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Organización y Digitalización CSA Ltda

Industria y Comercio

SUPERINTEN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098657- -00000-0000
Fecha: 2010-08-11 16:38:48 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACIÓN Folios: 643

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

1/3

21. **EXPEDIENTE No.** 10-98657

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 11, 2010

(FORMA P-10)

Título
13-09-2010

PETIT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098657- -00000-0000
Fecha: 2010-08-11 16:38:48 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 643

Industria y Comercio
SUPERINTENDENCIA

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

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

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

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

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

Dirección: 119 Place Mercure Candiac, Québec J5R 1B1 (CA); c/o Bristol Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US); 401-4905 Av. Colomb, Brossard, Québec J4Z 3T2 (CA); 52 High Hill Road Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway, Wallingford, CT 06492 (US); 500 Boulevard Quinn Longueuil, Québec J4H 2N4 (CA); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); 29 Rue Monette, Delson, Québec J5B 1G8 (CA); c/o Bristol Myers Squibb Company, 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company, 5 Research Parkway Wallingford, CT 06492 (US); 133 St. Charles Greenfield Park, Québec J4V 2K3 (CA); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol Myers Squibb Company, 5 Research Parkway Wallingford, Connecticut 06492 (US); 250 Massachusetts Avenue Cambridge, Massachusetts 02139 (US)

Nacionalidad o Domicilio: Canadá y Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2009/033380 Fecha 06.02.2009

Publicación Internacional No. WO/2009/102633 Fecha 20.08.2009

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

(7) Clasificación Internacional (51) C07D 403/14, A61K 31/4178, A61K 31/4184, A61K 31/4188, A61P 31/14, C07D 405/14, C07D 487/04, C07D 491/044, C07D 491/052

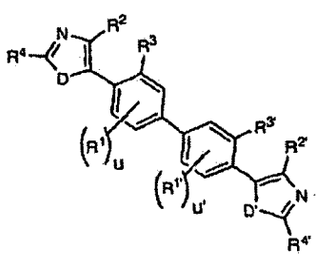
(8) Prioridad SI [ ] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	13-02-2008	61/028,277

(9) Comprobante de pago No. 10-63,484 - 10-54,857 – 10-54,912 – 10-63,467 **Fecha** 11-08, 2010

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso. Ver documento de Poder General radicado en el Expediente No. 08 129.339
- [ ] Documento de cesión del inventor al solicitante o a su causante (ver Declaración)
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) **FIGURA CARATERISTICA**



(I),

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

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

2010/014 3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 63,484
FECHA : AGOSTO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098657- -00000-0000
Fecha: 2010-08-11 16:38:48 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 643

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

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

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

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

2010/013

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 54,857
FECHA : JULIO 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098657- -00000-0000
Fecha: 2010-08-11 16:38:48 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 643

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

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

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	6,000.00
		TOTAL : $	6,000.00

SON: SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

2010/013

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 54,912
FECHA : JULIO 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098657- -00000-0000
Fecha: 2010-08-11 16:38:48 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 643

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	390489826	06/07/2010	51,604,000.00

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

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

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2010/014

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 63,467
FECHA : AGOSTO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098657- -00000-0000
Fecha: 2010-08-11 16:38:48 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIY:I Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 643

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

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

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** S.DISTINTIVO INSCRIPCION AFECTACI	290,000.00
		TOTAL : $	280,000.00

SON: DOSCIENTOS OCHENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio
SUPERINTENDENCIA

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

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

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

(51) Clasificación Internacional: C07D 403/14, A61K 31/4178, A61K 31/4184, A61K 31/4188, A61P 31/14, C07D 405/14, C07D 487/04, C07D 491/044, C07D 491/052

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

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

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/028,277	13-02-2008	US

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

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 06.02.2009
No. de solicitud: PCT/US2009/033380

(87) Publicación internacional
Fecha: 20.08.2009
N° publicación: WO/2009/102633

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

Industria y Comercio
SUPERINTENDENCIA

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

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

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

(51) Clasificación Internacional: C07D 403/14, A61K 31/4178, A61K 31/4184, A61K 31/4188, A61P 31/14, C07D 405/14, C07D 487/04, C07D 491/044, C07D 491/052

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

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

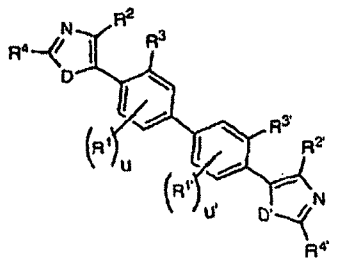
(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/028,277	13-02-2008	US

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

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 06.02.2009
No. de solicitud PCT/US2009/033380

(87) Publicación internacional:
Fecha: 20.08.2009
No. Publicación: WO/2009/102633



(I),

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

(57) Resumen: La presente invención se refiere compuesto de la fórmula (I)
La presente invención se refiere a compuestos, composiciones y procedimientos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se revelan composiciones farmacéuticas que contienen tales compuestos y procedimientos de uso de estos compuestos en el tratamiento de infección por VHC.

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***No.*** 61/028,277 32) ***Fecha*** 13-02-2008 (33) ***País*** US

(51) Int Cl: C07D 403/14, A61K 31/4178, A61K 31/4184, A61K 31/4188, A61P 31/14, C07D 405/14, C07D 487/04, C07D 491/044, C07D 491/052

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

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

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

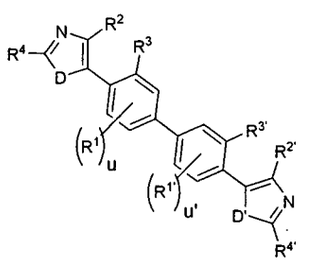
(85) Fecha limite inicio fase nacional: 13-09-2010

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 06.02.2009
No. de PCT/US2009/033380

(87) Publicación internacional
Fecha: 20.08.2009
N° publicación: WO/2009/102633

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

Reivindicación(es): 1. Un compuesto de fórmula (I)



(I),

o una de sus sales farmacéuticamente aceptables, caracterizado porque

u y u' son independientemente 0, 1, 2 ó 3;

D y D' se seleccionan cada uno independientemente de NR^5, O, y S; en donde cada R^5 se selecciona independientemente de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, hidroxi, (NR^aR^b)carbonilo y trialquilsililalcoxialquilo;

cada R^1 y $R^{1'}$ se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo;

R^2 se selecciona de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo y (NR^aR^b)carbonilo; y

R^3 se selecciona de hidrógeno, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo; o

R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; estando el anillo de cinco a ocho miembros opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo, (NR^aR^b)carbonilo, oxo y espirociclo;

R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; en donde el anillo de cinco a ocho miembros está opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo, (NR^aR^b)carbonilo, oxo y espirociclo;

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

(19) World Intellectual Property Organization
International Bureau

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

PCT

(10) International Publication Number
WO 2009/102633 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *A61K 31/4178* (2006.01)
C07D 405/14 (2006.01) *A61K 31/4184* (2006.01)
C07D 487/04 (2006.01) *A61K 31/4188* (2006.01)
C07D 491/044 (2006.01) *A61P 31/14* (2006.01)
C07D 491/052 (2006.01)

(21) International Application Number:
PCT/US2009/033380

(22) International Filing Date:
6 February 2009 (06.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/028,277 13 February 2008 (13.02.2008) US

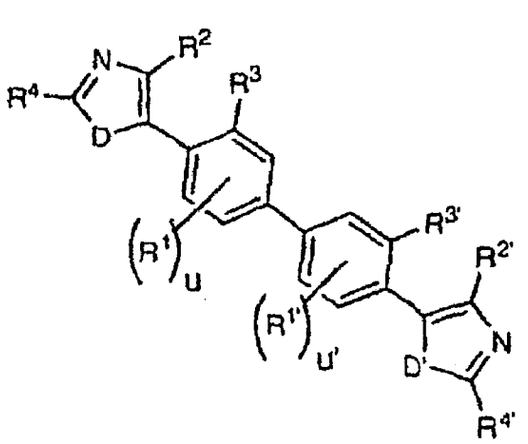
(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

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[Continued on next page]

(54) Title: HEPATITIS C VIRUS INHIBITORS



(I),

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

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(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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/028,277 filed February 13, 2008.

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

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

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

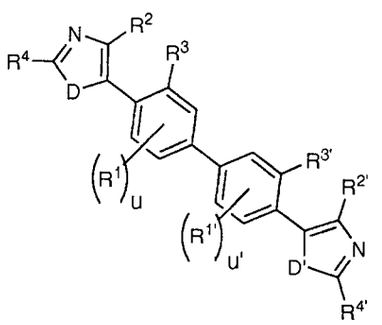
HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain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

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

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

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, *284*, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

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



(I),

or a pharmaceutically acceptable salt thereof, wherein

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

D and D' are each independently selected from NR^5, O, and S; wherein each R^5 is independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, hydroxy, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl;

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

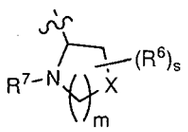
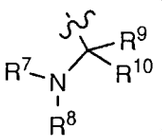
R^2 is selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

R^3 is selected from hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; or

R^2 and R^3, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, oxo, and spirocycle;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, oxo, and spirocycle;

R^4 and $R^{4'}$ are each independently selected from

and ; wherein

each m is independently 0, 1, or 2;

each s is independently 0, 1, 2, 3, or 4;

each X is independently selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$; provided that when n is 0, X is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each R^7 is independently selected from hydrogen and R^{11}-C(O)-, and R^{11}-C(S)-;

R^8 is selected from hydrogen and alkyl;

R^9 and R^{10} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

R^9 and R^{10}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^z, O, and S; wherein R^z is selected from hydrogen and alkyl; and

each R^{11} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a first embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein D and D' are each NR^5. In a second embodiment of the first aspect each R^5 is independently selected from hydrogen and hydroxy.

In a third embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein u and u' are each 0.

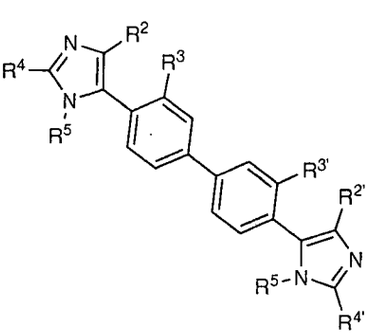
In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and haloalkyl.

In a fifth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen and halo.

In a sixth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3, together with the carbon atoms to which they are attached, form a six- or seven-membered carbocyclic ring.

In a seventh embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered ring optionally containing one heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups.

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



(II),

or a pharmaceutically acceptable salt thereof, wherein

R^2 is selected from hydrogen and haloalkyl; and

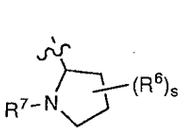
R^3 is selected from hydrogen and halo; or

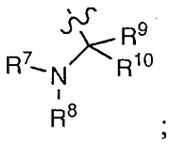
R^2 and R^3, together with the carbon atoms to which they are attached, form a five- or six-membered aromatic or non-aromatic carbocyclic ring;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered aromatic or non-aromatic ring optionally containing one

heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups;

R^4 and $R^{4'}$ are each independently selected from



and


; wherein

each s is 0 or 2;

each R^6 is independently selected from alkyl and halo, wherein the alkyl forms a fused three-membered ring with an adjacent carbon atom;

each R^7 is independently selected from hydrogen and R^{11}-C(O)-;

R^8 is selected from hydrogen and alkyl;

R^9 and R^{10} are each independently selected from hydrogen and alkyl; and

each R^{11} is independently selected from alkyl, arylalkoxy, arylalkyl, and (NR^cR^d)alkyl.

In a third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a first embodiment of the third aspect the composition comprises one or two additional compounds having anti-HCV activity. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment the 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 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 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 fourth aspect the present disclosure provides a 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 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 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^1, R^2, R^5, R^6, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

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

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

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

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

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

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

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

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

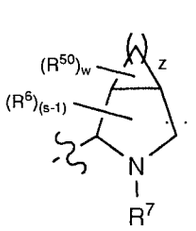
The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

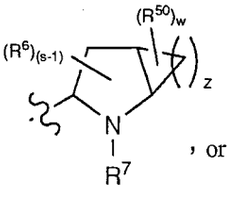
The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

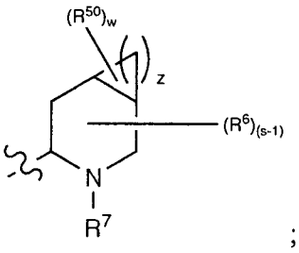
The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

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

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when m is 1 or 2; X is CHR^6, and R^6 is alkyl, each alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom to provide one of the structures shown below:



,


, or


;

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

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

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

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

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

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

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

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

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

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

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

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

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

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

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

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

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

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

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

The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring, i.e., the pyrrolidine rings of the compound of Formula (I). It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing ring or to the fragment in the final product, i.e., "Cap-51" or "The Cap-51 fragment found in Example 5".

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

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

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

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present

disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are futher optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

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

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

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

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

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

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

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

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

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

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

The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic

carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

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

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

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

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

unsubstitued arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and -NR^xR^y.

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

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

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

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

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

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

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

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

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

The term "-NR^aR^b," as used herein, refers to two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

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

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

The term "-NR^cR^d," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl,

heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and -C(NCN)NR^xR^y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one -NR^eR^f group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

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

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

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

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

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

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

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

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

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

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

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

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

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

The term "trialkylsilyl," as used herein, refers to $-SiR_3$, wherein R is alkyl. The R groups may be the same or different.

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

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

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

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

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

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

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

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, dihydrobromide, diydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can

be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

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

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present

disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

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

and 80% of the dosage normally administered in a monotherapy regimen.

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

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

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

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

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and

the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA

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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL

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 Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

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

The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

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

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: TFA for trifluoroacetic acid; Ph for phenyl; tBu or t-Bu for tert-butyl; DMSO for dimethylsulfoxide; DMF for N,N-dimethylformamide; EtOH for ethanol; Boc or BOC for tert-butoxycarbonyl; THF for tetrahydrofuran; Et_2O for diethyl ether; Et for ethyl; MeOH for methanol; EtOAc and EtOAC for ethyl acetate; RT for room temperature or retention time

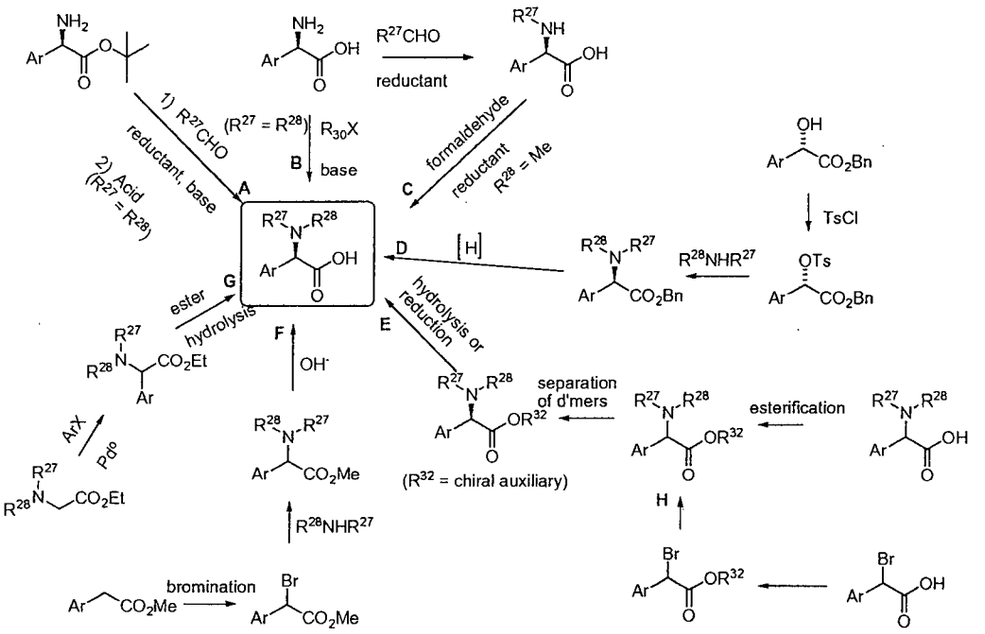
(context will dictate); R_t or t_R for retention time; h for hours; sat'd for saturated; PCC for pyridinium chlorochromate; TBDPS for tert-butyldiphenylsilyl; DMAP for 4-dimethylaminopyridine; TBAF for tetrabutylammonium fluoride; Et_3N or TEA for triethylamine; min for minutes; OAc for acetate; Cbz for carbobenzyloxy; SEM for 2-trimethylsilylethoxymethoxy; AIBN for azobisisobutyronitrile; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; DDQ for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; dppf for 1,1'-bis(diphenylphosphino)ferrocene; and iPr_2NEt or DIPEA or DIEA for diisopropylethylamine.

