosfino)bifenilo (11 mg, 0,03 mmol) en tolueno anhidro (1 ml) se añadió morfolina (61 µl, 0,70 mmol). La mezcla se calentó a 100 °C durante 16 h, se enfrió hasta 25 °C, se filtró a través de tierra de diatomeas (Celite®) y se concentró. La purificación del residuo sobre gel de sílice, (elución con gradiente de acetato de etilo del 10% a 70% enhexanos proporcionó *Cap-142, etapa b* (38 mg, 32%) como un sólido amarillo, que se llevó a etapas posteriores directamente. T_R = 1,26 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{14}N_3O$: 240,11; encontrado: 240,13.

Cap-142

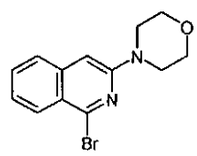


Cap-142 se preparó a partir de *Cap-142, etapa b* con hidróxido sódico 5*N* como se describe en el procedimiento para *Cap 138*. T_R = 0,72 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259,11; encontrado: 259,08.

Cap-143



Cap-143, etapa a



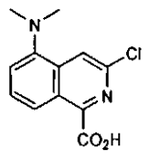
A una solución agitada de 3-amino-1-bromoisoquinolina (444 mg, 2,00 mmol) en dimetilformamida anhidra (10 ml) se añadió hidruro sódico (60%, sin lavar, 96 mg, 2,4 mmol) en una porción. Esta mezcla se agitó a 25 °C durante 5 min antes de añadir éter 2-bromoetílico (90%, 250 µl, 2,00 mmol). La mezcla se agitó otra vez a 25 °C durante 5 h y a 75 °C durante 72 h antes de enfriar hasta 25 °C, se inactivó con solución saturada de cloruro amónico y se diluyó con acetato de etilo. La fase orgánica se separó, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación del residuo sobre gel de sílice (elución con gradiente de acetato de etilo al 0% a 70% en hexanos proporcionó *Cap-143, etapa* (180 mg, 31%) *a* como un sólido amarillo. T_R =

1,75 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293,03; encontrado: 293,04.

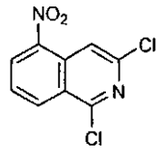
Cap-143

A una solución fría (-60 ºC) de *Cap-143, etapa a* (154 mg, 0,527 mmol) en tetrahidrofurano anhidro (5 ml) se añadió una solución de *n*-butil litio en hexanos (2,5 M, 0,25 ml, 0,633 mmol). Después de 10 min, se burbujeó dióxido de carbono en la mezcla de reacción durante 10 minutos antes que se inactivara con HCl 1N y se dejó calentar hasta 25ºC. La mezcla se extrajo entonces con diclorometano (3 x 30 ml) y los extractos orgánicos reunidos se concentraron a vacío. La purificación del residuo por una HPLC de fase inversa (MeOH/agua/TFA) proporcionó *Cap-143* (16 mg, 12%). T_R = 1,10 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259,11; encontrado: 259,08.

Cap-144

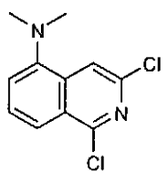


Cap-144, etapa a



Se añadió 1,3-dicloroisoquinolina (2,75 g, 13,89 mmol) en pequeñas porciones a una solución fría (0 °C) de ácido nítrico fumante (10 ml) y ácido sulfúrico concentrado (10 ml). La mezcla se agitó a 0°C durante 0,5 horas antes de que se calentara gradualmente hasta 25°C a la que se agitó durante 16 horas. La mezcla se vertió entonces en un vaso de precipitados que contenía hielo triturado y agua y la suspensión resultante se agitó durante 1 hora a 0°C antes de que se filtrara proporcionando *Cap-144, etapa a* (2,73 g, 81%) como un sólido amarillo que se usó directamente. T_R = 2,01 min. (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242,97; encontrado: 242,92.

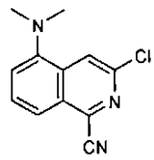
Cap-144, etapa b



Se suspendió *Cap-144, etapa a* (0,30 g, 1,23 mmol) en metanol (60 ml) y se trató con óxido de platino (30 mg) y la suspensión se sometió a hidrogenación de Parr a 48,26 kPa de H_2 durante 1,5 h. Antes se añadieron formalina (5 ml) y más óxido de platino (30 mg). La suspensión se volvió a someter a hidrogenación de Parr a 310,26 kPa de H_2 durante 13 h antes de someter a filtración por succión a través de tierra de diatomeas (Celite®) y se concentró hasta ¼ de su volumen. La filtración por succión del precipitado proporcionó el compuesto del epígrafe como un sólido amarillo que se sometió a cromatografía sobre gel de sílice (elución con gradiente de acetato de etilo al 5% en hexanos hasta acetato de etilo al 25% en hexanos) proporcionando

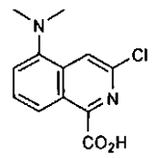
Cap-144, etapa b (231 mg, 78%) como un sólido amarillo pálido. T_R = 2,36 min (Condiciones-D1); índice de homogeneidad del 95%; RMN de ^1H (400 MHz, $CDCl_3$) δ 8,02 (s, 1H), 7,95 (d, *J* = 8,6 Hz, 1H), 7,57-7,53 (m, 1H), 7,30 (d, *J* = 7,3 Hz, 1H), 2,88 (s, 6H); CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241,03; encontrado: 241,02. EMAR: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241,0299; encontrado: 241,0296.

Cap-144, etapa c



Cap-144, etapa c se preparó a partir de *Cap-144, etapa b* de acuerdo con el procedimiento descrito para la preparación de *Cap-139, etapa a.* T_R = 2,19 min (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232,06; encontrado: 232,03. EMAR: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232,0642; encontrado: 232,0631.

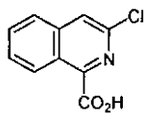
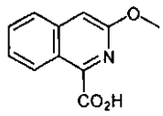
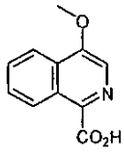
Cap-144

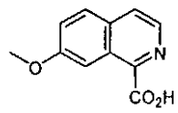
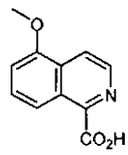
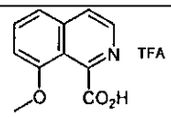
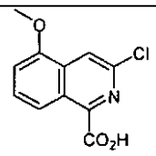
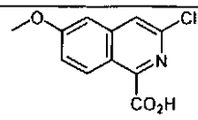


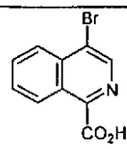
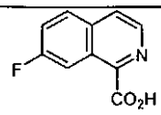
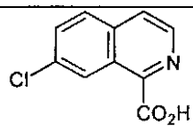
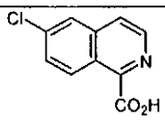
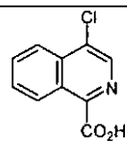
Cap-144 se preparó de acuerdo con el procedimiento descrito para *Cap-141.* T_R = 2,36 min (Condiciones-D1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238,01; encontrado: 238,09.

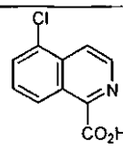
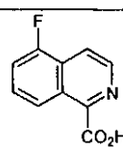
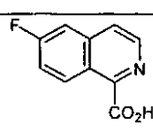
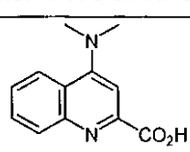
Caps-145 a 162

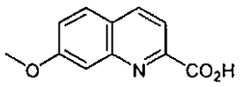
Caps-145 a *162* se prepararon a partir de las 1-cloroisoquinolinas apropiadas de acuerdo con el procedimiento descrito para la preparación de *Cap-138* (Procedimiento A) o *Cap-139* (Procedimiento B) a no ser que se describa de otro modo más adelante.

Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-145	 Preparado a partir de 1,3-dicloroisoquinolina disponible comercialmente	B	12*N* HCl	1,14 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,00.
Cap-146	 Preparado a partir de 3-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	1,40 min (Condiciones-D1); 95% ; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,06.
Cap-147	 Preparado a partir de 1-cloro-4-hidroxiisoquinolina disponible comercialmente	B	NaOH 5N	0,87 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

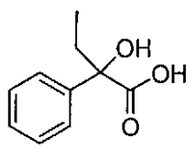
Cap-148	 Preparado a partir de 7-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0,70 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.
Cap-149	 Preparado a partir de 5-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0,70 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.
Cap-150	 Preparado a partir de 8-metoxi-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	A	HCl 12N	0,26 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,04.
Cap-151	 Preparado a partir de 5-metoxi-1,3-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2005 / 051410.	B	HCl 12N	1,78 min (Condiciones-D1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238,03; encontrado: 238,09.
Cap-152	 Preparado a partir de 6-metoxi-1,3-dicloroisoquinolina disponible comercialmente	B	HCl 12N	1,65 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$:

				238,00; encontrado: 238,09.
Cap-153	 Preparado a partir de 4-bromoisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 062241	A	HCl 6N	1,18 min (Condiciones de EM-W1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7BrNO_2$: 251,97; encontrado: 251,95.
Cap-154	 Preparado a partir de 7-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0,28 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03.
Cap-155	 Preparado a partir de 1,7-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0,59 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,00.
Cap-156	 Preparado a partir de 1,6-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0,60 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,03.
Cap-157		B	HCl 12N	1,49 min (Condiciones-D1); 95%; CLEM: Análisis

	Preparado a partir de 1,4-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 062241			calculado para $[M+H]^+$ $C_{10}H_{17}ClNO$: 208,02; encontrado: 208,00.
Cap-158	 Preparado a partir de 1,5-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0,69 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,01.
Cap-159	 Preparado a partir de 5-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0,41 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03.
Cap-160	 Preparado a partir de 6-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0,30 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03.
Cap-161	 Preparado a partir de ácido 4-bromoquinolin-2-carboxílico y dimetilamina (DMSO, 100 °C)	--	--	0,70 min (Cond. D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217,10; encontrado: 217,06.

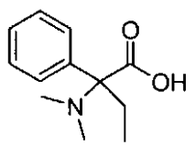
Cap-162	 Preparado a partir de *m*-anisidina siguiendo el procedimiento descrito en *J. Hetero. Chem.* **1993**, 17 y *Heterocycles*, **2003**, *60*, 953.	--	--	0,65 min (Condiciones-M3); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 203,94.

Cap-163



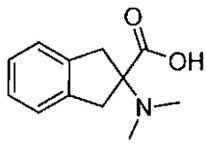
A una solución de ácido 2-cetobutírico (1,0 g, 9,8 mmol) en éter dietílico (25 ml) se añadió gota a gota bromuro de fenilmagnesio (22 ml, 1M en THF). La reacción se agitó a ~25 °C en nitrógeno durante 17,5h. La reacción se acidificó con HCl 1N y el producto se extrajo con acetato de etilo (3 x 100 ml). La fase orgánica reunida se lavó con agua seguido por salmuera y se secó sobre $MgSO_4$. Después de concentrar a vacío se obtuvo un sólido blanco. El sólido se recristalizó en hexanos/acetato de etilo proporcionando *Cap-163* como agujas blancas (883,5 mg). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 12,71 (s ancho, 1 H), 7,54-7,52 (m, 2H), 7,34-7,31 (m, 2H), 7,26-7,23 (m, 1H), 5,52-5,39 (s ancho, 1H), 2,11 (m, 1H), 1,88 (m, 1H), 0,79 (t ap, J = 7,4 Hz, 3H).

Cap-164



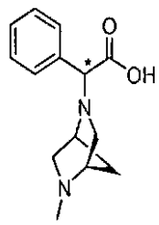
Se expuso a H_2 a 344,74 kPa en un frasco de Parr durante 42 horas una mezcla de ácido 2-amino-2-fenilbutírico (1,5 g, 8,4 mmol), formaldehído (14 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (0,5 mg) en MeOH (40 ml). La reacción se filtró sobre Celite y se concentró a vacío, el residuo se suspendió en MeOH (36 ml) y el producto se purificó con una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de *Cap-164* como un sólido blanco (1,7 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz) 7,54-7,47 (m, 5H), 2,63 (m, 1H), 2,55 (s, 6H), 2,31 (m, 1H), 0,95 (t ap, J = 7,3 Hz, 3H).

Cap-165



A una mezcla de ácido 2-amino-2-indanocarboxílico (258,6 mg, 1,46 mmol) y ácido fórmico (0,6 ml, 15,9 mmol) en 1,2-dicloroetano (7 ml) se añadió formaldehído (0,6 ml, 37% en agua). La mezcla se agitó a ~25 °C durante 15 min luego se calentó a 70 °C durante 8h. El componente volátil se eliminó a vacío y el residuo se disolvió en DMF (14 ml) y se purificó por una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de *Cap-165* como un aceite viscoso (120,2 mg). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 7,29-7,21 (m, 4 H), 3,61 (d, J = 17,4 Hz, 2H), 3,50 (d, J = 17,4 Hz, 2H), 2,75 (s, 6H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206,12; encontrado: 206,07.

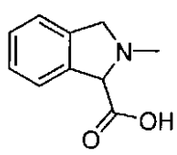
Cap-166a y -166b



Cap-166a: Diastereómero-1
Cap-166b: Diastereómero-2

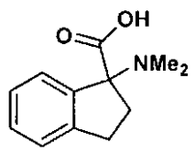
Caps-166a y *-166b* se prepararon a partir de (1S, 4S)-(+)-2-metil-2,5-diazabiciclo[2.2.1]heptano (2HBr) de acuerdo con el procedimiento descrito para la síntesis de *Cap-7a y Cap-7b*, con la salvedad de que se separó el éster bencílico intermedio usando una columna semipreparativa Chiralcel OJ, 20 x 250 mm, 10 μm eluyendo con una mezcla 85:15 de heptano/etanol a 10 ml/min de caudal de elución durante 25 min. *Cap-166b*: RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 7,45 (d, J = 7,3 Hz, 2H), 7,27-7,19 (m, 3H), 4,09 (s, 1H), 3,34 (s ancho ap, 1H), 3,16 (s ancho ap, 1H), 2,83 (d, *J*=10,1 Hz, 1H), 2,71 (m, 2H), 2,46 (m, 1H), 2,27 (s, 3H), 1,77 (d, J = 9,8 Hz, 1H), 1,63 (d, J = 9,8 Hz, 1H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247,14; encontrado: 247,11.

Cap-167



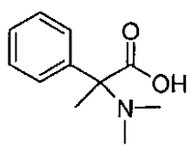
Se agitó una solución de ácido Boc-1,3-dihidro-2H-isoindol carboxílico racémico (1,0g, 3,8 mmol) en TFA al 20%/CH_2Cl_2 a ~25 °C durante 4h. Se eliminó todo el componente volátil a vacío. Se expuso una mezcla del material bruto resultante, formaldehído (15 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (10 mg) en MeOH a H_2 (275,71 kPa) en un frasco de Parr durante 23 h. La mezcla de reacción se filtró sobre Celite y se concentró a vacío proporcionando *Cap-167* como una espuma amarilla (873,5 mg). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz) 7,59-7,38 (m, 4H), 5,59 (s, 1H), 4,84 (d, J = 14 Hz, 1H), 4,50 (d, J = 14,1 Hz, 1H), 3,07 (s, 3H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_2$: 178,09; encontrado: 178,65.

Cap-168



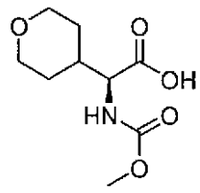
Se preparó *Cap-168* racémico a partir de ácido Boc-aminoindano-1-carboxílico racémico de acuerdo con el procedimiento descrito para la preparación de *Cap-167*. El producto bruto se empleó como tal.

Cap-169



Se colocó una mezcla de clorhidrato de ácido 2-amino-2-fenilpropanoico (5,0 g, 2,5 mmol), formaldehído (15 ml, 37% en agua), HCl 1N (15 ml) y Pd al 10%/C (1,32 g) en MeOH (60 ml) en un frasco de Parr y se agitó en hidrógeno (379,11 kPa) durante 4 días. La mezcla de reacción se filtró sobre Celite y se concentró a vacío. El residuo se suspendió en MeOH y se purificó por HPLC preparativa de fase inversa (MeOH/agua/TFA) proporcionando la sal TFA de *Cap-169* como un semisólido viscoso (2,1 g). RMN de ^{1}H ($CDCl_3$, δ = 7,26 ppm, 500 MHz): 7,58-7,52 (m, 2 H), 7,39-7,33 (m, 3H), 2,86 (s ancho, 3H), 2,47 (s ancho, 3H), 1,93 (s, 3H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,12; encontrado: 194,12.

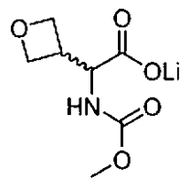
Cap-170



A ácido (*S*)-2-amino-2-(tetrahidro-2*H*-piran-4-il)acético (505 mg; 3,18 mmol; obtenido de Astatech) en agua (15ml) se añadió carbonato sódico (673 mg; 6,35 mmol) y la mezcla resultante se enfrió hasta 0ºC momento en el que se añadió cloroformiato de metilo (0,26ml; 3,33mmol) gota a gota durante 5 minutos. Se dejó agitando la reacción durante 18 horas llegando lentamente a temperatura ambiente a medida que se fundía el baño de hielo. La mezcla de reacción se repartió entonces entre HCl 1N y acetato de etilo. La fase orgánica se separó y la fase acuosa se extrajo de nuevo con dos porciones más de acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío

dando un residuo incoloro. RMN de ^{1}H (500 MHz, *DMSO-d$_6$*) δ ppm 12,65 (1 H, s ancho), 7,44 (1 H, d, *J*=8,24 Hz), 3,77 - 3,95 (3 H, m), 3,54 (3 H, s), 3,11 - 3,26 (2 H, m), 1,82 - 1,95 (1 H, m), 1,41 - 1,55 (2 H, m), 1,21 - 1,39 (2 H, m); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{16}NO_5$: 218,1; encontrado 218,1.

Cap-171

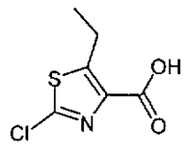


Una solución de 2-(benciloxicarbonilamino)-2-(oxetan-3-iliden)acetato de metilo (200 mg, 0,721 mmol; Il Farmaco (2001), 56, 609–613) en acetato de etilo (7 ml) y CH_2Cl_2 (4,00 ml) se desgasificó burbujeando nitrógeno durante 10min. Se añadieron entonces dicarbonato de dimetilo (0,116 ml, 1,082 mmol) y Pd/C (20 mg, 0,019 mmol), la mezcla de reacción se ajustó bajo un globo de hidrógeno y se dejó agitando a temperatura ambiente durante la noche momento en el que la TLC (95:5 CH_2Cl_2 / MeOH: visualizada con tinción realizada en 1g de $Ce(NH_4)_2SO_4$, 6g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua) indicó la conversión completa. La reacción se filtró a través de Celite y se concentró. El residuo se purificó por Biotage® (cada con diclorometano en 25 de muestra; elución en columna 25S con diclorometano para 3CV luego 0 a 5% de MeOH / diclorometano sobre 250ml luego mantenido a 5% de MeOH / diclorometano para 250ml; fracciones de 9 ml). Las fracciones obtenidas que contenían material deseado y se concentraron hasta 120 mg (81%) de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo como un aceite incoloro. RMN de ^{1}H (500 MHz, CLOROFORMO-D) δ ppm 3,29

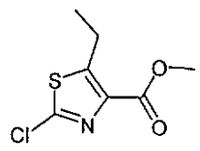
- 3,40 (m, *J*=6,71 Hz, 1 H) 3,70 (s, 3 H) 3,74 (s, 3 H) 4,55 (t, *J*=6,41 Hz, 1 H) 4,58 - 4,68 (m, 2 H) 4,67 - 4,78 (m, 2 H) 5,31 (s ancho, 1 H). CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{14}NO_5$: 204,2; encontrado 204,0.

Se añadió a 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo (50 mg, 0,246 mmol) en THF (2 ml) y agua (0,5 ml) hidróxido de litio monohidratado (10,33 mg, 0,246 mmol). La solución resultante se dejó agitando durante la noche a temperatura ambiente. La TLC (1:1 EA / Hex; tinción de Hanessian [1g de $Ce(NH_4)_2SO_4$, 6 g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua]) indicó que quedaba ~10% de material de partida. Se añadieron otros 3 mg de LiOH y se dejó agitando durante la noche momento en el que la TLC mostró que no quedaba material de partida. Se concentró a vacío y se colocó en alto vacío durante la noche proporcionando 55 mg de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de litio como un sólido incoloro. RMN de ^1H (500 MHz, MeOD) δ ppm 3,39 - 3,47 (m, 1 H) 3,67 (s, 3 H) 4,28 (d, *J*=7,93 Hz, 1 H) 4,64 (t, *J*=6,26 Hz, 1 H) 4,68 (t, *J*=7,02 Hz, 1 H) 4,73 (d, *J*=7,63 Hz, 2 H).

Cap-172



Cap-172, etapa a



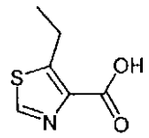
La siguiente etapa de diazotación se adaptó de Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: Se añadió una solución de $NaNO_2$ (166 mg, 2,4 mmol) en agua (0,6 ml) a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1,0 mmol), $CuSO_4 \cdot 5H_2O$ (330 mg, 1,32 mmol), NaCl (260 mg, 4,45 mmol) y H_2SO_4 (5,5 ml) en agua (7,5 ml). La mezcla se agitó a 0 °C durante 45 min y se dejó calentar hasta temperatura ambiente donde se agitó durante otra 1 h antes de añadir CuCl (118 mg). Esta mezcla se agitó de nuevo a temperatura ambiente durante 16 h antes de diluirse con salmuera y extraerse con éter dos veces. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 2-cloro-5-etiltiazol-4-carboxilato de metilo (es decir, *Cap-172, etapa a*) (175 mg, 85%) como un aceite naranja (80% de pureza) que se usó directamente en la siguiente reacción. T_R = 1,99 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_7H_9ClNO_2S$: 206,01; encontrado: 206,05.

Cap-172

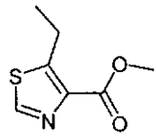
A una solución de 2-cloro-5-etiltiazol-4-carboxilato de metilo (175 mg) en THF/H_2O/MeOH (20 ml/ 3 ml/ 12 ml) se añadió LiOH (305 mg, 12,76 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando *Cap-172* (60 mg, 74%) como un sólido rojo que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 13,03-13,42 (1 H, m), 3,16 (2 H, q, J = 7,4 Hz), 1,23 (3 H, t, J = 7,5 Hz). T_R = 1,78 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$

$C_6H_7ClNO_2S$: 191,99; encontrado: 191,99.

Cap-173



Cap-173, etapa a

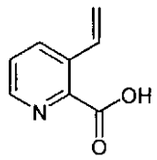


La siguiente etapa de diazotación se adaptó de Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: Se añadió una solución de $NaNO_2$ (150 mg, 2,17 mmol) en agua (1,0 ml) gota a gota a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1,0 mmol) en H_3PO_2 al 50% (3,2 ml). La mezcla se agitó a 0 °C durante 1 h y se dejó calentar hasta temperatura ambiente donde se agitó durante otras 2h. Después de volver a enfriar hasta 0 °C, la mezcla se trató lentamente con una solución de NaOH (85 mg) en agua (10 ml). La mezcla se diluyó entonces con solución saturada de $NaHCO_3$ y se extrajo dos veces con éter. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 5-etiltiazol-4-carboxilato de metilo (es decir, *Cap-173, etapa a*) (134 mg, 78%) como un aceite naranja (85% de pureza) que se usó directamente en la siguiente reacción. T_R = 1,58 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_7H_{10}NO_2S$: 172,05; encontrado: 172,05.

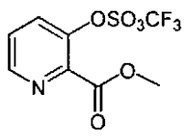
Cap-173

A una solución de 5-etiltiazol-4-carboxilato de metilo (134 mg) en THF/H_2O/MeOH (18 ml/ 2,7 ml/ 11 ml) se añadió LiOH (281 mg, 11,74 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando *Cap-173* (90 mg, 73%) como un sólido naranja que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 12,74-13,04 (1 H, m), 3,20 (2 H, q, *J* = 7,3 Hz), 1,25 (3 H, t, *J* = 7,5 Hz). T_R = 1,27 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_6H_8NO_2S$: 158,03; encontrado: 158,04.

Cap-174



Cap-174, etapa a



Se añadió anhídrido tríflico (5,0 g, 18,0 mmol) gota a gota a una solución fría (0 °C) de 3-hidroxipicolinato de metilo (2,5 g, 16,3 mmol) y TEA (2,5 ml,

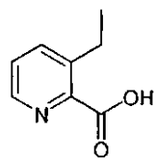
18,0 mmol) en CH_2Cl_2 (80 ml). La mezcla se agitó a 0 °C durante 1h antes de dejar calentar hasta temperatura ambiente, momento en el que se agitó durante una hora más. La mezcla se inactivó entonces con solución saturada de $NaHCO_3$ (40 ml) y la fase orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró dando 3-(trifluorometilsulfoniloxi)picolinato de metilo (*es decir, Cap-174, etapa a*) (3,38 g, 73%) como un aceite marrón oscuro (>95% de pureza) que se usó directamente sin purificación posterior. RMN de ^1H (300 MHz, $CDCl_3$) δ ppm 8,72-8,79 (1 H, m), 7,71 (1 H, d, J = 1,5 Hz), 7,58-7,65 (1 H, m), 4,04 (3 H, s). T_R = 1,93 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_7F_3NO_5S$: 286,00; encontrado: 286,08.

Cap-174

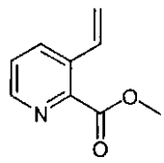
A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (570 mg, 2,0 mmol) en DMF (20 ml) se añadió LiCl (254 mg, 6,0 mmol), tributil(vinil)estannano (761 mg, 2,4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0,06 mmol). La mezcla se calentó a 100 °C durante la noche antes d añadir una solución saturada de KF (20 ml) a la mezcla de reacción a temperatura ambiente. Esta mezcla se agitó durante 4 h antes de filtrar a través de Celite y el lecho de Celite se lavó con acetato de etilo. La fase acuosa del filtrado se separó entonces y se concentró a vacío. El residuo se trató con HCl 4*N* en dioxanos (5 ml) y la mezcla resultante se extrajo con metanol, se filtró y se evaporó proporcionando *Cap-174* (260 mg) como un sólido verde que estaba ligeramente contaminado con sales inorgánicas pero que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 8,21 (1 H, d, J = 3,7 Hz), 7,81-7,90 (1 H, m), 7,09 (1 H, dd, J = 7,7, 4,8 Hz),

6,98 (1 H, dd, *J* = 17,9, 11,3 Hz), 5,74 (1 H, dd, *J* = 17,9, 1,5 Hz), 5,20 (1 H, d, *J* = 11,0 Hz). T_R = 0,39 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_8NO_2$: 150,06; encontrado: 150,07.

Cap-175



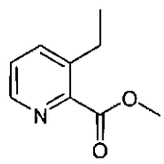
Cap-175, etapa a



A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (*es decir, Cap 173, etapa a*) (570 mg, 2,0 mmol), un intermedio en la preparación de *Cap-174*, en DMF (20 ml) se añadió LiCl (254 mg, 6,0 mmol), tributil(vinil)estannano (761 mg, 2,4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0,06 mmol). La mezcla se calentó a 100 °C durante 4 h antes de eliminar el disolvente a vacío. El residuo se suspendió en acetonitrilo (50 ml) y hexanos (50 ml) y la mezcla resultante se lavó dos veces con hexanos. Se separó entonces la fase de acetonitrilo, se filtró a través de Celite y se evaporó. La purificación del residuo por cromatografía ultrarrápida en un aparato Horizon (elución con gradiente de acetato de etilo al 25% en hexanos hasta acetato de etilo al 65% en hexanos) proporcionó 3-vinilpicolinato de metilo (es decir, *Cap-175, etapa a*) (130 mg, 40%) como un aceite amarillo.

RMN de ^{1}H (300 MHz, $CDCl_3$) δ ppm 8,60 (1 H, dd, *J* = 4,6, 1,7 Hz), 7,94 (1 H, d, *J* = 7,7 Hz), 7,33-7,51 (2 H, m), 5,72 (1 H, d, *J* = 17,2 Hz), 5,47 (1 H, d, *J* = 11,0 Hz), 3,99 (3 H, s). T_R = 1,29 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{10}NO_2$: 164,07; encontrado: 164,06.

Cap-175, etapa b



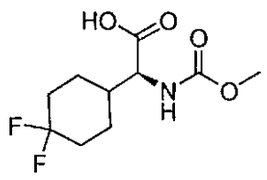
Se añadió paladio sobre carbón (10%, 25 mg) a una solución de 3-vinilpicolinato de metilo (120 mg, 0,74 mmol) en etanol (10 ml). La suspensión se agitó a temperatura ambiente en una atmósfera de hidrógeno durante 1 h antes de filtrar a través de Celite y se lavó el lecho de Celite con metanol. El filtrado se concentró hasta sequedad proporcionando 3-etilpicolinato de metilo (es decir, *Cap-175, etapa b*) que se llevó directamente a la siguiente reacción. T_R = 1,15 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{12}NO_2$: 166,09; encontrado: 166,09.

Cap-175

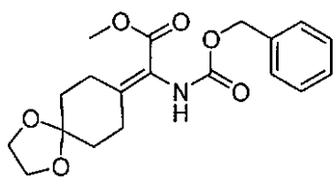
A una solución de 3-etilpicolinato de metilo en THF/H_2O/MeOH (5 ml/ 0,75 ml/ 3 ml) se añadió LiOH (35 mg, 1,47 mmol). La mezcla se agitó a temperatura ambiente durante 2 días antes de añadir más LiOH (80 mg). Después de otras 24 horas más a temperatura ambiente, la mezcla se filtró y el disolvente se eliminó a vacío. El residuo se trató entonces con HCl 4*N* en dioxanos (5 ml) y la suspensión resultante se concentró hasta sequedad

proporcionando *Cap-175* como un sólido amarillo que se usó sin purificación posterior. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 8,47 (1 H, dd, J = 4,8, 1,5 Hz), 7,82-7,89 (1 H, m), 7,53 (1 H, dd, J = 7,7, 4,8 Hz), 2,82 (2 H, q, J = 7,3 Hz), 1,17 (3 H, t, J = 7,5 Hz). T_R = 0,36 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{10}NO_2$: 152,07; encontrado: 152,10.

Cap-176



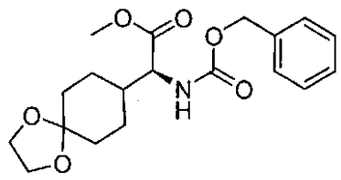
Cap-176, etapa a



Se añadió una solución de 1,4-dioxaspiro[4,5]decan-8-ona (15 g, 96 mmol) en EtOAc (150 ml) a una solución de 2-(benciloxicarbonilamino)-2-(dimetoxifosforil)acetato de metilo (21,21 g, 64,0 mmol) en 1,1,3,3-tetrametilguanidina (10,45 ml, 83 mmol) y EtOAc (150 ml). La solución resultante se agitó a temperatura ambiente durante 72 h y luego se diluyó con EtOAc (25 ml). La fase orgánica se lavó con HCl 1N (75 ml), H_2O (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por Biotage (EtOAc al 5% hasta 25 %/Hexanos; 300g columna). Las fracciones reunidas que contenían el producto se concentraron entonces a

vacío y el residuo se volvió a cristalizar en hexanos/EtOAc dando cristales blancos que corresponden a 2-(benciloxicarbonilamino)-2-(1,4-dioxaspiro[4,5]decan-8-iliden)acetato de metilo (6,2 g) RMN de ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 7,30 - 7,44 (5 H, m), 6,02 (1 H, s ancho), 5,15 (2 H, s), 3,97 (4 H, s), 3,76 (3 H, s ancho), 2,84 - 2,92 (2 H, m), 2,47 (2 H, t, *J*=6,40 Hz), 1,74 - 1,83 (4 H, m). LC (Cond. OL1): T_R = 2,89 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745,21; encontrado: 745,47

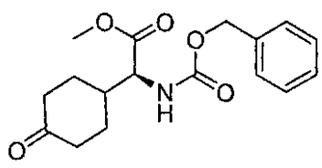
Cap 176, etapa b



Se preparó el éster *Cap 176, etapa b* a partir del alqueno *Cap 176, etapa a* de acuerdo con el procedimiento de Burk, M. J.; Gross, M. F. and Martinez J. P. (*J. Am. Chem. Soc.*, **1995**, *117*, 9375-9376 y referencias en el mismo): Se cargó una botella a alta presión de 500 ml con el alqueno *Cap 176, etapa a* (3,5 g, 9,68 mmol) en MeOH desgasificado (200 ml) en una capa de N_2. La solución se cargó entonces con tetrafluoroborato de (-)-1,2-bis((2S,5S)-2,5-dimetilfosfolano)etano(ciclooctadieno)rodio (I) (0,108 g, 0,194 mmol) y la mezcla resultante se cubrió con N_2 (3x) y se cargó con H_2 (3x). La solución se agitó vigorosamente a 482 kPa de H_2 a temperatura ambiente durante 72 h. El disolvente se eliminó a presión reducida y el residuo que quedó se suspendió en EtOAc. La solución pardusca se filtró entonces a través de un lecho de gel de sílice y se eluyó con EtOAc. El disolvente se concentró a vacío proporcionando un aceite transparente que correspondía al éster *Cap 176,*

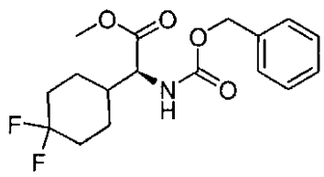
etapa b (3,4 g), RMN de ^{1}H (500 MHz, $CDCl_3$-*d*) δ ppm 7,28 - 7,43 (5 H, m), 5,32 (1 H, d, *J*=9,16 Hz), 5,06 - 5,16 (2 H, m), 4,37 (1 H, dd, *J*=9,00, 5,04 Hz), 3,92 (4 H, t, *J*=3,05 Hz), 3,75 (3 H, s), 1,64 - 1,92 (4 H, m), 1,37 - 1,60 (5 H, m). LC (Cond. OL1): T_R = 1,95 min. CL/EM: Análisis calculado para $[M+H]^+$ $C_{19}H_{26}NO_6$: 364,18; encontrado: 364,27.

Cap 176, etapa c



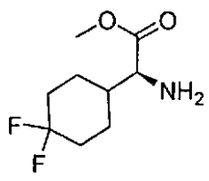
Se disolvió el éster *Cap 176, etapa b* (4,78 g, 13,15 mmol) en THF (15 ml) seguido por la adición secuencial de agua (10 ml), ácido acético glacial (26,4 ml, 460 mmol) y ácido dicloroacético (5,44 ml, 65,8 mmol). La mezcla resultante se agitó durante 72 h a temperatura ambiente, y la reacción se inactivó mediante la adición lente de Na_2CO_3 sólido con agitación vigorosa hasta que no fue visible la generación de gas. El producto bruto se extrajo en acetato de etilo al 10%-diclorometano y las fases orgánicas se reunieron, se secaron ($MgSO_4$), se filtraron y concentraron. El residuo resultante se purificó por Biotage (EtOAc al 0 hasta 30%/Hex; 25 g de columna) proporcionando la cetona *Cap 176, etapa c* (3,86g) como un aceite transparente. RMN de ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 7,28 - 7,41 (5 H, m), 5,55 (1 H, d, *J*=8,28 Hz), 5,09 (2 H, s), 4,46 (1 H, dd, *J*=8,16, 5,14 Hz), 3,74 (3 H, s), 2,18 - 2,46 (5 H, m), 1,96 - 2,06 (1 H, m), 1,90 (1 H, ddd, *J*=12,99, 5,96, 2,89 Hz), 1,44 - 1,68 (2 H, m, *J*=12,36, 12,36, 12,36, 12,36, 4,77 Hz). LC (Cond. OL1): T_R = 1,66 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342,13; encontrado: 342,10.

Cap 176, etapa d



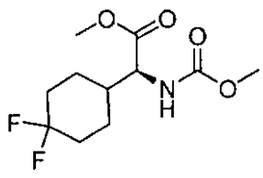
Se añadió Deoxo-Fluor® (3,13 ml, 16,97 mmol) a una solución de la cetona *Cap 176, etapa c* (2,71 g, 8,49 mmol) en CH_2Cl_2 (50 ml) seguido por la adición de una cantidad catalítica de EtOH (0,149 ml, 2,55 mmol). La solución amarillenta resultante se agitó a ta durante la noche. La reacción se inactivó mediante la adición de $NaHCO_3$ acuoso saturado (25 ml) y la mezcla se extrajo con EtOAc (3X75 ml)). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se secaron dando un aceite amarillento. El residuo se purificó por cromatografía en Biotage (EtOAc al 2% hasta 15%/Hex; 90g de columna) y se recuperó un sólido blanco correspondiente al difluoruro de difluoro aminoácido *Cap 176, etapa d* (1,5 g). RMN de ^1H (400 MHz, $CDCl_3$-*d*) δ ppm 7,29 - 7,46 (5 H, m), 5,34 (1 H, d, *J*=8,28 Hz), 5,12 (2 H, s), 4,41 (1 H, dd, *J*=8,66, 4,89 Hz), 3,77 (3 H, s), 2,06 - 2,20 (2 H, m), 1,83 - 1,98 (1 H, m), 1,60 - 1,81 (4 H, m), 1,38 - 1,55 (2 H, m). RMN de ^{19}F (376 MHz, $CDCl_3$-*d*) δ ppm -92,15 (1 F, d, *J*=237,55 Hz), -102,44 (1 F, d, *J*=235,82 Hz). LC (Cond. OL1): T_R = 1,66 min. CL/EM: Análisis calculado para $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705,28; encontrado: 705,18.

Cap 176, etapa e



Se disolvió el difluoruro *Cap 176, etapa d* (4 g, 11,72 mmol) en MeOH (120 ml) y se cargó con Pd/C (1,247 g, 1,172 mmol). Se inyectó en la suspensión N_2 (3x) y la mezcla de reacción se colocó bajo una presión de 101 kPa de H_2 (globo). La mezcla se agitó a temperatura ambiente durante 48 h. La suspensión se filtró entonces a través de un lecho de Celite y se concentró a vacío dando un aceite que corresponde al aminoácido *Cap 176, etapa e* (2,04 g) y que se usó sin purificación posterior. RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ ppm 3,62 (3 H, s), 3,20 (1 H, d, *J*=5,77 Hz), 1,91 - 2,09 (2 H, m), 1,50 - 1,88 (7 H, m), 1,20 - 1,45 (2 H, m). RMN de ^{19}F (376 MHz, *DMSO-d*$_6$) δ ppm -89,39 (1 F, d, *J*=232,35 Hz), -100,07 (1 F, d, *J*=232,35 Hz). RMN de ^{13}C (101 MHz, *DMSO-d*$_6$) δ ppm 175,51 (1 C, s), 124,10 (1 C, t, *J*=241,21, 238,90 Hz), 57,74 (1 C, s), 51,39 (1 C, s), 39,23 (1 C, s ancho), 32,02 - 33,83 (2 C, m), 25,36 (1 C, d, *J*=10,02 Hz), 23,74 (1 C, d, *J*=9,25 Hz). LC (Cond. OL2): T_R = 0,95 min. CL/EM: Análisis calculado para $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415,22; encontrado: 415,40.

Cap 176, etapa f



Se añadió cloroformiato de metilo (1,495 ml, 19,30 mmol) a una solución de aminoácido *Cap 176, etapa e* (2 g, 9,65 mmol) y DIEA (6,74 ml, 38,6 mmol)

en CH_2Cl_2 (100 ml). La solución resultante se agitó a ta durante 3 h y se eliminaron los volátiles a presión reducida. El residuo se purificó por Biotage (EtOAc al 0% hasta 20%/Hex; 90 g de columna). Se recuperó un aceite transparente que solidificó en reposo a vacío y que correspondía al carbamato *Cap-176, etapa f* (2,22 g). RMN de ^{1}H (500 MHz, $CDCl_3$-*d*) δ ppm 5,27 (1 H, d, *J*=8,55 Hz), 4,39 (1 H, dd, *J*=8,85, 4,88 Hz), 3,77 (3 H, s), 3,70 (3 H, s), 2,07 - 2,20 (2 H, m), 1,84 - 1,96 (1 H, m), 1,64 - 1,82 (4 H, m), 1,39 - 1,51 (2 H, m). RMN de ^{19}F (471 MHz, $CDCl_3$-*d*) δ ppm -92,55 (1 F, d, *J*=237,13 Hz), -102,93 (1 F, d, *J*=237,12 Hz). RMN de ^{13}C (126 MHz, $CDCl_3$-*d*) δ ppm 171,97 (1 C, s), 156,69 (1 C, s), 119,77 - 125,59 (1 C, m), 57,24 (1 C, s ancho), 52,48 (1 C, s ancho), 52,43 (1 C, s), 39,15 (1 C, s), 32,50 - 33,48 (2 C, m), 25,30 (1 C, d, *J*=9,60 Hz), 24,03 (1 C, d, *J*=9,60 Hz). LC (Cond. OL1): T_R = 1,49 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288,10; encontrado: 288,03.

Cap-176

Se añadió una solución de LiOH (0,379 g, 15,83 mmol) en agua (25 ml) a una solución de carbamato *Cap-176, etapa f* (2,1 g, 7,92 mmol) en THF (75 ml) y la mezcla resultante se agitó a temperatura ambiente durante 4 h. Se eliminó el THF a vacío y la fase acuosa restante se acidificó con solución de HCl 1N (2 ml) y luego se extrajo con EtOAc (2 X 50 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron dando una espuma que correspondía al *Cap-176* (1,92 g). RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ ppm 12,73 (1 H, s), 7,50 (1 H, d, *J*=8,78 Hz), 3,97 (1 H, dd, *J*=8,53, 6,02 Hz), 3,54 (3 H, s), 1,92 - 2,08 (2 H, m), 1,57 - 1,90 (5 H, m), 1,34 - 1,48 (1 H, m), 1,27 (1 H, qd, *J*=12,72, 3,26 Hz). RMN de ^{19}F (376 MHz, *DMSO-d*$_6$) δ ppm -89,62 (1 F, d,

J=232,35 Hz), -99,93 (1 F, d, *J*=232,35 Hz). CL (Cond. OL2): T_R = 0,76 min. CL/EM: Análisis calculado para $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250,09; encontrado: 250,10.

EJEMPLOS

La presente exposición se describirá ahora con relación a ciertas realizaciones que no pretenden limitar su alcance. Por el contrario, la presente exposición cubre todas las alternativas, modificaciones y equivalentes que se pueden incluir en el alcance de las reivindicaciones. Así, los siguientes ejemplos que incluyen realizaciones específicas, ilustrarán una práctica de la presente exposición, sobreentendiéndose que los ejemplos tienen fines ilustrativos de ciertas realizaciones y se presentan proporcionando lo que se cree es la descripción más útil y fácilmente comprensible de sus procedimientos y aspectos conceptuales.

Los porcentajes en solución expresan una relación peso a volumen y las relaciones de solución expresan una relación volumen a volumen, a no ser que se indique de otro modo. Los espectros de resonancia magnética nuclear (RMN) se registraron bien en un espectrómetro Bruker 300, 400 o 500 MHz; los desplazamientos químicos (δ) se expresan en partes por millón.

La valoración de la pureza y el análisis de masas de baja resolución se llevaron a cabo en un sistema de CL Shimadzu acoplado con un sistema de EM Waters Micromass ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. A no ser que se indique de otro modo, las condiciones de CL empleadas en la determinación del tiempo de retención (T_R) fueron:

Condiciones-J1

Columna = Phenomenex-Luna 3,0X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/agua al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/agua al 10%

Condiciones-J2

Columna = Phenomenex-Luna 3,0X50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Tiempo de parada = 5 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/agua al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/agua al 10%

Condiciones-J3

Columna = XTERRA C18 S7 (3,0 x 50mm)

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/agua al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/agua al 10%

Condiciones-D1

Columna = Phenomenex-Luna 3,0X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/agua al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/agua al 10%

Condiciones-D2

Columna = Phenomenex-Luna 4,6X50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en metanol al 10%/agua al 90%

Disolvente B = TFA al 0,1% en metanol al 90%/agua al 10%

Condiciones-JB-1

Columna = Water Sunfire 5 u C 18 4,6 x 30 mm

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

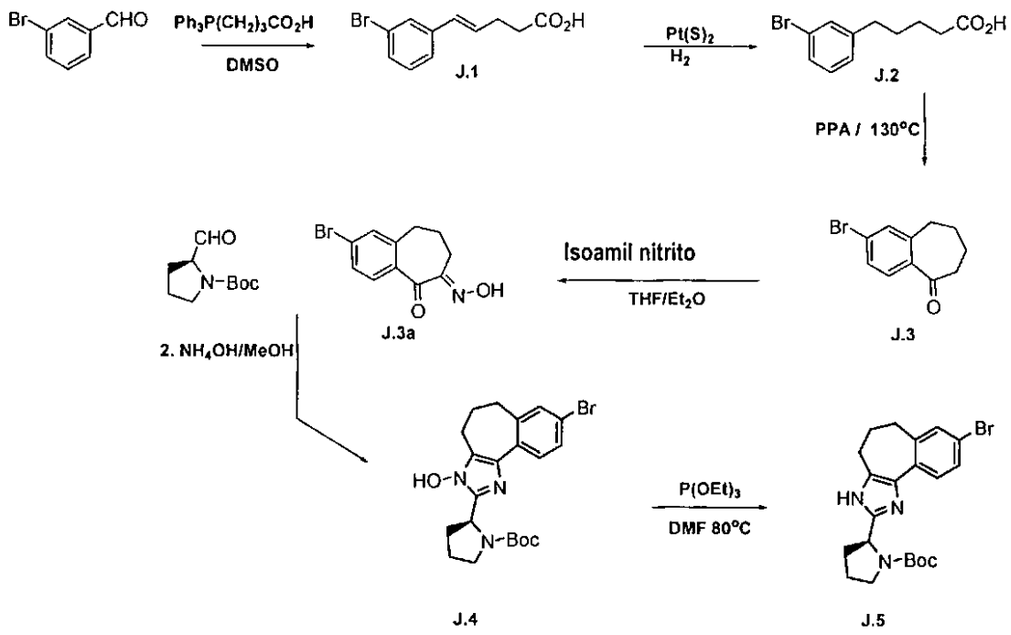
Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0,1% en acetonitrilo al 10%/agua al 90%

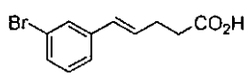
Disolvente B = TFA al 0,1% en acetonitrilo al 90%/agua al 10%

Ruta de síntesis 1:



Referencia: *J.Med.Chem.* (2005) 48, 7351.

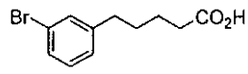
Ejemplos J.1 - J.5



J.1

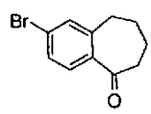
Se añadió una solución 1M de terc-butóxido potásico en tetrahidrofurano (80 ml) gota a gota a bromuro de (3-carboxipropil)trifenilfosfonio (17 g, 40 mol) en DMSO anhidro (20 ml) en nitrógeno a 24°C, y la solución se agitó 30 min. antes de la adición de 3-bromobenzaldehído (4,7 ml, 40 mmol). Después de varios minutos se observó un precipitado y se añadieron otros 20 ml de DMSO para ayudar a solvatar, y la reacción se agitó 18 horas. La solución se vertió en agua (120 ml) y se lavó con cloroformo. La fase acuosa se acidificó con HCl conc. y se extrajo con cloroformo (3 x 250 ml). La fase orgánica se concentró y

se aplicó a una columna de gel de sílice 65i Biotage, elución con gradiente desde 15-65% de B (A = Hexanos; B = acetato de etilo) durante 2 l dando J.1, ácido (E)-5-(3-bromofenil)pent-4-enoico, 8,2 g (82%). RMN de ^{1}H (300 MHz, $CDCl_3$) δ 7,45 (t, J = 1,5 Hz, 1H), 7,30 (dt, J = 7,7, 1,5 Hz, 1H), 7,2-7,16 (m, 1H), 7,12 (t, J = 7,7 Hz, 1H), 6,40-6,32 (m, 1H), 6,23-6,14 (m, 1H), 2,52 (s, 4H). CL (Condiciones-J1): T_R = 2,0 min; EMBR: Análisis calculado para $[M-H]^-$ $C_{11}H_{11}BrO_2$: 252,97; encontrado: 252,98.



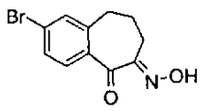
J.2

J.1, Se disolvió ácido (E)-5-(3-bromofenil)pent-4-enoico (4 g, 15,8 mmol) en etanol absoluto (200 ml) y se inyectó con nitrógeno antes de la adición de sulfuro de platino al 5% sobre carbón (2,5 g). La solución se inyectó con hidrógeno a presión atmosférica y se agitó 5 horas. El catalizador se separó por filtración sobre tierra de diatomeas (Celite®) y el disolvente se eliminó inmediatamente por evaporación rotatoria (con el fin de minimizar la esterificación) dando J.2, ácido 5-(3-bromofenil)pentanoico 4 g (99%) que se utilizó a continuación sin purificación adicional. RMN de ^{1}H (500 MHz, $CDCl_3$) δ 7,31-7,30 (m, 2H), 7,13 (t, J = 7,6 Hz, 1H), 7,09-7,07 (d, J = 7,6 Hz, 1H), 2,60 (t, J = 7,0 Hz, 2H), 2,37 (t, J = 7,0 Hz, 2H), 1,68-1,65 (m, 4H). CL (Condiciones-J1): T_R = 2,1 min; EMBR: Análisis calculado para $[M-H]^-$ $C_{11}H_{13}BrO_2$: 255,00; encontrado: 254,99.



J.3

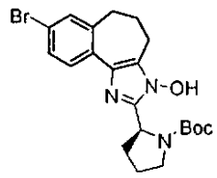
J.2, Se suspendió ácido 5-(3-bromofenil)pentanoico (4 g, 15,6 mmol) en ácido polifosfórico (15 g) y se calentó hasta 140°C durante 8 h en un recipiente a presión de 150 ml, tapado para evitar la pérdida de producto debido a sublimación. La mezcla de reacción se repartió entre 150 ml de agua y diclorometano (600 ml). [Precaución, es necesario evitar la ebullición del diclorometano.] La fase orgánica se lavó con agua, salmuera y se concentró. El producto bruto se aplicó a una columna de gel de sílice 40 (S) Biotage y se eluyó con gradiente desde 5 – 60% (acetato de etilo/hexanos) y dio J.3 2-bromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona 1,7 g (40%). RMN de ^{1}H (300 MHz, $CDCl_3$) δ 7,56 (d, J = 8,1 Hz, 1H), 7,41 (dd, J = 8,4 Hz, 1,8 Hz, 1H), 7,35 (d, J = 1,8 Hz, 1H), 2,86 (t, J = 5,9 Hz, 2H), 2,69 (t, J = 5,8 Hz, 2H), 1,90-1,73 (m, 4H). CL (Condiciones-J1): T_R = 2,1 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}BrO$: 239,00; encontrado: 239,14.



J.3a

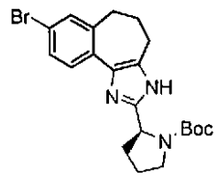
J.3, Se disolvió 2-bromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona (1,5 g, 5,9 mmol) en éter/tetrahidrofurano 2:1 (120 ml) y se añadió HCl 1N en éter (9 ml). La solución se enfrió hasta 0°C antes de añadir isoamil nitrito (1,2 ml, 9 mmol) y la reacción se agitó 18 h a 24°C, se concentró, y se aplicó a una columna de gel de sílice 25 (M) Biotage. Elución con gradiente desde 15-100% de B (A = Hexanos; B = acetato de etilo) durante 1 l y dio J.3a (E)-2-bromo-6-(hidroxiimino)-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona 1 g (64%). CL (Condiciones-J1); T_R = 1,9 min; CL/EM: Análisis calculado para $[M+H]^+$

$C_{11}H_{10}NBrO_2$: 268; encontrado: 268.



J.4

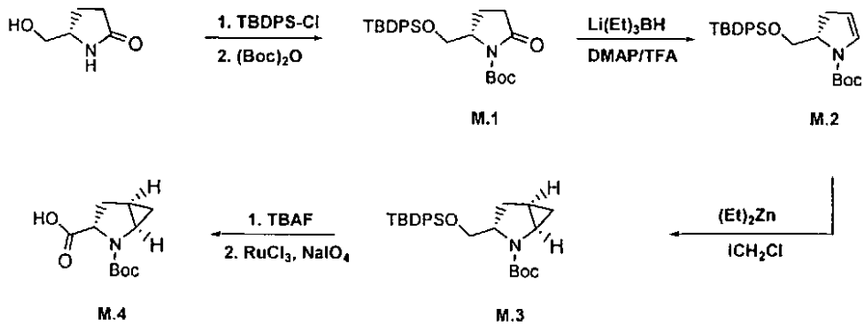
Se añadió hidróxido de amonio concentrado (12 ml, 28%) a una solución de J.3a(E)-2-bromo-6-(hidroxiimino)-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona (1g, 3,7 mmol) y N-Boc-L-prolinal (850 mg, 4,3 mmol) en metanol (35 ml) y la reacción se agitó 18 h a 24ºC. La mezcla de reacción se concentró para eliminar el metanol, la solución acuosa se extrajo con diclorometano, y la fase orgánica se lavó con agua. La aplicación del producto bruto en diclorometano a una columna de gel de sílice 40 (S) Biotage y someter a elución con gradiente; Segmento 1. 15%-30% de B durante 300 ml; Segmento 2. 30%-100% de B durante 700 ml (A = 1:1 hexanos/diclorometano; B = acetato de etilo) dio J.4 700 mg (44%). RMN de ^{1}H (300 MHz, DMSO-d_6) δ 11,3 (s ancho, 1H), 7,91 (d, J = 8,4 Hz, 1H), 7,35 (dd, J = 8,4, 1,5 Hz, 1H), 7,31 (d, J = 1,8 Hz, 1H), 5,0/4,87 (m, 1H), 3,51-3,46 (m, 1H), 3,42-3,36 (m, 1H), 2,90-2,70 (m, 4H), 2,27-1,80 (m, 6H), 1,38/1,11 (s, 9H). CL (Condiciones-J1): T_R = 1,9 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{21}H_{26}BrN_3O_3$: 488,12; encontrado: 488,14. EMAR: Análisis calculado para $[M+H]^+C_{21}H_{26}BrN_3O_3$: 488,1236; encontrado: 488,1242.



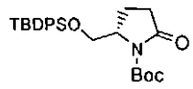
J.5

Se añadió trietilfosfito (0,78 ml, 4,7 mmol) a una solución de J.4 (700 mg, 1,57 mmol) en dimetilformamida (2 ml) y la solución se calentó a 80 °C durante 18 h en una atmósfera de nitrógeno. La mezcla de reacción se suspendió en acetato de etilo (100 ml) y se lavó con agua y salmuera. Después de concentrar el producto bruto se aplicó a una columna de gel de sílice 40 (S) Biotage y sometió a elución con gradiente; Segmento 1. 5%-15% de B durante 300 ml; Segmento 2. 15%-100% de B durante 600 ml (A = diclorometano; B = acetato de etilo) dando J.5 675 mg (100%). RMN de ^{1}H (300 MHz, DMSO-d_6) δ 11,7 (s ancho, 1H), 7,92 (d, J = 8,4 Hz, 1H), 7,82 (d, J = 8,4 Hz, 1H), 7,29 (s, 1H), 4,78/4,69 (s ancho, 1H), 3,57-3,48 (m, 1H), 3,38-3,32 (m, 1H), 2,85-2,78 (m, 4H), 2,28-1,77 (m, 6H), 1,39/1,14 (s, 9H). CL (Condiciones-J1): T_R = 1,9 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{21}H_{26}BrN_3O_2$: 432,13; encontrado: 432,14.

Ruta de síntesis 2



Ejemplos M.1 - M.4

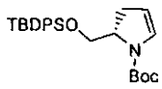


M.1

A una solución de (S)-5-(hidroximetil)pirrolidin-2-ona (10 g, 87 mmol) en diclorometano (50 ml) se añadió terc-butilclorodifenilsilano (25,6 g, 93 mmol), Et_3N (12,1 ml, 87 mmol) y DMAP (1,06 g, 8,7 mmol). La mezcla se agitó a temperatura ambiente hasta que la pirrolidinona de partida se consumió totalmente y luego se diluyó con diclorometano (50 ml) y se lavó con agua (50 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se concentró a vacío, y el material bruto se sometió a cromatografía ultrarrápida (gel de sílice; 30 hasta 100% de acetato de etilo/hexanos) proporcionando el éter de sililo como un aceite incoloro (22,7 g, 74% de rendimiento). RMN de ^1H (400 MHz, DMSO-d_6, δ = 2,5 ppm) 7,69 (s ancho, 1H), 7,64-7,61 (m, 4H), 7,50-7,42 (m, 6H), 3,67-3,62 (m, 1H), 3,58-3,51 (m, 2H), 2,24-2,04 (m, 3H), 1,87-1,81 (m, 1H), 1,00 (s, 9H). CL/EM $[M+H]^+$ = 354,58.

Se añadió dicarbonato de di-terc-butilo (38,5 g, 177 mmol) en porciones como un sólido durante 10 min a una solución en diclorometano (200 ml) de éter de sililo (31,2 g, 88,3 mmol), Et_3N (8,93 g, 88 mmol) y DMAP (1,08 g, 8,83 mmol) y se agitó durante 18 h a 24°C. La mayor parte del material volátil se eliminó a vacío y el material bruto se suspendió en acetato de etilo al 20%/hexanos y se aplicó a un embudo de 2 litros que contenía 1,3 l de gel de sílice y luego eluyó con 3 l de acetato de etilo al 20%/hexano y 2 l de acetato de etilo al 50%). Tras concentrar las fracciones deseadas en un evaporador rotatorio, una suspensión blanca del sólido formado que se filtró, se lavó con

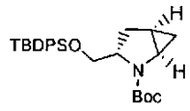
hexanos y se secó a vacío proporcionando carbamato M.1 como un sólido blanco (32,65 g, 82% de rendimiento). RMN de ^{1}H (400 MHz, DMSO-d_6, δ = 2,5 ppm) 7,61-7,59 (m, 2H), 7,56-7,54 (m, 2H), 7,50-7,38 (m, 6H), 4,18 (m, 1H), 3,90 (dd, J = 10,4, 3,6, 1H), 3,68 (dd, J = 10,4, 2,1, 1H), 2,68-2,58 (m, 1H), 2,40-2,33 (m, 1H), 2,22-2,12 (m, 1H), 2,01-1,96 (m, 1H), 1,35 (s, 9H), 0,97 (s, 9H). CL/EM $[M\text{-}Boc+H]^+$ = 354,58. Calculado 454,24.



M.2

Se cargó un matraz de tres bocas equipado con un termómetro y una entrada de nitrógeno con el carbamato M.1 (10,05 g, 22,16 mmol) y tolueno (36 ml), y se sumergió en un baño de enfriamiento a -55ºC. Cuando la temperatura interna de la mezcla alcanzó -50 °C, se añadió gota a gota durante 30 min trietilborohidruro de litio (23 ml de 1,0 M/tetrahidrofurano, 23,00 mmol) y la mezcla se agitó durante 35 min manteniendo la temperatura interna entre -50 °C y -45 °C. Se añadió gota a gota durante 10 min base de Hunig (16,5 ml, 94 mmol). A continuación, se añadió DMAP (34 mg, 0,278 mmol) en una porción, seguido por la adición de anhídrido trifluoroacético (3,6 ml, 25,5 mmol) durante 15 min, manteniendo la temperatura interna entre -50 °C y -45 °C. El baño se retiró 10 minutos después, y la mezcla de reacción se agitó durante 14 h mientras se dejaba llegar hasta temperatura ambiente. Se diluyó con tolueno (15 ml), se enfrió con un baño de hielo-agua, y se trató lentamente con agua (55 ml) durante 5 min. Se separaron las fases y la fase orgánica se lavó con agua (50 ml, 2x) y se concentró a vacío. El material bruto se purificó por cromatografía ultrarrápida (gel de sílice; acetato de etilo al 5%/hexanos)

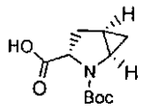
proporcionando dihidropirrol M.2 como un aceite viscoso incoloro (7,947 g, 82% de rendimiento). T_R = 2,41 min en las siguientes condiciones de HPLC: Gradiente de disolvente desde 100% de A : 0% de B hasta 0% de A : 100% de B (A = TFA al 0,1% en metanol/agua 1:9; B = TFA al 0,1% en 9:1 metanol/agua) durante 2 min y mantenido durante 1 min; detección a 220 nm; Columna Phenomenex-Luna 3,0X50 mm S10. RMN de ^{1}H (400 MHz, DMSO-d_6, δ = 2,5 ppm) 7,62-7,58 (m, 4H), 7,49-7,40 (m, 6H), 6,47 (s ancho, 1H), 5,07/5,01 (d ancho solapando 1H), 4,18 (s ancho, 1H), 3,89 (s ancho, 0,49H), 3,69 (s ancho, 1,51H), 2,90-2,58 (m ancho, 2H), 1,40/1,26 (s ancho solapando 9H), 0,98 (s, 9H). CL/EM: $[M+Na]^+$ = 460,19.



M.3

Se añadió gota a gota durante 15 min dietilcinc (19 ml de ~1,1 M en tolueno, 20,9 mmol) a una solución en tolueno (27 ml) enfriada (-30 °C) de dihidropirrol M.2 (3,94 g, 9,0 mmol). Se añadió gota a gota durante 10 min cloroyodometano (estabilizado sobre cobre; 3,0 ml, 41,2 mmol) y se agitó mientras se mantenía la temperatura del baño a -25 °C durante 1 h y de -25 °C a -21 °C durante 18,5 h. Se abrió al aire la mezcla de reacción y se inactivó mediante la adición lenta de solución saturada al 50% de $NaHCO_3$ (40 ml), y luego se retiró del baño de enfriamiento y se agitó a temperatura ambiente durante 20 min. Se filtró a través de un papel de filtro y la torta blanca se lavó con 50 ml de tolueno. La fase orgánica del filtrado se separó y se lavó con agua (40 ml, 2x), se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto

se purificó usando un sistema Biotage (350 g de gel de sílice; la muestra se cargó con acetato de etilo al 7%/hexanos; eluyó con acetato de etilo 7-20% /hexanos) proporcionando una mezcla de metanopirrolidinas (M.3 predomina) como un aceite viscoso incoloro (3,69 g, 90,7%). [Nota: la relación exacta de isómeros cis/trans no se determinó en esta etapa]. T_R = 2,39 min en las siguientes condiciones de HPLC: Gradiente de disolvente desde 100% de A : 0% de B hasta 0% de A : 100% de B (A = TFA al 0,1% en metanol/agua 1:9; B = TFA al 0,1% en 9:1 metanol/agua) durante 2 min, y mantenido durante 1 min; detección a 220 nm; columna Phenomenex-Luna 3,0X50 mm S10. RMN de ^{1}H (400 MHz, DMSO-d_6, δ= 2,5 ppm) 7,62-7,60 (m, 4H), 7,49-7,40 (m, 6H), 3,77/3,67 (s ancho solapando, 3H), 3,11-3,07 (m, 1H), 2,23 (s ancho aparente, 1H), 2,05-2,00 (m, 1H), 1,56-1,50 (m, 1H), 1,33 (s muy ancho, 9H), 1,00 (s, 9H), 0,80 (m, 1H), 0,30 (m, 1H). CL/EM: $[M+Na]^+$ = 474,14.



M.4

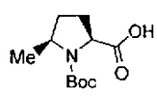
Se añadió gota a gota durante 5 min TBAF (7,27 ml de 1,0 M en tetrahidrofurano, 7,27 mmol) a una solución en tetrahidrofurano (30 ml) de éteres de sililo M.3 (3,13 g, 6,93 mmol) y la mezcla se agitó a temperatura ambiente durante 4,75 h. Después de la adición de solución saturada de cloruro amónico (5 ml), la mayor parte del material volátil se eliminó a vacío y el residuo se repartió entre diclorometano (70 ml) y solución saturada al 50% de cloruro amónico (30 ml). La fase acuosa se extrajo con diclorometano (30 ml), y la fase orgánica reunida se secó ($MgSO_4$), se filtró, se concentró a vacío y

luego se expuso a alto vacío durante la noche. El material bruto se purificó usando un sistema Biotage (gel de sílice; 40-50% de acetato de etilo/hexanos) proporcionando una mezcla de alcoholes, contaminada con trazas de una mancha de Rf menor, como un aceite incoloro (1,39 g, ~94% de rendimiento). [Nota: la relación exacta de isómeros cis/trans no se determinó en esta etapa.] RMN de ^{1}H (400 MHz, dimetilsulfóxido-d_6, δ= 2,5 ppm) 4,70 (t, J = 5,7, 1H), 3,62-3,56 (m, 1H), 3,49-3,44 (m, 1H), 3,33-3,27 (m, 1H), 3,08-3,04 (m, 1H), 2,07 (m ancho, 1H), 1,93-1,87 (m, 1H), 1,51-1,44 (m, 1H), 1,40 (s, 9H), 0,76-0,71 (m, 1H), 0,26 (m, 1H). CL/EM $[M+Na]^+$ = 236,20.

Una semisolución de peryodato sódico (6,46 g, 30,2 mmol) en agua (31 ml) se añadió a una solución de alcoholes (2,15 g, 10,08 mmol) en acetonitrilo (20 ml) y tetracloruro de carbono (20 ml). Se añadió inmediatamente tricloruro de rutenio (0,044 g, 0,212 mmol) y la mezcla de reacción heterogénea se agitó intensamente durante 75 min. La mezcla de reacción se diluyó con agua (60 ml) y se extrajo con diclorometano (50 ml, 3x). La fase orgánica reunida se trató con 1 ml metanol, se dejó reposar durante aproximadamente 5 min, y luego se filtró a través de tierra de diatomeas. El lecho se lavó con diclorometano (50 ml), y el filtrado se concentró a vacío proporcionando un sólido claro color carbón. El material bruto se disolvió en acetato de etilo (~10 ml) con calentamiento y se dejó reposar a temperatura ambiente con iniciadores. Aproximadamente 15 minutos en la fase de enfriamiento se observó una rápida formación de cristales. Aproximadamente 1 hora después, se añadieron hexanos (~6 ml) y la mezcla se refrigeró durante la noche (no parecía que precipitara material adicional). La mezcla se filtró y se lavó con hexanos/acetato de etilo enfriado con hielo/agua (relación 2:1; 20 ml) y se secó a alto vacío

proporcionando la primera tanda del ácido M.4 (cristales blanquecinos, 1,222 g). Las aguas madres se concentraron a vacío, y el residuo se volvió a disolver en ~3 ml de acetato de etilo con calentamiento, se dejó reposar a temperatura ambiente durante 1 h, y luego se añadieron 3 ml de hexanos y se almacenó en un frigorífico durante ~15 h. Se obtuvo igualmente una segunda tanda del ácido M.4 (cristales grises, 0,133 g), con un rendimiento combinado de 59%. T_R = 1,48 min en las siguientes condiciones de HPLC: Gradiente de disolvente desde 100% de A : 0% de B hasta 0% de A : 100% de B (A = TFA al 0,1% en metanol/agua 1:9; B = TFA al 0,1% en 9:1 metanol/agua) durante 3 min; detección a 220 nm; columna Phenomenex-Luna 3,0X50 mm S10. PF (desc.) para la primera tanda = 147,5-149,5 °C. RMN de ^{1}H (400 MHz, DMSO-d_6, δ = 2,5 ppm) 12,46 (s, 1H), 3,88 (s ancho aparente, 1H), 3,27 (s ancho aparente, 1H; solapado con la señal del agua), 2,28 (m ancho, 1H), 2,07 (s ancho aparente, 1H), 1,56 (s ap, 1H), 1,40/1,34 (dos s solapados, 9H), 0,71 (m, 1H), 0,45 (m, 1H). RMN de ^{13}C (100,6 MHz, DMSO-d_6, δ = 39,21 ppm) 172,96, 172,60, 154,45, 153,68, 78,74, 59,88, 59,58, 36,91, 31,97, 31,17, 27,77, 27,52, 14,86, 14,53, 13,69. CL/EM $[M+Na]^+$ = 250,22. Análisis calculado para C11H17NO4: C, 58,13; H, 7,54; N, 6,16. Encontrado (para la primera tanda): C, 58,24; H, 7,84; N, 6,07. Rotación óptica (10 mg/ml en $CHCl_3$): [α] D = -216 y -212 para la primera y segunda tanda, respectivamente.

Ejemplo M.4a

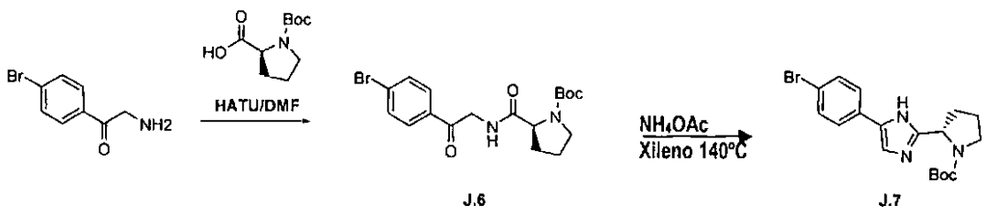


M.4a

La síntesis del ácido M.4a se describe en la solicitud de patente US

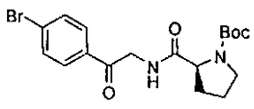
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Ruta de síntesis 3



J.6 J.7

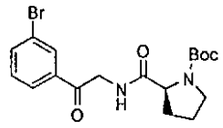
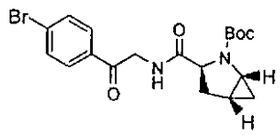
Ejemplos J.6 - J.7b

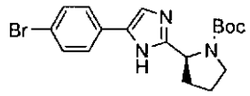


J.6

Se añadió gota a gota durante 15 minutos *N,N*-diisopropiletilamina (18 ml, 103,3 mmol) 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 2-amino-1-(4-bromo-fenil)etanona (8,127 g, 32,44 mmol), en dimetilformamida (105 ml) y se agitó en condiciones ambientales durante 55 minutos. Se eliminó la dimetilformamida a vacío, y el residuo resultante se repartió entre acetato de etilo (300 ml) y agua (200 ml). La fase orgánica se lavó con agua (200 ml) y salmuera, se secó ($MgSO_4$), se filtró y se concentró. Se preparó una malla de gel de sílice a partir del residuo y se sometió a cromatografía ultrarrápida (gel de sílice; acetato de etilo al 50-60%/hexanos) proporcionando J.6 2-(2-(4-bromofenil)-2-oxoetilcarbamoil)pirrolidin-1-carboxilato de (S)-terc-butilo como un sólido blanco (12,8 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 8,25-8,14 (m, 1H), 7,92 (d ancho, *J* = 8,0, 2H), 7,75 (d ancho, *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 s anchos aparentes, 9H). CL (Condiciones-J1): T_R = 1,70 min; CLEM: Análisis calculado para $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433,07; encontrado 433,09.

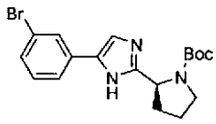
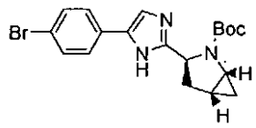
J.6a		EMBR: Análisis calculado para $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433,07; encontrado: 433,12
J.6b	 A partir de M.4	CL (Condiciones-J1): T_R = 1,7 min; Análisis calculado para $[M+Na]^+$ $C_{19}H_{23}BrN_2NaO_4$: 445,08; encontrado: 446,93.



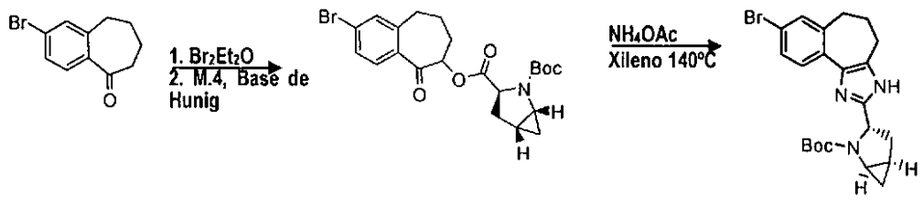
J.7

Se calentó en un tubo sellado a 140ºC durante 2 horas una mezcla de J.6 2-(2-(4-bromofenil)-2-oxoetilcarbamoil)-pirrolidin-1-carboxilato de (S)-terc-butilo (12,8 g, 31,12 mmol) y acetato amónico (12,0 g, 155,7 mmol) en xilenos (155 ml). El componente volátil se eliminó a vacío, y el residuo se repartió cuidadosamente entre acetato de etilo y agua, tras lo cual se añadió suficiente solución saturada de $NaHCO_3$ para que el pH de la fase acuosa fuera ligeramente básico después de agitar el sistema bifásico. Las fases se separaron, y la fase acuosa se extrajo con acetato de etilo adicional. La fase orgánica reunida se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El material resultante se recristalizó en acetato de etilo/hexanos proporcionando dos tandas de J.7 2-(5-(4-bromofenil)-1H-imidazol-2-

il)pirrolidin-1-carboxilato de (S)-terc-butilo, 5,85 g. Las aguas madres se concentraron a vacío y sometieron a una cromatografía ultrarrápida (gel de sílice; 30% acetato de etilo/hexanos) proporcionando otros 2,23 g. RMN de ^{1}H (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 (s ancho aparente, 1H), 3,36 (m, 1H), 2,30-1,75 (m, 4H), 1,40/1,15 (s ancho aparente, 9H). CL (Condiciones-J1): T_R = 1,71 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,10; encontrado 391,96. EMAR: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,0974; encontrado 392,0959.

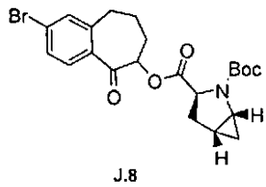
J.7a	 A partir de J.6a	EMBR: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,10; encontrado: 391,96.
J.7b	 A partir de J.6b	CL (Condiciones-J1): T_R = 1,5 min; Análisis calculado para $[M+H]^+$ $C_{19}H_{23}BrN_3O_2$: 405,09; encontrado: 406,04.

Ruta de síntesis 4



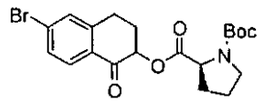
J.3 J.8 J.9

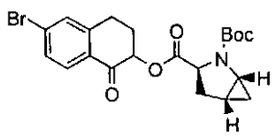
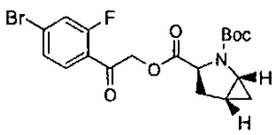
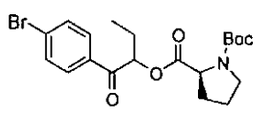
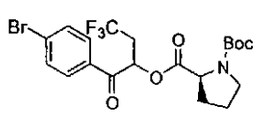
Ejemplos J.8 - J.9e

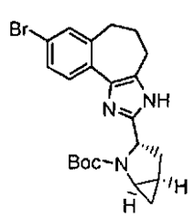


J.8

Se añadió bromo (0,23 ml, 4,18 mmol) gota a gota a una solución de J.3 2-bromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona (1,0 g, 4,18 mmol) en éter (50 ml), después de enfriarse hasta 0 °C. La solución se agitó 3 h y se añadieron unas pocas gotas de bromo adicional y mientras se seguía la reacción por TLC hasta finalización. El disolvente se eliminó por evaporación rotatoria, el residuo se suspendió en acetonitrilo (25 ml), M.4 (950 mg, 4,18 mmol) y se añadió gota a gota base de Hunig (1,4 ml). La reacción se agitó 18 horas a 60 °C antes de eliminar el disolvente por evaporación rotatoria. El producto bruto se cargó (diclorometano) en un cartucho de gel de sílice de 40 g Thompson y la elución con gradiente 15 - 100% de B durante 1 l (A/B hexanos/acetato de etilo) dio J.8 2-azabiciclo[3.1.0]hexano-2,3-dicarboxilato de (1R,3S,5R)-3-(2-bromo-5-oxo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-6-ilo) y 2-terc-butilo 1 g (51,5 %) como un aceite. T_R = 2,2 minutos (Condiciones-J1). CLEM: Análisis calculado para $C_{22}H_{26}BrNO_5Na$: 486,10; encontrado: 486,07 $(M+Na)^+$.

J.8a (Derivado de 6-bromo tetral-1-ona adquirido de *J* & W PharmLab, LLC)		T_R = 3,1 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{20}H_{25}BrNO_5$: 438; encontrado: 438.

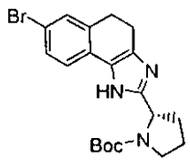
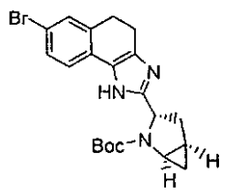
J.8b (Derivado de 6-bromo tetral-1-ona adquirido de *J* & W PharmLab, LLC)	 A partir de M.4	T_R = 2,99 min (Cond. D2), CLEM: Calculado para $C_{21}H_{25}BrNO_5$ $[M+Na]^+$ 472,07; encontrado: 472,10
J.8c (Derivado de 4-bromo 2-fluoroacetofenona)	 A partir de M.4	T_R = 2,87 min (Cond. D2), CLEM: Calculado para $C_{29}H_{22}BrFNO_5$ $[M+H]^+$ 464,05; encontrado: 463,98
J.8d Derivado de 1-(4-bromofenil)butan-1-ona)		T_R = 2,2 min, (Cond.-J1); Calculado para $C_{20}H_{27}BrNO_5$ $[M\text{-}Boc]^+$ 340,11; encontrado: 340,02.
J.8e Derivado de 1-(4-bromofenil)-4,4,4-trifluorobutan-1-ona		T_R = 2,21 min, (Cond.-J1); Calculado para $C_{20}H_{24}BrF_3NO_5$ $[M\text{-}Boc]^+$394,08; encontrado: 394,03.