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

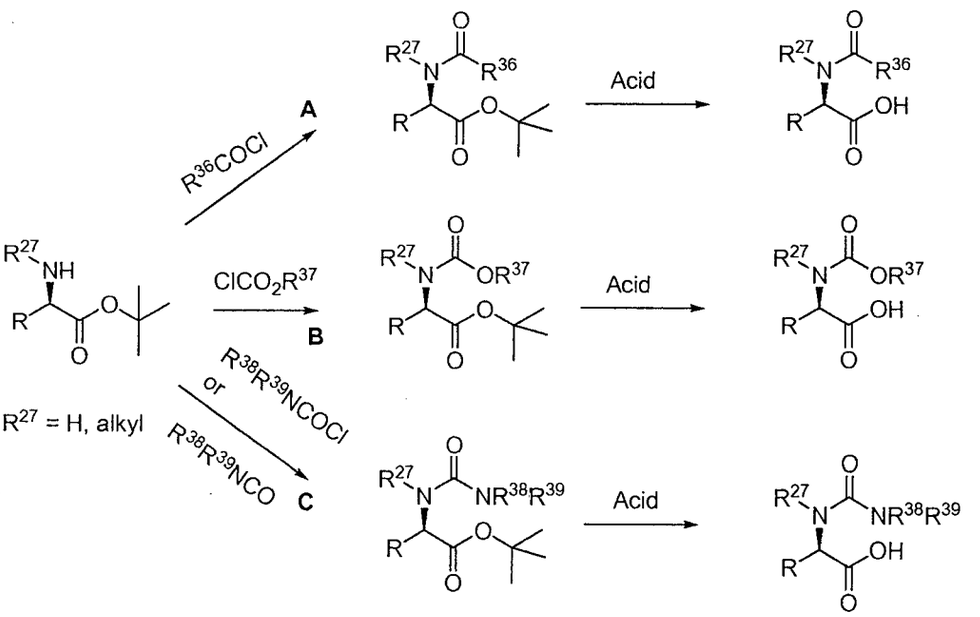
Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished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



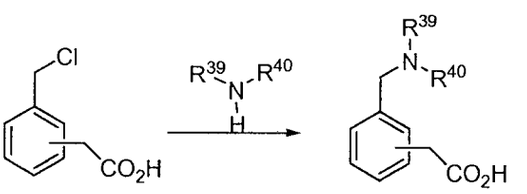
Scheme 2: Acylated Amino Acid Derivatives

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.



Compound analysis conditions

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Synthesis of common caps

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.-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 I

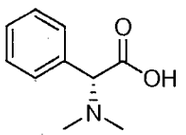
Column	= Phenomenex-Luna 3.0 X 50 mm S10

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

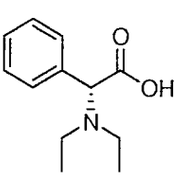
Condition III
Column = XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

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.

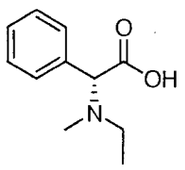
Cap-2



$NaBH_3CN$ (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

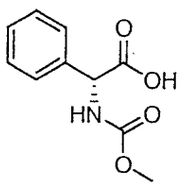


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under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

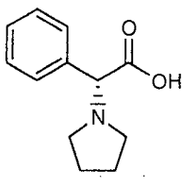


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-*tert*-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component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

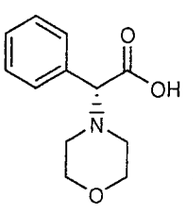
δ=2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, *J*=8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, *J*=8.3, 1H), 3.55 (s, 3H). LC (Cond. I): RT=1.01 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; 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.

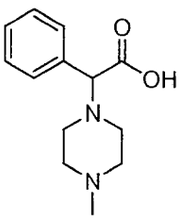
Cap-6



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. ^1H 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.

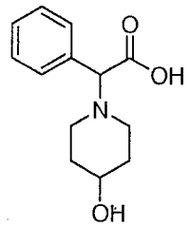
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed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

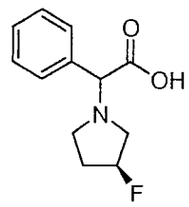
Cap-8



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

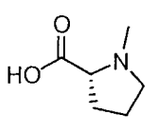


9a: diastereomer-1
9b: diastereomer-2

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

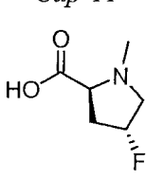
concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to prepare Caps 9a and 9b. Cap-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H_2O/methanol/TFA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

Cap-10



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

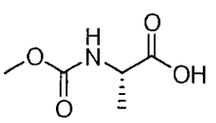
Cap-11



A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10%

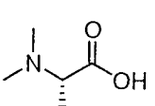
Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from isopropanol to provide the HCl salt of Cap-11 as a white solid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

Cap-12 (same as cap 52)



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

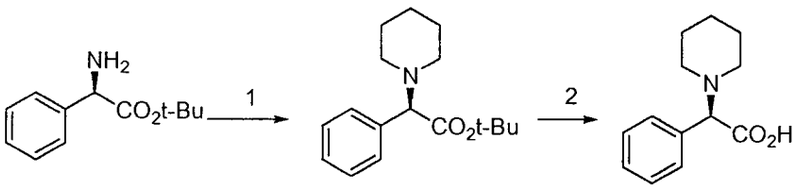
Cap-13



A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide the HCl salt of Cap-13 as an oil which solidified upon standing under vacuum (4.4 g; the

mass is above theoretical yield). The product was used without further purification. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, *J*=7.4, 1H), 2.76 (s, 6H), 1.46 (d, *J*=7.3, 3H).

Cap-14



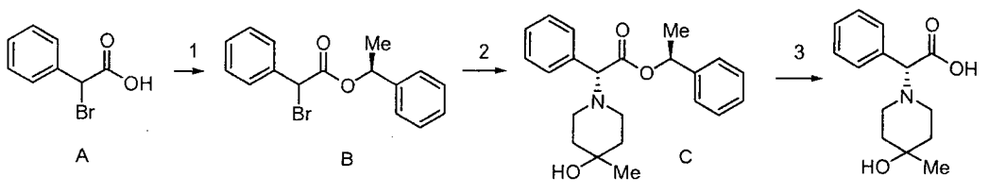
Cap-14

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

Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP

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

Cap-15



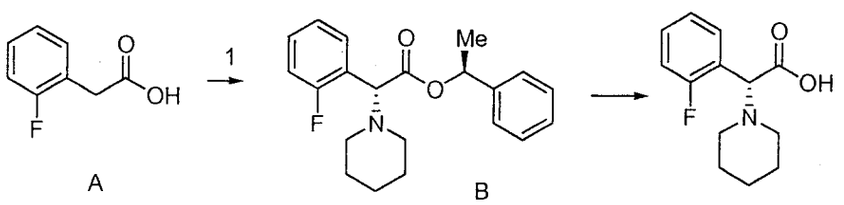
Step 1: (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred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

Step 2: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated.

The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ^{1}H NMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, *J*=6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, *J*=6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: ^{1}H NMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, *J*=6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, *J*=6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, *J*=6.8 Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

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

Cap-16



(R)-Cap-16

Step 1: (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O-ethyl acetate. The phases were

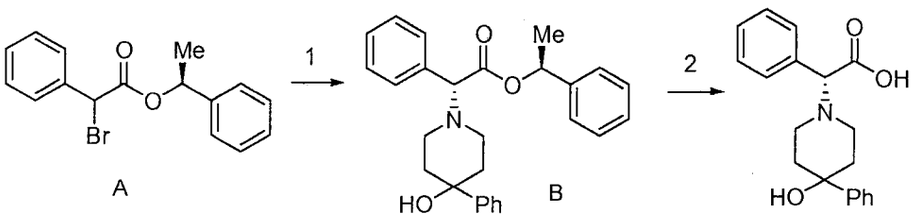
separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.32-7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, *J*=6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, *J*=6.5 Hz, 3H).

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

Step 3: (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated

in vacuo. This provided the title compound as a colorless solid (0.503 g, 98%). ^{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

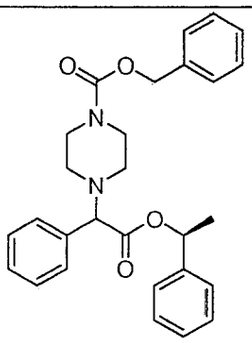


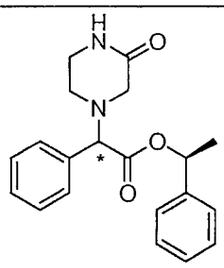
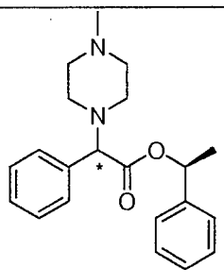
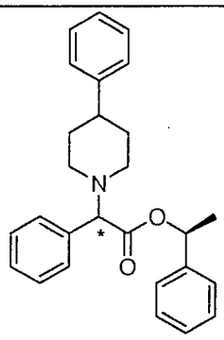
A B *(R)*-Cap-17

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

1H), 2.12 (dt, *J*=12.1, 4.6 Hz, 1H), 1.73 (dd, *J*=13.6, 3.0 Hz, 1H), 1.64 (dd, *J*=13.6, 3.0 Hz, 1H), 1.40 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

The following esters were prepared in similar fashion:

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

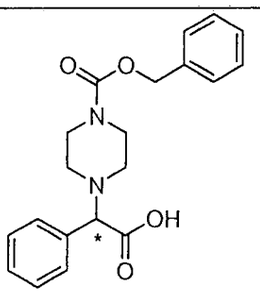
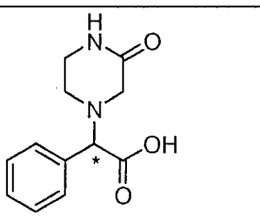
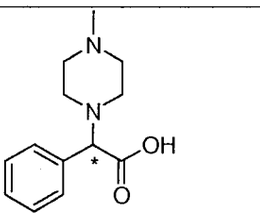
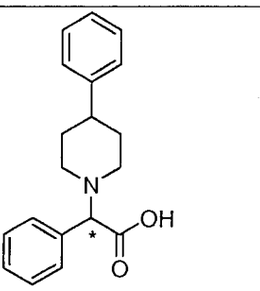
Flow rate: 2.0 mL/min.

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

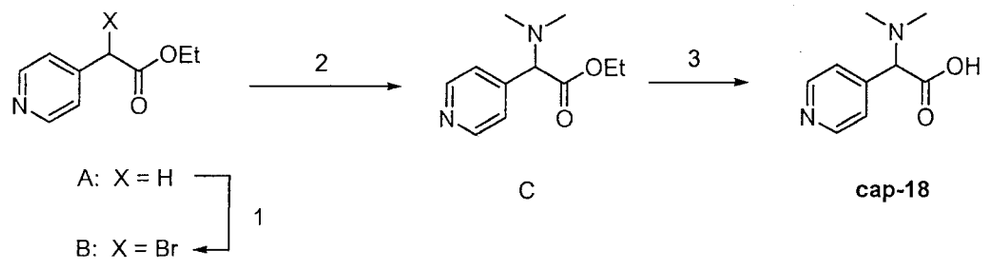
Flow Rate=4 mL/min

Wavelength=220

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

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

Cap-18



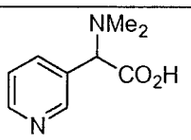
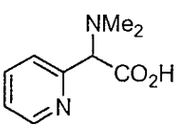
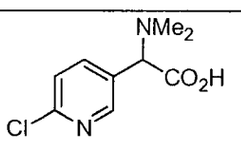
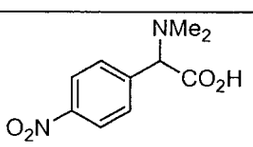
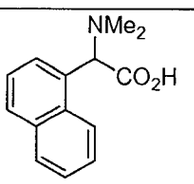
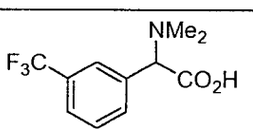
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this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

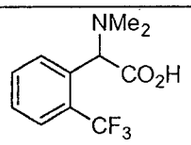
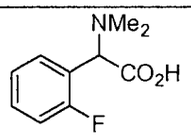
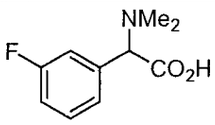
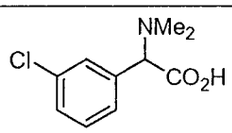
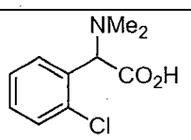
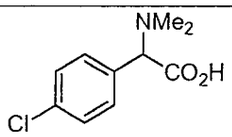
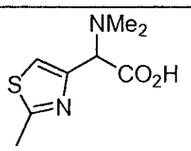
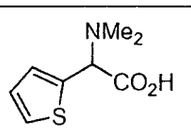
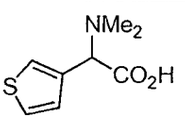
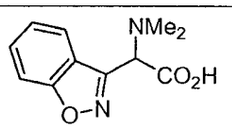
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography)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

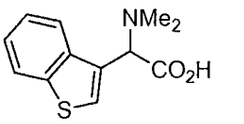
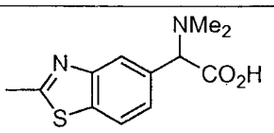
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in

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. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, *J*=5.7 Hz, 2H), 7.34 (d, *J*=5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

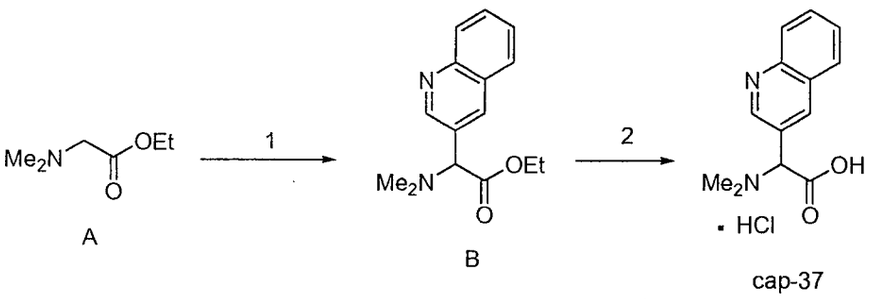
The following examples were prepared in similar fashion using the method described above;

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.
Cap-20		LCMS: no ionization. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (d, *J*=4.3 Hz, 1H), 7.84 (app t, *J*=5.3 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.37 (app t, *J*=5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.
Cap-22		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-23		LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 229; found: 230 $(M+H)^+$.
Cap-24		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.

Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{12}N_2O_2S$: 200; found: 201 $(M+H)^+$.
Cap-32		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-33		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-34		LCMS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$.

Cap-35		LCMS: Anal. Calcd. for $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$.
Cap-36		LCMS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$.

Cap-37

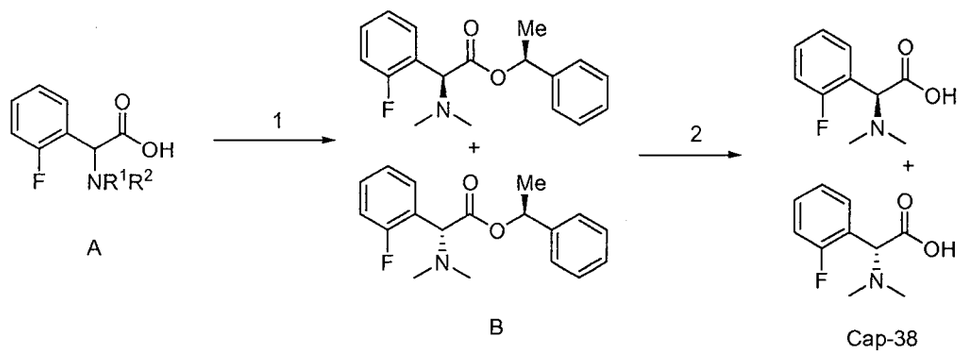


Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture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

Step 2; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent was removed *in vacuo* to provide the dihydrochloride of the title compound (0.169 g,

>100%) as a light yellow foam. The unpurified material was used in subsequent steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 $(M+H)^+$.

Cap-38



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

Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, *J*=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$.

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

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

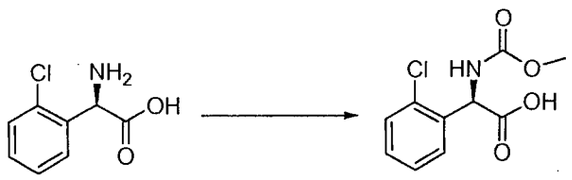
Cap-39



cap-39

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

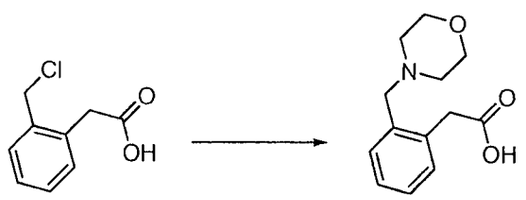
Cap-40



cap-40

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

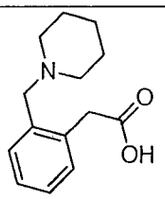
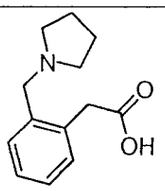
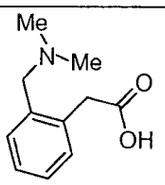
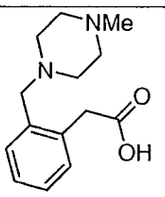
Cap-41



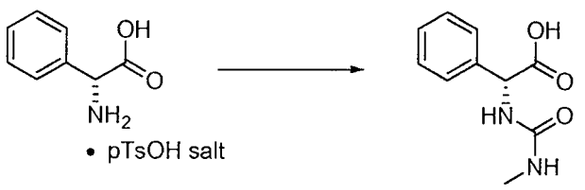
cap-41

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

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

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

Cap-45a

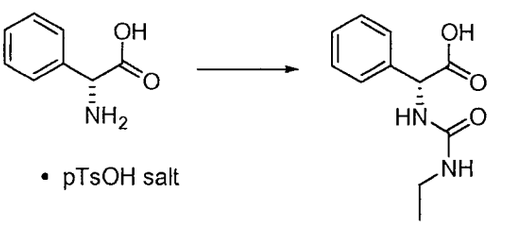


Cap-45a

HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used

without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26-7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^+$; HPLC Phenomenex C-18 3.0 × 46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.38 min, 90% homogeneity index.

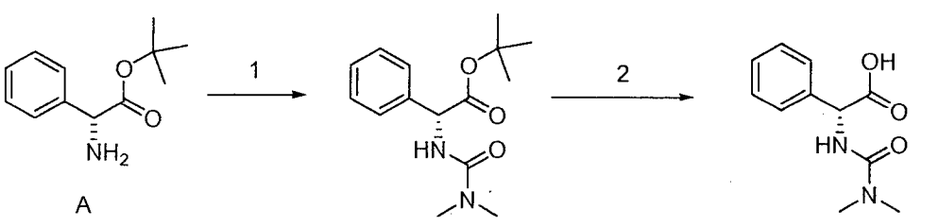
Cap-46



cap-46

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

Cap-47



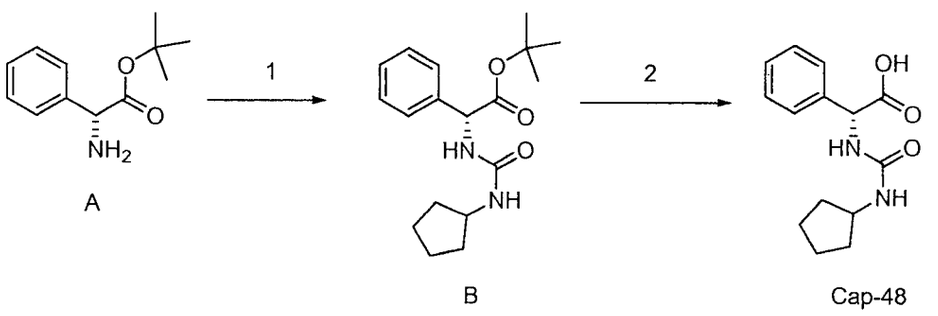
Cap-47

Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room

temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H_2O, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, J=7.63 Hz, 1H) 6.55 (d, J=7.32 Hz, 1H) 7.24-7.41 (m, 5H). LCMS: Anal. Calcd. for $C_{15}H_{22}N_2O_3$ 278.16 found 279.23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 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. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, J=7.32 Hz, 1H) 6.58 (d, J=7.32 Hz, 1H) 7.28 (t, J=7.17 Hz, 1H) 7.33 (t, J=7.32 Hz, 2H) 7.38-7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 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 trietheylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ^{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.

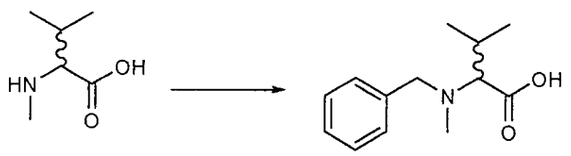
Cap-49



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 $(M+H)^+$.

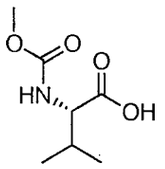
Cap-50



Cap-50

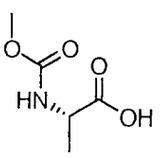
To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K_2CO_3 (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (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



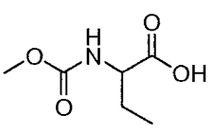
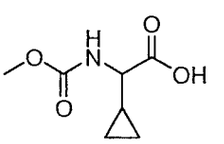
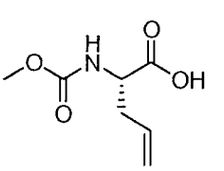
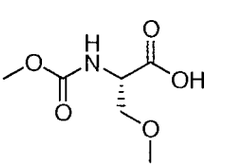
Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added dropwise over 15 min, the cooling bath was removed and the reaction mixture 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.

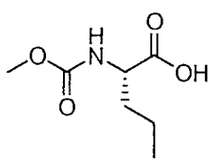
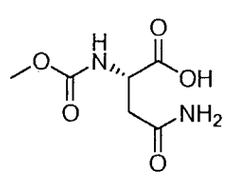
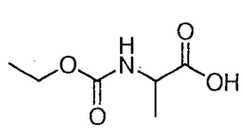
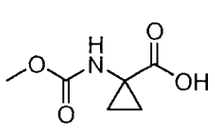
Cap-52 (Same as Cap-12)

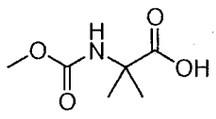
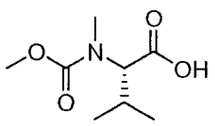
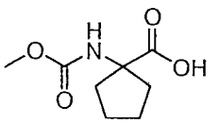
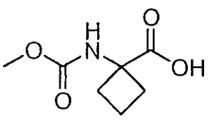


Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to afford Cap-52 as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ=2.5 ppm,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

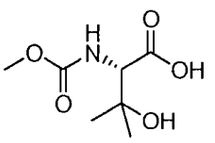
Cap-53 to *-64* were prepared from appropriate starting materials according to the procedure described for the synthesis of *Cap*-51, with noted modifications if any.

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).

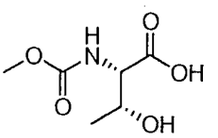
Cap-65



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).

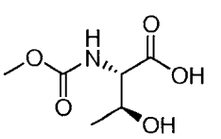
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



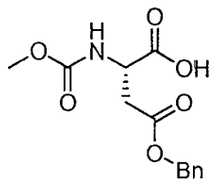
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, J = 8.3, 0.13H), 6.81 (d, J = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, J = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, J = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



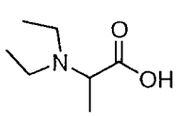
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (br d, *J* = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Note: only the dominant signals of NH were noted].

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

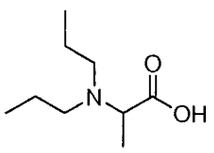
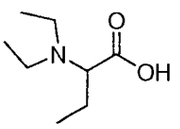
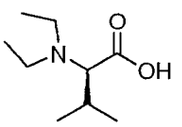
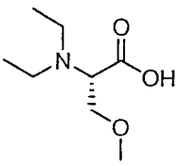


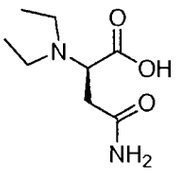
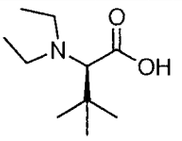
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

$NaCNBH_3$ (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

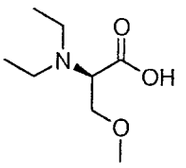
reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a Dowex ® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford *Cap*-69 (2.0 g) as an off-white soft hygroscopic solid. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, *J* = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, *J* = 7.1, 3H), 1.13 (t, *J* = 7.3, 6H).

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

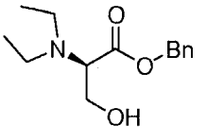
Cap-70a: (R) *Cap-70b*: (S)		^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, *J* = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, *J* = 7.3, 3H), 0.85 (t, *J* = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) *Cap-71b*: (S)		^1H NMR (DMSO-d_6,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

Cap-74		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, *J* = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, *J* = 15.6, 7.0, 1H), 2.36 (dd, *J* = 15.4, 6.3, 1H), 1.09 (t, *J* = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21

Cap-75



Cap-75, step a



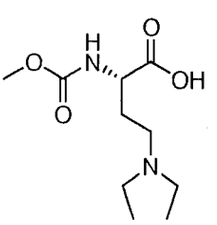
$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition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

7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 μL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH_3/Methanol. Removal of the volatile component *in vacuo* afforded *Cap*-75, contaminated with (R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

Cap-76

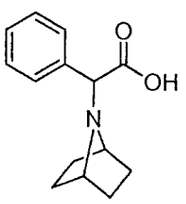


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed,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

compound was eluted with dilute NH_4OH, prepared from 18 ml of NH_4OH and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/H_2O, 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with CH_2Cl_2 (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M NH_3/MeOH) to afford impure *Cap*-76 as an off-white solid (704 mg). ^{1}H NMR (MeOH-d_4, 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

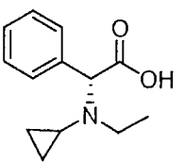


Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

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),

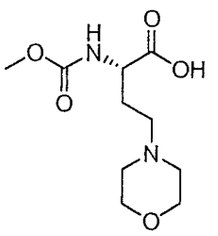
4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; found 232.1340.

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

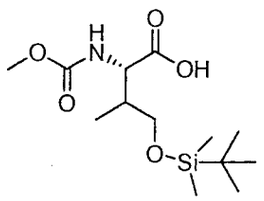


Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C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

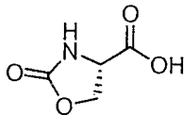
A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~ 21 hr, where the balloon was recharged 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.

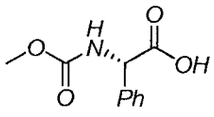
Cap-81



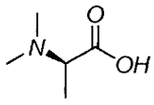
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 to Cap-85.

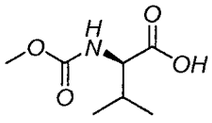
Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51 or *Cap*-13. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively).



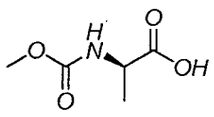
Cap-82



Cap-83

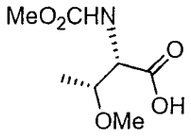


Cap-84



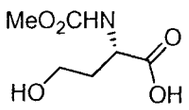
Cap-85

Cap-86



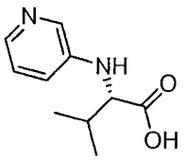
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10%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



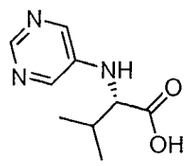
To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined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



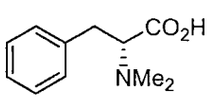
A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were 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



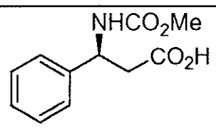
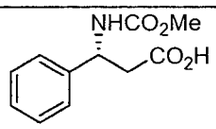
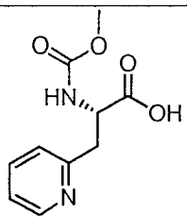
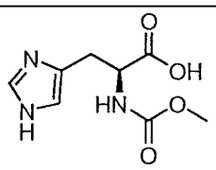
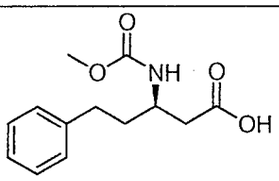
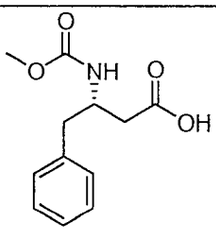
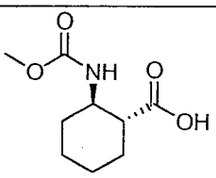
A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were 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 $(M+H)^+$.