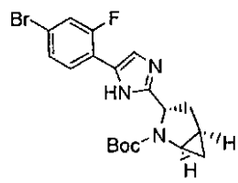
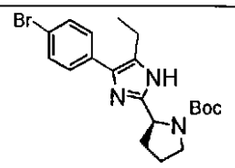
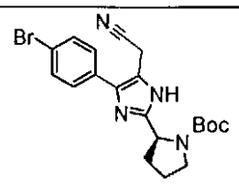


J.9

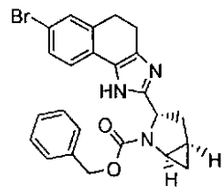
Se añadió acetato amónico (1,7 g, 21,54 mmol) a una solución de J.8 (1,0 g, 2,15 mmol) en xileno (15 ml) y la mezcla de reacción se agitó a 140 °C durante 3 h en un recipiente a presión con tapa a rosca. Después de enfriarse, la mezcla de reacción se repartió entre acetato de etilo y solución saturada de $NaHCO_3$, y la fase acuosa se extrajo con acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera, se concentraron, y el residuo se aplicó a una

columna de gel de sílice de 20 g Thomson. La elución con gradiente (10-50% de B durante 1 l; A/B hexanos/acetato de etilo). El producto mayoritario y menos polar (oxazol 450 mg) se separó proporcionando J.9 192 mg (20 %) como una mezcla diastereomérica (favoreciendo J.9; una mezcla 3:1 de S/R prolina). RMN de ^{1}H (300 MHz, $CDCl_3$) δ 10,6/10,3 (s ancho, 1H), 8,06 (d, J = 8,2 Hz, 0,6H), 7,34 (dd, J = 6,4, 1,8 Hz, 1H), 7,28 (s, 0,3H), 7,21 (d, J = 1,8 Hz, 0,7H), 7,11 (d, J = 8,6 Hz, 0,3H), 4,83-4,77 (m, 1H), 3,48 (m, 0,68H), 3,23 (m, 1,2H), 2,98 (t, J = 6,4 Hz, 0,65H), 2,88 (t, H = 6,7 Hz, 1,35H), 2,82-2,79 (m, 2H), 2,33 (t, J = 9,1 Hz, 1H), 2,01-1,95 (m, 2,4H), 1,76-1,72 (m, 1H), 1,57/1. 48 (s, 9H), 0,87-0,83 (m, 1,3H), 0,44 (s ancho, 1H). CL (Condiciones-J1): T_R = 1,7 min; CLEM: Análisis calculado para $[M+H]^+$ $C_{22}H_{26}BrN_3O_2$: 444,13; encontrado: 444,07.

J.9a	 A partir de J.8a	T_R = 2,4 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{20}H_{25}BrN_3O_2$: 418,11; encontrado: 418,10.
J.9b	 A partir de J.8b	T_R = 2,3 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430,11; encontrado: 430,16. EMAR: Análisis calculado para $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430,1125; encontrado 430,1123.

J.9c	 A partir de J.8c	T_R = 2,2 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{19}H_{22}BrFN_3O_2$: 422,09; encontrado: 422,10. EMAR: Análisis calculado para $[M+H]^+$ $C_{19}H_{22}BrFN_3O_2$: 422,0877; encontrado 422,0874.
J.9d	 A partir de J.8d	T_R = 1,69 min, (Cond.-J1); Calculado para $C_{20}H_{27}BrN_3O_2$ $[M+H]^+$ 420,13; encontrado: 420,13.
J.9e Obtenido como el producto más polar de una mezcla ~1:1 que contiene el análogo CF_3.	 A partir de J.8e	T_R =1,55 min, (Cond.-J1); Calculado para $C_{20}H_{24}BrN_4O_2$ $[M+H]^+$ 431,11; encontrado: 431,15.

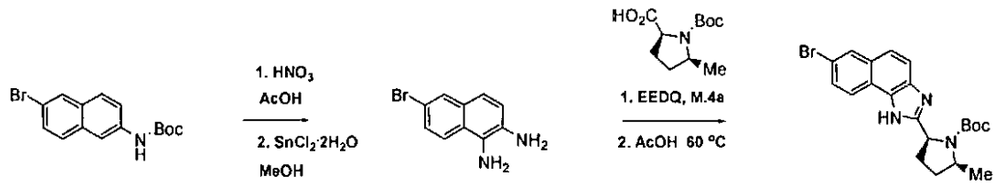
Ejemplo J.9f



Se añadió una solución fría (0 °C) de HCl (0,871 ml, 3,49 mmol, 4*N* en dioxanos) a una solución de J.9b (1,5 g, 3,49 mmol) en MeOH (20 ml). La mezcla se agitó durante 2 h antes de concentrar a sequedad. El sólido color

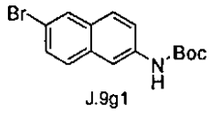
castaño se suspendió en dioxano (20 ml) y agua (20 ml), se enfrió hasta 0 °C, y se trató con carbonato sódico (0,369 g, 3,49 mmol) y CBZ-Cl (0,498 ml, 3,49 mmol). Se dejó calentar la mezcla de reacción hasta temperatura ambiente, se agitó durante 5 horas, se diluyó con acetato de etilo y se lavó con solución saturada de carbonato sódico. La fase orgánica se lavó con salmuera y se secó sobre sulfato sódico proporcionando J.9f (0,97 g, 60%) como una espuma color castaño, T_R = 2,47 min (Condición-D1); CL/EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{23}BrN_3O_2$: 464,10 y 466,10; encontrado: 463,95 y 465,98.

Ruta de síntesis 4.a



J.9g1 J.9g2 J.9g

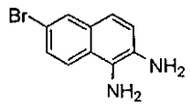
Ejemplos J.9g1 – J.9g



J.9g1

Se añadió azida de difenilfosforilo (17,09 ml, 79 mmol) a una solución de ácido 6-bromo-2-naftoico (16,5 g, 65,7 mmol), trietilamina (18,32 ml, 131 mmol) y alcohol *terc*-butílico (7,54 ml, 79 mmol) en tolueno (225 ml) y se agitó durante 4 h a 100 °C. Los volátiles se eliminaron por evaporación rotatoria y el residuo se suspendió en EtOAc (500 ml) y se lavó con agua y salmuera. Tras concentración se formó un precipitado que se aisló por filtración y se lavó con Et_2O/Hex 1:1 dando el Ejemplo J.9g1 (10,5 g). Se aisló una segunda tanda de

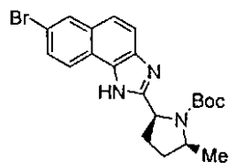
producto menos puro tras concentrar las aguas madres (9,8 g); rendimiento combinado (93%). CL/EM (Cond. J2): T_R = 3,44 min. CL/EM Análisis calculado para $[M+Na]^+$ $C_{15}H_{16}BrNO_2$: 345,02; encontrado 345,03.



J.9g2

Se diluyó el Ejemplo J.9g1 (5 g, 15,52 mmol) en ácido acético (50 ml) y se añadió gota a gota ácido nítrico fumante (2,3 ml) durante 20 min. La reacción se agitó durante 2 h y el producto se aisló por filtración, se repartió entre CH_2Cl_2 y solución saturada de $NaHCO_3$. La fase orgánica se concentró proporcionando 6-bromo-1-nitronaftalen-2-ilcarbamato de terc-butilo 5,7 g (cuant). CL/EM (Cond. J2): T_R = 3,52 min. CL/EM Análisis calculado para $[M+Na]^+$ $C_{15}H_{15}BrN_2O_4$: 390,02.; encontrado 390,99.

Se añadió cloruro de estaño (II) deshidratado (3 g, 16,34 mmol) a una solución de 6-bromo-1-nitronaftalen-2-ilcarbamato de terc-butilo (2 g, 5,47 mmol) en MeOH (100 ml) y la solución se agitó durante 18 h a 70 °C. El disolvente se eliminó por evaporación rotatoria y se secó el Ejemplo J.9g2 (se supone teórico 1,25 g) a alto vacío. CL/EM (Cond. J2): T_R = 1,49 min. CL/EM Análisis calculado para $[M+H]^+$ $C_{10}H_9BrN_2$: 237,00; encontrado 236,96.



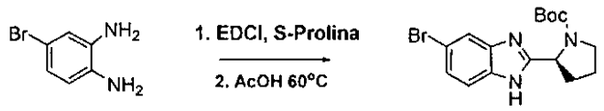
J.9g

Se añadió EEDQ (1,67 g, 6,75 mmol) a una solución de Ejemplo J.9g2

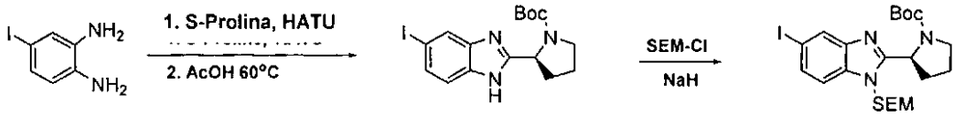
(1,6 g, 6,75 mmol) y M.4a (1,55 g, 6,75 mmol) en DCM (100 ml) y se agitó durante 6h. (Nota: La dianilina no era totalmente soluble). La mezcla de reacción se diluyó con DCM (1 vol) y se lavó con la mitad del volumen de solución saturada de $NaHCO_3$. La concentración dio un sólido (2,5 g). CL/EM (Cond. J2): T_R = 3,07 min. CL/EM Análisis calculado para $[M+H]^+$ $C_{21}H_{27}BrN_3O_3$: 448,13; encontrado 448,11.

El sólido bruto (2,5 g, 5,58 mmol) se suspendió en AcOH (200 ml) y se agitó durante 18 h a 60 °C. La concentración a alto vacío eliminó el disolvente. El residuo se suspendió en DCM, se lavó con solución saturada de $NaHCO_3$ y se concentró. El residuo se cargó (DCM) en un cartucho de gel de sílice de 80 g Thompson y se llevó a cabo una elución con gradiente desde 15% hasta 100% B durante 750 ml. (A/B Hex/EtOAc) dando el Ejemplo J.9g (2,6 g). RMN de ^1H (MeOD, 500 MHz, δ): 8,36-8,35 (m, 2H), 8,0 (d, J = 9Hz, 1H), 7,91 (dd, J = 9, 2 Hz, 1H), 7,87 (d, J = 9 Hz, 1H), 5,31-5,28 (m, 1H), 4,17 (s ancho, 1H), 2,59-2,56 (m, 1H), 2,39-2,31 (m, 2H) 1,86-1,83 (m, 1H), 1,52-1,19 (m, 12H). CL/EM (Cond. J2): T_R = 2,57 min. CL/EM Análisis calculado para $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430,12; encontrado 430,09.

Ruta de síntesis 5

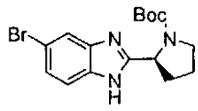


J.10



J.11 J.12

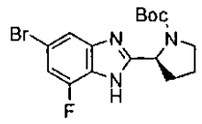
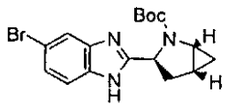
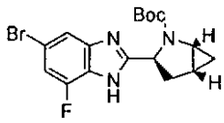
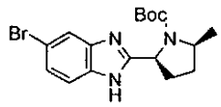
Ejemplos J.10 - J.12

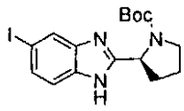


J.10

Se añadió EDCI•HCl (2,35 g, 12,25 mmol) a una mezcla de 4-bromobenceno-1,2-diamina (2,078 g, 11,11 mmol), N-Boc-L-prolina (2,311 g, 10,74 mmol) y 1-hidroxibenzotriazol (1,742 g, 12,89 mmol) en diclorometano (40 ml), y se agitó en condiciones ambientales durante 19 h. La mezcla se diluyó entonces con diclorometano, se lavó con agua (2x), se secó (salmuera; $MgSO_4$), se filtró y se concentró a vacío proporcionando una espuma marrón. Se añadió ácido acético (40 ml) a la espuma y la mezcla se calentó a 65 °C durante 90 min. El componente volátil se eliminó a vacío, y el residuo se disolvió en acetato de etilo y lavó cuidadosamente con solución saturada de $NaHCO_3$ (2x), y la fase orgánica se secó (salmuera; $MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se sometió a cromatografía ultrarrápida (gel de sílice; acetato de etilo) proporcionando J.10 como una espuma color castaño (2,5 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): 12,49-12,33 (cuatro s anchos, 1H), 7,71 (d, J = 2, 0,54H), 7,60 (s ancho

aparente, 0,46H), 7,50 (d, J = 8,6, 0,45H), 7,40 (d, J = 8,4, 0,55H), 7,26 (m, 1H), 4,96-4,87 (m, 1H), 3,64-3,51 (m, 1H), 3,44-3,38 (m, 1H), 2,38-2,21 (m, 1H), 1,99-1,85 (m, 3H), 1,39 (s, 3,7H), 1,06 (s, 5,3H). (Condiciones-D2) CL/EM: Análisis calculado para [M+H]+ $C_{16}H_{21}BrN_3O_2$: 368,03; encontrado: 368,18.

J.10a		T_R = 1,9 min (Condiciones-J1) CL/EM: Análisis calculado para $[M+Na]^+$ $C_{16}H_{20}BrN_3NaFO_2$: 406,06; encontrado: 406,06.
J.10b	 A partir de M.4	T_R = 1,7 min (Condiciones-D2) CL/EM: Análisis calculado para $[M+Na]^+$ $C_{17}H_{20}BrN_3NaO_2$: 400,06; encontrado: 400,09
J.10c	 A partir de M.4	T_R = 1,9 min (Condiciones-J1) CL/EM: Análisis calculado para $[M+Na]^+$ $C_{17}H_{20}BrN_3NaFO_2$: 418,06; encontrado: 418,06.
J.10d	 A partir de M.4a	T_R = 2,0 min (Cond.-J2) CL/EM: Análisis. Calculado para $[M+H]^+$ $C_{17}H_{23}BrN_3O_2$: 380,10; encontrado: 380,03.

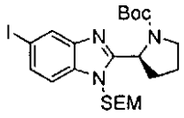


J.11

Se añadió 4-yodo-2-nitroanilina (35,2 g, 0,133 mol) en lotes a través de un embudo abierto durante 25 minutos a una mezcla calentada (65 °C) de $SnCl_2,2H_2O$ (106,86 g, 0,465 mol) y HCl 12N (200 ml). Se añadió más HCl 12N (30 ml) y la mezcla de reacción se calentó a 65 °C durante 1 hora más, y se agitó a temperatura ambiente durante 1 h. Se colocó en un frigorífico durante 15 h, y se filtró el precipitado. El sólido resultante se transfirió a un matraz que contenía agua (210 ml), se enfrió (hielo/agua), y se añadió al mismo durante 10 minutos con agitación una solución de NaOH (ac) (35 g en 70 ml de agua). Se retiró el baño de enfriamiento y se continuó con agitación vigorosa durante 45 min. La mezcla se filtró y el sólido se lavó con agua y se secó a vacío proporcionando 4-yodobenceno-1,2-diamina como un sólido color castaño (25,4 g). El producto se usó en la etapa siguiente sin purificación posterior. RMN de ^1H (DMSO-d_6, δ= 2,5 ppm, 500 MHz): 6,79 (d, J = 2,1H), 6,63 (dd, J = 1,9, 8,1, 1H), 6,31 (d, J = 8,1, 1H), 4,65 (s ancho, 2H), 4,59 (s ancho, 2H). CL/EM: Análisis calculado para [M+H]+ $C_6H_8IN_2$: 234,97; encontrado: 234,9.

Se añadió HATU (6,5 g, 17,1 mmol) a una solución de 4-yodobenceno-1,2-diamina (4 g, 17,1 mmol), ácido (S)-1-(terc-butoxicarbonil)pirrolidin-2-carboxílico (3,67 g, 17,1 mmol), y base de Hunig (3 ml) en dimetilformamida (100 ml). La mezcla de reacción se agitó durante 4 h antes de diluir con acetato de etilo (300 ml) y se lavó con $NaHCO_3$ saturado, salmuera y se secó (Na_2SO_4). La fase acuosa se extrajo dos veces más con acetato de etilo y se combinó con el extracto orgánico inicial antes de secar. La concentración dio

un residuo que se suspendió en ácido acético glacial (100 ml) y se calentó a 65 ºC durante 2h. La mezcla fría se concentró a vacío, se diluyó con acetato de etilo (300 ml) y solución 1N de NaOH (hasta pH = 10), se lavó con salmuera y se secó (Na_2SO_4). El producto bruto se aplicó a un cartucho de gel de sílice 65 (i) Biotage. Segmento 1. Mantenimiento 15% de B durante 450 ml; Segmento 2. Elución con gradiente desde 15% hasta 100% de B durante 4,5 l (A = hexano; B = acetato de etilo); Segmento 3. Mantenimiento 100% de B durante 2,5 l dando J.11 2-(5-yodo-1H-benzo[d]imidazol-2-il)pirrolidin-1-(S)-carboxilato de terc-butilo 7,0 g (99%). RMN de ^1H (500 MHz, DMSO-d_6) δ 7,85 (s ancho, 1H), 7,42 (d, J = 8,2 Hz, 1H), 7,34 (s ancho, 1H), 4,97-4,84 (m, 1H), 3,6 (s ancho, 1H), 3,44-3,40 (m, 1H), 2,37-2,25 (m, 1H), 1,99-1,87 (m, 3H), 1,4/ 1,07 (s, 9H). CL (Condiciones-D2): 2,1 min; CLEM: Análisis calculado para $[M+H]^+$ $C_{16}H_{20}IN_3O_2$: 414,07; encontrado: 414,08.

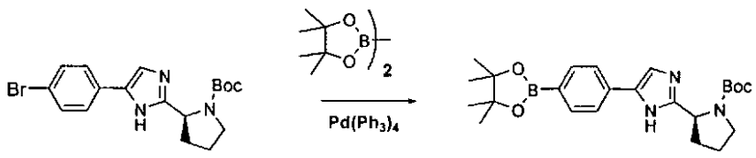


J.12

Se añadió en una porción hidruro sódico sin lavar al 60% (48 mg, 1,21 mmol) a una solución agitada de J.11 2-(5-yodo-1H-benzo[d]imidazol-2-il)pirrolidin-1-(S)-carboxilato de terc-butilo (500 mg, 1,21 mmol) en dimetilformamida seca (10 ml) en nitrógeno. La mezcla se agitó 5 min antes de la adición de SEM-Cl (0,21 ml, 1,21 mmol), se agitó durante 3 h, se inactivó con cloruro amónico saturado (1 ml), se diluyó con acetato de etilo (50 ml), y la fase orgánica se lavó con solución saturada de $NaHCO_3$ y salmuera. La fase acuosa se extrajo dos veces más con acetato de etilo y se combinó con el extracto

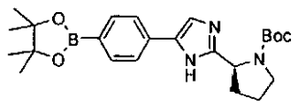
orgánico inicial antes de secar. La concentración dio un residuo que se aplicó (diclorometano) a un cartucho de gel de sílice 40 (i) Biotage. Segmento 1. Mantenimiento 5% de B durante 150 ml; Segmento 2. Elución con gradiente desde 5% hasta 100% de B durante 2,5 l (A = hexano; B = acetato de etilo) B dando productos regioisoméricos (localización SEM) J.12 316 mg (48 %). RMN de ^{1}H (500 MHz, DMSO-d_6) δ 7,99 (d, J = 5,8 Hz, 1H), 7,54-7,49 (m, 2H), 5,77-5,64 (m, 2H), 5,20-5,11 (m, 1H), 3,61-3,43 (m, 4H), 2,89-2,05 (m, 2H), 1,98-1,87 (m, 2H), 1,36/1,04 (s, 9H), 0,91-0,81 (m, 2H), -0,06 (s, 9H). CL (Condiciones-D2): T_R = 3,1 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{22}H_{34}IN_3O_3Si$: 544,15; encontrado: 544,15.

Ruta de síntesis 6.



J.7 J.13

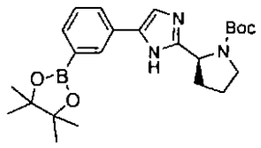
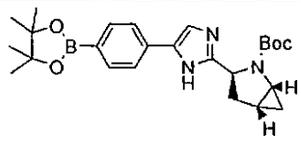
Ejemplos J.13 - J.13f

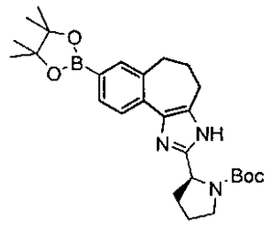
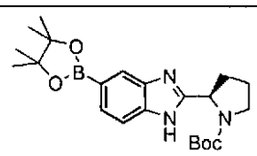
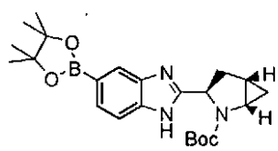
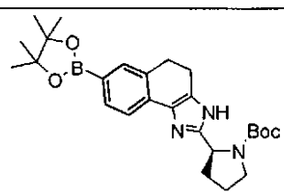


J.13

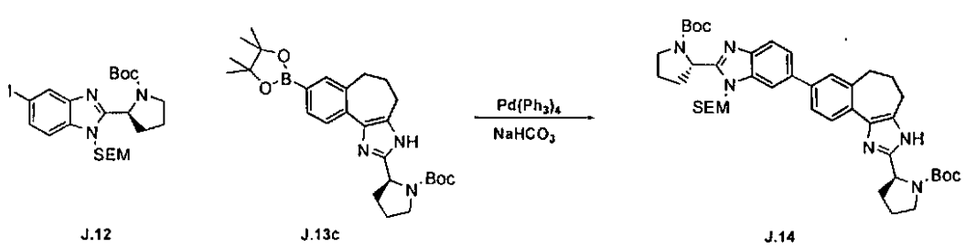
Se añadió $Pd(Ph_3P)_4$ (469 mg, 0,406 mmol) a un tubo de presión que contenía una mezcla de J.7 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (4 g, 10,22 mmol), bis(pinacolato)diboro (5,4 g, 21,35 mmol), acetato potásico (2,6 g, 26,21 mmol) y 1,4-dioxano (80 ml). El

matraz de reacción se purgó con nitrógeno, se tapó y se calentó (baño de aceite 80 °C) durante 16 horas. La mezcla de reacción se filtró y el filtrado se concentró a vacío. El material bruto se repartió cuidadosamente entre diclorometano (150 ml) y un medio acuoso (50 ml agua + 10 ml de solución saturada de $NaHCO_3$). La fase acuosa se extrajo con diclorometano, y la fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío. El material resultante se purificó con cromatografía ultrarrápida (la muestra se cargó con disolvente de elución; 20-35% de acetato de etilo/diclorometano) proporcionando J.13 2-(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo, contaminado con pinacol, como un sólido denso blanquecino; la relación molar relativa de J.13 a pinacol fue de aproximadamente 10:1 (RMN de ^1H). La muestra pesó 3,9 g después de ~2,5 días de exposición a alto vacío. RMN de ^1H (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 (s ancho aparente, 1H), 3,36 (m, 1H), 2,27-1,77 (m, 4H), 1,45-1,10 (m, 21H). CL (Condiciones-J1): T_R = 1,64 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440,27; encontrado 440,23.

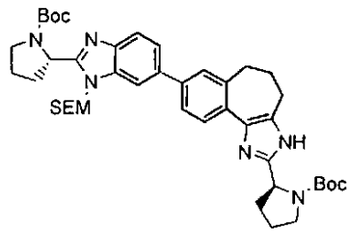
J.13a	 A partir de J.7a	T_R = 1,6 min (Condiciones-J1); CL/EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440,27; encontrado: 440,36.
J.13b		T_R = 1,6 min (Condiciones-J1); CL/EM: Análisis calculado para $[M+H]^+$ $C_{25}H_{35}BN_3O_4$: 452,27;

	A partir de J.7b	encontrado: 452,17.
J.13c	 A partir de J.5	T_R = 1,9 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{27}H_{38}BN_3O_4$: 480; encontrado: 480.
J.13d	 A partir de J.10	T_R = 1,7 (Condiciones-J1) CLEM: Análisis calculado para $[M+H]^+$ $C_{22}H_{33}BN_3O_4$ 414,25; encontrado: 414,28.
J.13e	 A partir de J.10a	T_R = 2,1 (Condiciones-D2) CLEM: Análisis calculado para $[M+H]^+$ $C_{23}H_{33}BN_3O_4$ 426,29; encontrado: 426,21.
J.13f	 A partir de J.9a	T_R = 2,46 (Cond.-D2) CLEM: Análisis calculado para $[M+H]^+$ $C_{26}H_{37}BN_3O_4$ 466,28; encontrado: 466,33.

Ruta de síntesis 7

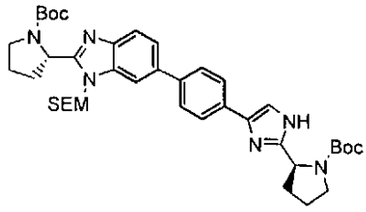
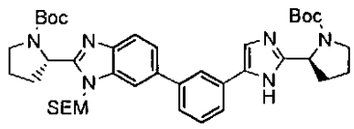
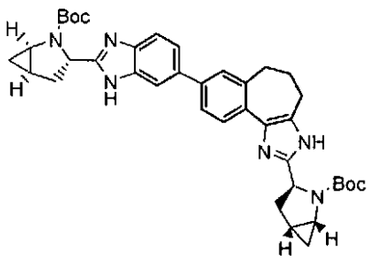


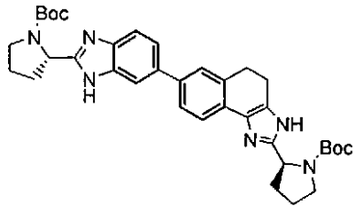
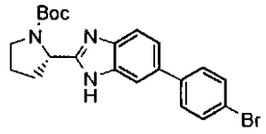
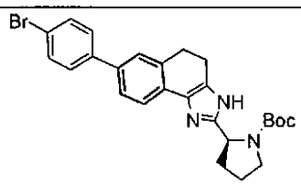
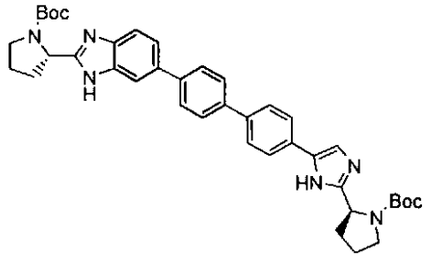
Ejemplos J.14 - J.14f.1

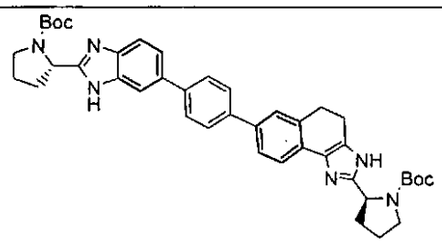


J.14

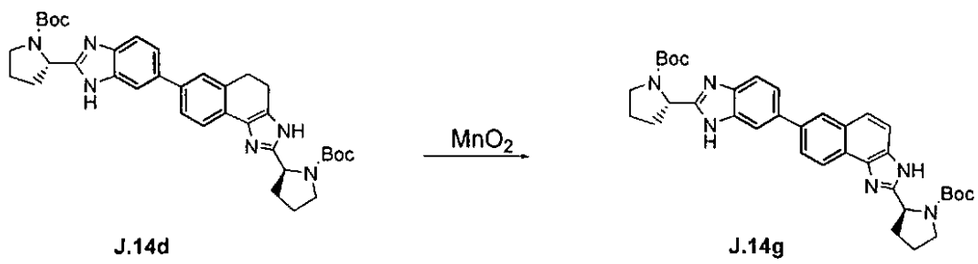
Se disolvieron el bencimidazol J.12 (250 mg, 0,46 mmol), éster borónico J.13c (217 mg, 0,46 mmol) y $NaHCO_3$ (95 mg, 1,13 mmol) en 1,2-dimetoxietano (4,5 ml) y se añadió agua (1,1 ml). La mezcla de reacción se evacuó y se inyectó nitrógeno (3x), se añadió $Pd(Ph_3P)_4$ (26 mg, 0,022 mmol), y la mezcla se calentó (baño de aceite a 80°C) en un recipiente a presión tapado durante 14 h. Después de enfriar, la solución se repartió en acetato de etilo/agua y la fase orgánica se lavó con $NaHCO_3$ saturado, salmuera y se secó (Na_2SO_4). La concentración dio un residuo que se aplicó a una columna 25M Biotage de SiO_2 previamente equilibrada con 25% de B (300 ml). Elución con gradiente: Segmento 1: 25% de B (60 ml); Segmento 2: 25-100% de B (1440 ml); Segmento 3: Mantenimiento a 100% (600 ml). A = Hexanos; B = acetato de etilo dio J.14, 101,1 mg (29%). RMN de ^1H (500 MHz, DMSO-d_6) δ 8,10-8,09 (m, 1H), 7,96/7,91 (s, 1H), 7,65-7,47 (m, 4H), 5,85-5,70 (m, 2H), 5,12/5,14 (s, 1H), 4,83/4,73 (s, 1H), 3,62-3,54 (m, 4H), 3,48-3,26 (m, 2H), 2,90 (s ancho, 4H), 2,37-1,84 (m, 10H), 1,42/1,08 (s, 9H), 1,37/1,06 (s, 9H), 0,92-0,83 (m, 2H), 0,06 (s, 9H). CL (Condiciones-D2): 2,8 min; CLEM: Análisis calculado para $[M+H]^+$ $C_{43}H_{61}N_6O_5Si$ 769,45; encontrado: 769,43. EMAR: Análisis calculado para $[M+H]^+$ $C_{43}H_{61}N_6O_5Si$: 769,4473; encontrado 769,4484.

J.14a	 A partir de J.12 y J.13	T_R = 2,71 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$ 729,42; encontrado: 729,43. EMAR: Análisis calculado para $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$: 729,4160; encontrado: 729,4188.
J.14b	 A partir de J.12 y J.13a	T_R = 2,75 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$ 729,42; encontrado: 729,44. EMAR: Análisis calculado para $[M+H]^+$ $C_{40}H_{57}N_6O_5Si$: 729,4160; encontrado: 729,4191.
J.14c	 A partir de J.13e y J.9	T_R = 1,6 min (Condiciones-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{39}H_{46}N_6O_4$ 663,37; encontrado: 663,46. EMAR: Análisis calculado para $[M+H]^+$ $C_{39}H_{46}N_6O_4$ 663,3653; encontrado: 663,3648.

J.14d	 A partir de J.13d y J.9a	T_R = 2,11 min, (Condiciones-D2); Calculado para $C_{36}H_{45}N_6O_4$ $[M+H]^+$ 625,35; encontrado: 625,42. EMAR: Calculado para $C_{36}H_{45}N_6O_4$ $[M+H]^+$ 625,3497; encontrado: 625,3486.
J.14e	 A partir de J.13d y 1,4-dibromobenceno	T_R = 1,83 min, (Condiciones-J1); Calculado para $C_{22}H_{25}BrN_3O_2$ $[M+H]^+$ 442,12; encontrado: 442,20.
J.14e.1	 A partir de J.13f y 1,4-dibromobenceno	T_R = 2,40 min, (Cond.-D2); Calculado para $C_{26}H_{29}BrN_3O_2$ $[M+H]^+$ 494,15; encontrado: 494,14.
J.14f	 A partir de J.14e y J.13	T_R = 1,66 min, (Condiciones-J1); Calculado para $C_{40}H_{47}N_6O_4$ $[M+H]^+$ 675,36; encontrado: 675,52.

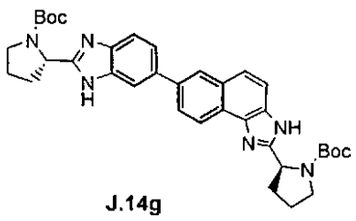
J.14f.1	 A partir de J.13d y J.14e.1	T_R: 2,15 min, (Cond.-D1); Calculado para $C_{42}H_{49}N_6O_4$ $[M+H]^+$ 701,38; encontrado: 701,35.

Ruta de síntesis 8



J.14d **J.14g**

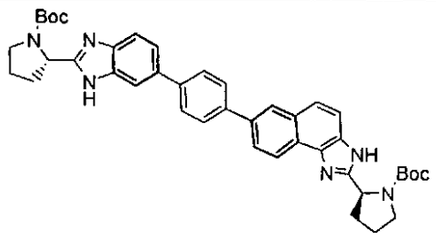
Ejemplos J.14g - J.14g.1



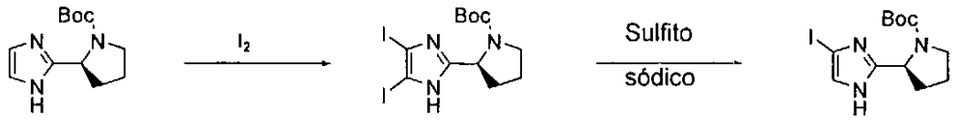
J.14g

Se añadió dióxido de manganeso activado (122 mg, 1,409 mmol) en una porción a una solución agitada de J.14d 2-(7-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (88 mg, 0,141 mmol) en diclorometano seco (2 ml). La suspensión se agitó durante 14 h y se añadió dióxido de manganeso adicional (1,5 g). La suspensión se agitó durante 16 h y se añadió de nuevo dióxido de manganeso (1,5 g) y se dejó continuar la

agitación durante 24h. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®), se concentró y se colocó en alto vacío durante 1 hora. Se aisló J.14g (85,0 mg, 92 %) como un sólido amarillento-naranja. CLEM: 2,14 min (Condiciones-D2) Calculado para $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623,33; encontrado: 623,46. EMAR: Calculado para $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623,3340; encontrado: 623,3327.

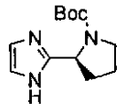
J.14g.1	 A partir de J.14f.1	T_R: 2,20 min, (Condición-D1); Calculado para $C_{42}H_{47}N_6O_4$ $[M+H]^+$ 699,37; encontrado: 699,32.

Ruta de síntesis 8a



JB.1 JB.2 JB.3

Ejemplos JB.1 – JB.3

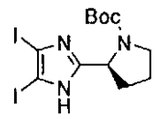


JB.1

Se añadió glioxal (2,0 ml de 40% en agua) gota a gota durante 11 minutos a una solución en metanol de NH_4OH (32 ml) y (S)-Boc-prolinal (8,56

g, 43,0mmol) y se agitó a temperatura ambiente durante 19 horas. El componente volátil se eliminó a vacío y el residuo se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc) seguido por recristalización (EtOAc, temperatura ambiente) proporcionando 2-(1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (4,43g) como un sólido blanco apelusado. RMN de ^{1}H (DMSO-d_6, 400 MHz): 11,68/11,59 (s ancho, 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).

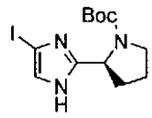
T_R = 0,87 min (Condición-JB,1) CL/EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{20}N_3O_2$: 238,16; encontrado 238,22. El compuesto mostró que tenía un ee del 98,9 % cuando se analizó en las condiciones de HPLC quiral indicadas a continuación. Columna: Chiralpak AD, 10 um, 4,6 x 50 mm Disolvente: 1,7% etanol/heptano (isocrático) Caudal: 1 ml/min Longitud de onda: bien 220 ó 256 nm. Tiempo de retención relativo: 3,25 min (*R*), 5,78 minutos (*S*)



JB.2

Se añadió yodo (16,17 g, 63,7 mmol) a una solución de Ejemplo JB.1 (6,87 g, 29,0 mmol) y carbonato sódico (9,21 g, 87 mmol) en dioxano (72 ml) y agua (72 ml) a temperatura ambiente. El matraz se cubrió con una lámina de aluminio y se agitó durante 16 horas. La mezcla de reacción se diluyó con EtOAc y una solución acuosa saturada de tiosulfato sódico. La mezcla se agitó durante 15 minuto y se separaron las fases. Se separaron las fases y la fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas reunidas se secaron (Na_2SO_4), se filtraron y concentraron a vacío

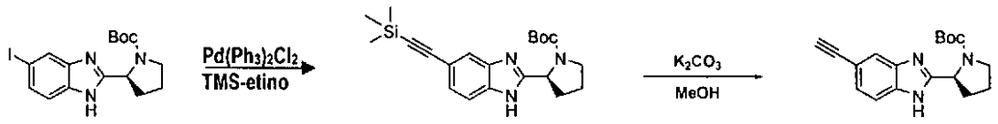
proporcionando 2-(4,5-diyodo-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (12,5 g) como un sólido color castaño. RMN de ^{1}H (500 MHz, MeOD) δ ppm 4,72 - 4,84 (m, 1H), 3,58 - 3,70 (m, 1H), 3,43 - 3,54 (m, 1H), 2,36 (s ancho, 1H), 1,88 - 2,08 (m, 3H), 1,47 (s ancho, 3H), 1,27 (s ancho, 6H). T_R = 1,40 min (Condición-JB,1) CL/EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{17}I_2N_3O_2$: 488,94 Encontrado; 489,96.



JB.3

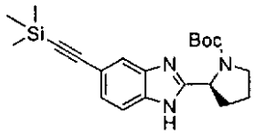
Se añadió sulfito sódico (10,31 g, 82 mmol) a una solución de Ejemplo JB.2 (4,0 g, 8,2 mmol) en etanol (75 ml) y agua (75 ml). La suspensión se calentó con un baño de aceite a 100°C durante 4 horas y a 90°C durante 16h. La reacción se diluyó con EtOAc y agua. Se separaron las fases y la fase acuosa se extrajo varias veces con EtOAc. Las fases orgánicas reunidas se secaron (salmuera, Na_2SO_4), se filtraron y concentraron a vacío. El residuo se purificó por cromatografía ultrarrápida (la muestra se cargó seca sobre gel de sílice y eluyó con 0 hasta 40% de acetato de etilo/CH_2Cl_2) proporcionando 2-(5-yodo-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (2,17 g) como un sólido blanco. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7,52-7,64 (m, 1H), 4,95 - 5,10 (m, 1H), 3,57 - 3,70 (m, 1H), 3,47 - 3,57 (m, 1H), 2,37 - 2,55 (m, 1H), 1,94 - 2,10 (m, 3H), 1,46 (s, 4H), 1,27 (s, 5H). T_R = 0,93 min (Condición-JB,1) CL/EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{18}IN_3O_2$ 363,04; Encontrado: 364,06.