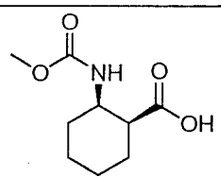
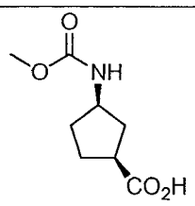
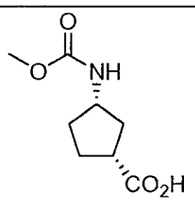
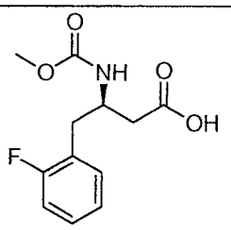
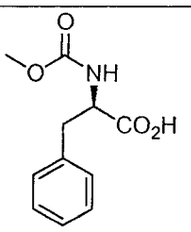
Cap–90

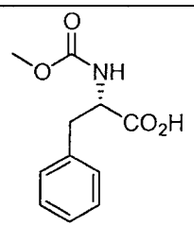
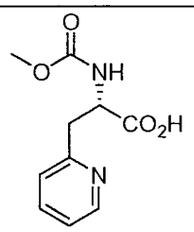
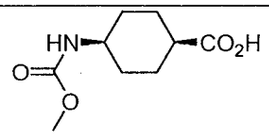
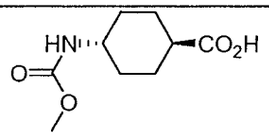
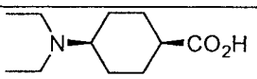


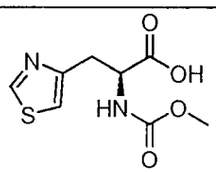
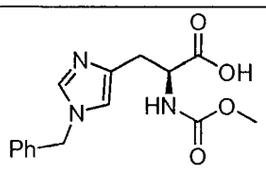
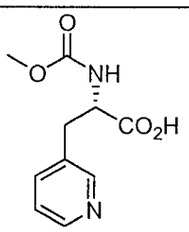
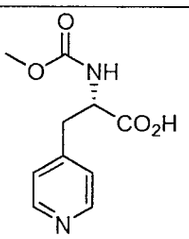
Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

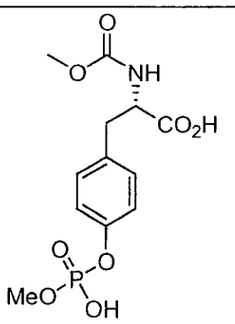
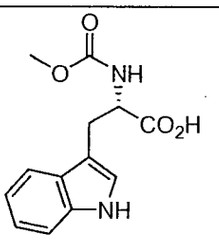
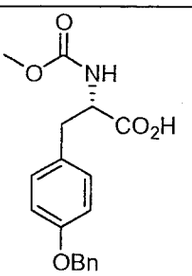
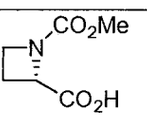
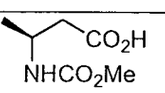
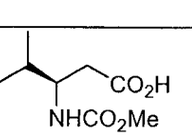
The following caps were prepared according to the method used for preparation of cap 51 unless noted otherwise:

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	^{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,

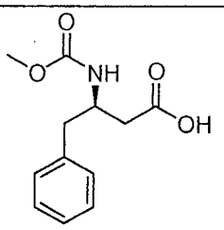
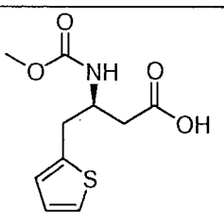
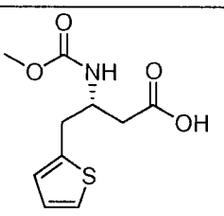
	acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX ($MeOH/H_2O/CH_2Cl_2$ wash; 2 N NH_3/MeOH elution) to afford an oil, which was dissolved in CH_3CN/H_2O and lyophilized to afford a tan solid.	12.5, 15.9 Hz, 2H), 1.46 (app dt 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 $(M+H)^+$.

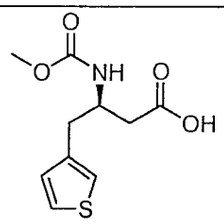
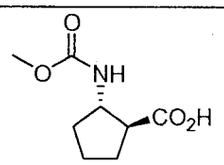
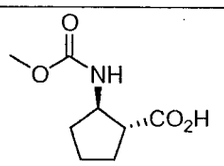
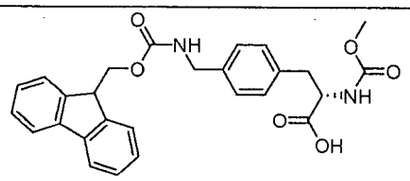
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$.
Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$.
Cap-114		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 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).

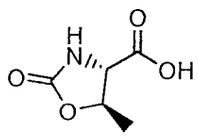
Cap-117 to Cap-123

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 $(M+H)^+$.

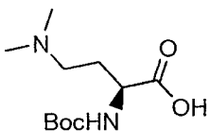
Cap-124



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

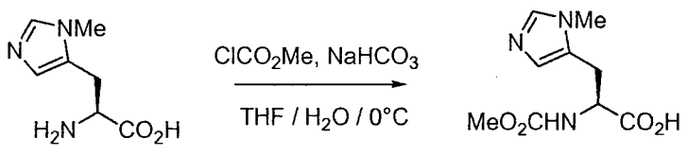
oil which was shown by LCMS to be the desired product. Both crops were combined to give 0.52 g of a solid. ^{1}HNMR (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). LCMS: Anal. Calcd. for $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

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



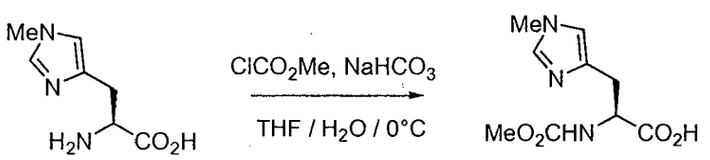
cj-25 *cap-126*

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 $(M+H)^+$.

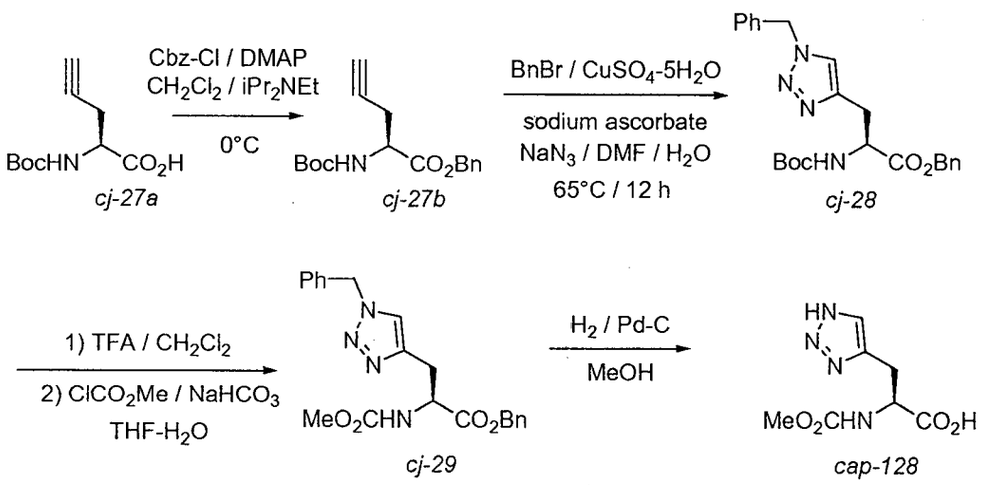
Cap-127



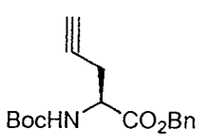
cj-26 *cap-127*

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 ^{1}H 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



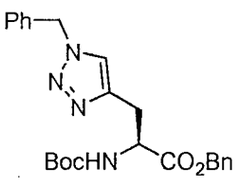
Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b).



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 $(M+H)^+$.

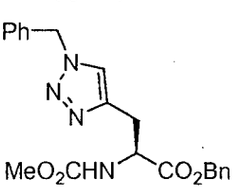
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28).



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).

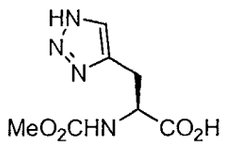


cj-29

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 $(M+H)^+$.

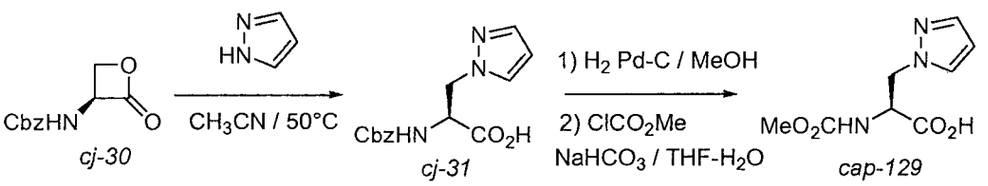
Step 4. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).



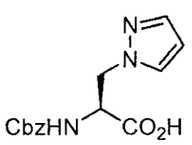
Cap-128

(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



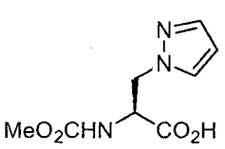
Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



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*).

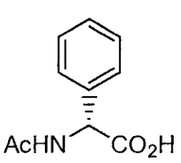


cap-129

(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,

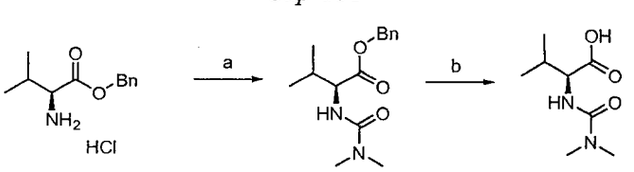
therefore the reaction mixture was diluted with 5mL H_2O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended 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

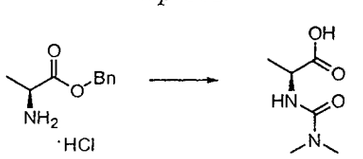


Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated

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.

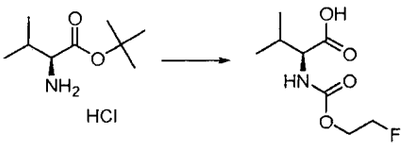
Step b: To a MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N_2 (3x) and placed under 1 atm of H_2. The mixture was stirred at room temperature overnight and filtered though a microfiber filter 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



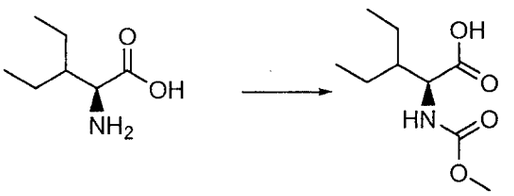
Cap-132 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for *Cap-131*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for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

Cap-133



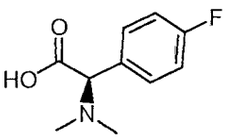
Cap-133 was prepared from (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap-47*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25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

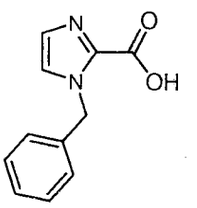
Cap-135



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

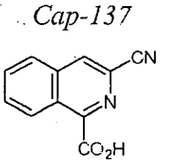
(dd, J = 8.80, 5.10 Hz, 2H), 7.29 (t, J = 8.6 Hz, 2H), 5.17 (s, 1H), 3.05 (v br s, 3H), 2.63 (v br s, 3H); R_t = 0.19 min (Cond.-MS-W5); 95% homogenity index; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; found: 198.10.

Cap-136

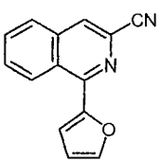


To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -50 °C, dry carbon dioxide (passed through Drierite) was bubbled 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

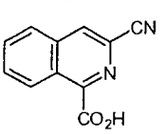


Cap-137, step a



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* as a white solid which was used as is (230 mg, 105%). 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.

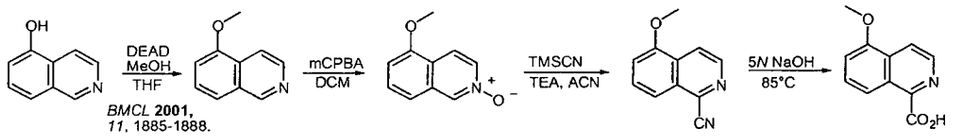
Cap-137



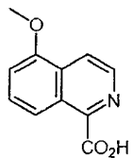
To a suspension of *Cap 137, step a*, (110 mg, 0.50 mmol) and sodium periodate (438 mg, 2.05 mmol) in carbon tetrachloride (1 mL), acetonitrile (1 mL) and water (1.5 mL) was added ruthenium trichloride hydrate (2 mg, 0.011 mmol). The mixture was stirred at 25 °C for 2 h and then partitioned between dichloromethane 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*

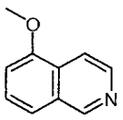
Synthetic Strategy. Method A.



Cap-138

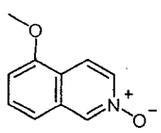


Cap-138, step a



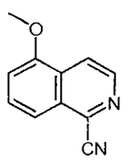
To a stirred suspension of 5-hydroxisoquinoline (prepared according to the procedure in WO 2003/ 099274) (2.0 g, 13.8 mmol) and triphenylphosphine (4.3 g, 16.5 mmol) in dry tetrahydrofuran (20 mL) was added dry methanol (0.8 mL) and diethyl azodicarboxylate (3.0 mL, 16.5 mmol) portionwise. The mixture 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 purified (elution with 40% ethyl acetate/hexanes) to afford *Cap-138, step a* as a light yellow solid (1.00 g, 45%). ^{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 160.10.

Cap-138, step b



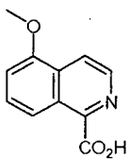
To a stirred solution of *Cap 138, step a* (2.34 g, 14.7 mmol) in anhydrous dichloromethane (50 mL) at room temperature was added *meta*-chloroperbenzoic acid (77%, 3.42 g, 19.8 mmol) in one portion. After being stirred for 20 h, powdered potassium carbonate (2.0 g) was added and the mixture was stirred for 1 h at room temperature before it was filtered and concentrated to afford *Cap-138, step b* as a pale, yellow solid which was sufficiently pure to carry forward (2.15 g, 83.3%). ^{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



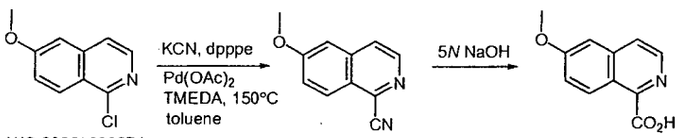
To a stirred solution of *Cap 138, step b* (0.70 g, 4.00 mmol) and triethylamine (1.1 mL, 8.00 mmol) in dry acetonitrile (20 mL) at room temperature under nitrogen was added trimethylsilylcyanide (1.60 mL, 12.00 mmol). The mixture was heated at 75 °C for 20 h before it was cooled to room temperature, 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 (elution with 5% ethyl acetate/hexanes) to 25% ethyl acetate/hexanes to afford *Cap-138, step c* (498.7 mg) as a white, crystalline solid along with 223 mg 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



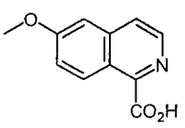
Cap-138, step c (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried over Na_2SO_4, concentrated to ¼ volume and filtered to afford *Cap-138* as a yellow solid (0.44g, 88.9%). ^{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).

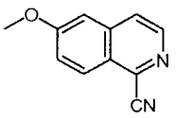


WO 2003/ 099274

Cap-139



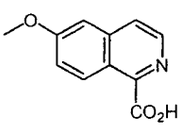
Cap-139, step a



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

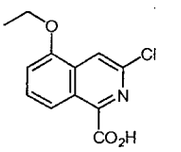
mg, 0.31 mmol) in anhydrous toluene (6 mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.29 mL, 2.48 mmol). The vial was sealed, heated at 150 °C for 22 h and then allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 5% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to afford *Cap-139, step a* as a white solid (669.7 mg). ^{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: 185.20.

Cap-139

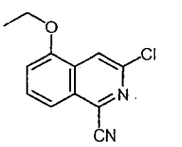


Cap-139 was prepared from the basic hydrolysis of *Cap-139, step a* with 5*N* NaOH according to the procedure described for *Cap 138*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (v br s, 1H), 8.60 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.44 (dd, 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

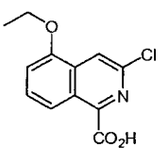


Cap-140, step a



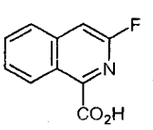
To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/ 051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry dimethylacetamide (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 eluting with 10% ethyl acetate/hexanes to 40% ethyl acetate/hexanes to afford *Cap-140, step a* as a yellow solid (160 mg, 34%). R_t = 2.46 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; found: 233.08.

Cap-140

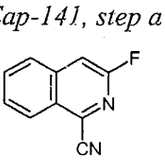


Cap-140 was prepared by the acid hydrolysis of *Cap-140, step a* with 12*N* HCl as described in the procedure for the preparation of *Cap 141*, described below. R_t = 2.24 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; found: 252.02.

Cap-141

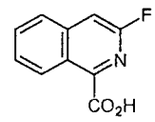


Cap-141, step a



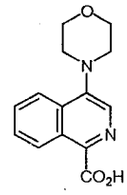
Cap-141, step a was prepared from 1-bromo-3-fluoroisoquinoline (prepared from 3-amino-1-bromoisoquinoline using the procedure outlined in *J. Med. Chem.* **1970**, *13*, 613) as described in the procedure for the preparation of *Cap-140, step a* (*vide supra*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d,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

Cap-141

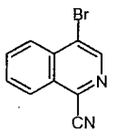


Cap-141, step a (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature and diluted with water (3 mL). The mixture was stirred for 10 min and then filtered to afford *Cap-141* as an off-white solid (44.1 mg, 47.8%). The filtrate was diluted with dichloromethane and washed with brine, dried over Na_2SO_4, and concentrated to afford additional *Cap-141* which was sufficiently pure to be carried forward directly (29.30 mg, 31.8%). ^{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

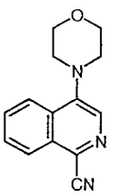


Cap-142, step a



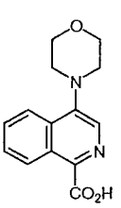
Cap-142, step a was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of *Cap-138, steps b and c*. R_t = 1.45 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

Cap-142, step b



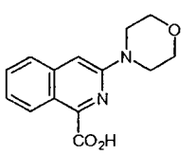
To an argon-degassed suspension of *Cap-142, step a* (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 μL, 0.70 mmol). The mixture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

Cap-142

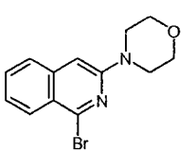


Cap-142 was prepared from *Cap-142, step b* with 5*N* sodium hydroxide as described in the procedure for *Cap 138*. R_t = 0.72 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-143

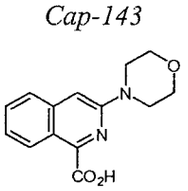


Cap-143, step a



To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 μL, 2.00 mmol) was added. The 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 eluting with 0% to 70% ethyl acetate/hexanes afforded *Cap-143, step a* as a yellow solid (180 mg, 31%). 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.

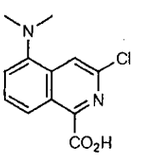
Cap-143



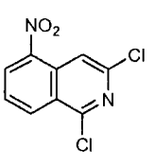
To a cold (-60 °C) solution of *Cap-143, step a* (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes

(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 a 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

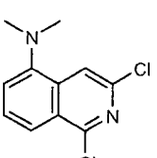


Cap-144, step a



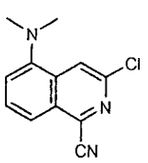
1,3-Dichloroisoquinoline (2.75 g, 13.89 mmol) was added in small portions to a cold (0 °C) solution of fuming nitric acid (10 mL) and concentrated sulfuric acid (10 mL). The mixture was stirred at 0 °C for 0.5 h before it was gradually warmed to 25 °C where it stirred for 16 h. The mixture was then poured 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



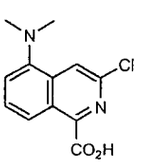
Cap-144, step a (0.30 g, 1.23 mmol) was taken up in methanol (60 mL) and treated with platinum oxide (30 mg), and the suspension was subjected to Parr hydrogenation at 7 psi H_2 for 1.5 h. Then formalin (5 mL) and additional platinum oxide (30 mg) were added, and the suspension was resubjected to Parr hydrogenation at 45 psi H_2 for 13 h. It was then 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 eluting 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.

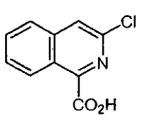
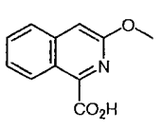
Cap-144

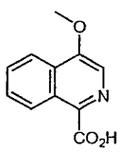
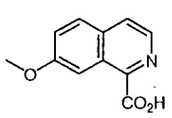
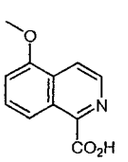
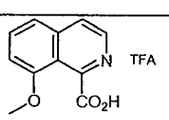


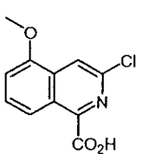
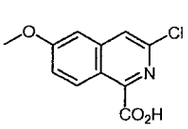
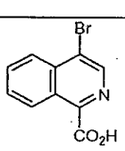
Cap-144 was prepared according to the procedure described for *Cap-141*. R_t = 2.36 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; found: 238.09.

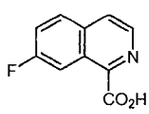
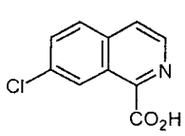
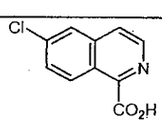
Caps-145 to 162

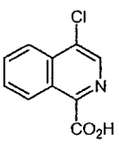
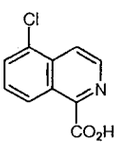
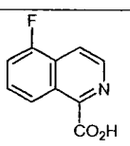
Caps-145 to *162* were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of *Cap-138* (Method A) or *Cap-139* (Method B) unless noted otherwise as outlined below.

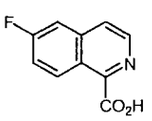
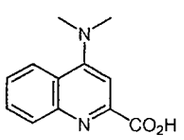
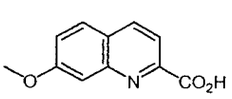
Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-145	 Prepared from commercially available 1,3-dichloroisoquinoline	B	12*N* HCl	1.14 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-146	 Prepared from commercially available 3-hydroxyisoquinoline	A	5*N* NaOH	1.40 min (Cond.-D1); 95% ; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.06.

Cap-147	 Prepared from commercially available 1-chloro-4-hydroxyisoquinoline	B	5*N* NaOH	0.87 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-148	 Prepared from commercially available 7-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; 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		A	12*N* HCl	0.26 min (Cond.-D1);

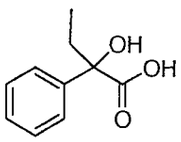
	Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274			95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.04.
Cap-151	 Prepared from 5-methoxy-1,3-dichloroisoquinoline, which can be synthesized following the procedure 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-	A	6*N* HCl	1.18 min (Cond.-MS-W1); 95%; LCMS: Anal.

	bromoisoquinoline, which can be synthesized 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/	B	5*N* NaOH	0.60 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$

	099274			$C_{10}H_7ClNO_2$: 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, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.69 min (Cond.-MS-W1); 90%; LCMS: 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;

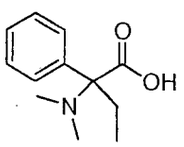
				found: 192.03.
Cap-160	 Prepared from 6-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.30 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-161	 Prepared from 4-bromoquinoline-2-carboxylic 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



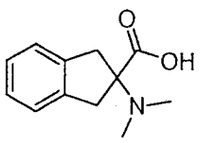
To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 x 100 ml). 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



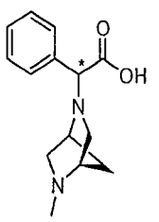
A mixture of 2-amino-2-phenylbutyric acid (1.5 g, 8.4 mmol), formaldehyde (14 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (0.5 mg) in MeOH (40 mL) was exposed to H_2 at 50 psi in a Parr bottle for 42 h. The reaction was filtered over Celite and concentrated *in vacuo*, the residue was taken up in 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, δ = 2.5 ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found: 206.07.

Cap-166a and -166b

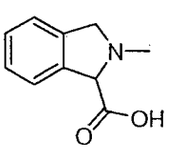


Cap-166a: Diastereomer-1
Cap-166b: Diastereomer-2

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

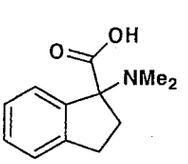
1.63 (d, J = 9.8 Hz, 1H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; found: 247.11.

Cap-167



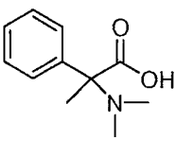
A solution of racemic Boc-1,3-dihydro-2H-isoindole carboxylic acid (1.0g, 3.8 mmol) in 20% TFA/CH_2Cl_2 was stirred at ~25 °C for 4h. All the volatile component was removed *in vacuo*. A mixture of the resultant crude material, formaldehyde (15 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (10 mg) in MeOH was exposed to H_2 (40 PSI) in a Parr bottle for 23 h. The reaction mixture was filtered over Celite and concentrated *in vacuo* to afford *Cap-167* as a yellow foam (873.5 mg). ^{1}H NMR (DMSO-d_6, 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



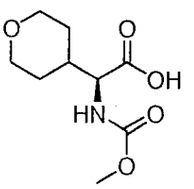
Racemic *Cap-168* was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of *Cap-167*. The crude material was employed as such.

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.

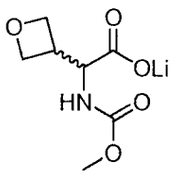
Cap-170



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).

EXAMPLES

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

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

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Retention times were determined according to the following LC/MS conditions:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Slovent A = 0.1% TFA in 10% methanol/90%H2O

Solvent B = 0.1% TFA in 90% methanol/10% H2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Slovent A = 0.1% TFA in 10% methanol/90%H2O

Solvent B = 0.1% TFA in 90% methanol/10% H2O

Condition 3

Column = LCMS. GEMINI C-18 4.6 □ 50 mm

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% NH4OAc in 10% acetonitrile /90%H2O

Solvent B = 0.1% NH4OAc in 90% acetonitrile /10% H2O

Condition 4

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

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

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

Condition 5

Column 30 mm x = Luna C18 4.6

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

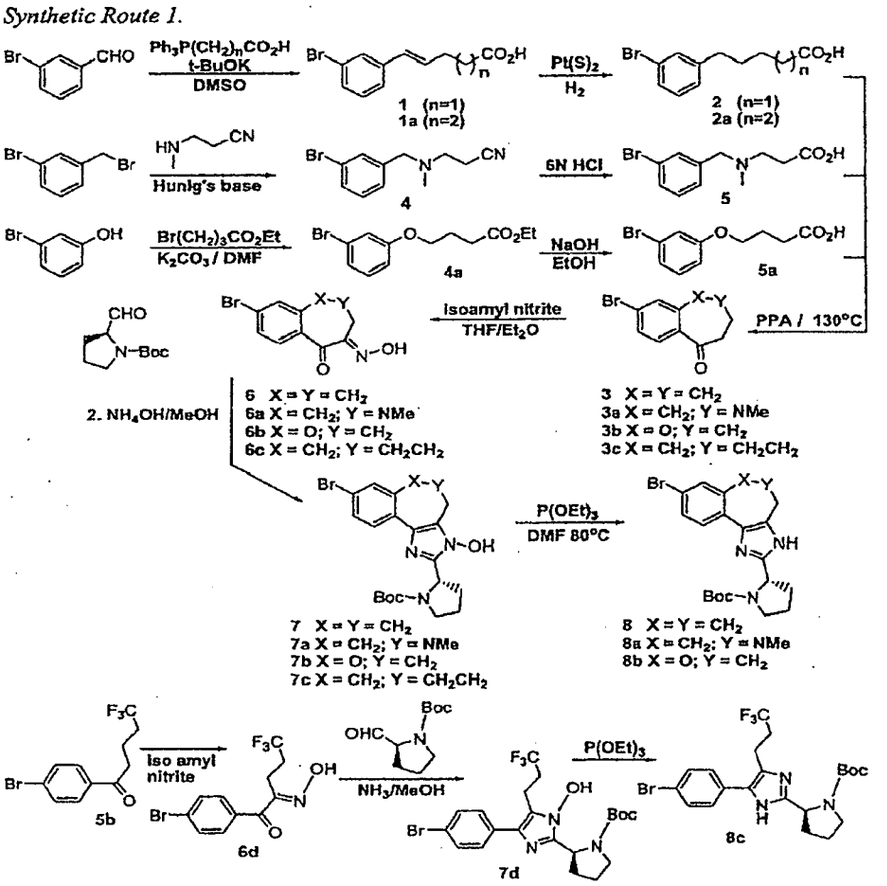
Flow Rate = 5 mL/min

Wavelength = 220 nm

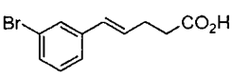
Solvent A = 0.1% NH4OAc in 10% acetonitrile /90%H2O

Solvent B = 0.1% NH4OAc in 90% acetonitrile /10% H2O

Synthetic Route 1.

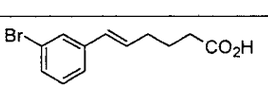


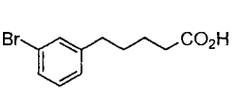
Reference: (Wittig/reduction/cyclization) *J.Med.Chem.* (2005) *48*, 7351-7362.



1

A 1M solution of potassium tert-butoxide in THF (80 mL) was added dropwise to (3-carboxypropyl)triphenylphosphoium bromide (17 g, 40 mmol) 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 hours. 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 65 (M) Biotage® silica gel column; Gradient elution from 15-65% B (A = Hexanes; B = EtOAc) over 2L to give Example 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). RT = 2.0 minutes (condition 1); LRMS: Anal. Calcd. for $C_{11}H_{11}BrO_2$: 252.97; found: 252.98 (M-H).

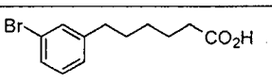
Example 1a		RT = 2.1 minutes (condition 1); LRMS: Anal. Calcd. for $C_{12}H_{13}BrO_2$: 267.00; found: 267.00 (M-H).