Ruta de síntesis 9



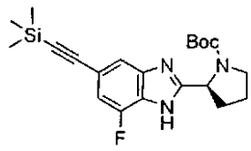
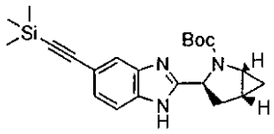
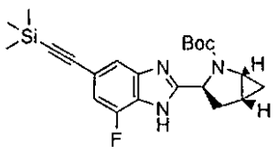
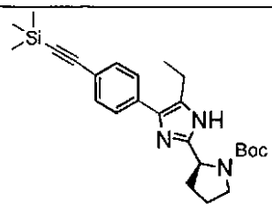
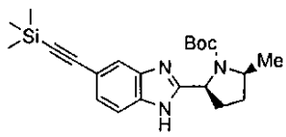
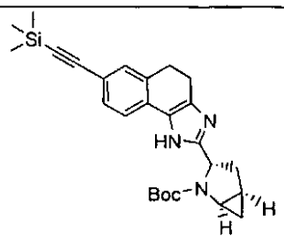
J.11 J.15 J.16

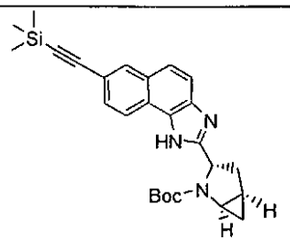
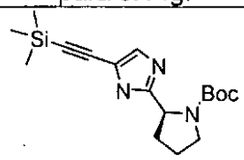
Ejemplos J.15 - JB.4



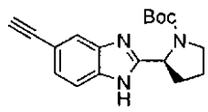
J.15

Se añadió una mezcla de yoduro de cobre (299,6 mg, 48,1 mmol) y $Pd(PPh_3)_2Cl_2$ (1,29 g, 4,41 mmol) a una solución en dimetilformamida (200 ml) de J.11 (16,0 g, 38,7 mmol), (trimetilsilil)acetileno (6,8 ml, 48,1 mmol), y trietilamina (16 ml), y la mezcla de reacción se agitó a ~25 °C durante 19,5 h. El componente volátil se eliminó a *vacío* y se preparó una malla de gel de sílice a partir del residuo y se sometió a una cromatografía ultrarrápida (gel de sílice; eluyendo con 40% acetato de etilo/hexanos) proporcionando el alquino J.15 como una espuma color castaño (13,96 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 12,52-12,38 (m, 1H), 7,62-7,41(m, 2H), 7,24-7,19 (m, 1H), 5,01-4,85 (m, 1H), 3,64-3,51 (m, 1H), 3,46-3,35 (m, 1H), 2,38-2,21 (m, 1H), 2,07-1,81 (m, 3H), 1,39 (s, 4H), 1,04 (s, 5H), 0,23 (s, 9H). T_R = 2,09 min (Condiciones-J1) CL/EM: Análisis calculado para $[M+H]^+$ $C_{21}H_{30}N_3O_2Si$: 384,21; encontrado: 384,27.

J.15a	 A partir de J.10a	T_R = 1,89 min, (Condiciones-J1); Calculado para $C_{21}H_{29}N_3O_2Si$ $[M+H]^+$ 402,20; encontrado: 402,26.
J.15b	 A partir de J.10b	T_R = 1,92 min, (Condiciones-J1); Calculado para $C_{22}H_{30}N_3O_2Si$ $[M+H]^+$ 396,21; encontrado: 396,22.
J.15c	 A partir de J.10c	T_R = 2,2 min, (Condiciones-J1); Calculado para $C_{22}H_{29}FN_3O_2Si$ $[M+H]^+$ 414,20; encontrado: 414,26.
J.15d	 A partir de J.9d	T_R = 1,70 min, (Cond.-J1); Calculado para$C_{25}H_{36}N_3O_2Si$ $[M+H]^+$ 438,26; encontrado: 438,33.
J.15d.1	 A partir de J.10.d	T_R =1,70 min, (Cond.-J1); Calculado para$C_{22}H_{32}N_3O_2Si$ $[M+H]^+$ 398,23; encontrado: 398,19.
J.15e	 A partir de J.9b	T_R = 2,43 min, (Cond.-D1); Calculado para$C_{26}H_{34}N_3O_2Si$ $[M+H]^+$ 448,24; encontrado: 448,82.

J.15f	 A partir de J.15e de acuerdo con el procedimiento descrito para J.14g.	LCMS: 2,51 min, (Cond.-D1); Calculado para $C_{26}H_{32}N_3O_2Si$ $(M+H)^+$ 446,23; encontrado: 446,05.
JB.4	 A partir de JB.3	LCMS: 1,5 min, (Cond.-JB.1); Calculado para $C_{17}H_{28}N_3O_2Si$ $(M+H)^+$ 334,20; encontrado: 334,14.

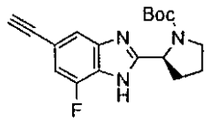
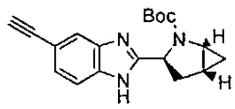
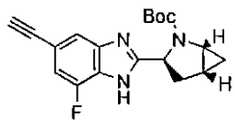
Ejemplo J.16 - JB.5

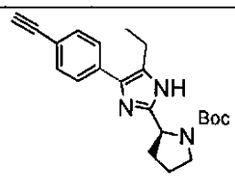
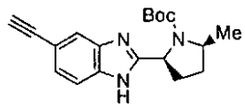


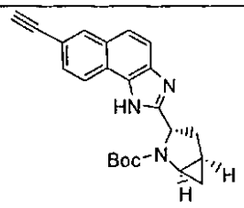
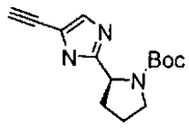
J.16

Se añadió carbonato potásico (0,5526 g, 4 mmol) a solución del alquino J.15 (13,9 g, 36 ,2 mmol) en metanol (200 ml) y la mezcla se agitó a temperatura ambiente durante 17 h. El componente volátil se eliminó a *vacío*, y el residuo se repartió entre acetato de etilo y solución de cloruro amónico saturado (ac) y la fase orgánica se separó y se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró *a vacío* proporcionando el alquino J.16 como una espuma color castaño (9,3 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): 12,58-12,30 (s ancho, 1H), 7,72-7,36 (dos s anchos aparentes solapando, 2H), 7,23 (d, *J* = 8,1, 1H), 4,97-4,88 (m, 1H), 4,02 (s, 1H), 3,64-3,52 (m, 1H), 3,44-3,36 (m, 1H), 2,40-2,20 (m, 1H), 2,06-1,81 (m, 3H), 1,39 (s, 4H), 1,05 (s, 5H). CL/EM: Análisis calculado para $[M+Na]^+$ $C_{18}H_{21}N_3NaO_2$: 334,15;

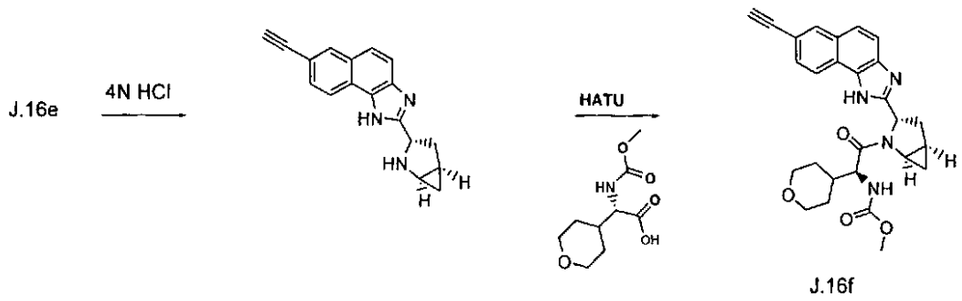
encontrado: 334,24.

J.16a	 A partir de J.15a	T_R = 1,69 min, (Condiciones-J1); Calculado para $C_{18}H_{20}N_3O_2$ $[M+Na]^+$ 352,14; encontrado: 352,15.
J.16b	 A partir de J.15b	T_R = 1,40 min, (Condiciones-J1); Calculado para $C_{19}H_{21}N_3O_2$ $[M+Na]^+$ 346,15; encontrado: 346,19.
J.16c	 A partir de J.15c	T_R = 1,36 min, (Condiciones-J1); Calculado para $C_{19}H_{20}FN_3O_2$ $[M+Na]^+$ 364,14; encontrado: 364,15.

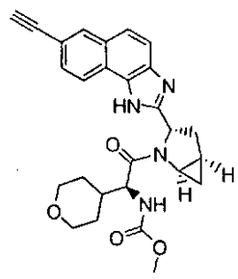
J.16d	 A partir de J.15d	T_R = 1,30 min, (Condición-J1); Calculado para $C_{22}H_{28}N_3O_2$ $[M+H]^+$ 366,22; encontrado: 366,25.
J.16d.1	 A partir de J.15d.1	T_R = 2,74 min, (Condición-J2); Calculado para $C_{19}H_{24}N_3O_2$ $[M+H]^+$ 326,19; encontrado: 326,13.

J.16e	 A partir de J.15f	CLEM: 1,88 min, (Condición-D1) Calculado para $C_{23}H_{24}N_3O_2$ $(M+H)^+$ 374,19; encontrado: 374,04.
JB.5	 A partir de JB.4	CLEM: 0,88 min, (Condición-JB-1) Calculado para $C_{10}H_{11}N_3O_2$ (M+H; -tBu)$^+$ 206,10; encontrado: 206,05.

Ruta de síntesis 9a



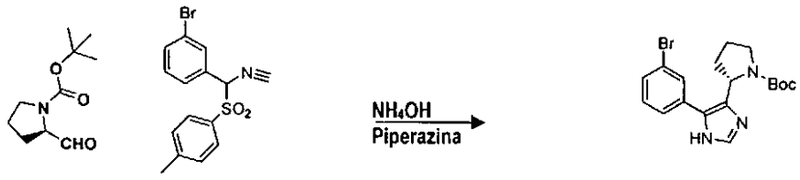
Ejemplo J.16f



J.16f

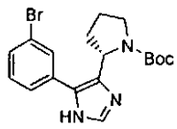
El Ejemplo J.16f se obtuvo a partir del Ejemplo J.16e de acuerdo con el procedimiento en dos etapas descrito a continuación. Desprotección como en la preparación de J.19 para formar una sal HCl que se acopló con cap-170 con HATU de acuerdo con la preparación de J.21 siguiendo dando J.16f T_R = 1,59 min, (Condición-D1); Calculado para $C_{27}H_{29}N_4O_4$ $[M+H]^+$ 473,22; encontrado: 473,06.

Ruta de síntesis 10



J.17

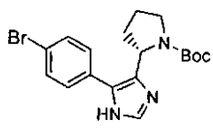
Ejemplo J.17 - 17.a



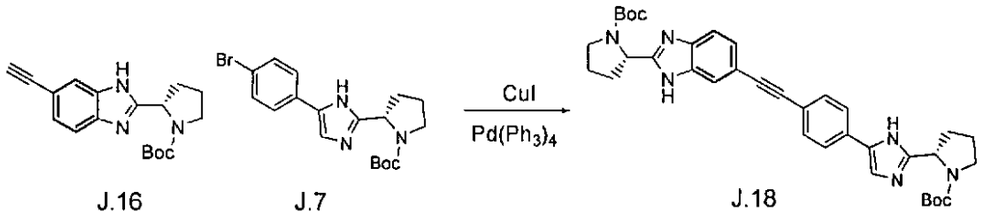
J.17

El hidróxido de amonio (4 ml) se añadió a una solución de (S)-prolinal

(650 mg, 3,26 mmol) en tetrahidrofurano (15 ml) y se agitó durante 6 h a 48 °C en un recipiente a presión sellado. Se añadieron isocianuro de α-tosil-(3-bromobencilo) (974 mg, 2,77 mmol) y piperazina (281 mg, 3,26 mmol) y la mezcla de reacción se agitó 18 h a 48 °C. Después de enfriarse, la mezcla de reacción se diluyó con acetato de etilo (200 ml) y se lavó con agua y salmuera y se concentró. El producto bruto se suspendió en diclorometano y se cargó en un cartucho de gel de sílice de 40 g Thomson. La elución con gradiente realizada desde 20-100% de B durante 750 ml dio J.17 2-(5-(3-bromofenil)-1H-imidazol-4-il)pirrolidin-1-carboxilato de (S)-terc-butilo 413 mg (31%). RMN de ^1H ($CDCl_3$, δ 500 MHz): 10,36/9,90 (s ancho, 1H), 7,75 (s ancho, 1H), 7,53 (s ancho, 2H), 7,38 (s ancho, 1H), 7,24 (s ancho, 1H), 5,11 (s ancho, 1H), 3,54 (s ancho, 2H), 2,32/2,19 (m, 1H), 1,95-1,85 (m, 2H), 1,74 (s, 1H), 1,45/1,18 (s, 9H). T_R = 1,7 (Condiciones-J1) CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,09; encontrado: 392,13.

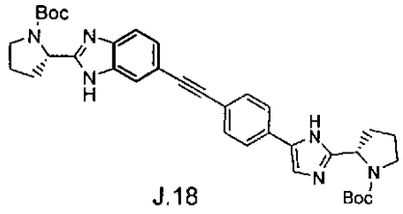
J.17a	 A partir de isocianuro de α-tosil-(4-bromobencilo)	T_R = 1,7 min, (Condiciones-J1); Calculado para $C_{18}H_{23}BrN_3O_2$ $[M+H]^+$ 392,09; encontrado: 392,13.

Ruta de síntesis 11.



J.16 J.7 J.18

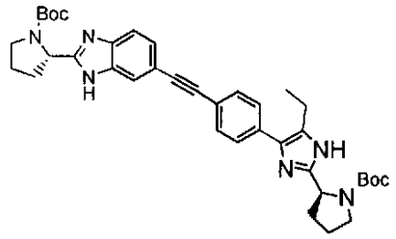
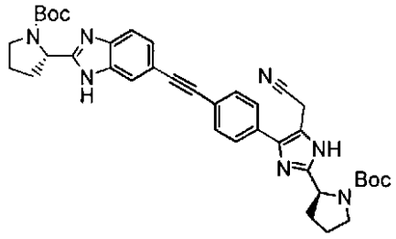
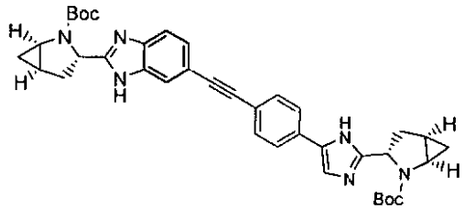
Ejemplos J.18 JB.6

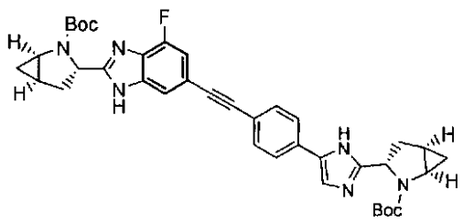
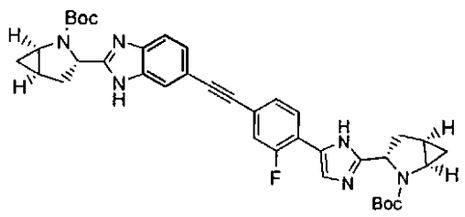
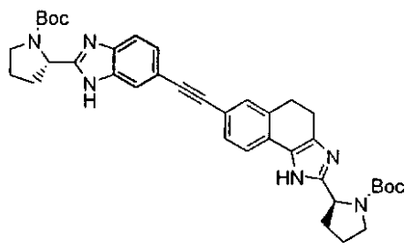


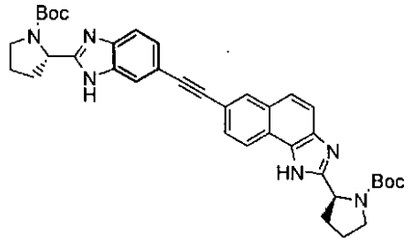
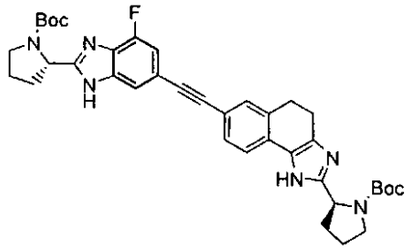
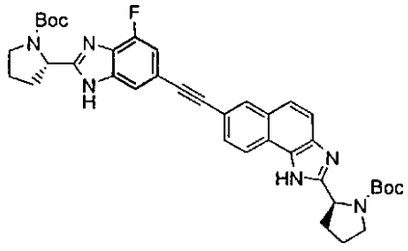
J.18

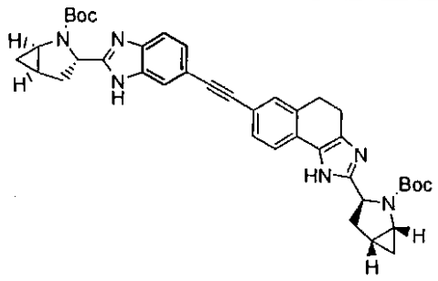
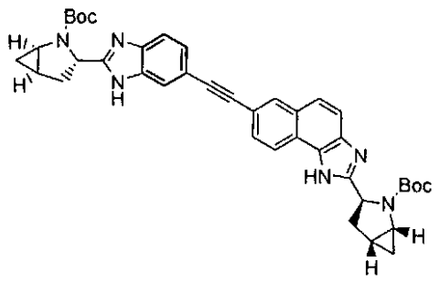
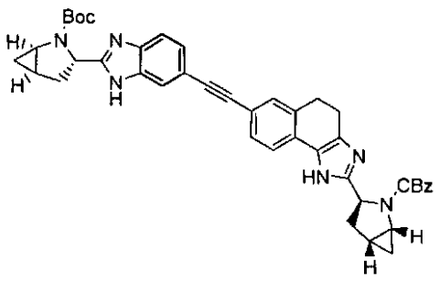
Se añadieron yoduro de cobre (9,8 mg, 0,051 mmol) y $Pd(PPh_3)_4$ (59,4 mg, 0,051 mmol) a una solución purgada en nitrógeno de J.16 2-(5-etinil-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (160 mg, 0,514 mmol) y J.7 2-(4-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (171 mg, 0,437 mmol) que contenía Et_3N (0,2 ml) en dimetilformamida (3 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 48 h. El componente volátil se eliminó a *vacío* y el residuo se aplicó (diclorometano) a una columna de 20 g Thomson y eluyó con 50-100 % de B durante 500 ml (A/B diclorometano /20% de metanol en acetato de etilo) proporcionando J.18; 87 mg (26%). RMN de ^1H ($CDCl_3$, δ, 500 MHz): 10,97-10,51 (m, 2H), 7,9 (s, 0,41H), 7,75 (d, *J* = 8,2, 1,26H), 7,69-7,66 (m, 0,55H), 7,59 (s, 0,54H), 7,54-7,51 (m, 1,85H), 7,42-7,32 (m, 2H), 7,25 (s, 1H), 7,22 (s ancho, 0,32) (s ancho, 1H), 4,99-4,94 (m, 1H), 3,31 (s ancho, 3H), 3,04/2,92 (s ancho, 2H), 2,19-2,15 (m, 3H), 2,03-1,95 (m, 2H), 1,62/1,50 (s ancho, 20H). CL

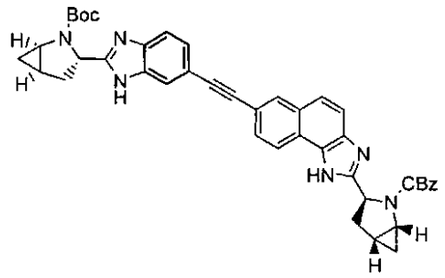
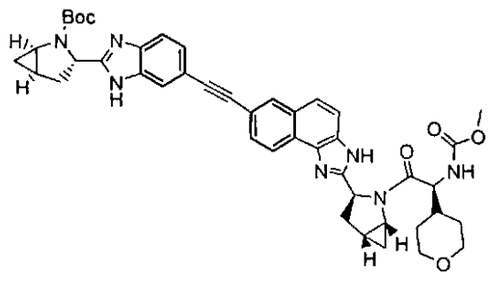
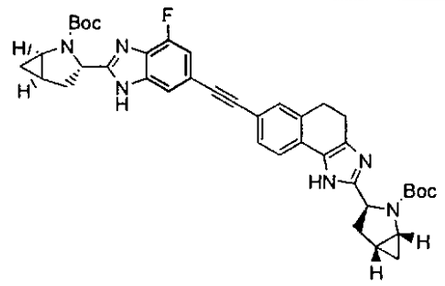
(Cond-J1): 1,6 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_6O_4$: 623,34; encontrado: 623,52; EMAR: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_6O_4$: 623,3340; encontrado: 623,3344.

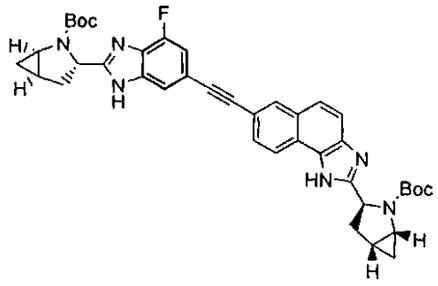
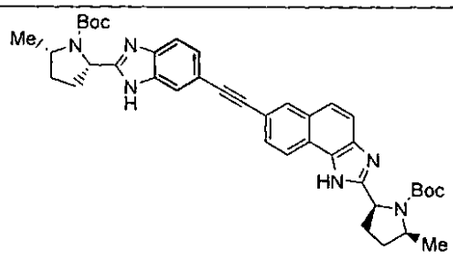
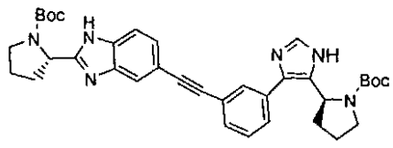
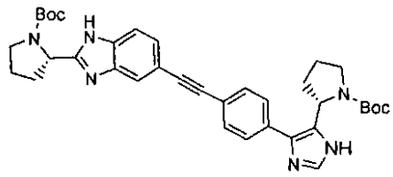
J.18,1	 A partir de J.10 y J.16d	T_R = 1,4 min (Condición-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_6O_4$ 651,36; encontrado: 651,46.
J.18,2	 A partir de J.16 y J.9e	T_R = 1,34 min (Condición-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{44}N_7O_4$ 662,35; encontrado: 662,35.
J.18a	 A partir de J.16b y J.7b	T_R = 1,6 min (Condición-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{43}N_6O_4$ 647,33; encontrado: 647,39.

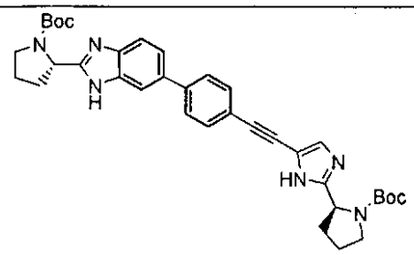
J.18b	 A partir de J.16c y J.7b	T_R = 1,57 min (Condición-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{42}FN_6O_4$ 665,33; encontrado: 665,49.
J.18c	 A partir de J.16b y J.9c	T_R = 1,42 min (Condición-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{42}FN_6O_4$ 665,33; encontrado: 665,49.
J.18d	 A partir de J.16 y J.9a	T_R: 2,27 min, (Condición-D2); Calculado para $C_{38}H_{45}N_6O_4$ $[M+H]^+$ 649,35; encontrado: 649,49. EMAR: Calculado para $C_{38}H_{45}N_6O_4$ $[M+H]^+$ 649,3497; encontrado:

		649,3484.
J.18e	 A partir de J.18d de acuerdo con el procedimiento descrito para J.14g.	T_R: 2,31 min, (Condición-D2); Calculado para $C_{38}H_{43}N_6O_4$ $[M+H]^+$ 647,33; encontrado: 647,46. EMAR: Calculado para $C_{38}H_{43}N_6O_4$ $[M+H]^+$ 647,3340; encontrado: 647,3328.
J.18f	 A partir de J.16a y J.9a	T_R: 1,61 min, (Condición-J1); Calculado para $C_{38}H_{44}FN_6O_4$ $[M+H]^+$ 667,34; encontrado: 667,46.
J.18g		T_R: 1,64 min, (Condición-J1); Calculado para $C_{38}H_{42}FN_6O_4$ $[M+H]^+$ 665,33; encontrado: 665,49.

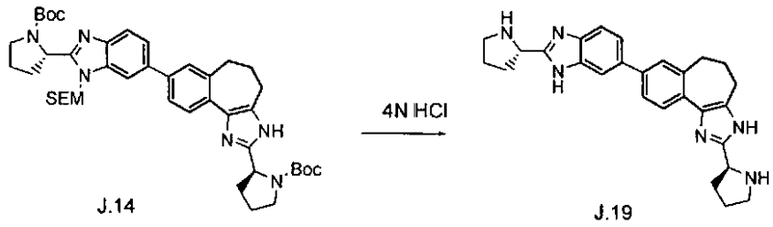
	A partir de J.18f de acuerdo con el procedimiento descrito para J.14g.	
J.18h	 A partir de J.16b y J.9b	T_R: 1,44 min, (Condición-J1); Calculado para $C_{40}H_{45}N_6O_4$ $[M+H]^+$ 673,35; encontrado: 673,43.
J.18i	 A partir de J.18h de acuerdo con el procedimiento descrito para J.14g.	T_R: 1,48 min, (Condición-J1); Calculado para $C_{40}H_{43}N_6O_4$ $[M+H]^+$ 670,34; encontrado: 670,46.
J.18i.1	 A partir de J.16b y J.9f	T_R: 2,03 min, (Condición-D1); Calculado para $C_{43}H_{43}N_6O_4$ $[M+H]^+$ 707,34; encontrado: 707,28.

J.18i.2	 A partir de J.18i,1 de acuerdo con el procedimiento descrito para J.14g.	T_R: 2,10 min, (Condición-D1); Calculado para $C_{43}H_{41}N_6O_4$ $[M+H]^+$ 705,32; encontrado: 705,19.
J.18i.3	 A partir de J.16f y J.10b	T_R = 1,92 min (Condición-D1); CLEM: Calculado para $C_{44}H_{48}N_7O_6$ $(M+H)^+$ 770,37; encontrado: 770,29.
J.18j	 A partir de J.16c y J.9b	T_R: 1,62 min, (Condición-J1); Calculado para $C_{40}H_{44}FN_6O_4$ $[M+H]^+$ 691,34; encontrado: 691,46.

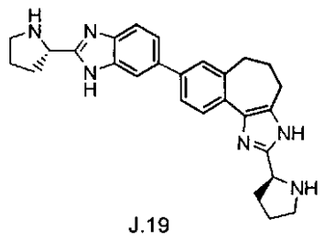
J.18k	 A partir de J.18j de acuerdo con el procedimiento descrito para J.14g.	T_R: 1,66 min, (Condición-J1); Calculado para $C_{40}H_{42}FN_6O_4$ $[M+H]^+$ 689,33; encontrado: 689,43.
J.18k.1	 A partir de J.16d.1 y J.9g	T_R: 3,44 min, (Condición-J2); Calculado para $C_{40}H_{47}N_6O_4$ $[M+H]^+$ 675,37; encontrado: 675,33
J.18l	 A partir de J.16 y J.17	T_R = 1,67 min, (Condición-J1); Calculado para $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623,34; encontrado: 623,46.
J.18m	 A partir de J.16 y J.17a	T_R = 1,67 min, (Condición-J1); Calculado para $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623,34; encontrado: 623,46.

JB,6	 A partir de J.14e y JB.5	T_R = 1,33 min, (Condición-JB,1); Calculado para $C_{36}H_{43}N_6O_4$ $[M+H]^+$ 623,34; encontrado: 623,24.

Ruta de síntesis 12

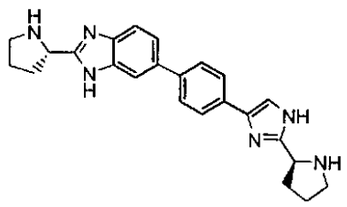
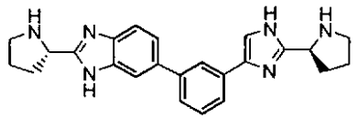


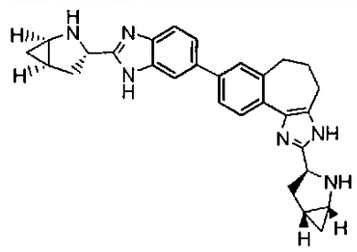
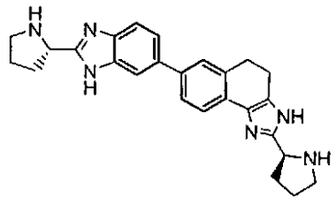
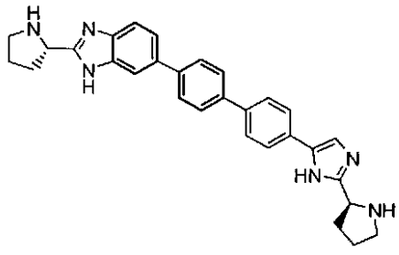
Ejemplos J.19 - JB.7

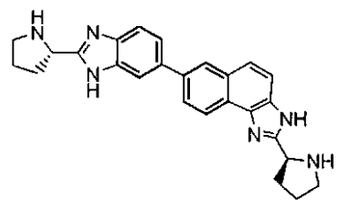
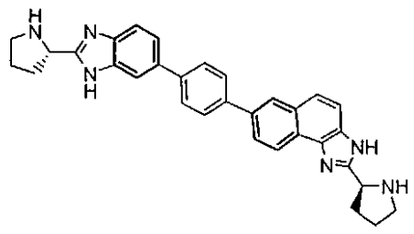
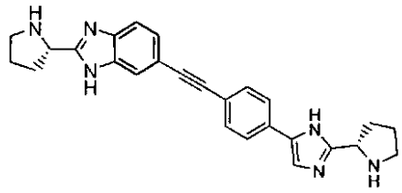


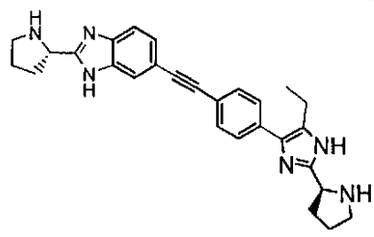
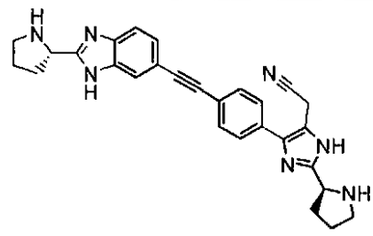
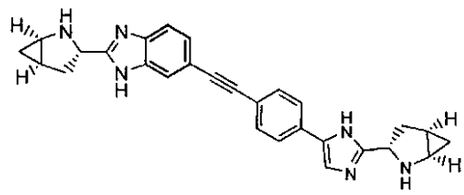
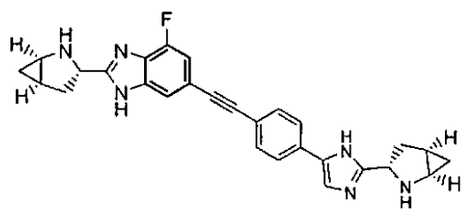
El Ejemplo J.14 (85 mg, 0,11 mmol) se disolvió en metanol (1 ml) y se añadió HCl 4N/Dioxano (5 ml) y la reacción se agitó 16 hr. Los disolventes se eliminaron a vacío, y la sal tetra HCl J.19 se expuso a alto vacío durante 18 h. CL (Cond-D2): 1,4 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{27}H_{31}N_6$:

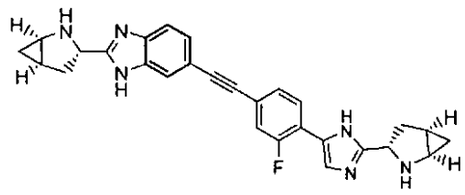
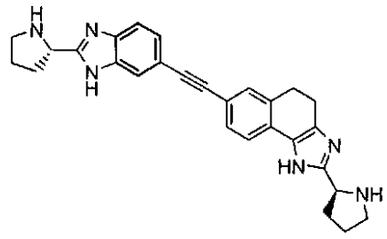
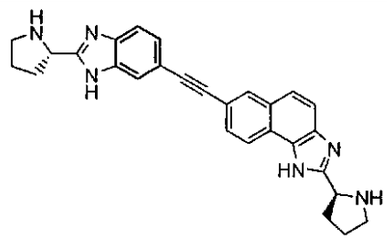
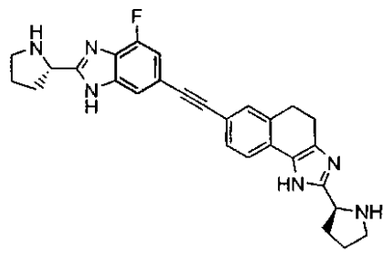
439,26; encontrado: 439,29. EMAR: Análisis calculado para $[M+H]^+$ $C_{27}H_{31}N_6$: 439,2610; encontrado 439,2593.

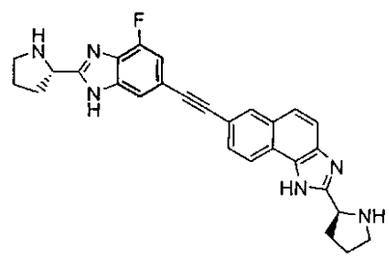
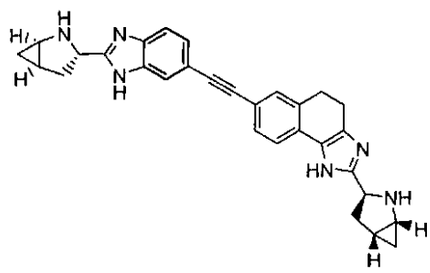
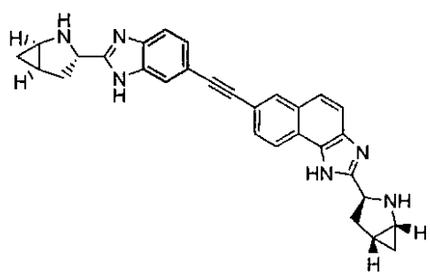
J.19a	 A partir de J.14a	T_R = 1,34 min (Condición-D2) CLEM: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}N_6$: 399,23; encontrado: 399,24. EMAR: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}N_6$: 399,2297; encontrado: 399,2316.
J.19b	 A partir de J.14b	T_R = 1,46 min (Condición-D2) CLEM: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}N_6$: 399,23; encontrado: 399,24. EMAR: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}N_6$: 399,2297; encontrado: 399,2298.

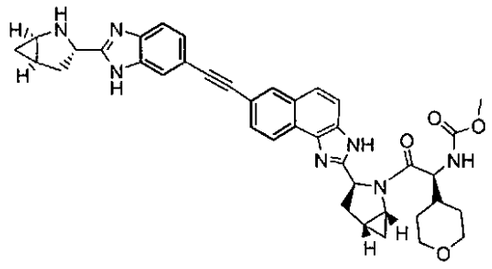
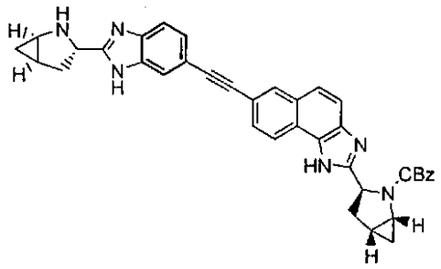
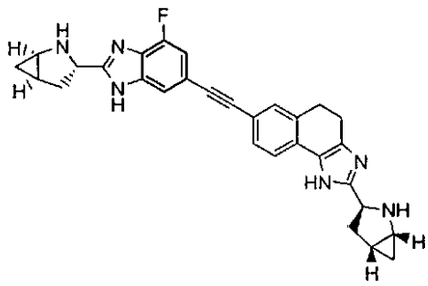
J.19c	 A partir de J.14c	T_R = 1,13 min (Condición-J1) CLEM: Análisis calculado para $[M+H]^+$ $C_{29}H_{30}N_6$: 463,26; encontrado: 463,38.
J.19d	 A partir de J.14d	T_R = 1,27 min, (Condición-D2) CLEM: Calculado para $C_{26}H_{29}N_6$ $[M+H]^+$ 425,24; encontrado:425,28. EMAR: Calculado para $C_{26}H_{29}N_6$ $[M+H]^+$ 425,2448; encontrado: 425,2444.
J.19e	 A partir de J.14f	T_R = 1,30 min, (Condición-J1) CLEM: Calculado para $C_{30}H_{31}N_6$ $[M+H]^+$ 475,26; encontrado: 475,25.

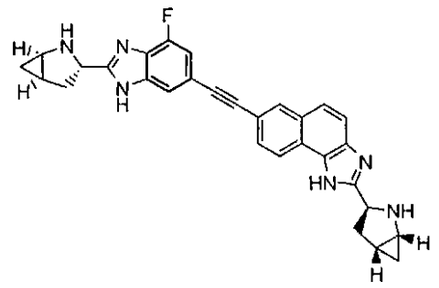
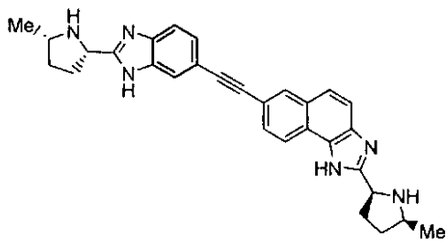
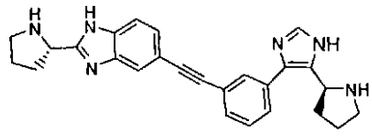
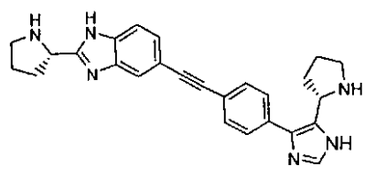
J.19f	 A partir de J.14g	T_R = 1,46 min, (Condición-D2) CLEM: Calculado para $C_{26}H_{27}N_6$ $[M+H]^+$ 423,23; encontrado:423,31. EMAR: Calculado para $C_{26}H_{27}N_6$ $[M+H]^+$ 423,2292; encontrado: 423,2287.
J.19f.1	 A partir de J.14g.1	T_R: 1,73 min, (Condición-D1); Calculado para $C_{32}H_{31}N_6$ $[M+H]^+$ 499,26; encontrado: 499,22.
J.20	 A partir de J.18	T_R = 1,18 min, (Condición-J1) CLEM: Calculado para $C_{26}H_{27}N_6$ $[M+H]^+$ 423,23; encontrado:423,24.

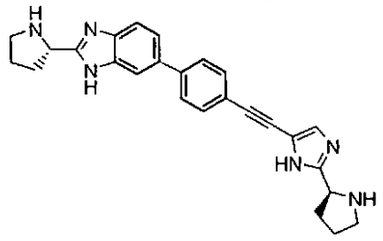
J.20.1	 A partir de J.18.1	T_R = 0,99 min (Condición-J1); CLEM Calculado para $C_{28}H_{31}N_6$ $(M+H)^+$ 451,25; encontrado: 451,28.
J.20.2	 A partir de J.18.2	T_R = 0,98 min (Condición-J1); CLEM Calculado para $C_{28}H_{28}N_7$ $(M+H)^+$ 462,24; encontrado: 462,24.
J.20a	 A partir de J.18a	T_R = 1,21 min, (Condición-J1) CLEM: Calculado para $C_{28}H_{27}N_6$ $[M+H]^+$ 447,23; encontrado: 447,18.
J.20b	 A partir de J.18b	T_R = 1,04 min, (Condición-J1) CLEM: Calculado para $C_{28}H_{26}FN_6$ $[M+H]^+$ 465,21; encontrado: 465,28.

J.20c	 A partir de J.18c	T_R = 1,07 min, (Condición-J1) CLEM: Calculado para $C_{28}H_{26}FN_6$ $[M+H]^+$ 465,21; encontrado: 465,28.
J.20d	 A partir de J.18d	T_R = 1,60 min, (Condición-D2) CLEM: Calculado para $C_{28}H_{29}N_6$ $[M+H]^+$ 449,24; encontrado: 449,28.
J.20e	 A partir de J.18e	T_R = 1,78 min, (Condición-D2) CLEM: Calculado para $C_{28}H_{27}N_6$ $[M+H]^+$ 447,23; encontrado: 447,25.
J.20f	 A partir de J.18f	T_R = 1,07 min, (Condición-J1) CLEM: Calculado para $C_{28}H_{28}FN_6$ $[M+H]^+$ 467,24; encontrado: 467,25.

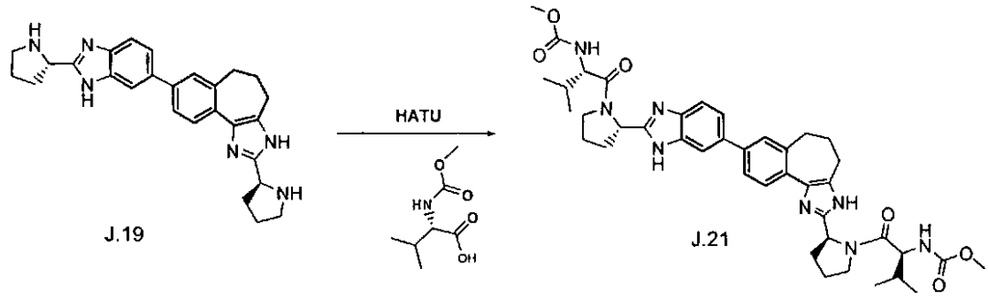
J.20g	 A partir de J.18g	T_R = 1,17 min, (Condición-J1) CLEM: Calculado para $C_{28}H_{26}FN_6$ $[M+H]^+$ 465,22; encontrado: 465,28.
J.20g.1	 A partir de J.18h	T_R = 1,43 min, (Condición-D1) CLEM: Calculado para $C_{30}H_{29}N_6$ $[M+H]^+$ 473,25; encontrado: 473,13.
J.20h	 A partir de J.18i	T_R = 1,09 min, (Condición-J1) CLEM: Calculado para $C_{30}H_{27}N_6$ $[M+H]^+$ 471,23; encontrado: 471,25.

J.20h.1	 A partir de J.18i.3	T_R: 1,60 min, (Condición-D1); Calculado para $C_{39}H_{40}N_7O_4$ $[M+H]^+$ 670,32; encontrado: 670,24.
J.20h.2	 A partir de J.18i.2	T_R: 1,77 min, (Condición-D1); Calculado para $C_{38}H_{33}N_8O_2$ $[M+H]^+$ 605,27; encontrado: 605,20.
J.20i	 A partir de J.18j	T_R = 1,09 min, (Condición-J1) CLEM: Calculado para $C_{30}H_{28}FN_6$ $[M+H]^+$ 491,24; encontrado: 491,25.

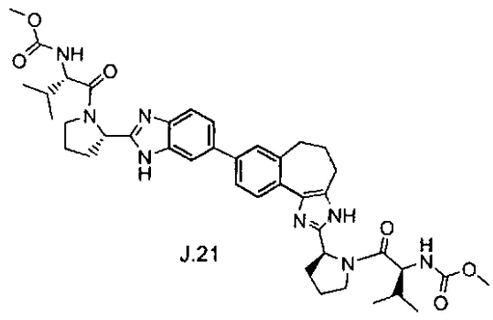
J.20j	 A partir de J.18k	T_R = 1,17 min, (Condición-J1) CLEM: Calculado para $C_{30}H_{26}FN_6$ $[M+H]^+$ 489,22; encontrado: 489,22.
J.20j.1	 A partir de J.18k.1	T_R = 2,73 min, (Condición-J2) CLEM: Calculado para $C_{30}H_{31}N_6$ $[M+H]^+$ 475,26; encontrado: 475,17.
J.20k	 A partir de J.18l	T_R = 1,0 min (Condición-J1) CLEM: Calculado para $C_{26}H_{27}N_6$ $[M+H]^+$ 423,23; encontrado: 423,24.
J.20l		T_R = 1,01 min (Condición-J1) CLEM: Calculado para $C_{26}H_{27}N_6$ $[M+H]^+$

	A partir de J.18m	423,23; encontrado: 423,31.
JB.7	 A partir de JB.6	T_R = 1,0 min (Condición-JB,1) CLEM: Calculado para $C_{26}H_{27}N_6$ $[M+H]^+$ 423,23; encontrado: 423,17.

Ruta de síntesis 13.

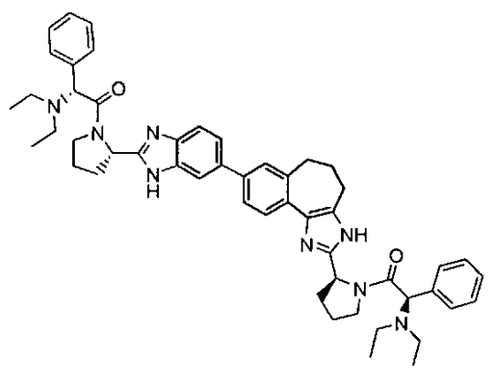


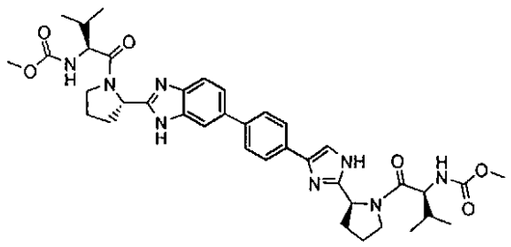
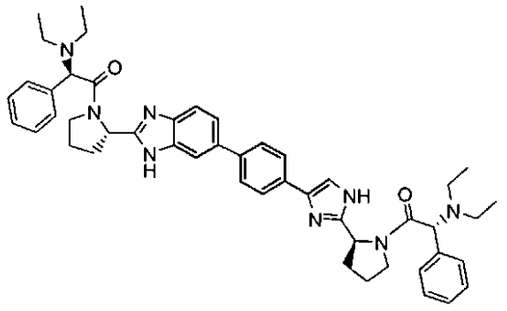
Ejemplos J.21 a JB.12

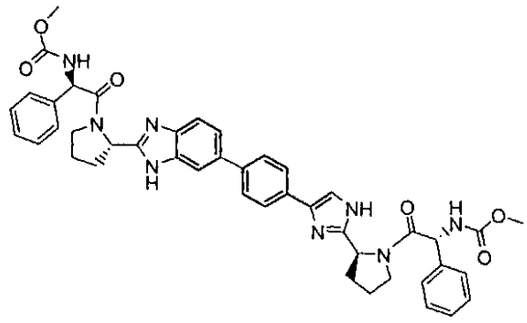
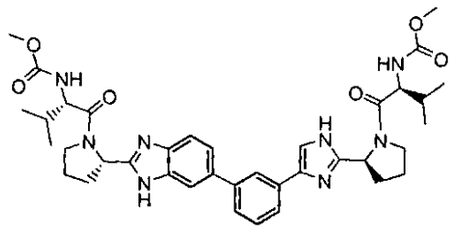
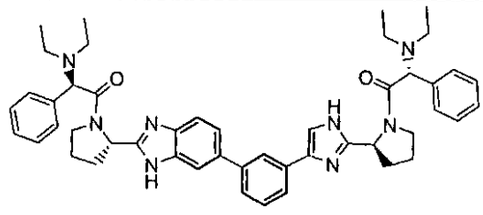


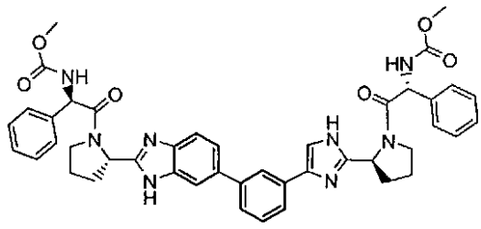
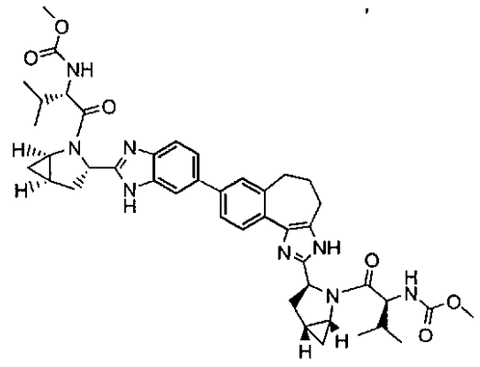
Se añadió HATU (60 mg, 0,16 mmol) a una solución rápidamente

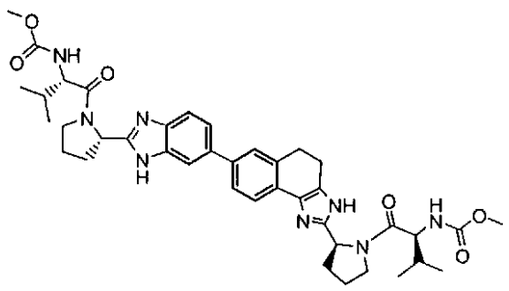
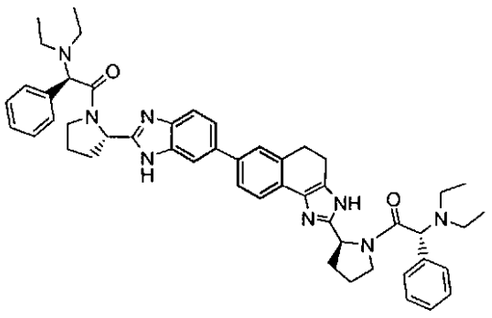
agitada del Ejemplo J.19 (38,18 mg, 0,075 mmol), N-metoxicarbonil-L-valina (26,2 mg, 0,15 mmol), y base de Hunig (0,095 ml, 0,54 mmol) en dimetilformamida (1,5 ml). La mezcla de reacción se agitó durante 2 h y el disolvente se eliminó en purga de nitrógeno. El residuo se diluyó con metanol y se sometió a HPLC prep. (Phenomenex LUNA C18 (30 x 100 mm); 5% - 100% de B durante 40 min; Caudal = 40 ml/min; Longitud de onda = 220 nm; Disolvente A = TFA al 0,1% en 10% metanol / 90% agua; Disolvente B = TFA al 0,1% en 90% metanol /10% agua) dando la sal bis TFA de J.21, 17,6 mg (24%). RMN de ^{1}H (500 MHz, DMSO-d_6) δ 7,91-7,84 (m, 1H), 7,72-7,57 (serie m, 5H), 7,30-6,8 (m, 2H), 5,50-5,17 (serie m, 4H), 4,20 (m, 1H), 4,10 (s ancho, 1H), 3,34-3,25 (m, 6H), 3,17 (s, 6H), 3,14-2,90 (serie m, 4H), 2,23-2,20 (m, 2H), 2,13-1,93 (m, 8H), 1,32-1,03 (m, 12H). CL (Condiciones-D2): 1,8 min; CLEM: Análisis calculado para $[M+H]^+$ $C_{41}H_{53}N_8O_6$ 753,41; encontrado: 753,55. EMAR: Análisis calculado para $[M+H]^+$ $C_{41}H_{53}N_8O_6$ 753,4088; encontrado: 753,4108.

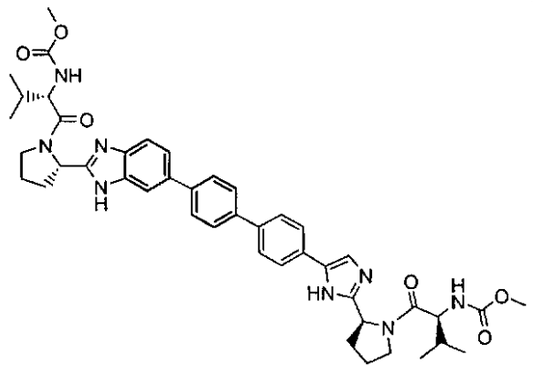
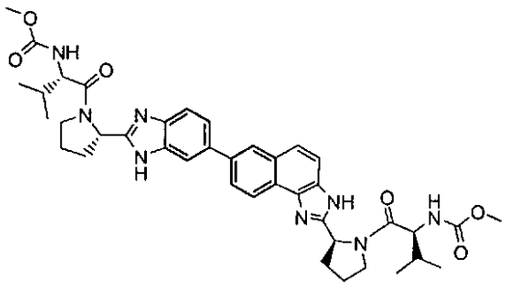
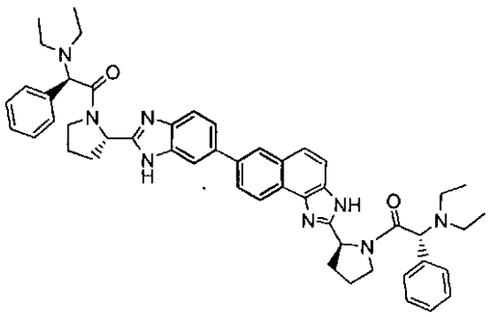
J.21a	 A partir de J.19	T_R= 2,1 min (Condición-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{51}H_{61}N_8O_2$: 817,49; encontrado: 817,63. EMAR: Análisis calculado para $[M+H]^+$ $C_{51}H_{61}N_8O_2$: 817,4917; encontrado: 817,4927.

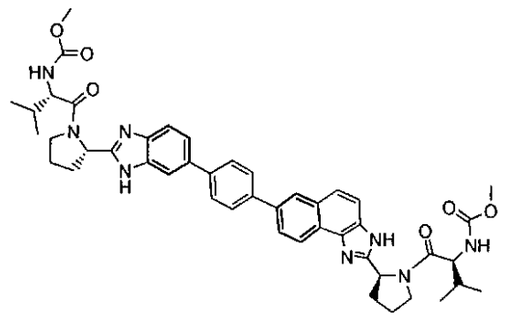
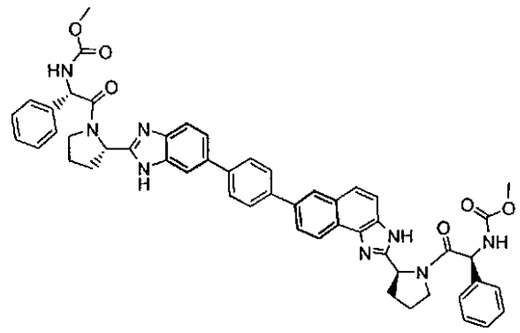
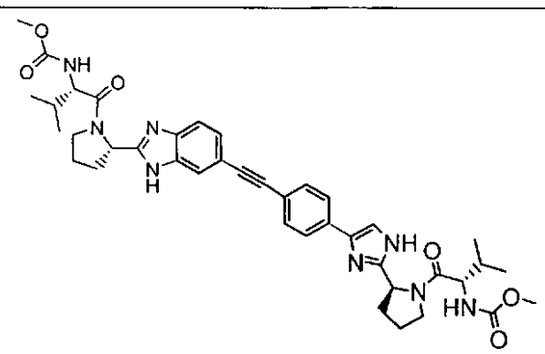
J.22	 A partir de J.19a	T_R = 1,88 min (Condición-D2) CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713,38; encontrado: 713,31. EMAR: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713,3775; encontrado: 713,3804.
J.22a	 A partir de J.19a	T_R = 1,65 min (Condición-D2) CLEM: Análisis calculado para $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777,46; encontrado: 777,48. EMAR: Análisis calculado para $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777,4604; encontrado: 777,4636.

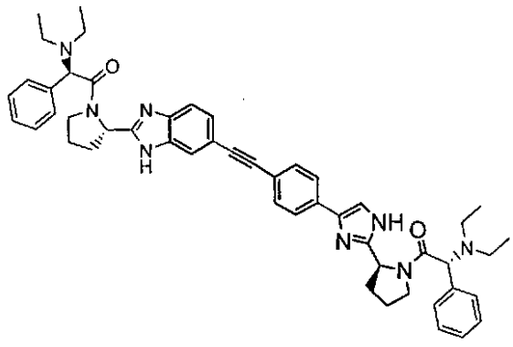
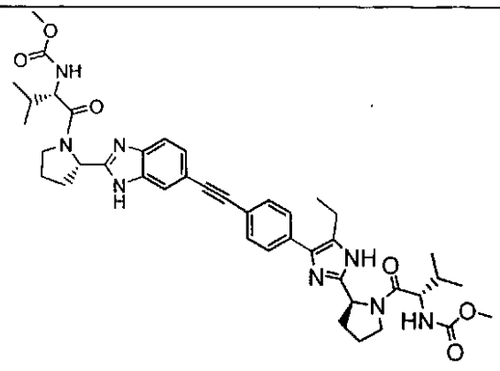
J.22b	 A partir de J.19a	T_R = 1,99 min (Condición-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781,35; encontrado: 781,37. EMAR: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781,3462; encontrado: 781,3483.
J.23	 A partir de J.19b	T_R = 1,92 min (Condición-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713,38; encontrado: 713,40. EMAR: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_6$: 713,3804; encontrado: 713,3798.
J.23a		T_R = 1,72 min (Condición-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{48}H_{56}N_8O_2$:

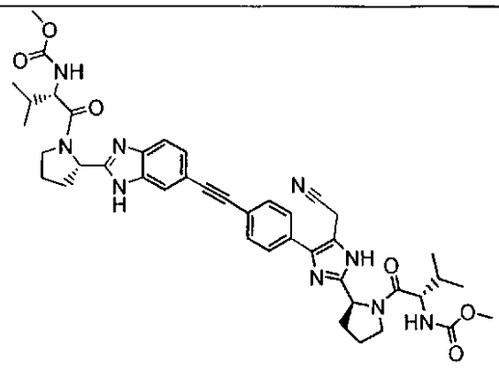
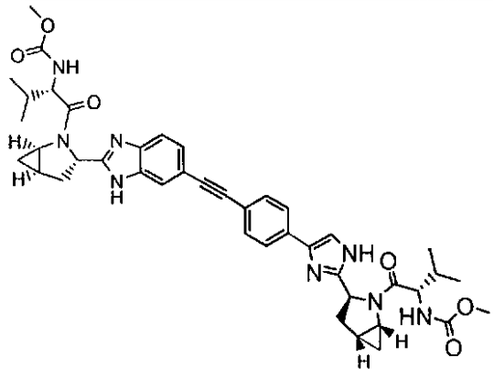
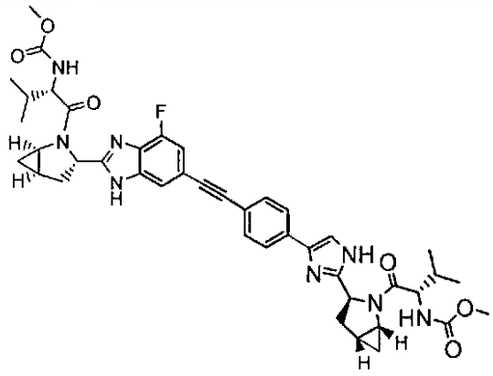
	A partir de J.19b	777,46; encontrado: 777,48. EMAR: Análisis calculado para $[M+H]^+$ $C_{48}H_{56}N_8O_2$: 777,4604; encontrado: 777,4579.
J.23b	 A partir de J.19b	T_R = 2,02 min (Condición-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781,35; encontrado: 781,37. EMAR: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_8O_6$: 781,3462; encontrado: 781,3497.
J.24	 A partir de J.19c	T_R = 1,5 min (Condición-J1); 87%, CLEM: Calculado para $C_{43}H_{53}N_8O_6$ $(M+H)^+$ 777,41; encontrado: 777,49. EMAR: Calculado para $C_{43}H_{53}N_8O_6$ $(M+H)^+$

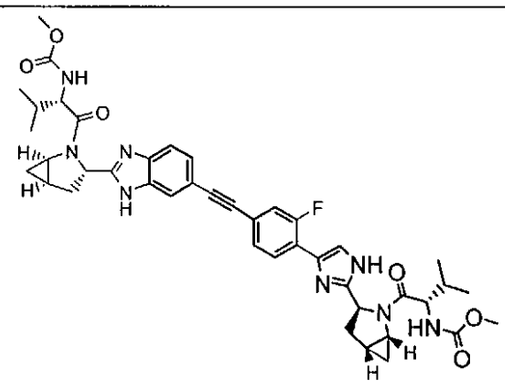
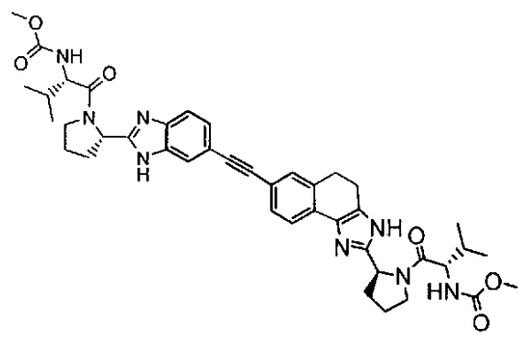
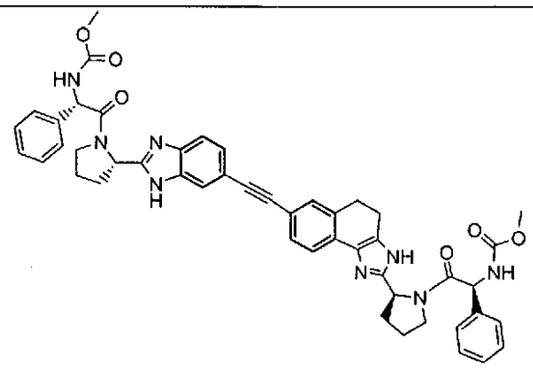
		777,4083; encontrado: 777,4088.
J.25	 A partir de J.19d	T_R = 1,83 min (Condición-D2); CLEM: 95%, Calculado para $C_{40}H_{51}N_8O_6$ $(M+H)^+$ 739,39; encontrado: 739,59. EMAR: Calculado para $C_{40}H_{51}N_8O_6$ $(M+H)^+$ 739,3926; encontrado: 739,3916.
J.25.a	 A partir de J.19d	T_R = 1,58 min (Condición-D2); CLEM: Calculado para $C_{50}H_{59}N_8O_2$ $(M+H)^+$ 803,47; encontrado: 803,65. EMAR: Calculado para $C_{50}H_{59}N_8O_2$ $(M+H)^+$ 803,4755; encontrado: 803,4749.

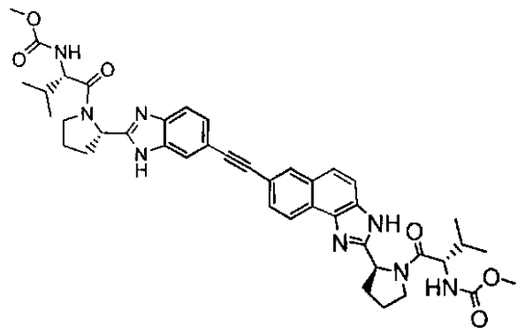
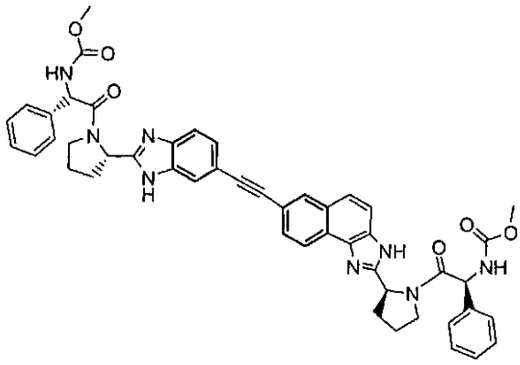
J.26	 A partir de J.19e	T_R = 1,51 min (Condición-J1); CLEM Calculado para $C_{44}H_{53}N_8O_6$ $(M+H)^+$ 789,41; encontrado: 789,55.
J.27	 A partir de J.19f	T_R = 1,94 min (Condición-D2); CLEM: 95%, Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,38; encontrado: 737,56. EMAR: Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,3770; encontrado: 737,3756.
J.27a	 A partir de J.19f	T_R = 1,67 min (Condición-D2); CLEM: Calculado para $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801,46; encontrado: 801,68.

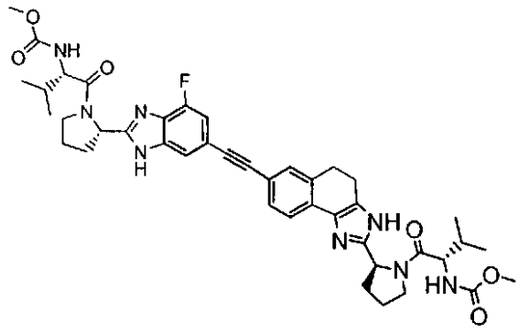
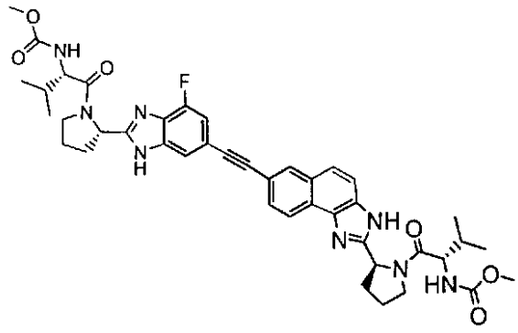
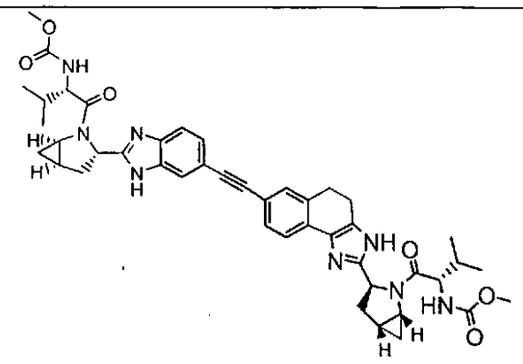
		EMAR: Calculado para $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801,4599; encontrado: 801,4592.
J.27b	 A partir de J.19f.1	T_R = 1,94 min (Condición-D1); CLEM: Calculado para $C_{46}H_{53}N_8O_6$ $(M+H)^+$ 813,41; encontrado: 813,46.
J.27c	 A partir de J.19f.1	T_R = 2,01 min (Condición-D1); CLEM: Calculado para $C_{52}H_{49}N_8O_6$ $(M+H)^+$ 881,38; encontrado: 881,37.
J.28		T_R = 1,46 min (Condición-J1); CLEM Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,38; encontrado: 737,42.

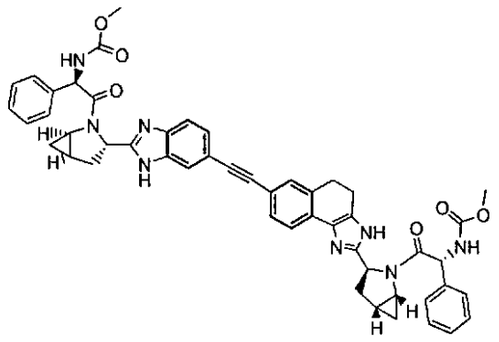
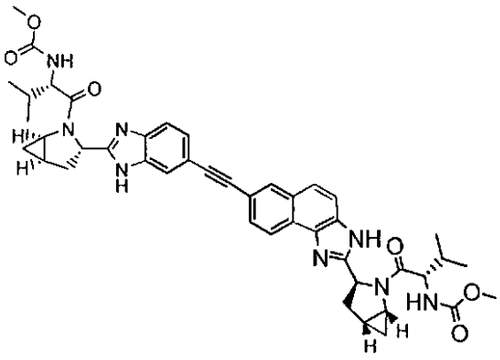
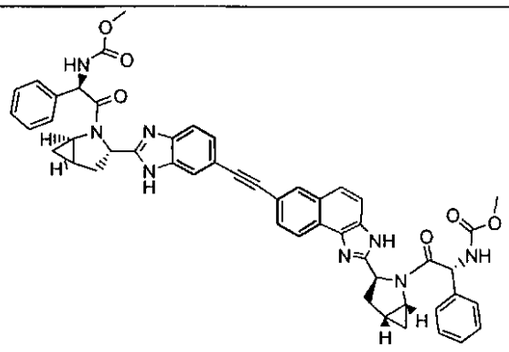
	A partir de J.20	EMAR: Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,3770; encontrado: 737,3774.
J.28a	 A partir de J.20	T_R = 1,30 min (Condición-J1); CLEM Calculado para $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801,46; encontrado: 801,62. EMAR: Calculado para $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801,4599; encontrado: 801,4585.
J.28a.1	 A partir de J.20.1	T_R = 1,29 min (Condición-J1); CLEM Calculado para $C_{42}H_{53}N_8O_6$ $(M+H)^+$ 765,41; encontrado: 765,49.

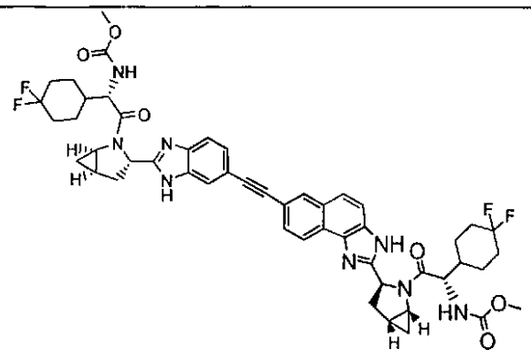
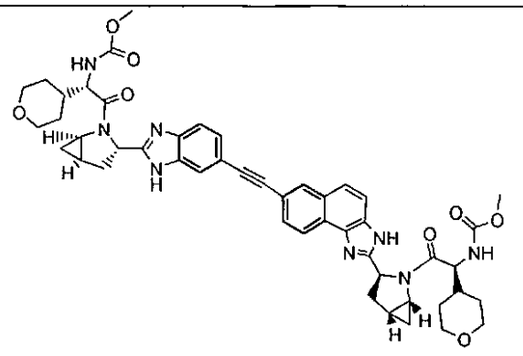
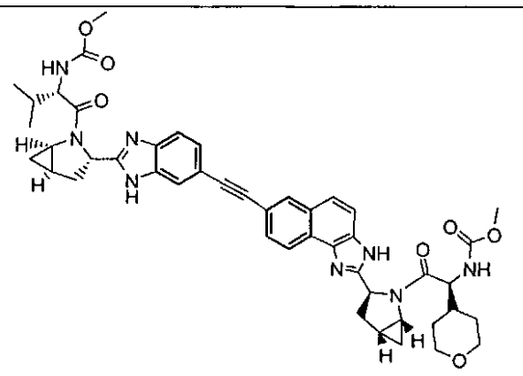
J.28a.2	 A partir de J.20.2	T_R = 1,22 min (Condición-J1); CLEM Calculado para $C_{42}H_{50}N_9O_6$ $(M+H)^+$ 776,39; encontrado: 776,42.
J.28b	 A partir de J.20a	T_R = 1,25 min (Condición-J1); CLEM Calculado para $C_{42}H_{49}N_8O_6$ $(M+H)^+$ 761,38; encontrado: 761,49.
J.28c	 A partir de J.20b	T_R = 1,44 min (Condición-J1); CLEM Calculado para $C_{42}H_{48}FN_8O_6$ $(M+H)^+$ 779,37; encontrado: 779,45.

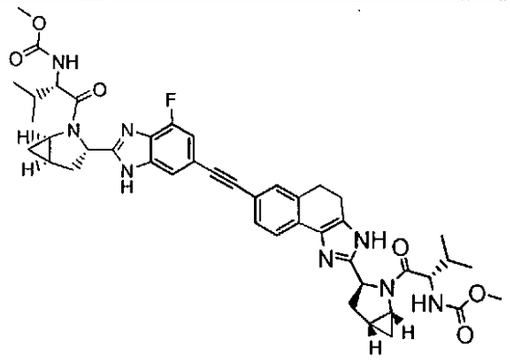
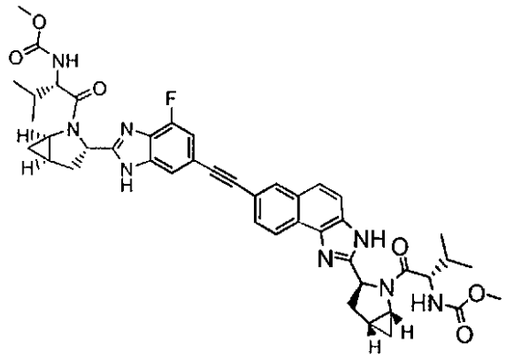
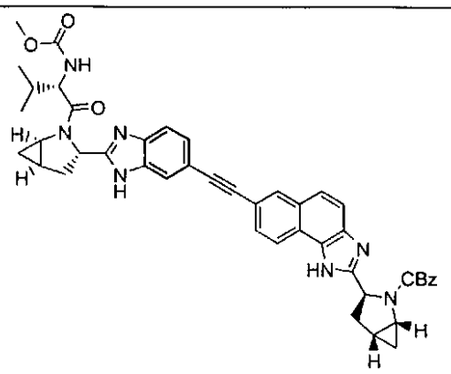
J.28d	 J.20c	T_R = 1,30 min (Condición-J1); CLEM Calculado para $C_{42}H_{48}FN_8O_6$ $(M+H)^+$ 779,37; encontrado: 779,45.
J.28e	 A partir de J.20d	T_R = 2,02 min (Condición-D2); 95%, Calculado para $C_{42}H_{51}N_8O_6$ $(M+H)^+$ 763,39; encontrado: 763,59. EMAR: Calculado para $C_{42}H_{51}N_8O_6$ $(M+H)^+$ 763,3926; encontrado: 763,3918.
J.28e.1		T_R = 1,97 min (Condición-D1); CLEM: Calculado para $C_{48}H_{47}N_8O_6$ $(M+H)^+$ 831,43; encontrado: 831,36.

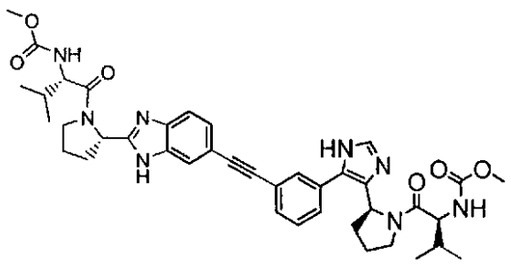
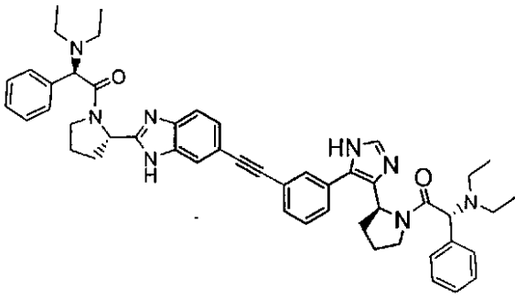
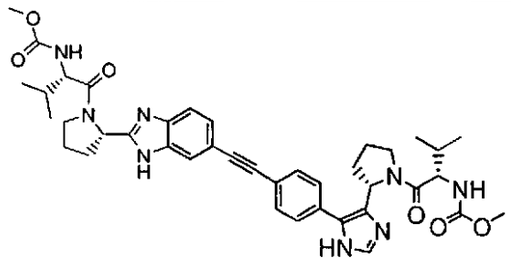
	A partir de J.20d	
J.28f	 A partir de J.20e	T_R = 2,10 min (Condición-D2); 95%, Calculado para $C_{42}H_{49}N_8O_6$ $(M+H)^+$ 761,38; encontrado: 761,55. EMAR: Calculado para $C_{42}H_{49}N_8O_6$ $(M+H)^+$ 761,3770; encontrado: 761,3765.
J.28f,1	 A partir de J.20e	T_R = 1,95 min (Condición-D1); CLEM: Calculado para $C_{48}H_{45}N_8O_6$ $(M+H)^+$ 829,35; encontrado: 829,45.

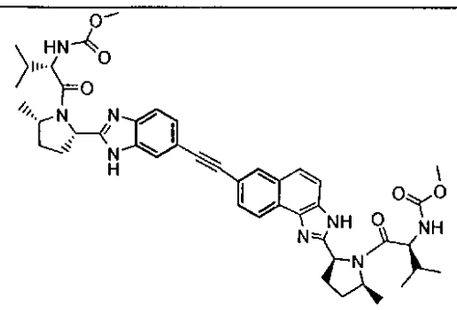
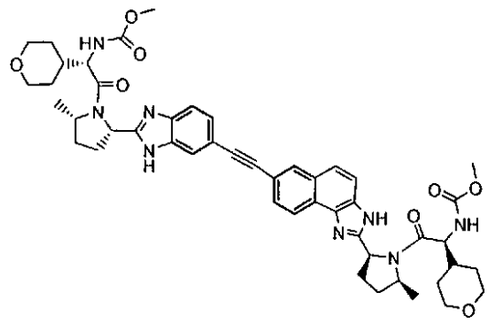
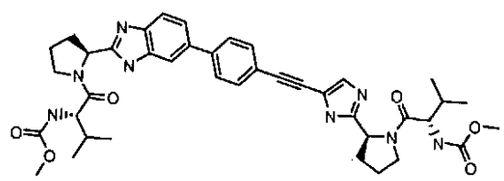
J.28g	 A partir de J.20f	T_R = 1,46 min (Condición-J1); CLEM Calculado para $C_{42}H_{50}FN_8O_6$ $(M+H)^+$ 781,39; encontrado: 781,49.
J.28h	 A partir de J.20g	T_R: 1,52 min, (Condición-J1); Calculado para $C_{42}H_{48}FN_8O_6$ $[M+H]^+$ 779,37; encontrado: 779,52.
J.28h.1	 A partir de J.20g.1	T_R = 1,83 min (Condición-D1); CLEM: Calculado para $C_{44}H_{51}N_8O_6$ $(M+H)^+$ 787,23; encontrado: 787,40.

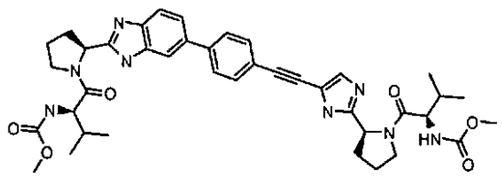
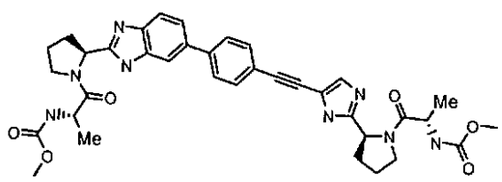
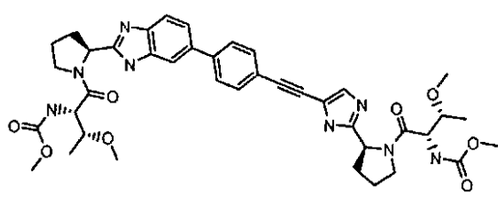
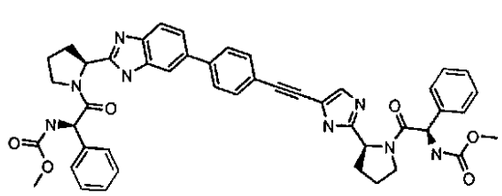
J.28h.2	 A partir de J.20g.1	T_R = 1,92 min (Condición-D1); CLEM: Calculado para $C_{50}H_{47}N_8O_6$ $(M+H)^+$ 855,36; encontrado: 855,21.
J.28i	 A partir de J.20h	T_R: 1,34 min, (Condición-J1); Calculado para $C_{44}H_{49}N_8O_6$ $[M+H]^+$ 785,38; encontrado: 785,55.
J.28i.1	 A partir de J.20h	T_R = 2,01 min (Condición-D1); CLEM: Calculado para $C_{50}H_{45}N_8O_6$ $(M+H)^+$ 853,35; encontrado: 853,25.