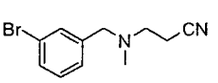
2

Example 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 hours. The catalyst was removed by filtration through diatomaceous earth (Celite ®) and the solvent immediately removed by rotory evaporation (in order to minimized esterification) to give Example 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). RT = 2.1 minutes (condition 1); LRMS: Anal. Calcd. for $C_{11}H_{13}BrO_2$: 255.00; found: 254.99 (M-H).

Example 2a (Derived from Example 1a).		RT = 2.2 minutes (condition 1); LRMS: Anal. Calcd. for $C_{12}H_{15}BrO_2$: 269.02; found: 269.04 (M-H).

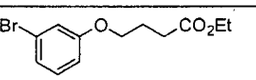
Reference: (Alkylation/hydrolysis) *J.Am.Chem.Soc.* (1946) *68*, 1468-1470.

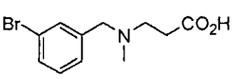


4

Hunig's base (26.5 mL, 0.15 mol) was added to 3-bromobenzyl bromide (38g, 0.15 mol) and N-methyl-β-alanine nitrile (14.2 mL, 0.15 mol) in dry DMF (400 mL). The solution was stirred 16 h, concentrated *in vacuo* to near dryness, triturated with ether/EtOAc, and filtered. [A second reaction was repeated on 12 g]. The combined filtrates were concentrated by rotory evaporation and the residue was charged (CH_2Cl_2) to a 65 (M) Biotage® silica gel column; Segment 1: Gradient elution from 5-15% B over 1.3 L; Segment 2: 15%-100% B (A = Hexanes; B = EtOAc) over 6.75 L to give Example 4, 3-((3-bromobenzyl)(methyl)amino)-propanenitrile 44.4 g (88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 3.54 (s, 2H), 2.71 (t, J = 6.4 Hz, 2H),

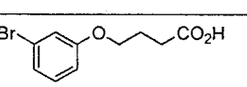
2.63 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H). RT = 1.1 minutes (condition 2); LRMS: Anal. Calcd. for $C_{11}H_{13}BrN_2$: 253.03; found: 253.05 (M+H).

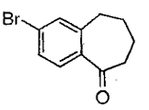
Example 4a Prepared as in J.Med.Chem.**2000** *43*, 2049		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{12}H_{15}BrO_3$: 287.14; found: 289.2 (M+2H).



5

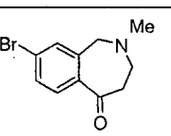
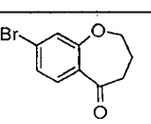
6N HCl was added to Example 4, 3-((3-bromobenzyl)(methyl)amino)-propanenitrile (44.4 g, 0.175 mol) in a 1 L screw cap pressure vessel and the sealed solution was heated at 90 °C for 40 hours. After being cooled, the solution was concentrated *in vacuo* to ¼ vol. Filtration, concentration of mother liquor, and filtration (2x) gave a quantitative yield of Example 5, 3-((N-(3-bromobenzyl)-N-methyl)amino)propanoic acid as a white solid (HCl salt). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (t, J = 1.5 Hz, 1H), 7.67 (dd, J = 7.3, 1.5 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 4.33 (br. s, 2H), 3.34 (br. s, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.63 (s, 3H). RT = 1.3 minutes (condition 2); LRMS: Anal. Calcd. for $C_{11}H_{11}BrNO_2$: 272.03; found: 272.10 (M+H).

Example 5a Derived from 4a as in J.Med.Chem.**2000** *43*, 2049		RT = 1.05 minutes (condition2); LCMS: Anal. Calcd. for $C_{10}H_{11}BrO_3$: 259.09; found: 259.2. (M+2).

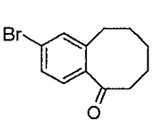


3

Example 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 hours 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 CH_2Cl_2 (600 mL). [Caution is necessary to avoid boiling of CH_2Cl_2.] 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% (EtOAc/Hex) and gave Example 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). RT = 2.1 minutes (condition 1); LRMS: Anal. Calcd. for $C_{11}H_{11}BrO$: 239.00; found: 239.14 (M+H).

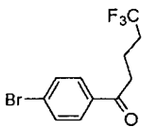
Example 3a (Derived from Example 5)		RT = 1.17 minutes (condition 1); LRMS: Anal. Calcd. for $C_{11}H_{13}BrNO$: 254.02; found: 254.16 (M+H).
Example 3b (Derived from Example 5a)		RT = 1.7 minutes (condition 2); LCMS: Anal. Calcd. for $C_{10}H_9BrO_2$: 241.08; found: 241.2 (M+2).

Reference: (Cyclization) *JACS* **1962** *27*, 70-76.



3c

Thionyl chloride (13.2 mL, 181 mmol) was added (neat) to Example 2a, 6-(3-bromophenyl)hexanoic acid (16 g, 59.2 mmol) in a 1L round-bottomed flask under a nitrogen atmosphere. The mixture was warmed to 60°C for 2 h, excess reagent was removed *in vacuo*, and the residue was subjected to azeotropic conditions (benzene 3x). The acid chloride was dissolved in carbon disulfide (550 mL) and cannulated into a solution of aluminum trichloride (26.3 g, 198 mmol) in carbon disulfide (1315 mL) heated at reflux. The reaction was stirred 20 h, cooled, decanted, concentrated, and the resultant solids were stirred in diethyl ether/THF (1:1, 1L), and 1N HCl (500 mL) for 1.5 hours. The organic layer was filtered, washed with water, and brine to give Example 3c, 2-bromo-7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one 10.1 g (66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 2.99 (t, J = 6.6 Hz, 2H), 2.89 (t, J = 6.6 Hz, 2H), 1.85-1.73 (m, 4H), 1.52-1.44 (m, 2H). RT = 2.8 minutes (condition 2); LRMS: Anal. Calcd. for $C_{12}H_{13}BrO$: 253.02; found: 253.15 (M+H). Reference: J.Org.Chem. USSR (Engl.Transl.) (1985) p 2201-2205.

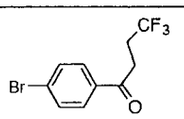


5b

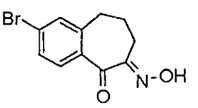
Magnesium (0.636 g, 26.2 mmol) was added to a solution of 4-bromo-1,1,1-trifluorobutane (5 g, 26.2 mmol) in THF (100 mL) and under nitrogen. The solution was stirred for 18 h at 24 °C, and the Grignard reagent was transfered via cannula to a solution of 4-bromobenzaldehyde (4.85 g, 26.2 mmol) in THF (50 mL) at -78 °C under nitrogen. The cold bath was removed and the reaction allowed to warm and stirred 18 h, diluted with Et_2O (1 vol), quenched with sat'd NH_4Cl soln, and washed with brine. Concentrate, take up in CH_2Cl_2 and charged to a 40M Biotage® silica gel cartridge. Gradient elution was performed from 15% to 100% B over 1 L (A/B Hexanes/EtOAc) to give 1-(4-bromophenyl)-5,5,5-trifluoropentan-1-ol 6.4 g (82%).

PCC (9.29 g, 43.1 mmol) was admixed with 9 g SiO_2 and ground with mortar & pestle before being added in one portion to a solution of 1-(4-bromophenyl)-5,5,5-trifluoropentan-1-ol (6.4 g, 21.54 mmol) dissolved in dichloromethane (350 mL). The reaction was stirred 4h, filtered through diatomaceous earth (Celite®),

concentrated, and applied to a 160 g Thomson® silica gel column. Elution: 10 - 60% B over 1.5 L (A/B Hexanes/EtOAc) gave Example 5b, 1-(4-bromophenyl)-5,5,5-trifluoropentan-1-one 6.1 g (86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 3.04 (t, J = 7.0 Hz, 2H), 2.25-2.16 (m, 2H), 2.05-1.99 (m, 2H). RT = 2.1 minutes (condition 1). LCMS: Anal. Calcd. For $C_{11}H_{11}BrF_3O$: 295.00; found: 295.00 (M+H).

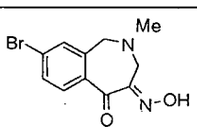
Example 5b.1 (Prepared from 3-bromo-1,1,1-trifluoropropane)		RT = 1.7 minutes (condition 1); LCMS: Anal. Calcd. For $C_{10}H_9BrF_3O$: 278.97; found: 278.98 (M-H).

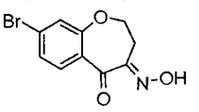
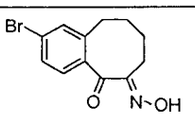
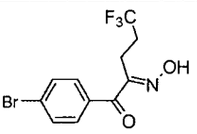
Reference: (Imidazole synthesis) *Bioorg. Med. Chem. Lett.* **2002** 1009-1011.

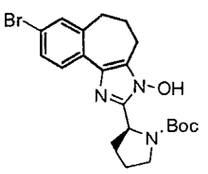


6

Example 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 Et_2O/THF (120 mL) and 1N HCl in Et_2O (9 mL) was added. The solution was cooled to 0°C before addition of *iso*-amylnitrite (1.2 mL, 9 mmol) and the reaction was stirred 18 hours at 24 °C, concentrated, and applied to 25 (M) Biotage® silica gel column. Gradient elution from 15-100% B (A = Hexanes; B = EtOAc) over 1L and gave Example 6, (E)-2-bromo-6-(hydroxyimino)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 1 g (64%). RT = 1.9 minutes (condition 1). LCMS: Anal. Calcd. For $C_{11}H_{10}NBrO_2$: 268; found: 268 (M+H).

Example 6a (Derived from Example 3a)		RT = 1.35 minutes (condition 2); LCMS: Anal. Calcd. For $C_{11}H_{11}BrN_2O_2$: 283.00; found: 283.03 (M+H).

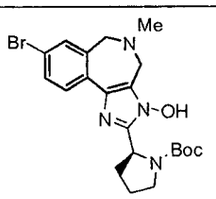
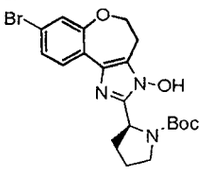
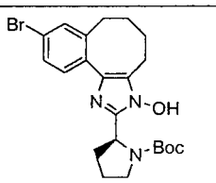
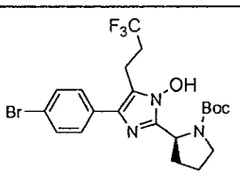
Example 6b (Derived from Example 3b)		RT = 1.55 minutes (condition 2); LCMS: Anal. Calcd. for $C_{10}H_8BrNO_3$: 270.08; found: 270 (M+H).
Example 6c (Derived from Example 3c)		RT = 2.51 minutes (condition 2); LCMS: Anal. Calcd. For $C_{12}H_{12}BrNO_2$: 282.02; found: 282.13 (M+H).
Example 6d (Derived from Example 5b)		RT = 2.1 minutes (condition 1); LCMS: Anal. Calcd. For $C_{11}H_{10}BrF_3NO_2$: 323.98; found: 323.99 (M+H).

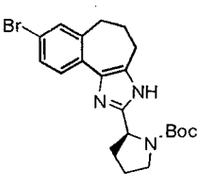


7

Concentrated 28% ammonium hydroxide solution (12 mL,) was added to a solution of Example 6, (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 mixture was stirred 18 hours at 24 °C, partially concentrated to remove methanol, and the aqueous residue extracted with CH_2Cl_2. The organic phase washed with water and concentrated and the crude product charged (CH_2Cl_2) to a 40 (S) Biotage® silica gel column; Gradient elution Segment 1. 15%-30% B over 300 mL; Segment 2. 30%-100% B over 700 mL (A = 1:1 hexanes/CH_2Cl_2; B = EtOAc) gave Example 7, 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),

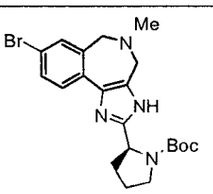
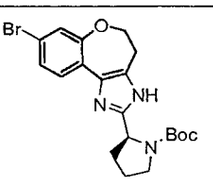
7.31 (d, J = 1.8 Hz, 1H), 5.0/4.87 (m, 1H), 3.51-3.46 (m, 1H), 3.42-3.36 (m, 1H), 2.90-2.70 (m, 4H), 2.27-1.80 (m, 6H), 1.38/1.11 (s, 9H). RT = 1.9 minutes (condition 1). LRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_3$: 488.12; found: 488.14 (M+H). HRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_3$: 488.1236; found: 488.1242 (M+H).

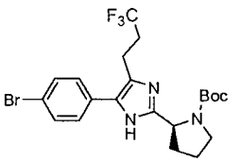
Example 7a (Derived from Example 6a)		RT = 2.29 minutes (condition 2); LCMS: Anal. Calcd. For $C_{21}H_{28}N_4BrO_3$: 463.13; found: 463.16 (M+H).
Example 7b (Derived from Example 6b)		RT = 1.67 minutes (condition 1); LCMS: Anal. Calcd. For $C_{20}H_{24}N_3BrO_4$: 450.34; found: 450 (M+H).
Example 7c (Derived from Example 6c)		RT = 2.53 minutes (condition 2); LCMS: Anal. Calcd. For $C_{22}H_{29}N_3BrO_3$: 462.13; found: 462.31 (M+H).
Example 7d (Derived from Example 6d)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{26}N_3BrF_3O_3$: 504.11; found: 504.17 (M+H).



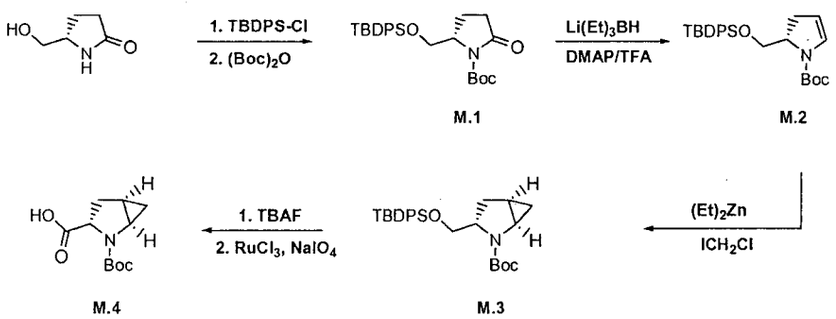
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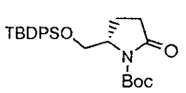
Triethyl phosphite (0.78 mL, 4.7 mmol) was added to a solution Example 7, (700 mg, 1.57 mmol) in DMF (2 mL) and the solution heated at 80°C for 18 hours under a nitrogen atmosphere. The reaction mixture was taken up in ethyl acetate (100 mL) and washed with water and brine. After concentration the crude 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 = CH_2Cl_2; B = EtOAc) to give Example 8, 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). RT = 1.9 minutes (condition 1). LRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_2$: 432.13; found: 432.14 (M+H).

Example 8a (Derived from Example 7a)		RT = 1.83 minutes (condition 2); LCMS: Anal. Calcd. For $C_{21}H_{28}BrN_4O_2$: 447.14; found: 447.06 (M+H).
Example 8b (Derived from Example 7b)		RT = 1.95 minutes (condition 2); LCMS: Anal. Calcd. For $C_{20}H_{24}N_3BrO_3$: 433.24; found: 434 (M+H).