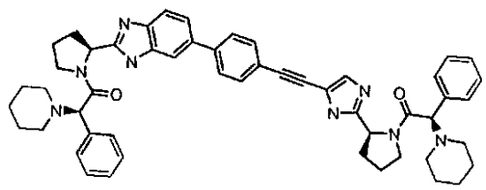
J.28i.2	 A partir de J.20h	T_R = 2,14 min (Condición-D1); CLEM: Calculado para $C_{50}H_{55}F_2N_8O_6$ $(M+H)^+$ 937,40; encontrado: 937,46.
J.28i.3	 A partir de J.20h	T_R = 2,83 min (Condición-D1); CLEM: Calculado para $C_{48}H_{53}N_8O_8$ $(M+H)^+$ 869,40; encontrado: 869,35.
J.28i.4	 A partir de J.20h.1	T_R = 1,81 min (Condición-D1); CLEM: Calculado para $C_{46}H_{51}N_8O_7$ $(M+H)^+$ 827,39; encontrado: 827,26.

J.28j	 A partir de J.20i	T_R: 1,49 min, (Condición-J1); Calculado para $C_{44}H_{50}FN_8O_6$ $[M+H]^+$ 805,39; encontrado: 805,55.
J.28k	 A partir de J.20j	T_R: 1,54 min, (Condición-J1); Calculado para $C_{44}H_{48}FN_8O_6$ $[M+H]^+$ 803,37; encontrado: 803,58.
J.28k.1	 A partir de J.20h.2	T_R: 2,01 min, (Condición-D1); Calculado para $C_{45}H_{44}N_7O_5$ $[M+H]^+$ 762,34; encontrado: 762,16.

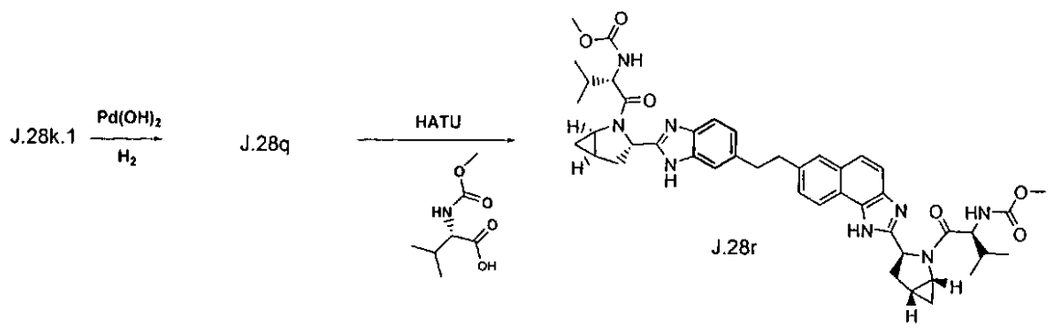
J.28l	 A partir de J.20k	T_R = 1,46 min (Condición-J1); CLEM Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,38; encontrado: 737,56. EMAR: Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,3770; encontrado: 737,3760.
J.28m	 A partir de J.20k	T_R = 1,36 min (Condición-J1); CLEM Calculado para $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801,46; encontrado: 801,62. EMAR: Calculado para $C_{50}H_{57}N_8O_2$ $(M+H)^+$ 801,4599; encontrado: 801,4597.
J.28n		T_R = 1,43 min (Condición-J1); CLEM Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,38; encontrado: no

	A partir de J.20l	aparente EMAR: Calculado para $C_{40}H_{49}N_8O_6$ $(M+H)^+$ 737,3770; encontrado: 737,3759.
J.28o	 A partir de J.20j.1	T_R: 1,88 min, (Condición-J2); Calculado para $C_{44}H_{53}N_8O_6$ $[M+H]^+$ 789,41; encontrado: 789,36.
J.28p	 A partir de J.20j.1	T_R: 1,76 min, (Condición-J2); Calculado para $C_{48}H_{57}N_8O_8$ $[M+H]^+$ 873,43; encontrado: 873,43.
JB.8	 A partir de JB.7	T_R: 1,17 min, (Condición-JB,1); Calculado para $C_{40}H_{49}N_8O_6$ $[M+H]^+$ 737,38; encontrado: 737,31.

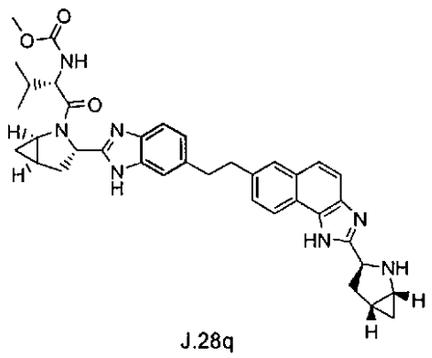
JB.8.1	 A partir de JB.7	T_R: 1,23 min, (Condición-JB,1); Calculado para $C_{40}H_{49}N_8O_6$ $[M+H]^+$ 737,38; encontrado: 737,33.
JB.9	 A partir de JB.7	T_R: 1,39 min, (Condición-JB,1); Calculado para $C_{36}H_{41}N_8O_6$ $[M+H]^+$ 681,32; encontrado: 681,21.
JB.10	 A partir de JB.7	T_R: 1,08 min, (Condición-JB,1); Calculado para $C_{40}H_{49}N_8O_8$ $[M+H]^+$ 769,37; encontrado: 769,31.
JB.11	 A partir de JB.7	T_R: 1,33 min, (Condición-JB,1); Calculado para $C_{46}H_{45}N_8O_6$ $[M+H]^+$ 805,35; encontrado: 805,27.

JB.12	 A partir de JB.7	T_R: 1,35 min, (Condición-JB,1); Calculado para $C_{52}H_{56}N_8O_2$ $[M+H]^+$ 825,46; encontrado: 825,34.

Ruta de síntesis 13a.

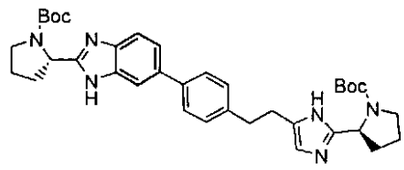


Ejemplos J.28q – JB.13



J.28q

Se añadió una solución del Ejemplo J.28k,1 (286,6 mg, 0,376 mmol) en MeOH (2 ml) a una suspensión agitada de hidróxido de paladio al 20% sobre carbón (52,8 mg, 0,376 mmol) y carbonato potásico (104 mg, 0,752 mmol) en MeOH (4 ml) en una atmósfera de nitrógeno. El matraz se evacuó y se cargó con hidrógeno (3x; globo, 96,5 kPa) y se agitó durante 3 h. **Nota:** Si se deja más de 3 horas se forman cantidades significativas de producto N-metilado. La mezcla se filtró sobre Celite y se lavó el lecho de Celite con MeOH (100 ml), cloruro de metileno (50 ml) y MeOH (100 ml) de nuevo. El filtrado se concentró y se colocó a alto vacío durante 0,5 h antes de que se suspendiera en MeOH y se hiciera pasar a través de una frita de jeringa de nailon (para eliminar las trazas de catalizador). El Ejemplo, J.28q se obtuvo (202 mg, 85 % de rendimiento) como un sólido amarillo. T_R: 1,62 min, (Condición-D1); Calculado para $C_{37}H_{42}N_7O_2$ $[M+H]^+$ 632,34; encontrado: 632,21.

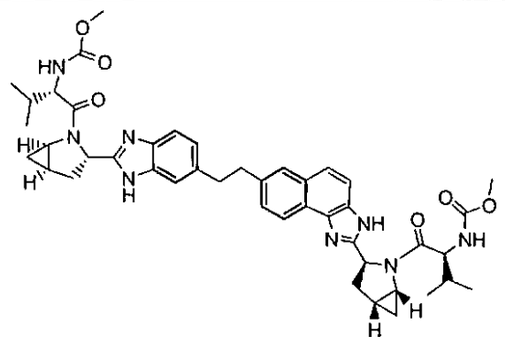


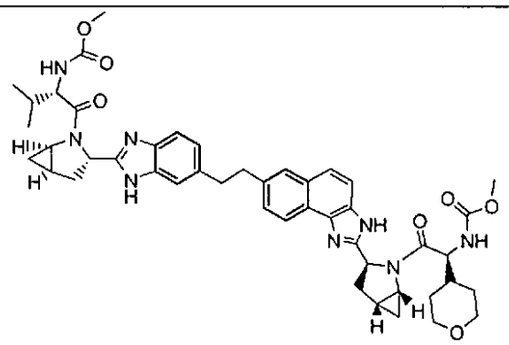
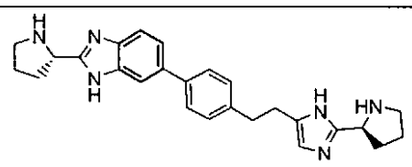
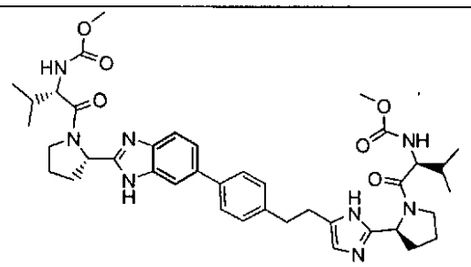
JB.13

Se añadió Pd al 10%/C (50 mg, 0,470 mmol) en una porción a una suspensión de una sal TFA del Ejemplo JB.6 (100 mg, 0,118 mmol) en MeOH

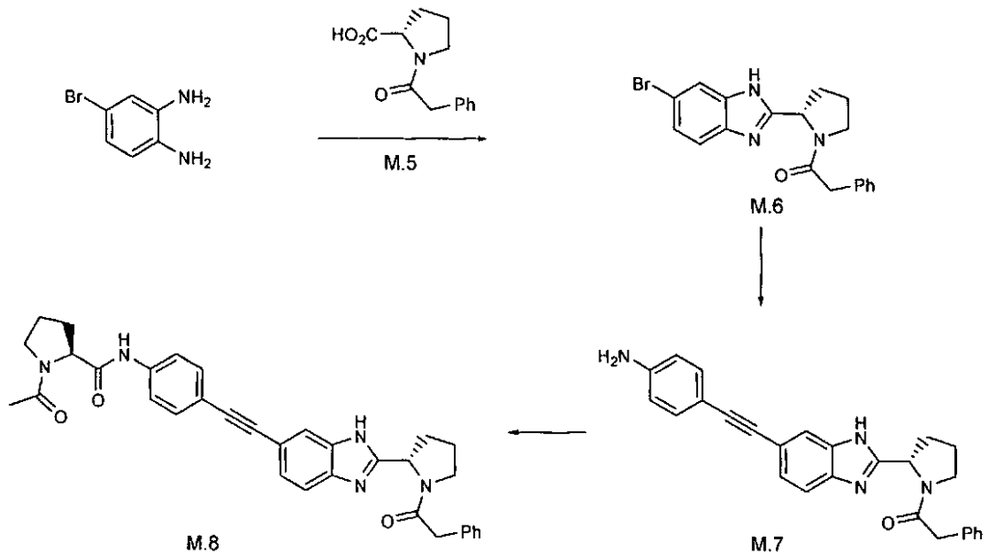
(10 ml). La mezcla de reacción se purgó con hidrógeno y se agitó bajo un globo de hidrógeno durante la noche a ta. La mezcla de reacción se filtró a través de Celite y se concentró. El residuo se purificó por HPLC prep (columna Waters Sunfire C18 30 X 150 mm 5u que eluyó con un gradiente de 10 hasta 100 % de ACN -agua + TFA al 0,1 %) proporcionando una sal TFA de (2S)-2-(4-(2-(4-(2-((2S)-1-(terc-butoxicarbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)etil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de terc-butilo (70 mg) como un sólido blanco. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7,95 (d, *J*=9,5 Hz, 1H), 7,85 (d, *J*=9,2 Hz, 2H), 7,66 (s ancho, 2H), 7,31 - 7,44 (m, 2H), 7,26 (s, 0,5H), 7,14 (s, 0,5H), 5,29 (s ancho, 1H), 5,04 (s ancho, 1H), 3,73 - 3,82 (m, 1H), 3,64 (s ancho, 2H), 3,55 (s ancho, 1H), 3,02 - 3,15 (m, 4H), 2,56 - 2,70 (m, 1H), 2,41 - 2,55 (m, 1H), 2,24 (s ancho, 1H), 2,08 - 2,18 (m, 2H), 2,03 (s ancho, 3H), 1,49 (d, *J*=7,9 Hz, 9H), 1,26 (s ancho, 4,5H), 1,22 (s ancho, 4,5H). T_R: 1,16 min, (Condición-JB-1); Calculado para $C_{36}H_{46}N_6O_4$ $[M+H]^+$ 627,37; encontrado: 627,31$[M+H]^+$.

Ejemplos J.28r – JB.15

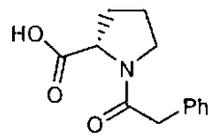
J.28r	 A partir de J.28q de acuerdo con el procedimiento descrito para J.21	T_R = 1,78 min (Condición-D1); CLEM: Calculado para $C_{44}H_{53}N_8O_6$ $(M+H)^+$ 789,41; encontrado: 789,24.

J.28s	 A partir de J.28q de acuerdo con el procedimiento descrito para J.21	T_R = 1,67 min (Condición-D1); CLEM: Calculado para $C_{46}H_{55}N_8O_7$ $(M+H)^+$ 831,42; encontrado: 831,26.
JB.14	 A partir de JB.13 de acuerdo con el procedimiento descrito para J.19	T_R = 0,82 min (Condición-JB-1); LC MS: Calculado para $C_{26}H_{31}N_6$ $(M+H)^+$ 427,26; encontrado: 427,28.
JB.15	 A partir de JB.14 de acuerdo con el procedimiento descrito para J.21	T_R = 1,06 min (Condición-JB-1); LC MS: Calculado para $C_{40}H_{56}N_6O_6$ $(M+H)^+$ 741,41; encontrado: 741,39.

Ruta de síntesis 14.

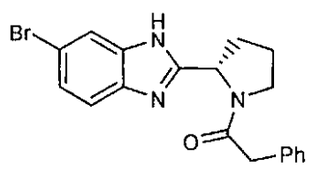


Ejemplos M.5 – M.9



M.5

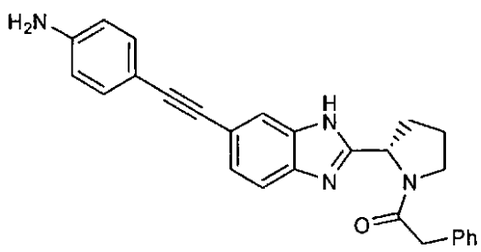
El Ejemplo M.5 se preparó a partir de l-prolina de acuerdo con el procedimiento descrito en Gudasheva, et al. Eur. J. Med. Chem. 1996, 31, 151.



M.6

Se añadió EDCI•HCl (1,76 g, 9,22 mmol) a una mezcla de 4-bromobenceno-1,2-diamina (1,50 g, 8,03 mmol), M.5 (1,88 g, 8,06 mmol) y 1-

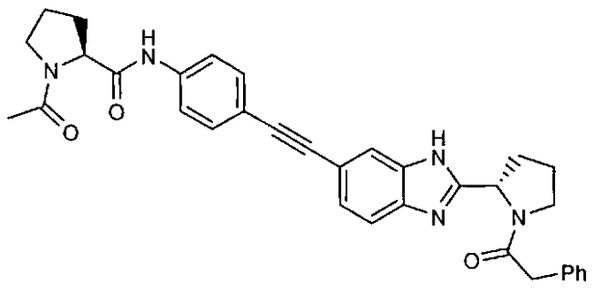
hidroxibenzotriazol (1,31 g, 9,70 mmol) en diclorometano (30 ml) y se agitó en condiciones ambientales durante 19 horas. La mezcla se diluyó entonces con diclorometano, se lavó con agua (2x), se secó (salmuera; $MgSO_4$), se filtró y se concentró a vacío proporcionando una espuma marrón. Se añadió ácido acético (30 ml) a la espuma y la mezcla se calentó a 65°C durante 90 minutos. El componente volátil se eliminó a vacío y el residuo se disolvió en acetato de etilo y se lavó cuidadosamente con solución saturada de $NaHCO_3$ (2x), y la fase orgánica se secó (salmuera; $MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se sometió a cromatografía ultrarrápida (gel de sílice; acetato de etilo) proporcionando el Ejemplo M.6 como una espuma color castaño (1,67 g). RMN de ^1H ($CDCl_3$, δ= 7,24 ppm, 500 MHz): 10,71/10,68 (s ancho solapando, 1H), 7,85 (s, 0,48H), 7,56 (d, J = 8,6, 0,52H), 7,50 (s, 0,52H), 7,35-7,22 (m, 6,48H), 5,38 (d ancho aparente, J = 8,1, 1H), 3,73 (d, J = 15,7, 1H), 3,67 (d, J = 15,6, 1H), 3,64-3,51 (m, 2H), 3,12-3,04 (m, 1H), 2,41-2,28 (m, 1H), 2,20-2,08 (m, 2H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{19}H_{18}BrN_3O$: 386,07; encontrado: 386,10.



M.7

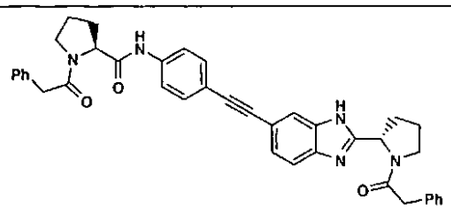
Se añadió $Pd(Ph_3P)_2Cl_2$ (13,3 mg, 0,019 mmol) a una mezcla de M.6 (152,9 mg, 0,40 mmol), 4-etinilanilina (69,6 mg, 0,59 mmol) y Et_3N (2,20 ml) en dimetilformamida (2,0 ml) y la reacción se calentó hasta 50 °C durante 8,5

horas. El componente volátil se eliminó a vacío y el residuo se sometió a cromatografía ultrarrápida (metanol al 0-30%/diclorometano), luego se volvió a purificar sobre HPLC de fase inversa (metanol/agua/TFA) proporcionando la sal TFA de M.7 (50 mg). CL/EM: Análisis calculado para $[M+H]^+$ $C_{27}H_{25}N_4O$: 421,2; Encontrado 421,21.

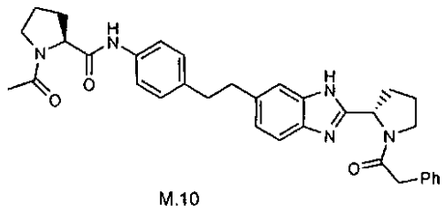


M.8

Se añadió diclorometano (3,0 ml) a una mezcla de M.7 (57,0 mg, 0,14 mmol), ácido (S)-1-acetilpirrolidin-2-carboxílico (23,3 mg, 0,15 mmol) y EEDQ (39,0 mg, 0,16 mmol) y se agitó en condiciones ambientales durante 16 horas. Los componentes volátiles se eliminaron a vacío y el residuo se disolvió en metanol y se sometió a purificación por HPLC de fase inversa (metanol/agua/TFA), seguido por desbasificación (columna SCX; lavado con metanol; elución con amoníaco 2,0 M/metanol) y purificación por cromatografía ultrarrápida (metanol al 5-15%/acetato de etilo) proporcionando M.8 como un sólido marrón (38,0 mg). CL/EM: Análisis calculado para $[M+H]^+$ $C_{34}H_{34}N_5O_3$: 560,27; encontrado: 560,28.

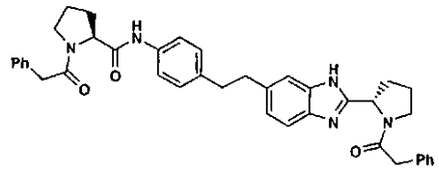
M.9	 A partir de M.5 y M.7	CL/EM: Análisis calculado para $[M+H]^+$ $C_{40}H_{37}N_5O_3$: 636,30; encontrado: 636,29.

Ejemplos M.10 - M.11

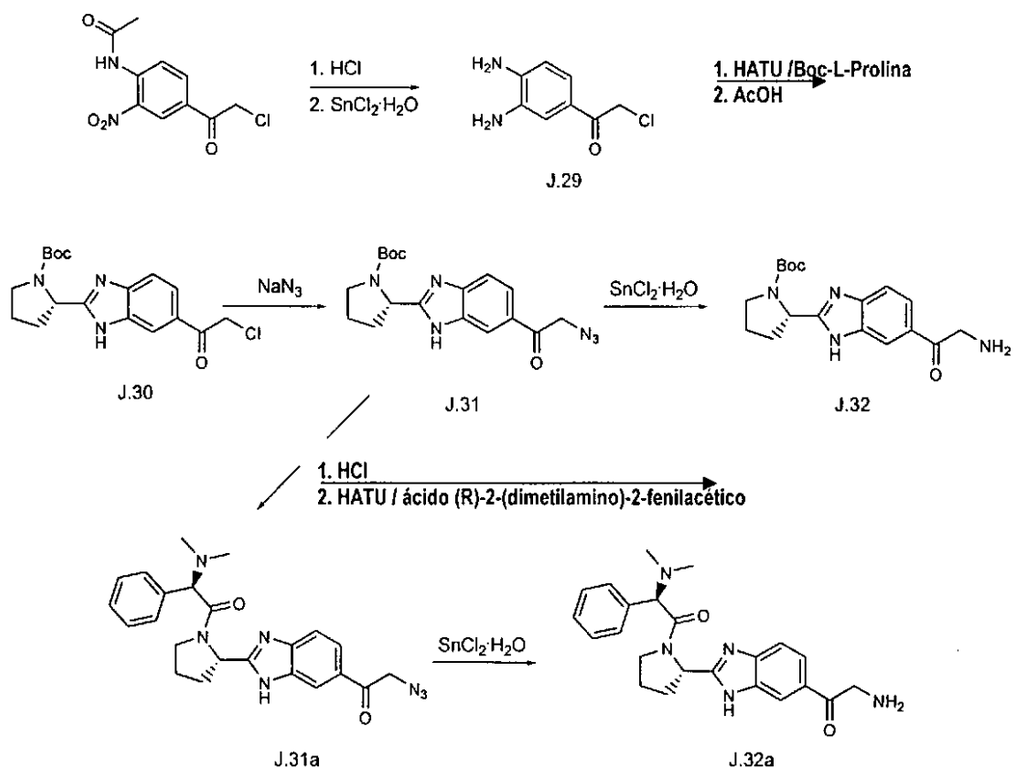


M.10

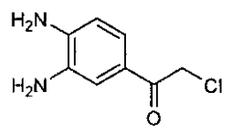
Se agitó una mezcla de M.8 (24,0 mg, 0,04 mmol) y Pd/C (10%, 14,1 mg) en metanol (3,0 ml) bajo un globo de H_2 (101 kPa) durante 3 horas. La suspensión se filtró a través de un lecho de tierra de diatomeas (Celite®) y se concentró a vacío proporcionando M.10 como una espuma blanquecina (22,0 mg). CL/EM: Análisis calculado para [M+H]+ $C_{34}H_{38}N_5O_3$: 564,30; encontrado: 564,43.

M.11	 A partir de M.9	CL/EM: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_5O_3$: 640,33; encontrado: 640,35.

Ruta de síntesis 15



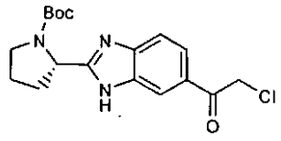
Ejemplos J.29 - J.32a



J.29

Se suspendió N-(4-(2-cloroacetil)-2-nitrofenil)acetamida (25,7 g, 0,1 mol) en 250 ml de HCl 3N y se calentó a 80 °C en un recipiente a presión de 1 litro durante 20 h. Después de enfriarse hasta temperatura ambiente, se aisló 1-(4-amino-3-nitrofenil)-2-cloroetanona•HCl (23,2 g, 92%) por filtración a vacío como

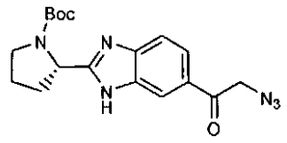
un sólido amarillo brillante. La sal (23,2 g, 0,092 mol) se suspendió en metanol (600 ml) y se añadió en una porción cloruro de estaño dihidrato (65 g, 0,29 mol). La mezcla se calentó a 70 °C durante 14 h mientras se agitaba intensamente. Se añadieron otros 20 g más de cloruro de estaño dihidrato y la reacción se agitó 8 h. El disolvente se eliminó por evaporación rotatoria y el residuo se suspendió en solución de acetato de etilo/$NaHCO_3$ (precaución: gran generación de dióxido de carbono. Las sales precipitadas se separaron por filtración y la fase orgánica se separó. La fase acuosa se extrajo dos veces más (acetato de etilo) y las fases orgánicas reunidas se lavaron con salmuera, se secaron (Na_2SO_4) y concentraron hasta ¼ del volumen. Se aisló 2-cloro-1-(3,4-diaminofenil) etanona, J.29, 10,03 g (59%) por filtración a vacío como un sólido color rojo ladrillo. RMN de ^1H (400 MHz, DMSO-d_6) δ: 8,17 (dd, J = 8,3, 2,3 Hz, 1H), 7,14 (d, J = 2,0 Hz, 1H), 6,51 (d, J = 8,0 Hz, 1H), 5,57 (s ancho, 2H), 4,85 (s, 2H), 4,78 (s ancho, 2H). CL (Condiciones-D2): 0,65 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{10}ClN_2O$: 185,05; encontrado: 185,02. EMAR: Análisis calculado para $[M+H]^+$ $C_8H_{10}ClN_2O$: 185,0482; encontrado: 185,0480. La reacción se repitió para suministrar más material.



J.30

Se añadió HATU (38,5 g, 101,3 mmol) en varias porciones a una solución intensamente agitada de J.29 (17,0 g, 92 mmol), N-Boc-L-prolina (19,82 g, 92 mmol) y base de Hunig (17,6 ml, 101,3 mmol) en dimetilformamida (200 ml). Después de 6 h, la mezcla de reacción se concentró a vacío para

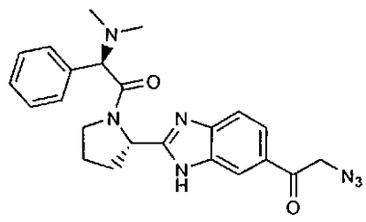
eliminar el disolvente y el residuo se suspendió en acetato de etilo, se lavó con solución saturada de $NaHCO_3$, salmuera y se secó (Na_2SO_4). La concentración proporcionó un aceite viscoso que se suspendió en ácido acético glacial (100 ml) y se calentó a 60 ºC durante 20 h. El disolvente se eliminó a vacío y el residuo se suspendió en acetato de etilo, se lavó con solución saturada de $NaHCO_3$ (ajustando con solución 1N de NaOH hasta pH = 9), salmuera y se secó (Na_2SO_4). El residuo obtenido tras concentrar se adsorbió previamente sobre SiO_2 (diclorometano) y se sometió a cromatografía ultrarrápida sucesivamente eluyendo con acetato de etilo al 50%, 75%, 100%/hexanos dando J.30 2-(6-(2-cloroacetil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo, se obtuvieron 22,37 g (67%) como una espuma amarilla. RMN de ^1H (400 MHz, DMSO-d_6) δ: 8,20 (s, 1H), 7,81 (dd, J = 8,3, 2,3 Hz, 1H), 7,59 (d, J = 8,0 Hz, 1H), 5,24 (s, 2H), 4,99/4,93 (s, 1H), 3,60 (s ancho, 1H), 3,46-3,41 (m, 1H), 2,36-2,30 (m, 1H), 2,01-1,89 (m, 3H), 1,39/1,06 (s, 9H). CL (Condiciones-D2): 1,85 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}ClN_3O_3$: 364,14; encontrado: 364,20. EMAR: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}ClN_3O_3$: 364,1428; encontrado: 364,1427.



J.31

Se añadió azida de sodio (1,79 g, 27,48 mmol) en una porción a una solución de J.30 2-(6-(2-cloroacetil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (10,0 g, 27,48 mmol) en acetonitrilo (200 ml) y se agitó a 60 ºC durante 16 h. La mezcla de reacción se concentró hasta 1/5 del

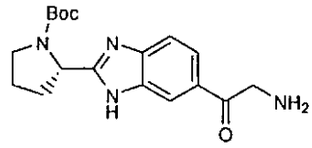
volumen, se diluyó con acetato de etilo, y se lavó con agua y salmuera antes de secar (Na_2SO_4). La concentración dio J.31 2-(6-(2-azidoacetil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo 6,8 g (48%) como una espuma naranja dorada. RMN de ^1H (500 MHz, DMSO-d_6) δ: 8,22/8,03 (s, 1H), 7,80-7,75 (m, 1H), 7,65/7,56 (d, J = 8,5 Hz, 1H), 4,99-4,93 (m, 3H), 3,60 (s ancho, 1H), 3,46-3,41 (m, 1H), 2,38-2,27 (m, 1H), 2,01-1,89 (m, 3H), 1,40/1,06 (s, 9H). CL (Condiciones-D2): 1,97 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}N_6O_3$: 371,19; encontrado: 371,32. EMAR: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}N_6O_3$: 371,1832; encontrado: 371,1825.



J.31a

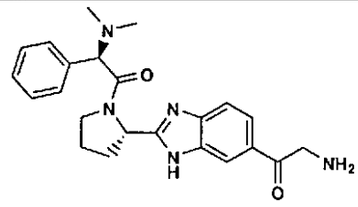
A una solución de J.31 (1,8 g, 4,86 mmol) en acetato de etilo (5 ml) se añadió HCl/dioxano (10 ml de 4N), y la reacción se agitó 4 horas. Los disolventes se eliminaron a vacío, y la sal HCl se expuso a alto vacío durante 18 h dando (S)-2-azido-1-(2-(pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etanona·2HCl como un sólido amarillo. Se añadió HATU (1,94 g, 5,10 mmol) a la sal HCl de (S)-2-azido-1-(2-(pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etanona (1,8 g, 4,86 mmol), ácido (R)-2-(dimetilamino)-2-fenilacético, sal HCl (1,05 g, 4,86 mmol), y base de Hunig (3,4 ml, 19,4 mmol) en dimetilformamida (50 ml) mientras se agitaba rápidamente 6 h. El disolvente se eliminó a vacío y el residuo se repartió en dos lotes y se preadsorbió por separado sobre SiO_2 (diclorometano), y se sometió a cromatografía ultrarrápida en una columna de

gel de sílice 40 M Biotage previamente equilibrada con B al 2%, y eluyó con 2% de B (150 ml); Segmento 2: 2-40% de B (1200 ml); Segmento 3: 40 – 80% (600 ml). A = diclorometano; B = 25% metanol/ diclorometano dando J.31a (R)-1-((S)-2-(6-(2-azidoacetil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-il)-2-(dimetilamino)-2-feniletanona (lotes combinados: 1,05 g (50%)) como una espuma amarilla. RMN de ^{1}H (500 MHz, DMSO-d_6) δ: 8,16 (s, 1H), 7,82 (dd, J = 8,8, 1,5 Hz, 1H), 7,65 (d, J = 8,5 Hz, 1H), 7,60-7,56 (m, 5H), 5,51 (s, 1H), 5,22 (dd, J = 8,2, 2,8, 1H), 4,95 (m, 2H), 4,09-4,05 (m, 1H), 3,17-3,12 (m, 1H), 2,90/2,84 (s ancho, 6H), 2,23-2,19 (m, 1H), 2,21-1,89 (m, 3H). CL (D-Cond. 1): T_R =1,5 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{23}H_{26}N_7O_2$: 432,22; encontrado: 431,93. EMAR: Análisis calculado para $[M+H]^+$ $C_{23}H_{26}N_7O_2$: 432,2148; encontrado: 432,2127.

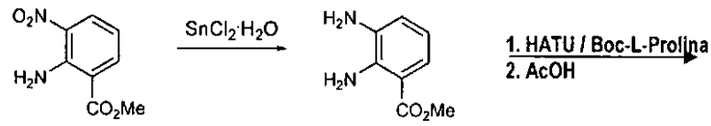


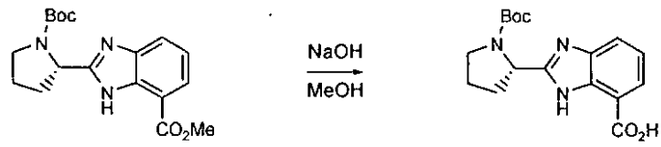
J.32

Se añadió dicloruro de estaño (II) deshidratado (12,24 g, 54,26 mmol) a J.31 (6,8 g, 18,08 mmol) disuelto en metanol (200 ml). La mezcla de reacción se calentó a 60 °C durante 6 h y se concentró y secó a alto vacío dando la sal HCl de J.32 2-(6-(2-aminoacetil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo, 16,6 g que contenía sales de estaño. CL (Condiciones-D2): 1,21 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{25}N_4O_3$: 345,18; encontrado: 345. El material se usó sin purificación.

J.32 a		

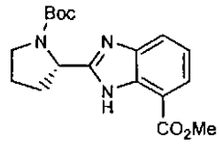
Ruta de síntesis 16





J.33 J.34

Ejemplos J.33 - J34.a



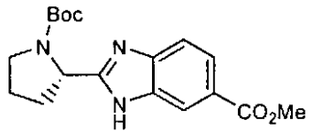
J.33

Se añadió cloruro de estaño (II) dihidratado (17,25 g, 76,5 mmol) en una porción a 2-amino-3-nitrobenzoato de metilo (5,0 g, 25,5 mmol) en metanol (100 ml) en nitrógeno. La mezcla amarilla se agitó intensamente a 65 °C durante 16 h, y el disolvente se eliminó por evaporación rotatoria casi hasta sequedad. El residuo se suspendió en acetato de etilo y la solución se vertió en

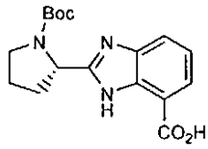
un vaso de precipitados grande que contenía solución 1:1 de acetato de etilo/$NaHCO_3$ (300 ml) y se agitó 15 min. Los precipitados se eliminaron por filtración y la fase orgánica se separó. La fase acuosa se extrajo dos veces con acetato de etilo, y las fases orgánicas reunidas se lavaron con solución saturada de $NaHCO_3$, salmuera y se secó (Na_2SO_4). La concentración dio 2,3-diaminobenzoato de metilo como un aceite viscoso rojo intenso 4,1 g (97%).

Se añadió HATU (10,66 g, 28,0 mmol) en una porción a una solución agitada de 2,3-diaminobenzoato de metilo (4,1 g, 24,7 mmol), N-Boc-L-prolina (5,49 g, 25,5 mmol) y base de Hunig (4,9 ml, 28,0 mmol) en dimetilformamida (50 ml). La mezcla de reacción se agitó 3 h y el disolvente se eliminó a vacío, y el residuo se diluyó con acetato de etilo, se lavó con HCl 0,1N, $NaHCO_3$ saturado, salmuera y se secó (Na_2SO_4). La concentración dio un aceite viscoso rojizo que se suspendió en ácido acético glacial (60 ml) y se calentó a 60 °C durante 16 h. El disolvente se eliminó a vacío, y el residuo se diluyó con acetato de etilo, se lavó con solución saturada de $NaHCO_3$, salmuera y se secó (Na_2SO_4). La concentración dio un residuo que se dividió en dos lotes, y se preadsorbió cada lote sobre SiO_2 (diclorometano), se aplicó a una columna 40 M Biotage de SiO_2, y eluyó en gradiente 10% - 100% de B (1440 ml); A = hexanos; B = acetato de etilo dando J.33 2-(1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-7-carboxilato de (S)-metilo 7,05 g (83%) como un aceite rojizo. RMN de ^1H (500 MHz, DMSO-d_6) δ: 7,86 (d, J = 7,9 Hz, 1H), 7,78 (t, J = 5 Hz, 1H), 7,28-7,24 (m, 1H), 5,20-5,11 (m, 1H), 3,95 (s, 3H), 3,60-3,52 (m, 1H), 3,43-3,38 (m, 1H), 2,33-2,22 (m, 1H), 2,15-2,0 (m, 2H), 1,91-1,86 (m, 1H), 1,40/1,05 (s, 9H). CL (Condiciones-D2): T_R =1,86 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{24}N_3O_4$: 346,18; encontrado 346,26; EMAR: Análisis

calculado para $[M+H]^+$ $C_{18}H_{24}N_3O_4$: 346,1767; encontrado: 346,1776.

J.33a		T_R = 0,72 min (Condiciones-J3); CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{24}N_3O_4$: 346,18; encontrado: 346.

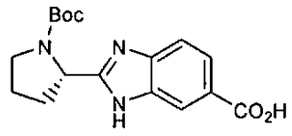
Ejemplo J.34



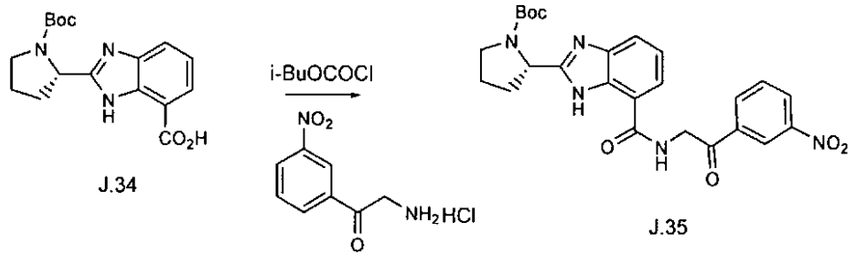
J.34

Se añadió una solución de hidróxido sódico 5N (8 ml) a éster metílico J.33 (7,0 g, 20,3 mmol) en metanol (80 ml) y se agitó 8 h. Se añadieron otros 4 ml y se continuó agitando durante 18 h, momento en el que se elevó la temperatura hasta 45 °C durante las 8 horas finales hasta completar la hidrólisis. Se eliminó la mayor parte del metanol por evaporación rotatoria, y la solución acuosa básica se diluyó con acetato de etilo. Se formó un precipitado y se aisló por filtración. La fase orgánica se separó y se lavó con salmuera. Se formaron lotes adicionales de precipitado durante la concentración parcial hasta ¼ del volumen y los lotes reunidos de J.34 ácido (S)-2-(1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-7-carboxílico totalizaron 5,49 g (82%) . RMN de ^1H (500 MHz, DMSO-d_6) δ: 8,04-8,0 (m, 2H), 7,58 (s ancho, 1H), 5,32 (s, 1H), 3,67-3,63 (m, 1H), 3,47-3,43 (m, 1H), 2,44-2,36 (m, 1H), 2,17-2,11 (m, 1H), 2,05-1,93 (m, 2H), 1,40/1,06 (s, 9H). CL (Condiciones-D2): 1,68

min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 332,16; encontrado: 332,25. EMAR: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 322,1610; encontrado: 322,1625.

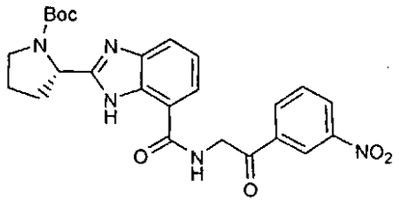
J.34a		T_R = 1,64 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 332,16; encontrado: 332,14. EMAR: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}N_3O_4$: 322,1605; encontrado: 322,1603.

Ruta de síntesis 17.



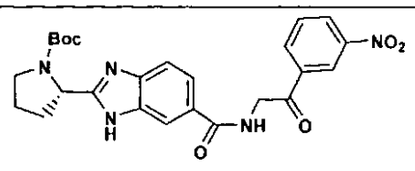
J.34 J.35

Ejemplos J.35 - J35.a



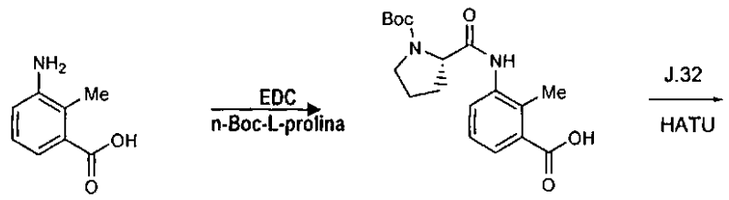
J.35

Se añadió cloroformiato de *iso*-butilo (0,45 ml, 3,4 mmol) gota a gota a una solución del ácido J.34 (1,0 g, 3,02 mmol) y N-metilmorfolina (1,2 ml, 10 mmol) en tetrahidrofurano (50 ml) enfriada hasta 0 °C en nitrógeno, y se retiró el baño de hielo y la reacción se agitó 30 min. La solución se volvió a enfriar y se añadieron otros 0,5 ml de base seguido por 2-nitrofenacilamina·HCl (700 mg, 3,2 mmol). La mezcla de reacción se agitó durante 18 h a temperatura ambiente y se diluyó con acetato de etilo y solución saturada de $NaHCO_3$. Se separó un precipitado por filtración y la fase orgánica se concentró. El residuo se suspendió en metanol y se filtró proporcionando un segundo lote de precipitado. Los lotes reunidos de J.35, 796 mg (65%) se llevaron a la siguiente etapa sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ: 10,5 (s ancho, 1H), 8,73 (s, 1H), 8,52-8,49 (m, 1H), 7,88 (t, J = 8,0 Hz, 1H), 7,80 (d, J = 7,7 Hz, 1H), 7,65 (d, J = 7,7 Hz, 1H), 7,25 (t, J = 7,7 Hz, 1H), 5,11-5,05 (m, 3H), 3,70-3,33 (m, 2H), 2,39-2,31 (m, 1H), 2,14-1,89 (m, 3H), 1,38/1,07 (s, 9H). CL (Condiciones-J1): 1,64 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{25}H_{28}N_5O_6$: 494,21; encontrado: 494,17.

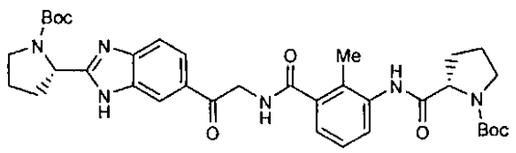
J.35a		T_R = 1,5 min (Condiciones-J1); CLEM: Análisis calculado para $[M+H]^+$

	A partir de J.34a y 2-amino-1-(3-nitrofenil)etanona	$C_{25}H_{28}N_5O_6$: 494,20; encontrado 494.

Ruta de síntesis 18

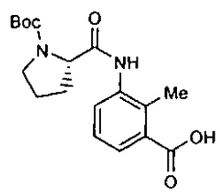


J.36



J.37

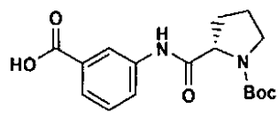
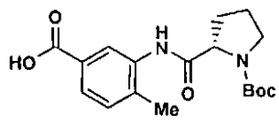
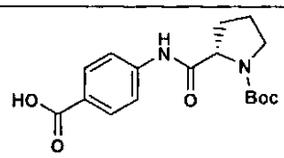
Ejemplos J.36 - J37.e

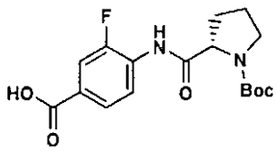


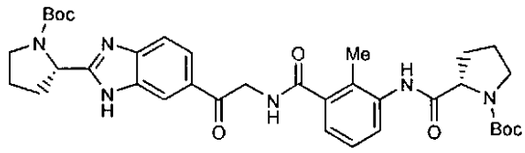
J.36

Se añadió sal HCl de N-(3-dimetilaminopropil)-N-etilcarbodimida (3,1 g, 16,6 mmol) a una suspensión de ácido 3-amino-2-metilbenzoico (2,5 g, 16,6 mmol) y N-Boc-L-prolina (3,5 g, 16,6 mmol) en diclorometano (40 ml). La mezcla de reacción se agitó en nitrógeno durante 18 h, se diluyó con disolvente (1 vol) y se lavó con HCl 1N, salmuera y se secó ($MgSO_4$). La concentración dio una espuma que se aplicó a una columna 40 M Biotage de SiO_2, y eluyó

con gradiente de 20% - 60% de B (1000 ml); A = ácido acético al 1% / hexanos; B = ácido acético al 1% / acetato de etilo dando J.36 ácido (S)-3-(1-(terc-butoxicarbonil)pirrolidin-2-carboxamido)-2-metilbenzoico 2,6 g (45%). RMN de ^{1}H (300 MHz, DMSO-d_6) δ: 12,5 (s ancho, 1H), 9,52/9,46 (s, 1H), 7,57 (d, J = 7,3 Hz, 1H), 7,44-7,40 (m, 1H), 7,29-7,24 (m, 1H), 4,32-4,28 (m, 1H), 3,47-3,48 (m, 1H), 3,34-3,29 (m, 1H), 2,33 (s, 3H), 1,93-1,80 (m, 4H), 1,41/1,36 (s, 9H). CL (Condiciones-J1): 1,55 min; CLEM: Análisis calculado para $[M+H]^+$ $C_{18}H_{25}N_2O_5$: 349,18; encontrado 349,33.

J.36a		T_R = 2,12 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{17}H_{23}N_2O_5$: 335,16; encontrado 335,26. EMAR: Análisis calculado para $[M-H]^-$ $C_{17}H_{21}N_2O_5$: 333,1450; encontrado: 333,1440.
J.36b		T_R = 2,14 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{18}H_{25}N_2O_5$: 349,18; encontrado 349,25. EMAR: Análisis calculado para $[M+H]^+$ $C_{18}H_{25}N_2O_5$: 349,1763; encontrado: 349,1748.
J.36c		T_R = 2,09 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{17}H_{23}N_2O_5$: 335,16; encontrado 335,25.

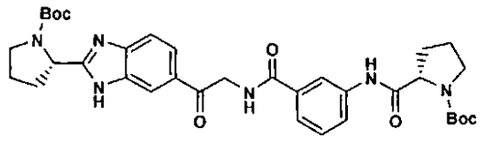
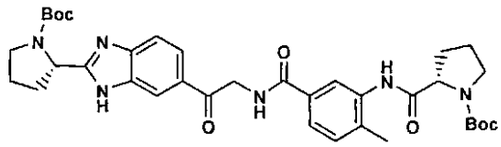
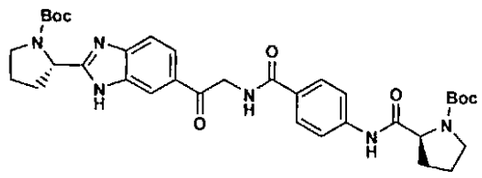
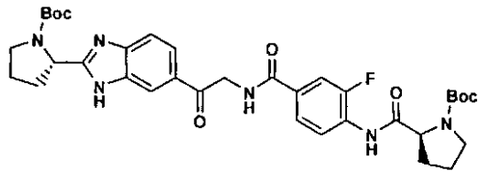
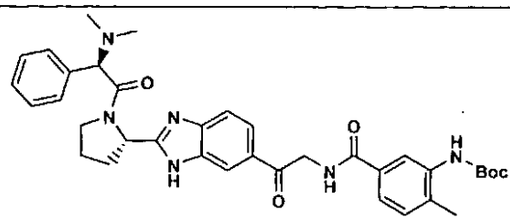
		EMAR: Análisis calculado para $[M-H]^-$ $C_{17}H_{23}N_2O_5$: 333,1450; encontrado: 333,1467.
J.36d	 (Obtenido tras desprotección del éster alilo mediante $Pd(Ph_3)_4$).	T_R = 2,24 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}FN_2O_5$: 353,15; encontrado 353,22. EMAR: Análisis calculado para $[M-H]^-$ $C_{17}H_{20}FN_2O_5$: 351,1356; encontrado: 351,1369.



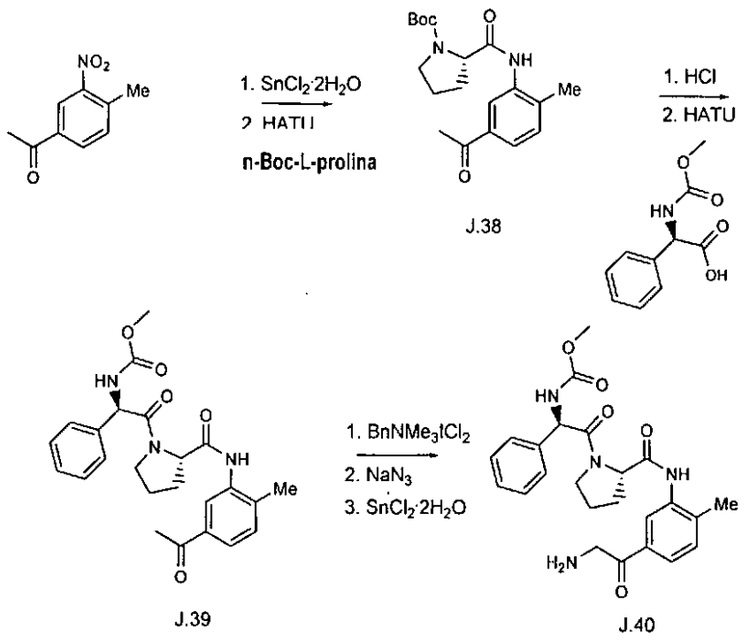
J.37

Se añadió HATU (462 mg, 1,22 mmol) en una porción a una solución agitada de J.32 (450 mg, 1,22 mmol), J.36 (423 mg, 1,22 mmol), y base de Hunig (1,0 ml) en dimetilformamida (10 ml) y la mezcla de reacción se agitó 18 h. El disolvente se eliminó a vacío y el residuo se aplicó a una columna 25 M Biotage de SiO_2, y eluyó con gradiente de 5% - 60% de B (500 ml); A = acetato de etilo; B = 10% metanol/acetato de etilo dando J.37, 439,6 mg (50%). RMN de ^1H (300 MHz, DMSO-d_6) δ: 12,73-12,58 (m, 1H), 9,45/9,35 (s, 1H), 8,59 (s ancho, 1H), 8,33/8,12 (s, 1H) 7,86 (d, J = 8,4 Hz, 1H), 7,66/7,56 (d, J = 8,4 Hz, 1H), 7,40-7,36 (m, 1H), 7,25 (s ancho aparente, 2H), 5,0-4,92 (m, 1H), 4,79 (d, J = 4,8 H, 2H), 4,33-4,30 (m, 1H), 3,60 (s ancho, 1H), 3,47-3,41(m, 2H), 3,35-3,29 (m, 1H), 2,24 (s, 3H), 2,02-1,87 (m, 8H), 1,42-1,37/1,05 (m, 18H). CL

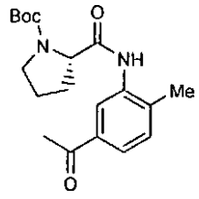
(Condiciones-J1): 1,65 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{36}H_{47}N_6O_7$: 675,35; encontrado 675,30.

J.37a	 A partir de J.32 y J.36a	T_R = 2,29 min (Condiciones-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661,34; encontrado 661,42.
J.37b	 A partir de J.32 y J.36b	T_R = 1,73 min (Condiciones-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{36}H_{47}N_6O_7$: 675,37; encontrado 675,31.
J.37c	 A partir de J.32 y J.36c	T_R = 2,25 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661,34; encontrado 661,42.
J.37d	 A partir de J.32 y J.36d	T_R = 2,33 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{35}H_{44}FN_6O_7$: 679,33; encontrado 679,42.
J.37e	 A partir de J.32a y ácido 3-(t-butoxicarbonil-amino)-4-metilbenzoico	T_R = 2,08 min (Condiciones-D2); CLEM: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_6O_5$: 639,33; encontrado 639,67.

Ruta de síntesis 19



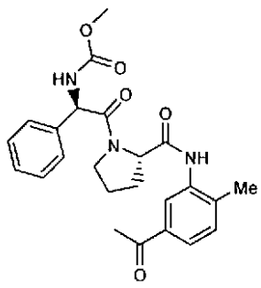
Ejemplos J.38 - J.40



J.38

Se añadió dicloruro de estaño (II) dihidratado (37 g, 168 mmol) a 4-metil-3-nitroacetofenona (10 g, 56 mmol) disuelta en metanol (350 ml). La mezcla de reacción se calentó a 60 °C durante 18 h, se concentró y se secó bajo alto vacío dando 1-(3-amino-4-metilfenil)etanona que contenía sales de estaño. CL

(Condiciones-J1): 0,73 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{11}NO$: 150,08; encontrado: 150. El material se usó sin purificación. Se añadió HATU (10,6 g, 28 mmol) en una porción a una solución agitada de 1-(3-amino-4-metilfenil)etanona (4,1 g, 28 mmol), N-Boc-L-prolina (6 g, 28 mmol), y base de Hunig (25 ml) en DMF (225 ml) y la mezcla de reacción se agitó 18 h. Se eliminó el disolvente a vacío y el residuo se suspendió en acetato de etilo/metanol (1:1) y se aplicó a una columna ultrarrápida de SiO_2. Se llevó a cabo una etapa de elución con gradiente de 20%; 50%; 75%; 100% de B (volumen total de elución 1500 ml); A = hexanos; B = acetato de etilo; y una elución final con;10% de metanol/acetato de etilo dando J.38, 4,4 g (46%). RMN de ^1H (300 MHz, DMSO-d_6) δ: 9,51/9,45 (s, 1H), 7,95-7,92 (m, 1H), 7,70 (d, J = 8,0 Hz, 1H), 7,37 (d, J = 7,7 Hz, 1H), 4,33-4,29 (m, 1H), 3,48-3,29 (m, 2H), 2,50 (s, 3H), 2,26 (s, 3H), 1,98-1,80 (m, 4H), 1,41/1,36 (m, 9H). CL (Condiciones-J1): 1,70 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{19}H_{27}N_2O_4$: 347,20; encontrado 347,41.

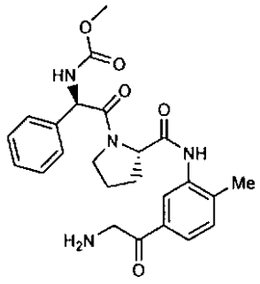


J.39

Se disolvió el Ejemplo J.38 (3 g, 83 mmol) en metanol (30 ml) y se añadió HCl 4N/dioxano (50 ml) y la reacción se agitó 18 horas. Los disolventes se eliminaron a vacío, y se expuso a vacío la sal HCl de (S)-N-(5-acetil-2-

metilfenil)pirrolidin-2-carboxamida. CL (Cond-J1): 0,9 min. HATU (1,4 g, 3,5 mmol) se añadió en una porción a una solución agitada de (S)-N-(5-acetil-2-metilfenil)pirrolidin-2-carboxamida·HCl (1,0 g, 3,5 mmol), ácido (R)-2-(metoxicarbonilamino)-2-fenilacético (740 mg, 3,5 mmol), y base de Hunig (2,9 ml) en dimetilformamida (25 ml) y la mezcla de reacción se agitó 18 h. El disolvente se eliminó a vacío y el residuo se aplicó a una columna 40 M Biotage de SiO_2, y eluyó con gradiente de 50% - 100% de B (500 ml); A = hexanos; B = acetato de etilo dando J.39, (R)-2-((S)-2-(5-acetil-2-metilfenilcarbamoil)pirrolidin-1-il)-2-oxo-1-feniletilcarbamato de metilo 1,25 g (87%). RMN de ^1H (300 MHz, DMSO-d_6) δ: 9,42 (s, 1H), 7,95 (s, 1H), 7,75-7,69 (m, 2H), 7,43-7,19 (m, 6H), 5,50/5,40 (d, J = 7,7 Hz, 1H), 4,49-4,47 (m, 1H), 3,87-3,81 (m, 1H), 3,58-3,54 (m, 1H), 3,50 (s, 3H), 2,54 (s, 3H), 2,27 (s, 3H), 1,99-1,83 (m, 4H). CL (Condiciones-J1): 1,65 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{24}H_{28}N_3O_5$: 438,20; encontrado 438,20.

Referencia: Synthesis (1988) página 545. (Chlorination).



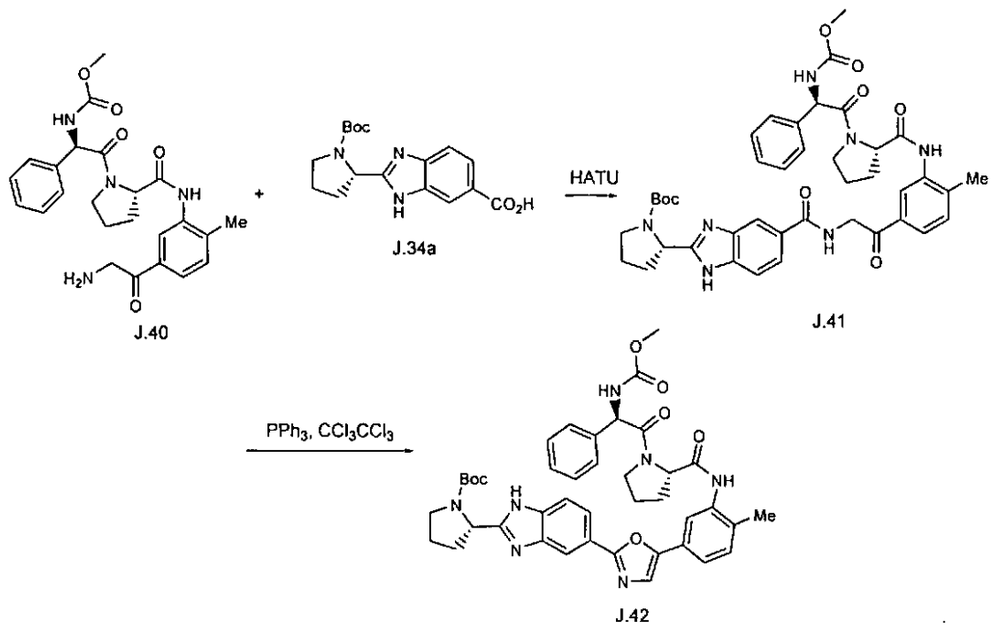
J.40

Se añadió trimetildicloroyodato de bencilo (2,0 g, 5,72 mmol) a una solución de J.39 (1,25 g, 2,86 mmol) en diclorometano (65 ml) y metanol (20 ml). La reacción se calentó durante 3 h a 75 °C antes de concentrase por evaporación rotatoria. El residuo se suspendió en acetato de etilo y se lavó con

solución de tiosulfato sódico, salmuera y se secó ($MgSO_4$) proporcionando una α-clorocetona. CL (Condiciones-J1): 1,70 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}ClN_3O_5$: 471,16; encontrado: 471.

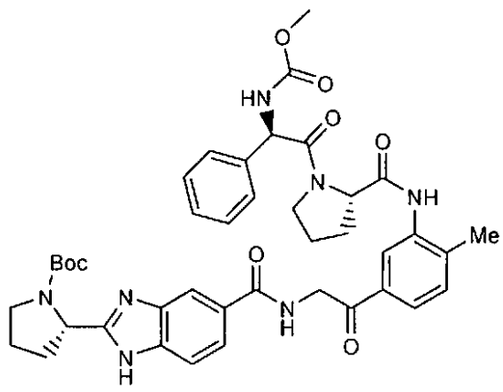
La α-clorocetona se convirtió en la α-aminocetona J.40 como se describe en el Ejemplo J.31. [α-azidocetona: CL (Condiciones-J1): 1,70 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}N_6O_5$: 479,20; encontrado: 479,20.] J.26 CL (Condiciones-J1): 1,70 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{24}H_{29}N_4O_5$: 453,21; encontrado: 453.

Ruta de síntesis 20.



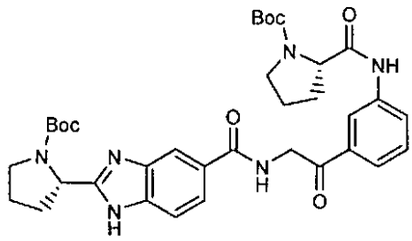
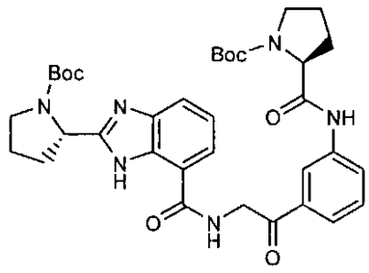
J.40 J.34a J.41 J.42

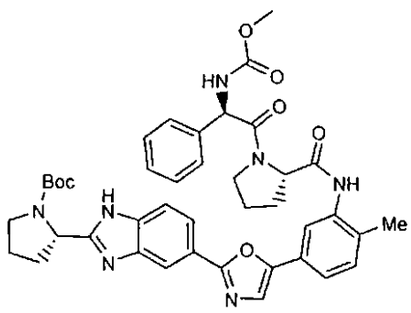
Ejemplo J.41- J.42h



J.41

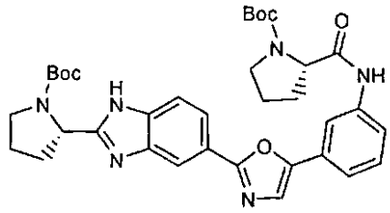
La α-aminocetona J.40 se acopló con J.34a como se describe en el Ejemplo J.37 dando J.41: CL (Condiciones-J1): 1,90 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_8$: 766,36; encontrado: 766,37.

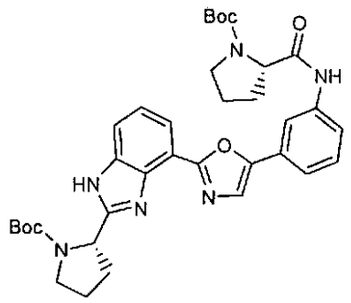
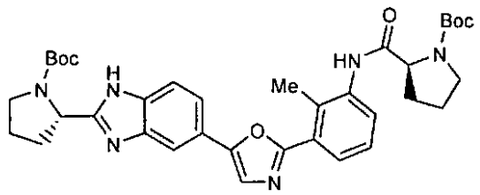
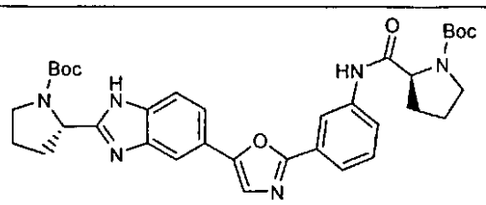
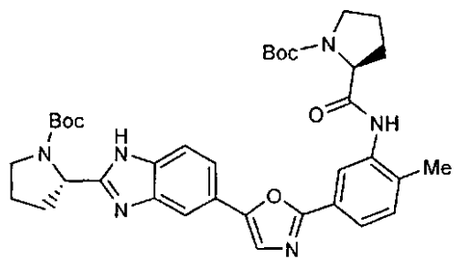
J.41a	 A partir de J.35a y N-Boc-L-prolina, preparado como se describe en la ruta para J.38.	T_R = 1,64 min (Condiciones-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661,34; encontrado 661,30.
J.41b	 A partir de J.35 y N-Boc-L-prolina, preparado como se describe en la ruta para J.38.	T_R = 1,82 min (Condiciones-J1); CLEM: Análisis calculado para $[M+H]^+$ $C_{35}H_{45}N_6O_7$: 661,34; encontrado 661,32.

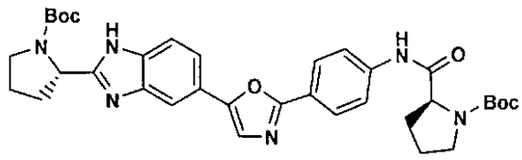
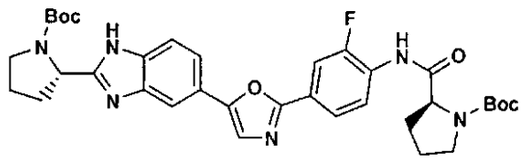
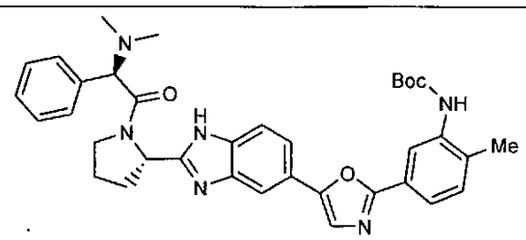


J.42

Se agitó aproximadamente 5 minutos en atmósfera de nitrógeno antes de la adición de hexacloroetano (146 mg, 0,62 mmol) en una porción una solución de J.41 (237 mg, 0,31 mmol), trifenilfosfina (162 mg, 0,62 mmol) y trietilamina (0,2 ml, 1,74 mmol) en diclorometano (3 ml). La mezcla de reacción se agitó 18 h, se concentró parcialmente, y se aplicó a una columna de gel de sílice 12 M Biotage y eluyó con gradiente de 40% - 100% de B. A = hexanos; B = acetato de etilo dando J.42, 95 mg (41%). CL (Condiciones-J1): 1,95 min; EMBR: Análisis calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_7$: 748,36; encontrado: 748,29.

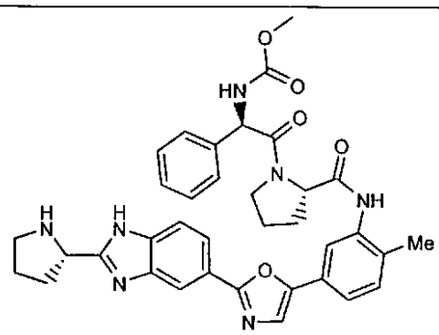
J.42a	 A partir de J.41a	T_R = 2,64 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643,32; encontrado: 643,35. EMAR: Análisis calculado para $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643,3244; encontrado 643,3242.

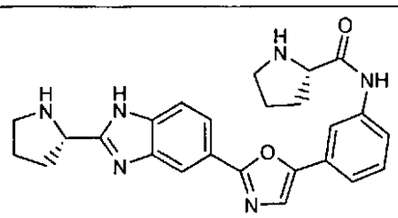
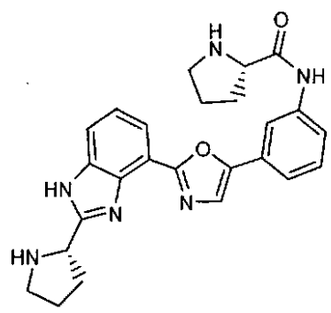
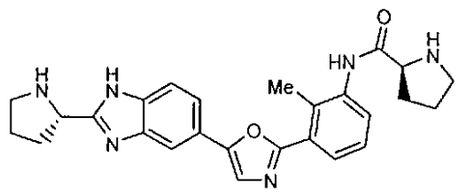
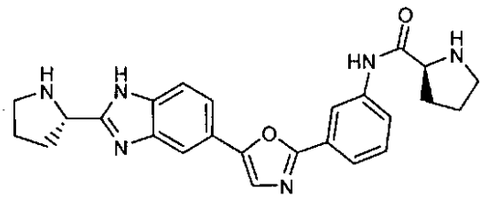
J.42b	 A partir de J.41b	T_R = 2,97 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643,32; encontrado: 643,37. EMAR: Análisis calculado para $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643,3244; encontrado 643,3265.
J.42c	 A partir de J.37	T_R = 2,51 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657,34; encontrado: 657,36. EMAR: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657,3401; encontrado 657,3407.
J.42d	 A partir de J.37a	T_R = 2,61 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643,32; encontrado: 643,41.
J.42e	 A partir de J.37b	T_R = 2,63 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657,34; encontrado: 657,73. EMAR: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_6$: 657,3401;

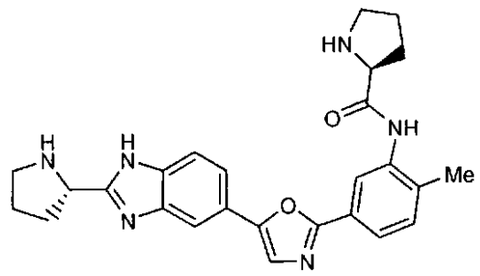
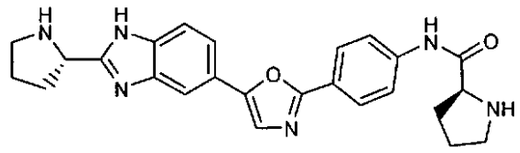
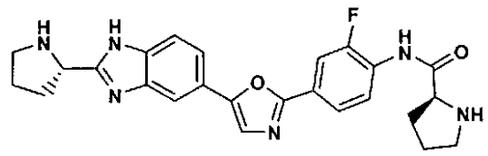
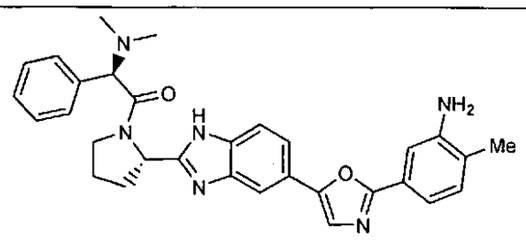
		encontrado 657,3397.
J.42f	 A partir de J.37c	T_R = 1,59 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{35}H_{43}N_6O_6$: 643,32; encontrado: 643,41.
J.42g	 A partir de J.37d	T_R = 2,64 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{35}H_{42}FN_6O_6$: 661,32; encontrado: 661,40.
J.42h	 A partir de J.37e	T_R = 2,41 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621,32; encontrado: 621,21.

Ejemplos J.43 - J.43j

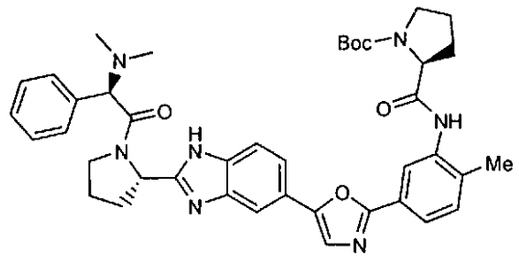
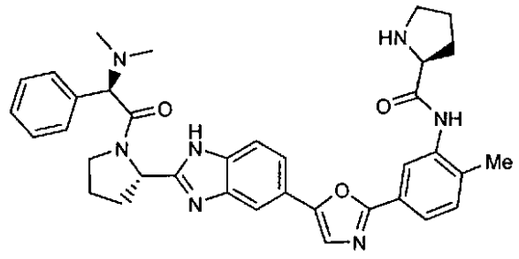
Las pirrolidinas ejemplos J.42 – J.42h se trataron con HCl como se describe en el Ejemplo J.39 dando los ejemplos J.43 – J.43j como sales HCl.

J.43	 A partir de J.42	T_R = 1,80 min (Condiciones-J1) CLEM: Análisis calculado para $[M+H]^+$ $C_{36}H_{38}N_7O_5$: 648,29; encontrado 648.

J.43a	 A partir de J.42a	T_R = 1,69 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,22; encontrado: 443,23.
J.43b	 A partir de J.42b	T_R = 1,86 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,22; encontrado: 443,07. EMAR: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,2195; encontrado 443,2213.
J.43c	 A partir de J.42c	T_R = 1,51 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6O_2$: 457,24; encontrado: 457,19.
J.43d	 A partir de J.42d	T_R = 1,64 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,22; encontrado: 443,31. EMAR: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,2195; encontrado 443,2205.

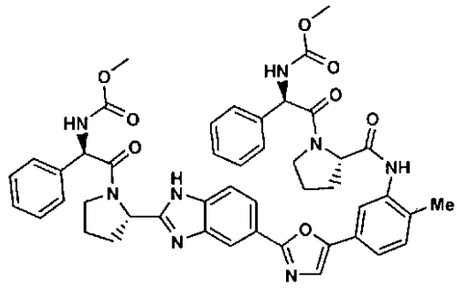
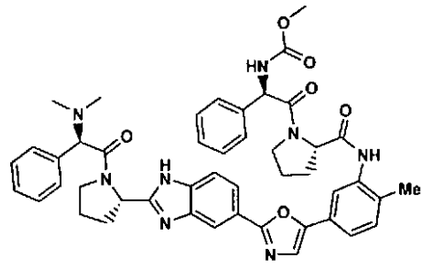
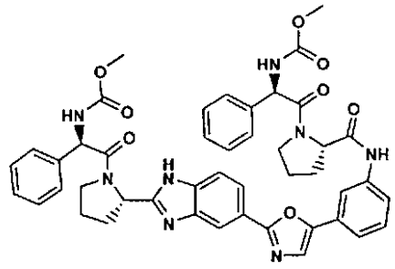
J.43e	 A partir de J.42e	T_R = 1,70 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6O_2$: 457,24; encontrado: 457,29. EMAR: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6O_2$: 457,2352; encontrado 457,2332.
J.43f	 A partir de J.42f	T_R = 1,59 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,22; encontrado: 443,31. EMAR: Análisis calculado para $[M+H]^+$ $C_{25}H_{27}N_6O_2$: 443,2195; encontrado 443,2206.
J.43g	 A partir de J.42g	T_R = 1,61 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{25}H_{26}FN_6O_2$: 461,21; encontrado: 461,31. EMAR: Análisis calculado para $[M+H]^+$ $C_{25}H_{26}FN_6O_2$: 461,2101; encontrado 461,2101.
J.43h		T_R = 1,70 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{31}H_{33}N_6O_2$: 521,27; encontrado: 521,48.

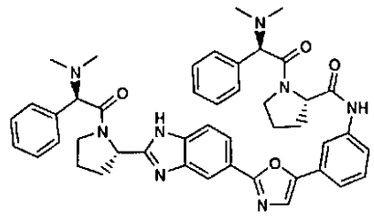
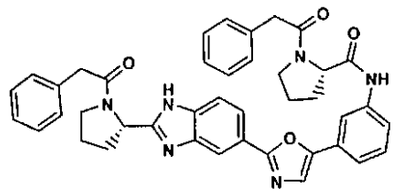
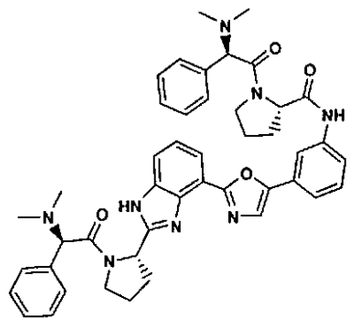
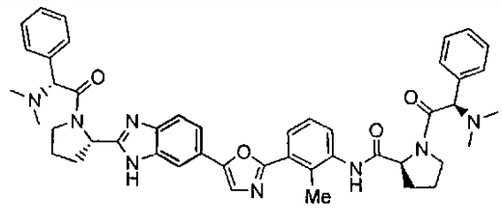
	A partir de J.42h	EMAR: Análisis calculado para $[M+H]^+$ $C_{31}H_{33}N_6O_2$: 521,2665; encontrado 521,2673.

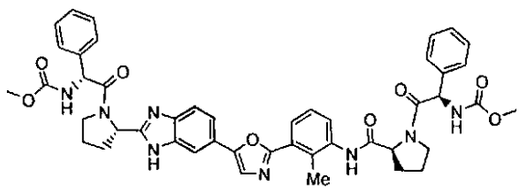
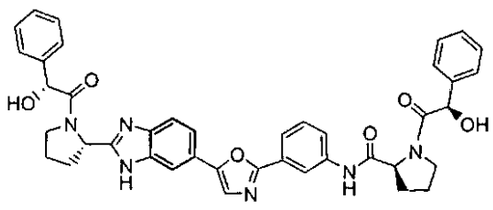
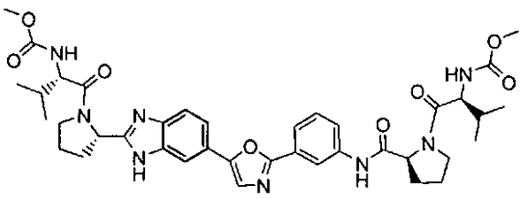
J.43i	 A partir de J.43h y N-Boc-L-prolina como se describe en el Ejemplo J.38.	T_R = 2,33 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_5$: 718,37; encontrado: 718,19. EMAR: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_5$: 718,3717; encontrado 718,3692.
J.43j	 A partir de J.43i como se describe en el Ejemplo J.39	T_R = 1,69 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{36}H_{40}N_7O_3$: 618,32; encontrado: 618,38.

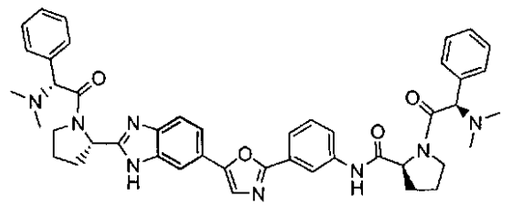
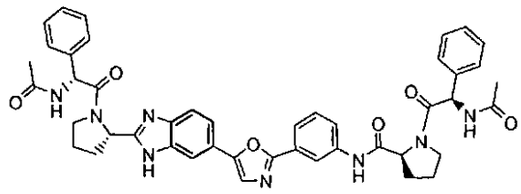
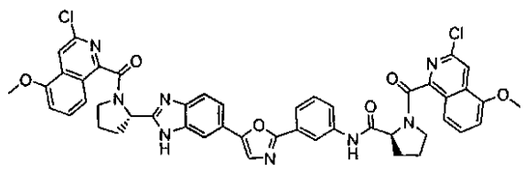
Ejemplos J.44 - J53.a

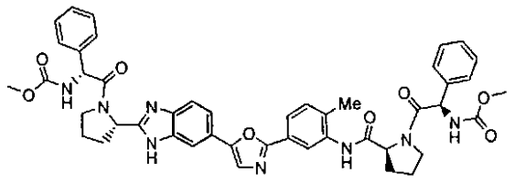
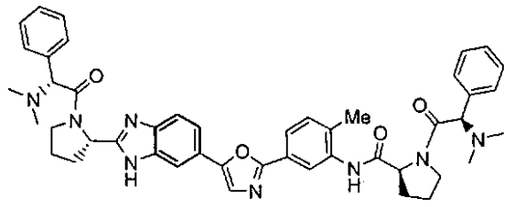
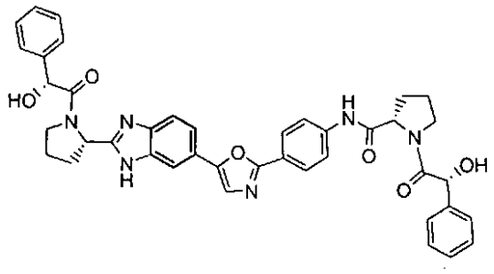
Los Ejemplos J.44 – J.53a se prepararon como se describe en el Ejemplo J.21.