Example 8c (Derived from Example 7d)		RT = 1.80 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{26}BrF_3N_3O_2$: 488.11; found: 488.17 (M+H).

Synthetic route 2.



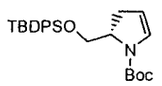


M.1

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-d6, 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

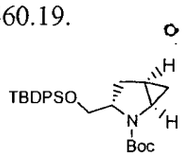
mmol), Et_3N (8.93 g, 88 mmol), and DMAP (1.08 g, 8.83 mmol) and stirred for 18 h at 24 °C. Most of the volatile material was removed in vacuo and the crude material taken up in 20% ethyl acetate/hexanes and applied to a 2 L funnel containing 1.3 L of silica gel and then eluted with 3 L of 20% ethyl 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-d6, 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-Boc+H) = 354.58. Calcd. 454.24.



M.2

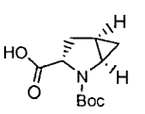
A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with carbamate M.1 (10.05 g, 22.16 mmol) and toluene (36 mL), and lowered into -55 °C cooling bath. When the internal temperature of the mixture reached -50 °C, lithium triethylborohydride (23 mL of 1.0 M/tetrahydrofuran, 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-d6, 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.



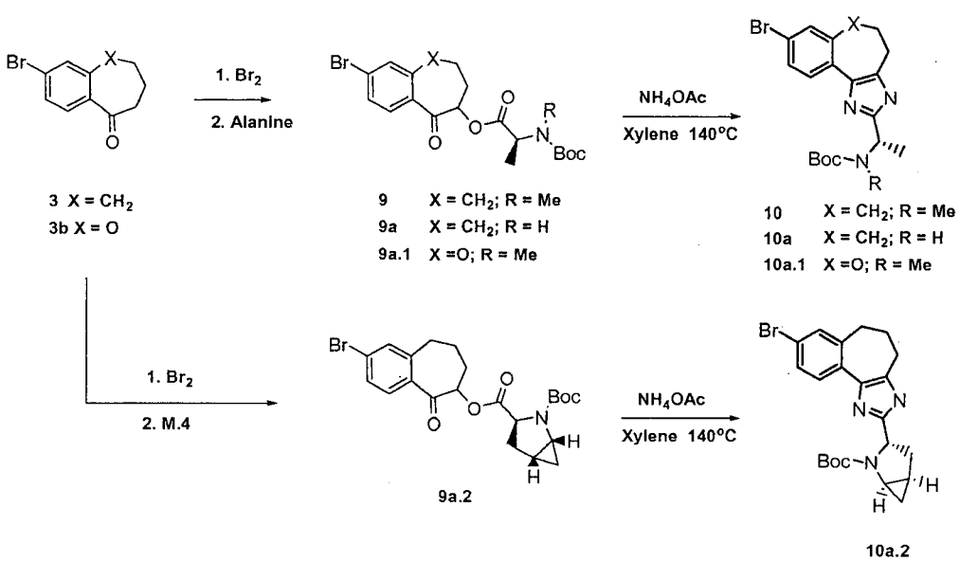
M.4

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-d6, 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 (Celite®). 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

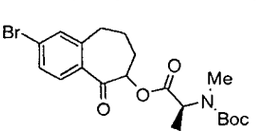
ambient temperature for 1 h, and then 3 mL hexanes was added and stored in a refrigerator for ~15 h. A second crop of acid M.4 was retrieved similarly (grey crystals, 0.133 g), for a combined yield of 59%. Rt = 1.48 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 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). 13C-NMR (100.6 MHz, DMSO-d_6, δ = 39.21 ppm) 172.96, 172.60, 154.45, 153.68, 78.74, 59.88, 59.58, 36.91, 31.97, 31.17, 27.77, 27.52, 14.86, 14.53, 13.69. LC/MS (M+Na) = 250.22. Anal. Calcd. For $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found (for first crop): C, 58.24; H, 7.84; N, 6.07. Optical rotation (10 mg/mL in CHCl3): [α] D = -216 and -212 for the first and second crop, respectively.

Synthetic route 3.



Reference: (Bromination) *JACS* (1952) *74*, 6263.

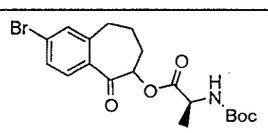
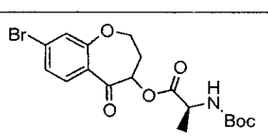
Reference: (Displacement/Cyclization) *J.Med.Chem.* (2001) *44*, 2990.

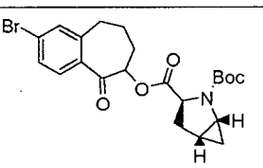


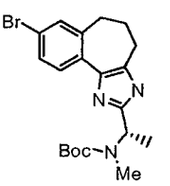
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Example 3, 2-Bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1.5 g, 5.9 mmol) was dissolved Et_2O (25 mL), cooled to 0°C and bromine (0.35 mL, 6.6 mmol) was added dropwise. The solution was stirred at 24°C until TLC indicated reaction complete (2-18 h; scale dependent). The solvent was removed by rotory evaporation and the crude product applied to a 25 (M) Biotage® silica gel column. Gradient elution from 50-100% B (A = Hexanes; B = 10% EtOAc/hex) over 500 mL and gave 2,6-dibromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 700 mg, and 1.5 g of a second fraction containing dibromide (1:1). RT = 2.2 minutes (condition 1).

The 2,6-dibromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (700 mg, 2.22 mmol), and N-methyl-L-alanine (493 mg, 2.4 mmol) were dissolved in acetonitrile (8 mL) and 1.1 mL of Hunig's base was added dropwise, and the reaction was stirred 18 hours at 55°C. The solvent was removed by rotory evaporation, and the residue taken up in EtOAc and washed with 0.1N HCl soln, sat'd $NaHCO_3$ soln, and brine and concentration gave Example 9, (2S)-2-bromo-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl 2-(tert-butoxycarbonyl(methyl)amino)propan-oate 960 mg (98%) which was carried forward without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.4, 1.8 Hz, 1H), 7.40 (dd, J = 8.4, 1.8 Hz, 1H), 7.38 (s, 1H), 5.51-5.45/5.36-5.31 (m, 1H), 4.96-4.79/4.72-4.53 (m, 1H), 3.8 (br s., 3H), 2.94 (t, J = 4.8 Hz, 2H), 2.82 (t, J = 5.1 Hz, 2H), 2.10-1.95 (m, 2H), 1.43 (s, 9H). RT = 2.3 minutes (condition 1). LRMS: Anal. Calcd. for $C_{20}H_{26}BrNO_5$: 440.11; found: 440.10 (M+H).

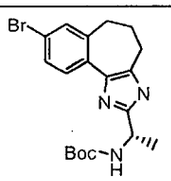
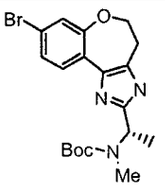
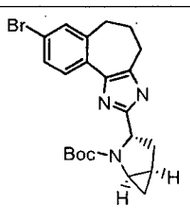
Example 9a (Derived from Example 3)		RT = 2.2 minutes (condition 1); LCMS: Anal. Calcd. For $C_{19}H_{24}BrNO_5$: 425; found: 425 (M+H).
Example 9a.1 (Derived from Example 3b)		RT = 2.05 minutes (condition 2); LCMS: Anal. Calcd. for $C_{19}H_{24}BrNO_6$: 442.30;

		found: 344.2 (M-100), (M+2H).
Example 9a.2 (Derived from Example 3)		RT = 2.18 minutes (condition 1); LCMS: Anal. Calcd. For $C_{22}H_{27}BrNO_5$: 464.10; found: 463.99 (M+H).

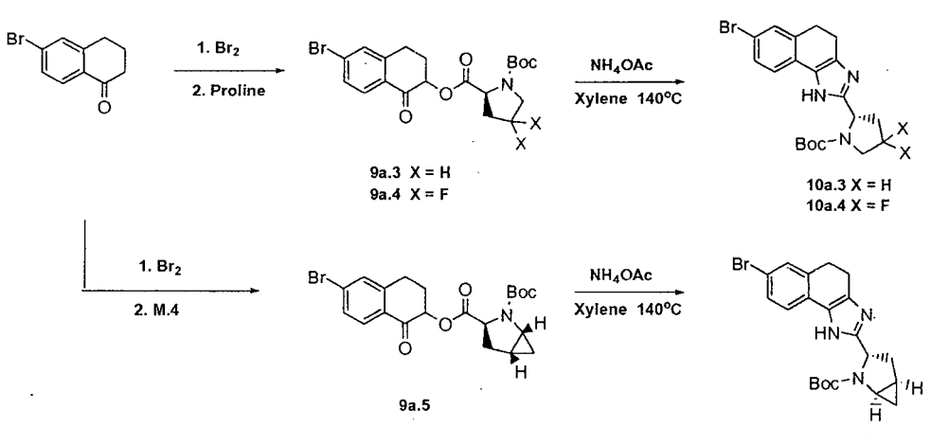


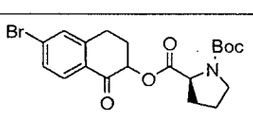
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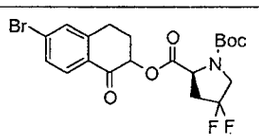
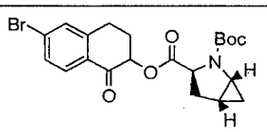
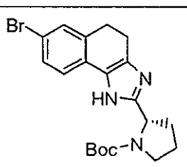
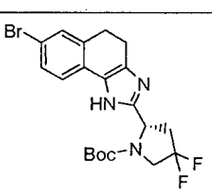
Example 9, (2S)-2-bromo-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl 2-(tert-butoxycarbonyl(methyl)amino)propanoate (960 mg, 2.2 mmol) was taken up in xylene (20 mL) and placed in a 100 mL screw cap pressure vessel. Ammonium acetate (1.7 g, 10 equiv) was added and the mixture was heated at 120°C (oil bath temperature) for 4 hours. The cooled mixture was diluted with ethyl acetate (150 mL) and sat'd $NaHCO_3$ soln and the organic phase concentrated. The crude product was applied (CH_2Cl_2) to a 25 (M) Biotage® silica gel cartridge. Segment 1. Hold 15% B for 300 mL; Segment 2. Gradient elution from 10 - 100% B over 600 mL (A = hexanes; B = EtOAc) to give Example 10, 150 mg (16%) NOTE: Compound loss occurred during chromatography (yield should be higher). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-.42 (m, 2H), 7.35 (s, 1H), 5.25 (q, J = 7.0 Hz, 1H), 3.02 (t, J = 6.4 Hz, 2H), 2.96 (s, 3H), 2.83-2.81 (m, 2H), 2.0-1.98 (m, 2H), 1.74 (d, J = 7.0 Hz, 3H), 1.47 (s, 9H). RT = 1.8 minutes (condition 1). LRMS: Anal. Calcd. for $C_{20}H_{26}BrN_3O_2$: 420.13; found: 420.10 (M+H).

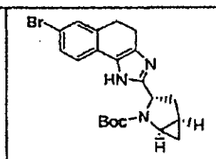
Example 10a (Derived from Example 9a)		RT = 1.9 minutes (condition 1); LRMS: Anal. Calcd. For $C_{19}H_{24}BrN_3O_2$: 406.11; found: 406.23 (M+H).
Example 10a.1 (Derived from Example 9a.1)		RT=1.59 minutes (condition 1); LCMS: Anal. Calcd. for $C_{19}H_{24}BrN_3O_3$: 422.33; found: 424.2 (M+2H).
Example 10a.2 (Derived from Example 9a.2)		RT = 1.74 minutes (condition 1); LRMS: Anal. Calcd. For $C_{22}H_{27}BrN_3O_2$: 443.11; found: 443.07 (M+H).

Synthetic route 4.

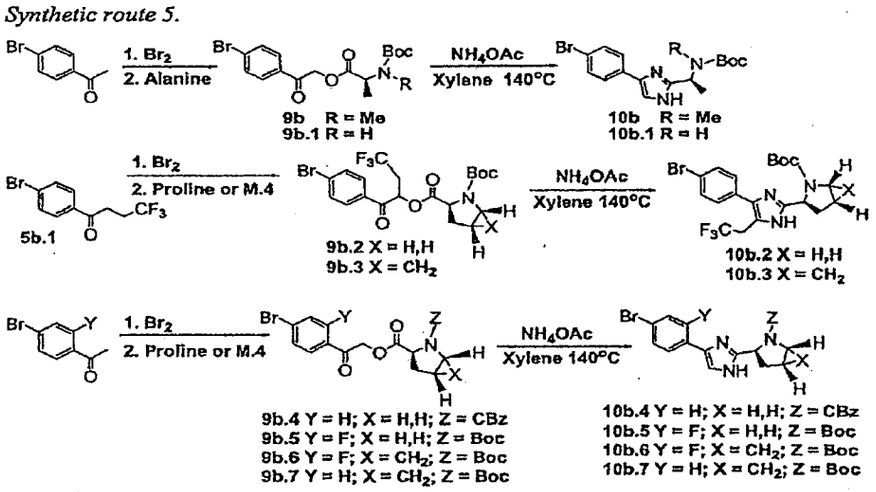


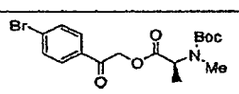
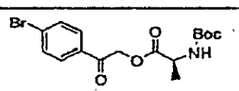
Example 9a.3 (Derived 6-bromo tetral-1-one purchased from J & W PharmLab, LLC.		RT = 3.1 minutes (condition 2); LCMS: Anal. Calcd. For $C_{20}H_{24}BrNO_5$: 438;

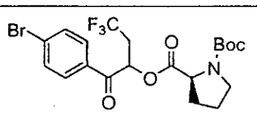
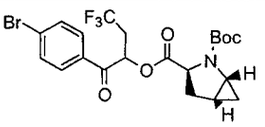
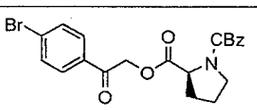
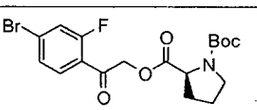
Example 9a.3 was prepared as described for Example 9.)		found: 438 (M+H).
Example 9a.4 (Derived 6-bromo tetral-1-one purchased from *J* & W PharmLab, LLC)		RT = 3.0 minutes (condition 2); LCMS: Anal. Calcd. For $C_{20}H_{22}BrF_2NO_5$: 474; found: 474 (M+H).
Example 9a.5 (Derived 6-bromo tetral-1-one purchased from J & W PharmLab, LLC)		RT = 2.95 minutes (condition 2); LCMS: Anal. Calcd. For $C_{21}H_{25}BrNO_5$: 472.07, 474.07; found: 472.02, 474.02 (M+Na).
Example 10a.3 (Derived from Example 9a.3 and prepared as described for Example 10.)		RT = 2.37 minutes (condition 2); LRMS: Anal. Calcd. for $C_{20}H_{25}BrN_3O_2$: 418.11 and 420.10; found: 418.21 and 420.17 (M+H).
Example 10a.4 (Derived from Example 9a.4)		RT = 2.3 minutes (condition 2); HRMS: Anal. Calcd. for $C_{20}H_{22}BrF_2N_3O_2$ 454.09573; found: 454.09362 (M+H).