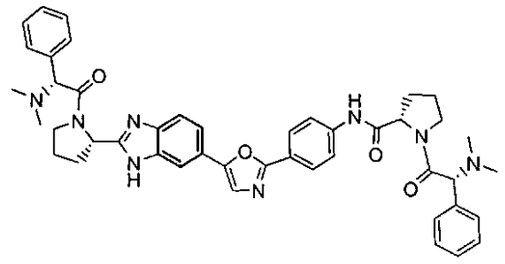
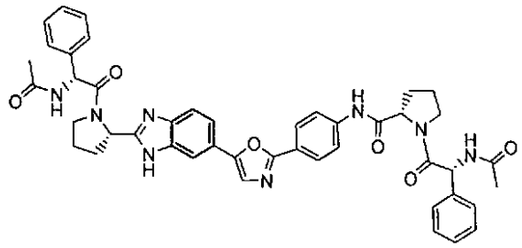
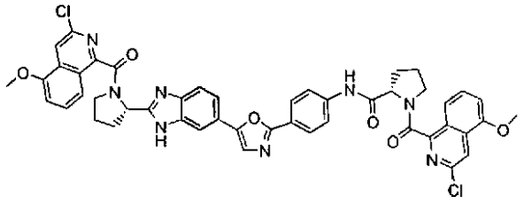
J.44	 A partir de J.43	T_R = 1,91 min (Condiciones-J1) EMBR: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839,35; encontrado 839,29. EMAR: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839,3517; encontrado 839,3492.
J.44a	 A partir de J.43	T_R = 1,80 min (Condiciones-J1) EMBR: Análisis calculado para $[M+H]^+$ $C_{46}H_{49}N_8O_6$: 809,38; encontrado 809,29. EMAR: Análisis calculado para $[M+H]^+$ $C_{46}H_{49}N_8O_6$: 809,3775; encontrado 809,3768.
J.45	 A partir de J.43a	T_R = 2,42 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{45}H_{45}N_8O_8$: 825,34; encontrado: 825,40. EMAR: Análisis calculado para $[M+H]^+$ $C_{45}H_{45}N_8O_8$: 825,3360; encontrado 825,3366.

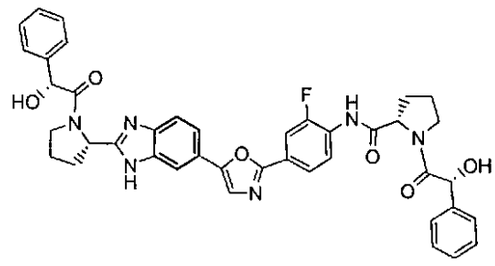
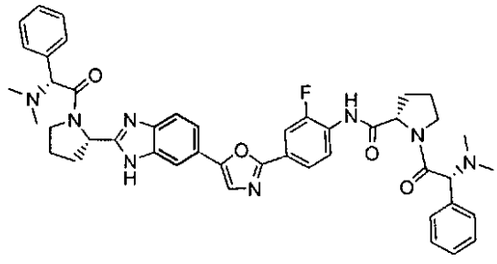
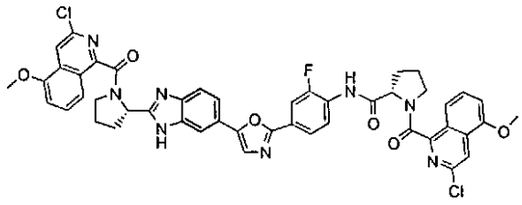
J.45a	 A partir de J.43a	T_R = 2,27 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765,39; encontrado: 765,36. EMAR: Análisis calculado para $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765,3877; encontrado 765,3879.
J.45b	 A partir de J.43a	T_R = 2,48 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{41}H_{39}N_6O_4$: 679,30; encontrado: 679,37. EMAR: Análisis calculado para $[M+H]^+$ $C_{41}H_{39}N_6O_4$: 679,3033; encontrado 679,3037.
J.46	 A partir de J.43b	T_R = 2,10 min (D-Cond. 2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765,39; encontrado: 765,72. EMAR: Análisis calculado para $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765,3877; encontrado 765,3899.
J.47		T_R = 1,77 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_4$: 779,40; encontrado: 779,49.

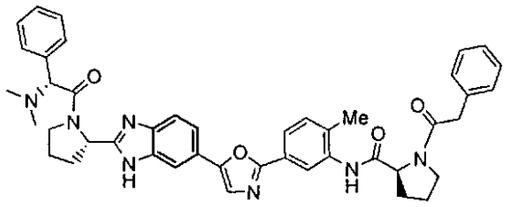
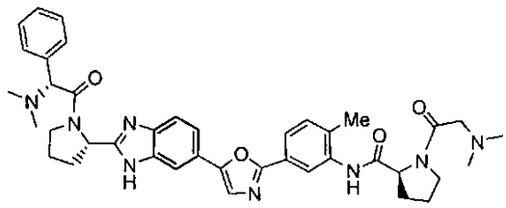
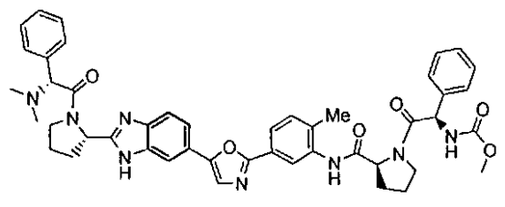
	A partir de J.43c	EMAR: Análisis calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_4$: 779,4033; encontrado: 779,4042.
J.47a	 A partir de J.43c	T_R = 2,28 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839,35; encontrado: 839,43. EMAR: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839,3517; encontrado: 839,3519.
J.48	 A partir de J.43d	T_R = 2,21 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{41}H_{39}N_6O_6$: 711,29; encontrado: 711,46. EMAR: Análisis calculado para $[M+H]^+$ $C_{41}H_{39}N_6O_6$: 711,2931; encontrado: 711,2942.
J.48a	 A partir de J.43d	T_R = 2,37 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_8$: 757,37; encontrado: 757,37. EMAR: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_8$:

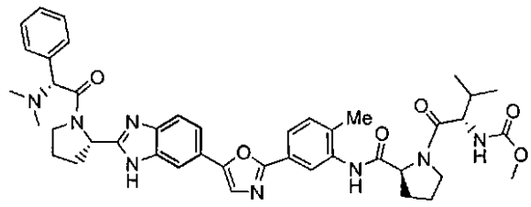
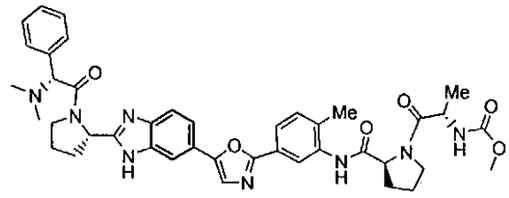
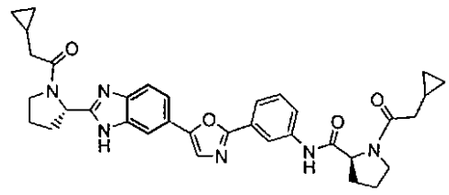
		757,3673; encontrado: 757,3705.
J.48b	 A partir de J.43d	T_R = 1,92 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765,39; encontrado: 765,59. EMAR: Análisis calculado para $[M+H]^+$ $C_{45}H_{49}N_8O_4$: 765,3877; encontrado: 765,3841.
J.48c	 A partir de J.43d	T_R = 2,26 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{45}H_{45}N_8O_6$: 793,35; encontrado: 793,52. EMAR: Análisis calculado para $[M+H]^+$ $C_{45}H_{45}N_8O_6$: 793,3462; encontrado: 793,3452.
J.48d	 A partir de J.43d	T_R = 2,88 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{47}H_{39}Cl_2N_8O_6$: 881,24; encontrado: 881,50. EMAR: Análisis calculado para $[M+H]^+$ $C_{47}H_{39}Cl_2N_8O_6$: 881,2370; encontrado: 881,2347.

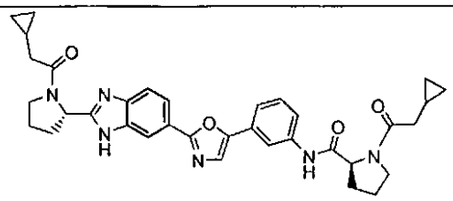
J.49	 A partir de J.43e	T_R = 2,41 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839,35; encontrado: 839,27. EMAR: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_8$: 839,3517; encontrado: 839,3535.
J.49a	 A partir de J.43e	T_R = 2,07 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C46H51N8O4: 779,40; encontrado: no apparente. EMAR: Análisis calculado para $[M+H]^+$ C46H51N8O4: 779,4033; encontrado: 779,4014.
J.50	 A partir de J.43f	T_R = 2,26 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C41H39N6O6: 711,29; encontrado: 711,39. EMAR: Análisis calculado para $[M+H]^+$ C41H39N6O6: 711,2931; encontrado: 711,2958.

J.50a	 A partir de J.43f	T_R = 1,92 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C45H49N8O4: 765,39; encontrado: 765,53. EMAR: Análisis calculado para $[M+H]^+$ C45H49N8O4: 765,3877; encontrado: 765,3843.
J.50b	 A partir de J.43f	T_R = 2,29 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C45H45N8O6: 793,35; encontrado: 793,49. EMAR: Análisis calculado para $[M+H]^+$ C45H45N8O6: 793,3462; encontrado: 793,3442.
J.50c	 A partir de J.43f	T_R = 2,99 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C47H39Cl2N8O6: 881,24; encontrado: 883,41. EMAR: Análisis calculado para $[M+H]^+$ C47H39Cl2N8O6: 881,2370; encontrado: 881,2349.

J.51	 A partir de J.43g	T_R = 2,29 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C41H38FN6O6: 729,28; encontrado: 729,36. EMAR: Análisis calculado para $[M+H]^+$ C41H38FN6O6: 729,2837; encontrado: 729,2847.
J.51a	 A partir de J.43g	T_R = 1,93 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C45H48FN8O4: 783,38; encontrado: 783,52. EMAR: Análisis calculado para $[M+H]^+$ C45H48FN8O4: 783,3783; encontrado: 783,3764.
J.51b	 A partir de J.43g	T_R = 2,89 min (Condiciones-D2); EMBR: Análisis calculado para $[M+H]^+$ C47H38ClFN8O6: 899,23; encontrado: 897,19. EMAR: Análisis calculado para $[M+H]^+$ C47H38ClFN8O6: 899,2275; encontrado: 899,2287.

J.52	 A partir de J.43j	T_R = 2,23 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C44H46N7O4: 736,36; encontrado: 737,00. EMAR: Análisis calculado para $[M+H]^+$ C44H46N7O4: 736,3611; encontrado: 736,3622.
J.52a	 A partir de J.43j	T_R = 1,75 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C40H47N8O4: 703,37; encontrado: 703,81. EMAR: Análisis calculado para $[M+H]^+$ C40H47N8O4: 703,3720; encontrado: 703,3748.
J.52b	 A partir de J.43j	T_R = 2,22 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C46H49N8O6: 809,38; encontrado: 809,57. EMAR: Análisis calculado para $[M+H]^+$ C46H49N8O6: 809,3775; encontrado: 809,3803.

J.52c	 A partir de J.43j	T_R = 2,27 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C43H51N8O6: 775,39; encontrado: 775,39. EMAR: Análisis calculado para $[M+H]^+$ C43H51N8O6: 775,3932; encontrado: 775,3921.
J.52d	 A partir de J.43j	T_R = 2,09 min (Condiciones-D2); CL/EM: Análisis calculado para $[M+H]^+$ C41H47N8O6: 747,36; encontrado: 747,34. EMAR: Análisis calculado para $[M+H]^+$ C41H47N8O6: 747,3619; encontrado: 747,3610.
J.53	 A partir de J.43d	T_R = 2,22 min (Cond.-D2); CLC/EM: Análisis calculado para $[M+H]^+$ $C_{35}H_{39}N_6O_4$: 607,30; encontrado: 607,71. EMAR: Análisis calculado para $[M+H]^+$ $C_{35}H_{39}N_6O_4$: 607,3033; encontrado: 607,3015.

J.53a	 A partir de J.43a	T_R = 2,28 min (Cond.-D2); CL/ES: Análisis calculado para $[M+H]^+$ $C_{35}H_{39}N_6O_4$: 607,30; encontrado: 607,34.

ACTIVIDAD BIOLÓGICA

Se utilizó un ensayo de replicón del VHC en la presente exposición y se preparó, llevó a cabo y validó como se describe en el documento PCT/US2006/022197 del mismo solicitante y en O'Boile et. al. *Antimicrob Agents Chemother.* **2005** Apr;49(4):1346-53. También se han usado procedimientos de ensayo que incorporan informadores de luciferasa como se describe (Apath. com).

Se usaron células de replicón de VCH y células de replicón que contienen mutaciones en la región NS5A para ensayar la familia de compuestos. Los compuestos se determinó que tenían más de 10 veces menos actividad inhibidora sobre células que contienen las mutaciciones sobre las células naturales. Así, los compuestos de la presente exposición pueden ser eficaces en la inhibición de la función de la proteína NS5A del VHC y se sobreentiende que son eficaces en combinaciones que se han descrito previamente en la solicitud PCT/US2006/022197 y el documento WO/O4014852 del mismo solicitante. Además, los compuestos de la presente exposición pueden ser eficaces contra el genotipo 1b del VHC. Se sobreentiende que los compuestos de la presente exposición pueden inhibir múltiples genotipos de VHC. La tabla 2 muestra los valores de CE_{50} (concentración inhibidora eficaz al 50%) de compuestos representativos de la

presente exposición contra el genotipo 1b del VHC. En una realización los compuestos de la presente exposición son inhibidores contra genotipos 1a, 1b, 2a, 2b, 3a, 4a y 5a. Los valores de CE_{50} contra VHC 1b son como sigue: A (1-10 μM); B (100-999 nM); C (4,57-99 nM); D (2 pM-4,57 nM).

Los compuestos de la presente exposición pueden inhibir VHC por mecanismos diferentes o distintos de la inhibición de NS5A. En una realización los compuestos de la presente exposición inhiben el replicón del VHC y en otra realización los compuestos de la presente exposición inhiben NS5A.

Tabla 2

Ejemplo	*EC50*	*Intervalo*	*Nombre*
J.21		D	((1S)-1-(((2S)-2-(8-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)-1,4,5,6-tetrahidrobenzo[3,4]ciclohepta[1,2-d]imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.21a		D	(1R)-2-((2S)-2-(8-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,4,5,6-tetrahidrobenzo[3,4]ciclohepta[1,2-d]imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina
J.22		D	((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.22a		D	(1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina

J.22b		D	((1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo
J.23		D	((1S)-1-(((2S)-2-(5-(3-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.23a		D	(1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina
J.23b		D	((1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo
J.24	10 pM	D	((1S)-1-(((1R,3S,5R)-3-(8-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-1,4,5,6-tetrahidrobenzo[3,4]ciclohepta[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo
J.25		D	((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-3H-nafto[1,2-d]imidazol-7-il)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.26	5 pM	D	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

J.27		D	((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-3H-nafto[1,2-d]imidazol-7-il)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.27a		D	(1R)-2-((2R)-2-(7-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine
J.27b		D	methyl ((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.27c	3.0 pM	D	methyl ((1R)-2-((2S)-2-(7-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.28		D	((1S)-1-(((2S)-2-(5-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28a		D	(1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina
J.28a.1		D	methyl ((1S)-1-(((2S)-2-(5-((4-(4-ethyl-2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

J.28a.2		D	methyl ((1S)-1-(((2S)-2-(4-(cyanomethyl)-5-(4-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28b		D	((1S)-1-(((1R,3S,5R)-3-(5-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo
J.28c		D	((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-fluoro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo
J.28d		D	((1S)-1-(((1R,3S,5R)-3-(4-(2-fluoro-4-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo
J.28e		D	((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-3H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28e.1		D	methyl ((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-1-

			pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
J.28f		D	((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-3H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28g		D	((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28h	120 pM	D	((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28h.1		D	methyl ((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28h.2		D	methyl ((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate
J.28i		D	((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-2-

			azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo
J.28i.1		D	methyl ((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate
J.28i.2	0.51 pM	D	methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate
J.28i.3		D	methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
J.28i.4		D	methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
J.28j		D	((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

J.28k		D	methyl ((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28k.1		D	benzyl (1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-valyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate
J.28l	7 nM	C	((1S)-1-(((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-4-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28m	55,7 nM	C	(1R)-2-((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-4-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina
J.28n		D	((1S)-1-(((2S)-2-(5-((4-(4-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.28o		D	methyl ((1S)-1-(((2S,5S)-2-(5-((2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-benzimidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
J.28p		D	methyl ((1S)-2-((2S,5S)-2-(7-((2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-

			benzimidazol-5-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
JB.8		D	methyl ((1S)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
JB.8.1		B	methyl ((1R)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
JB.9		D	methyl ((1S)-2-((2S)-2-(5-(4-((2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate
JB.10		D	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4-((2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)phenyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate
JB.11		D	methyl ((1R)-2-((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate
JB.12	65.2 pM	D	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-4-yl)ethynyl)phenyl)-1H-benzimidazole
J.28r	15.5	D	methyl ((1S)-1-(((1R,3S,5R)-3-(7-(2-(2-

	pM		((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate
J.28s		D	methyl ((1S)-2-((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)ethyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate
JB.15		D	methyl ((1S)-1-(((2S)-2-(4-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)phenyl)ethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate
M.8	46,4 nM	C	(S)-1-acetil-N-(4-((2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etinil)fenil)pirrolidin-2-carboxamida
M.9		C	(S)-1-(2-fenilacetil)-N-(4-((2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etinil)fenil)pirrolidin-2-carboxamida
M.10	202 nM	B	(S)-1-acetil-N-(4-(2-(2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etil)fenil)pirrolidin-2-carboxamida
M.11		C	(S)-1-(2-fenilacetil)-N-(4-(2-(2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etil)fenil)pirrolidin-2-carboxamida
J.44		D	((1R)-2-((2S)-2-((5-(2-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo

J.44a		D	(R)-2-((S)-2-(5-(2-(2-((S)-1-((R)-2-(dimetilamino)-2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)oxazol-5-il)-2-metilfenilcarbamoil)pirrolidin-1-il)-2-oxo-1-feniletilcarbamato de metilo
J.45		D	((1R)-2-((2S)-2-((3-(2-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)fenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo
J.45a		D	1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(3-(2-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)fenil)-L-prolinamida
J.45b		D	(S)-1-(2-fenilacetil)-N-(3-(2-(2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)oxazol-5-il)fenil)pirrolidin-2-carboxamida
J.46		D	(S)-1-((R)-2-(dimetilamino)-2-fenilacetil)-N-(3-(2-(2-((S)-1-((R)-2-(dimetilamino)-2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-4-il)oxazol-5-il)fenil)pirrolidin-2-carboxamida
J.47		D	1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida
J.47a		D	((1R)-2-((2S)-2-((3-(5-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo
J.48		D	1-((2R)-2-hidroxi-2-fenilacetil)-N-(3-(5-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida

J.48a		D	((1S)-1-(((2S)-2-(5-(2-(3-((((2S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-1-pirrolidinil)carbonil)amino)fenil)-1,3-oxazol-5-il)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo
J.48b		C	(2R)-2-(dimetilamino)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-2-fenilacetamida
J.48c		D	1-((2R)-2-acetamido-2-fenilacetil)-N-(3-(5-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida
J.48d	147 nM	B	1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-N-(3-(5-(2-((2S)-1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida
J.49		D	((1R)-2-((2S)-2-((5-(5-(2-(1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo
J.49a		D	(S)-1-((R)-2-(dimetilamino)-2-fenilacetil)-N-(5-(5-(2-((S)-1-((R)-2-(dimetilamino)-2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)oxazol-2-il)-2-metilfenil)pirrolidin-2-carboxamida
J.50		C	1-((2R)-2-hidroxi-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida
J.50a		D	1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-

			pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida
J.50b		D	1-((2R)-2-acetamido-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida
J.50c	>10 μM	A	1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-N-(4-(5-(2-((2S)-1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida
J.51		C	N-(2-fluoro-4-(5-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-1-((2R)-2-hidroxi-2-fenilacetil)-L-prolinamida
J.51a		D	1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-fluorofenil)-L-prolinamida
J.51b		B	1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-N-(4-(5-(2-((2S)-1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-fluorofenil)-L-prolinamida
J.52		D	N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-1-(fenilacetil)-L-prolinamida
J.52a		C	N,N-dimetilglicil-N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida
J.52b		D	((1R)-2-((2S)-2-((5-(5-(2-((2S)-1-((2R)-2-

			(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo
J.52c		D	N-(metoxicarbonil)-L-valil-N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida
J.52d		D	N-(metoxicarbonil)-L-alanil-N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida
J.53		B	1-(ciclopropilacetyl)-N-(3-(5-(2-((2S)-1-(ciclopropylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-2-yl)phenyl)-L-prolinamide
J.53a		A	1-(ciclopropylacetyl)-N-(3-(2-(2-((2S)-1-(ciclopropylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-1,3-oxazol-5-yl)phenyl)-L-prolinamide

Será evidente para un experto en la técnica que la presente exposición no está limitada a los anteriores ejemplos ilustrativos y que puede llevarse a la práctica en otras formas específicas sin apartarse de sus atributos esenciales. Por tanto se desea que los ejemplos sean considerados en todos los aspectos como ilustrativos y no restrictivos, haciéndose referencia a las reivindicaciones adjuntas, en lugar de a los ejemplos anteriores, y se pretende que todos los cambios que están dentro del significado y alcance de equivalencia de las reivindicaciones por tanto estén incluidos en la presente.

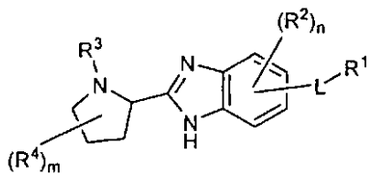
Los compuestos de la presente exposición pueden inhibir VHC por

mecanismos diferentes o distintos a la inhibición de NS5A. En una realización los compuestos de la presente exposición inhiben el replicón del VHC y en otra realización los compuestos de la presente exposición inhiben NS5A. Los compuestos de la presente exposición pueden inhibir múltiples genotipos de VHC.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula (I)

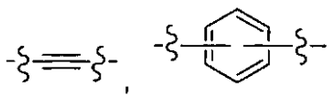
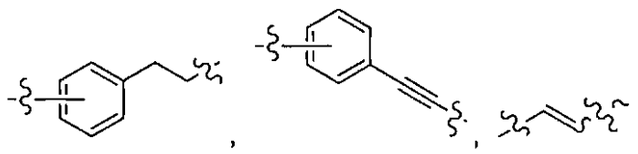
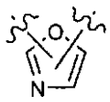


(I),

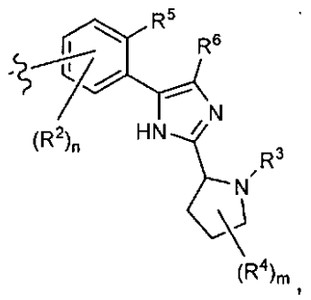
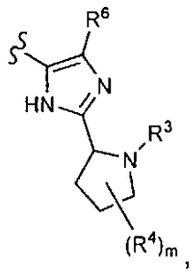
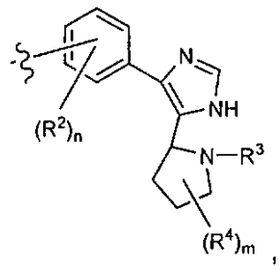
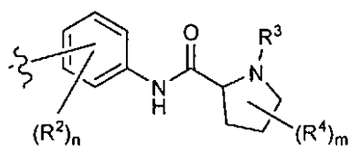
o una de sus sales farmacéuticamente aceptables, en la que

cada m es independientemente 0 ó 1;

cada n es independientemente 0 ó 1;

L es un enlace o se selecciona de  ,  , y  ; en los que cada grupo está representado con su extremo izquierdo unido al bencimidazol y su extremo derecho unido a R^1;

R^1 se selecciona de

cada R^2 se selecciona independientemente de alquilo y halo;

cada R^3 se selecciona independientemente de hidrógeno y $-C(O)R^7$;

R^4 es alquilo;

R^5 y R^6 se seleccionan independientemente de hidrógeno, alquilo, cianoalquilo y halo, o

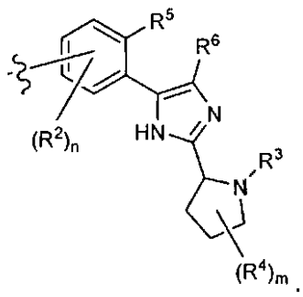
R^5 y R^6, junto con los átomos de carbono a los que están unidos, forman un anillo de seis o siete miembros que opcionalmente contiene un heteroátomo seleccionado de nitrógeno y oxígeno y opcionalmente un doble enlace adicional; y

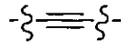
cada R^7 se selecciona independientemente de alcoxi, alquilo, arilalcoxi, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo.

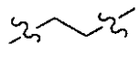
2. Un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, en el que L es un enlace.

3. Un compuesto de la reivindicación 2, o una de sus sales

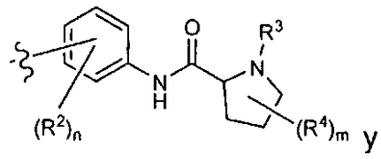
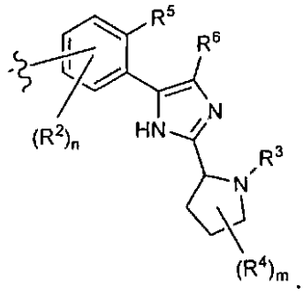
farmacéuticamente aceptables, en el que, en el que R^1 es

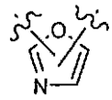


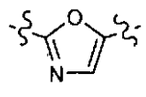
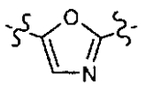
4. Un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, en el que L es  .

5. Un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, en el que L es  .

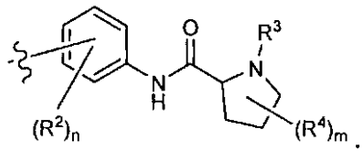
6. Un compuesto de la reivindicación 5, o una de sus sales farmacéuticamente aceptables, en el que R^1 se selecciona de

 y  .

7. Un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, en el que L es  .

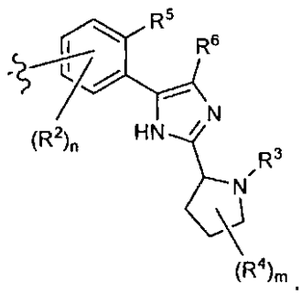
8. Un compuesto de la reivindicación 7, o una de sus sales farmacéuticamente aceptables, en el que L se selecciona de  y  .

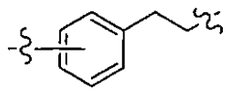
9. Un compuesto de la reivindicación 8, o una de sus sales farmacéuticamente aceptables, en el que R^1 es

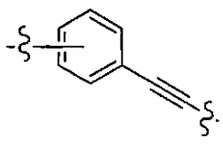


10. Un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, en el que L es  .

11. Un compuesto de la reivindicación 10, o una de sus sales farmacéuticamente aceptables, en el que R^1 es

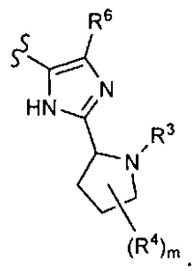


12. Un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, en el que L se selecciona de 

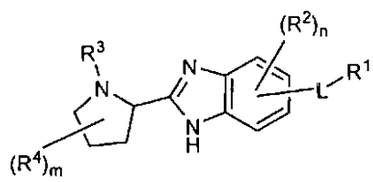


y ; en los que cada grupo está representado con su extremo izquierdo unido al bencimidazol y su extremo derecho unido a R^1.

13. Un compuesto de la reivindicación 12, o una de sus sales farmacéuticamente aceptables, en el que R^1 es



14. Un compuesto de Fórmula (II)



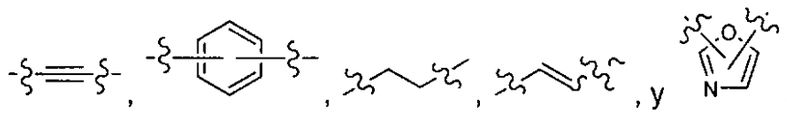
(II),

o una de sus sales farmacéuticamente aceptables, en la que

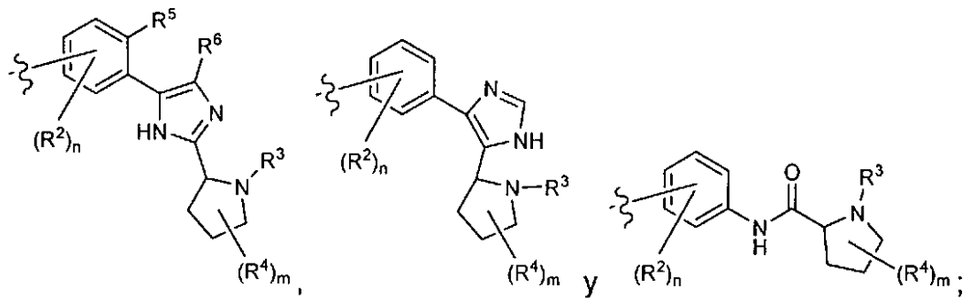
cada m es independientemente 0 ó 1;

cada n es independientemente 0 ó 1

L es un enlace o se selecciona de



R^1 se selecciona de



cada R^2 se selecciona independientemente de alquilo y halo;

cada R^3 se selecciona independientemente de hidrógeno y $-C(O)R^7$;

R^4 es alquilo;

R^5 y R^6 son independientemente hidrógeno o halo, o

R^5 y R^6, junto con los átomos de carbono a los que están unidos, forman un anillo de seis o siete miembros que opcionalmente contiene un heteroátomo seleccionado de nitrógeno y oxígeno y que opcionalmente ocntiene un doble enlace adicional; y

cada R^7 se selecciona independientemente de alcoxi, alquilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo.

15. Un compuesto seleccionado de

((1S)-1-(((2S)-2-(8-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)-1,4,5,6-tetrahidrobenzo[3,4]ciclohepta[1,2-d]imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1R)-2-((2S)-2-(8-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-

pirrolidinil)-1H-bencimidazol-5-il)-1,4,5,6-tetrahidrobenzo[3,4]ciclohepta[1,2-d]imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1R)-2-((2S)-2-(4-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((2S)-2-(5-(3-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1R)-2-((2S)-2-(4-(3-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(8-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-1,4,5,6-tetrahidrobenzo[3,4]ciclohepta[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-

metilbutanoil)-2-pirrolidinil)-4,5-dihidro-3H-nafto[1,2-d]imidazol-7-il)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

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

((1S)-1-(((2S)-2-(5-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-3H-nafto[1,2-d]imidazol-7-il)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1R)-2-((2R)-2-(7-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1H-nafto[1,2-d]imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(5-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-nafto[1,2-d]imidazol-7-il)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((2S)-2-(7-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)-1H-nafto[1,2-d]imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((2S)-2-(5-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(5-((4-(4-etil-2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)-1H-bencimidazol-2-il)-1-

pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(cianometil)-5-(4-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(5-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-fluoro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-(2-fluoro-4-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-3H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((2S)-2-(5-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-3H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-

2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((2S)-2-(7-((2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-fluoro-6-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(5-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-

2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(4,4-difluorociclohexil)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorociclohexil)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil)carbamato de metilo;

((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-fluoro-6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

(1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-(N-(metoxicarbonil)-L-valil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de bencilo;

((1S)-1-(((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-4-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1R)-2-((2S)-2-(5-(3-((2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)fenil)-1H-imidazol-4-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(5-((4-(4-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S,5S)-2-(5-((2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-bencimidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((2S,5S)-2-(7-((2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-bencimidazol-5-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

(S)-1-acetil-N-(4-((2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etinil)fenil)pirrolidin-2-carboxamida;

(S)-1-(2-fenilacetil)-N-(4-((2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etinil)fenil)pirrolidin-2-carboxamida;

(S)-1-acetil-N-(4-(2-(2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etil)fenil)pirrolidin-2-carboxamida;

(S)-1-(2-fenilacetil)-N-(4-(2-(2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)etil)fenil)pirrolidin-2-carboxamida;

((1R)-2-((2S)-2-((5-(2-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

(R)-2-((S)-2-(5-(2-(2-((S)-1-((R)-2-(dimetilamino)-2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)oxazol-5-il)-2-metilfenilcarbamoil)pirrolidin-1-il)-2-oxo-1-feniletilcarbamato de metilo;

((1R)-2-((2S)-2-((3-(2-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)fenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(3-(2-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)fenil)-L-prolinamida;

(S)-1-(2-fenilacetil)-N-(3-(2-(2-((S)-1-(2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)oxazol-5-il)fenil)pirrolidin-2-carboxamida;

(S)-1-((R)-2-(dimetilamino)-2-fenilacetil)-N-(3-(2-(2-((S)-1-((R)-2-(dimetilamino)-2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-4-il)oxazol-5-il)fenil)pirrolidin-2-carboxamida;

1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida;

((1R)-2-((2S)-2-((3-(5-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

1-((2R)-2-hidroxi-2-fenilacetil)-N-(3-(5-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

((1S)-1-(((2S)-2-(5-(2-(3-((((2S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-1-pirrolidinil)carbonil)amino)fenil)-1,3-oxazol-5-il)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(2R)-2-(dimetilamino)-N-(3-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-2-fenilacetamida;

1-((2R)-2-acetamido-2-fenilacetil)-N-(3-(5-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-N-(3-(5-(2-((2S)-1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

((1R)-2-((2S)-2-((5-(5-(2-(1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

(S)-1-((R)-2-(dimetilamino)-2-fenilacetil)-N-(5-(5-(2-((S)-1-((R)-2-

(dimetilamino)-2-fenilacetil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)oxazol-2-il)-2-metilfenil)pirrolidin-2-carboxamida;

1-((2R)-2-hidroxi-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

1-((2R)-2-acetamido-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-N-(4-(5-(2-((2S)-1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida;

N-(2-fluoro-4-(5-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-1-((2R)-2-hidroxi-2-fenilacetil)-L-prolinamida;

1-((2R)-2-(dimetilamino)-2-fenilacetil)-N-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-fluorofenil)-L-prolinamida;

1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-N-(4-(5-(2-((2S)-1-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-fluorofenil)-L-prolinamida;

N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-1-(fenilacetil)-L-prolinamida;

N,N-dimetilglicil-N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida;

((1R)-2-((2S)-2-((5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)carbamoil)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

N-(metoxicarbonil)-L-valil-N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida;

N-(metoxicarbonil)-L-alanil-N-(5-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)-2-metilfenil)-L-prolinamida;

((1S)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)etinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-1-(((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)etinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((2S)-2-(5-(4-((2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)etinil)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

((1S,2R)-2-metoxi-1-(((2S)-2-(5-(4-((2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-4-il)etinil)fenil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1R)-2-((2S)-2-(4-((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)etinil)-1H-imidazol-2-il)-1-

pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

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-4-il)etinil)fenil)-1H-bencimidazol;

((1S)-1-(((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((1R,3S,5R)-3-(7-(2-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)etil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(2-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)fenil)etil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

1-(ciclopropilacetil)-N-(3-(5-(2-((2S)-1-(ciclopropilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-2-il)fenil)-L-prolinamida; y

1-(ciclopropilacetil)-N-(3-(2-(2-((2S)-1-(ciclopropilacetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-1,3-oxazol-5-il)fenil)-L-prolinamida;

o una de sus sales farmacéuticamente aceptables.

16. Una composición que comprende un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables, y un vehículo farmacéuticamente aceptable.

17. La composición de la reivindicación 16, que comprende además uno o dos compuestos adicionales que tienen actividad contra el VHC.

18. La composición de la reivindicación 17, en la que al menos uno de los compuestos adicionales es un interferón o una ribavirina.

19. La composición de la reivindicación 18, en la que el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón tau linfoblastoide.

20. La composición de la reivindicación 17, en la que al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de la respuesta de linfocitos T colaboradores de tipo 1, ARN de interferencia, ARN antisentido, imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

21. La composición de la reivindicación 17, en la que al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamble del VHC, salida del VHC, proteína NS5A del VHC y IMPDH para el tratamiento de una infección por el VHC.

22. Un procedimiento para tratar una infección por VHC en un paciente, que

comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables.

23. El procedimiento de la reivindicación 22, que comprende además administrar uno o dos compuestos adicionales que tienen actividad contra el VHC antes de, después de o simultáneamente con el compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables.

24. El procedimiento de la reivindicación 23, en el que al menos uno de los compuestos adicionales es un interferón o una ribavirina.

25. El procedimiento de la reivindicación 24, en el que el interferón se selecciona de entre interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón tau linfoblastoide.

26. El procedimiento de la reivindicación 23, en el que al menos uno de los compuestos adicionales se selecciona de entre interleucina 2, interleucina 6, interleucina12, un compuesto que potencia el desarrollo de la respuesta de linfocitos T colaboradores de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

27. El procedimiento de la reivindicación 23, en el que al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana

seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamble del VHC, salida del VHC, proteína NS5A del VHC y IMPDH para el tratamiento de una infección por el VHC.

5

RESUMEN

La presente exposición se refiere a compuestos, composiciones y procedimientos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se exponen composiciones farmacéuticas que contienen tales compuestos y procedimientos para usar estos compuestos en el tratamiento de infección por VHC.

PODERES

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

Hayden

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)

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04 AGO 2011
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA D.C

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
RES. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

1

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

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JAIME A. GARAVITO B
TRADUCTOR E INTÉRPRETE OFICIAL
DEC. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

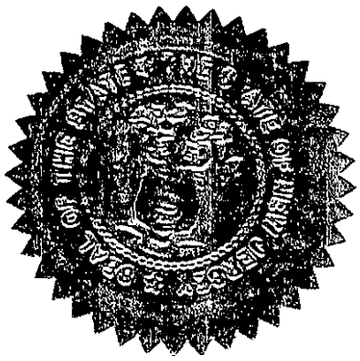
6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE



Bradley Abelow

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04 AGO 2011

Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

BAKER & MCKENZIE

Raisbeck, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

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

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

REPRESENTACIÓN DE COPIA DE ORIGINAL
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BOGOTÁ D.C.
04 AGO 2011
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTÁ D.C.

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power** Anastasia P. Winslow of legal age and domiciled in Princeton, NJ USA **Address, city, state, country** set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as Senior Patent Counsel **Position of the person issuing the Power** of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY** having its home office in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public

SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow mayor y domiciliado en Princeton, NJ Estados Unidos de América suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de Abogados de Patentes Senior de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY** con sede en

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

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

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04 AGO 2011
Eduardo Durán Gómez
NOTARIO 38 DE BOGOTA, D.C.

Industria y Comercio
SUPERINTENDENCIA

A SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-098732- -00000-0000
Fecha: 2011-08-04 15:57:28 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 613

PATENTE DE INVENCIÓN ☐ **MODELO DE UTIL**

- ☐ 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 ☐