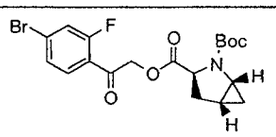
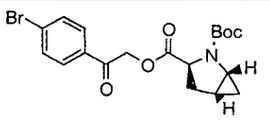
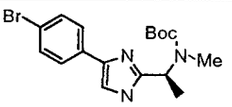
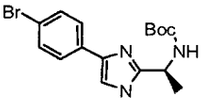
Example 10a.5 (Derived from Example 9a.5)		RT = 2.25 minutes (condition 2); LCMS: Anal. Calcd. For $C_{21}H_{25}BrN_3O_2$: 430.12, 432.12; found: 430.02, 432.02 (M+H).

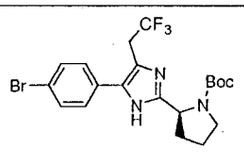
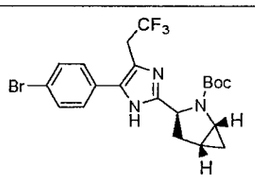
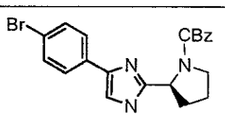
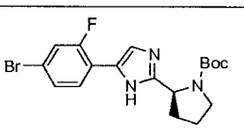
Synthetic route 5.

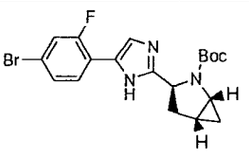
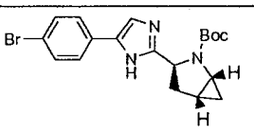


Example 9b (Prepared described in Example 9.)		RT = 2.2 minutes (condition 1); LCMS: Anal. Calcd. For $C_{15}H_{18}BrNO_5$: 371; found: 371 (M+H).
Example 9b.1		RT = 2.7 minutes (condition 1); LCMS: Anal. Calcd. For

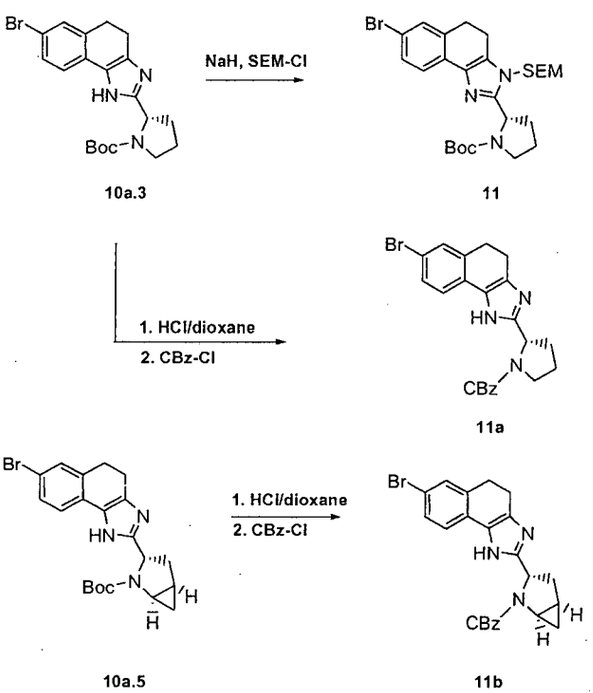
		$C_{16}H_{20}BrNO_5$: 385; found: 385 (M+H).
Example 9b.2 (Derived from Example Example 5b.1)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. For $C_{20}H_{24}BrF_3NO_5$ 494.08; found: 494.03 (M+H).
Example 9b.3 (Derived from Example Example 5b.1 and M.4)		RT = 2.1 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{24}BrF_3NO_5$: 526.07; found: 525.91 (M+H).
Example 9b.4		RT = 2.2 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{20}BrNO_5$: 445; found: 445 (M+H).
Example 9b.5		RT = 2.94 minutes (condition 2); LCMS: Anal. Calcd. For $C_{18}H_{22}BrFNO_5$: 452.05, 454.05, 466.05; found: 452.06, 454.06

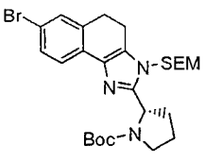
		(M+Na).
Example 9b.6 (Derived from Example M.4)		RT = 2.78 minutes (condition 2); LCMS: Anal. Calcd. For $C_{19}H_{21}BrFNO_5$: 464.05, 466.05; found: 463.92, 465.92 (M+Na).
Example 9b.7 (Derived from Example M.4)		RT = 2.05 minutes (condition 1); LRMS: Anal. Calcd. For $C_{19}H_{23}BrNO_5Na$: 446.07; found: 446.08 (M+Na), (M+2).
Example 10b (Derived from Example 9b as described for Example 10)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. For $C_{17}H_{22}BrN_3O2$: 380.10; found: 379.98 (M+H).
Example 10b.1 (Derived from Example 9b.1)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. For $C_{16}H_{20}BrN_3O_2$: 365; found: 365

		(M+H).
Example 10b.2 (Derived from Example 9b.2)		RT = 1.66 minutes (condition 1); LCMS: Anal. Calcd. for $C_{20}H_{24}BrF_3N_3O_2$ 474.10; found: 473.99 (M+H).
Example 10b.3 (Derived from Example 9b.3)		RT = 1.7 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{24}BrF_3N_3O_2$: 486.10; found: 486.10 (M+H).
Example 10b.4 (Derived from Example 9b.4)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. For $C_{21}H_{20}BrN_3O_2$: 426.08; found: 426.09 (M+H).
Example 10b.5 (Derived from Example 9b.5)		RT = 2.27 minutes (condition 2); LCMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09; found: 410.08 (M+H).

Example 10b.6 (Derived from Example 9b.6)		RT = 2.15 minutes (condition 2); LCMS: Anal. Calcd. For $C_{19}H_{22}BrFN_3O_2$: 422.09; found: 421.96 (M+H).
Example 10b.7 (Derived from Example 9b.7)		RT = 1.58 minutes (condition 1); LCMS: Anal. Calcd. For $C_{19}H_{23}BrN_3O_2$: 404.10; found: 404.09 (M+H).

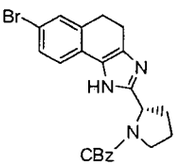
Synthetic route 6.





11

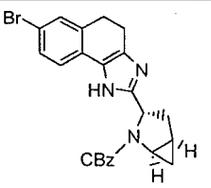
Unwashed 60% sodium hydride (54 mg, 1.35 mmol) was added in one portion to a stirred solution of Example 10a.3 (565 mg, 1.35 mmol) in dry DMF (10 mL) under nitrogen. The mixture was stirred 5 min before addition of SEM-Cl (0.24 mL, 1.35 mmol), stirred for 3 h, quenched with sat'd ammonium chloride (1 mL), diluted with EtOAc (50 mL), and the organic phase was washed with sat'd $NaHCO_3$ solution and brine. The aqueous phase was extracted twice more with EtOAc and combined with the initial organic extract prior to drying. Concentration gave a residue applied which was applied (CH_2Cl_2) to a 40 (S) Biotage® silica gel cartridge. Segment 1. Hold 15% B for 75 mL; Segment 2. Gradient elution from 15% to 50% B over 750 mL; Segment 3: 50-100%B over 750 mL (A = hex; B = EtOAc) B to give regioisomeric products Example 11, 497 mg (67 %). RT = 3.0 minutes (condition 2). ^1H NMR (500 MHz, DMSO-d_6) δ 7.42-7.35 (m, 3H), 5.65/5.39 (d, J = 11.6 Hz, 1H), 5.29-5.27 (m, 1H), 5.00/4.93 (s, 1H), 3.54-3.51 (m, 3H), 3.43-3.41 (m, 1H), 3.02-2.99 (m, 2H), 2.89-2.81 (m, 1H), 2.29-2.08 (m, 2H), 1.95 -1.84 (m, 2H), 1.37/1.13 (s, 9H), 0.89-0.86 (m, 2H), -0.02 (s, 9H). LRMS: Anal. Calcd. for $C_{26}H_{39}BrN_3O_3Si$: 548.19; found: 548.23 (M+H).



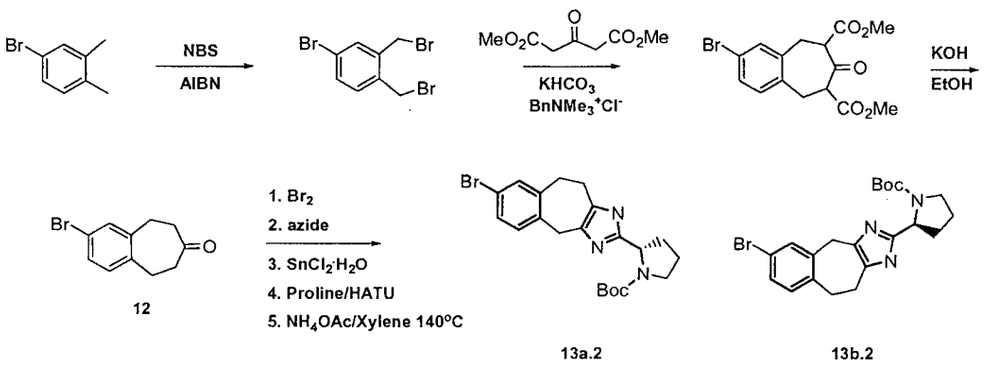
11a

Cold 4N HCl in dioxane (0.871 mL, 3.49 mmol) was added to a solution of 10a.3 (1R,3S,5R)-tert-butyl 3-(7-bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.5 g, 3.49 mmol) in MeOH (20 mL) and the reaction was stirred for 2h at room temperature. Concentration yielded a tan solid which was taken up in dioxane (20 mL) / water (20 mL) and cooled to 0°C. Na_2CO_3 (0.369 g, 3.49 mmol) and CBz-Cl (0.498 mL, 3.49 mmol) were added and the reaction mixture was stirred as it warmed to room temperature over 5h before

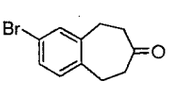
being partitioned between EtOAc and sat'd $NaHCO_3$ soln. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was charged (CH_2Cl_2) to a 110 g Thompson® silica gel cartridge and eluted 20% - 100% B over 1.5 L (A/B = hexanes/EtOAc). The combined yield of 11a (1R,3S,5R)-benzyl 3-(7-bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0] hexane-2-carboxylate from three fractions of various purities was 1.4 g (75%). LCMS Calcd for $C_{24}H_{23}BrN_3O_2$ $(M+H)^+$ 464.10 and 466.10; found: 463.95 and 465.98.

Example 11b (Derived from Example 10a.5)		RT = 2.01 minutes (condition 2); LCMS: Anal. Calcd. For $C_{24}H_{23}BrN_3O_2$: 464.10, 466.10; found: 464.11, 466.11 $(M+H)^+$.

Synthetic route 7.



Reference: *J.Chem.Soc. Perkin Trans 2* (1993) p 1305.



12

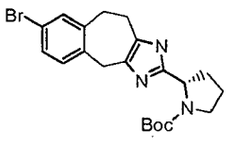
AIBN (98 mg, 0.59 mmol) was added to 4-bromo-1,2-dimethylbenzene (11 g, 59.4 mmol) and freshly recrystallized N-bromosuccinimide (21.1 g, 119 mmol) in CCl_4 (50 ml). The reaction mixture was heated at reflux for 2 hours under nitrogen.

After being cooled to room temperature, the solution was filtered and concentrated by rotory evaporation to give 21 g of a mixture containing approximately (75%) 4-bromo-1,2-bis(bromomethyl)benzene along with 3-bromo-1,2-bis(bromomethyl)benzene. [NOTE: The starting material was contaminated with 25% 3-bromo-1,2-dimethylbenzene]. RT = 2.2/2.3 min (condition 1).

The crude mixture of 4- and 3-bromo-1,2-bis(bromomethyl)benzene (21 g) was taken up in CH_2Cl_2 (313 ml) and dimethyl 3-oxopentanedioate (12.8 g, 73.5 mmol) was added and the solution was diluted with a 20% solution of $KHCO_3$ (64 g, 0.64 mol) in water (250 ml). Phase transfer catalyst benzyltrimethylammonium chloride (1.7 g, 9.19 mmol) was added and the reaction mixture was stirred 18h under nitrogen at 50 °C. After separation of the organic phase, the aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine. Concentration gave 23 g of a complex mixture (both regio isomers and ester diastereomers) containing dimethyl 2-bromo-7-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6,8-dicarboxylate which was carried forward without purification. RT = 1.87 min (condition 1); LCMS: Anal. Calcd. for $C_{15}H_{15}BrO_5$: 377.01; found 377.05 [M+Na].

The 23 g mixture of crude dimethyl 2-bromo-7-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6,8-dicarboxylate (contained ~ 8g, 22.5 mmol) was placed in a 1 L round-bottomed flask fitted with a reflux condenser and dissolved in ethanol (250 ml). A solution of KOH (8.8 g, 0.23 mol) dissolved in water (250 ml) was added and the initially tan suspension turned black upon heating at reflux for 16 hours. The reaction mixture was poured onto EtOAc (1 vol) and the organic phase separated. Brine (1/4 vol) was added to the aqueous layer which was extracted with EtOAc, and the combined organic layers were washed with brine. After being concentrated by rotory evaporation, the residue was charged (CH_2Cl_2) to a 40 (M) Biotage® silica gel column (apply vacuum from beneath column to aid adsorption) and gradient eluted 10-100% B (A = Hexanes; B = EtOAc) to give a 4:1 mixture of bromides which favored Example 12, 2-bromo-8,9-dihydro-5H-benzo[7]annulen-7(6H)-one and contained 1-bromo-8,9-dihydro-5H-benzo[7]annulen-7(6H)-one, 8.3 g (61%). The mixture was carried forward without further purification, but a pure sample of Example 12 was obtained upon crystallization by allowing the mixture to stand for 3 weeks at -5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 2.1 Hz, 1H), 7.33 (dd, J =

7.9, 2.1 Hz, 1H), 7.09 (d, J = 7.9 HZ, 1H), 2.87-2.84 (m, 4H), 2.61-2.57 (m, 4H). RT = 1.96 minutes (condition 1). LCMS: Anal. Calcd. for $C_{11}H_{11}BrO$: 239.0; found: 239.04 (M+H).



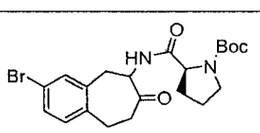
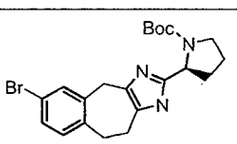
13a.2

Bromine (1.4 mL, 26.8 mmol) was added to a solution of the 4:1 mixture, respectively, of 2- and 1-bromo-8,9-dihydro-5H-benzo[7]annulen-7(6H)-one (6.4 g, 26.8 mmol) in diethyl ether (250 mL). The reaction was stirred for 4 h, concentrated, and the crude α-bromo ketones were taken up in acetonitrile (200 mL). Sodium azide (1.7 g, 26.8 mmol) was added and the reaction was stirred 16 h before being concentrated. The residue was partitioned between EtOAc and sat'd $NaHCO_3$ soln, and the organic layer was washed with water, brine, and concentrated. RT = 2.0 minutes (broad peak, condition 1).

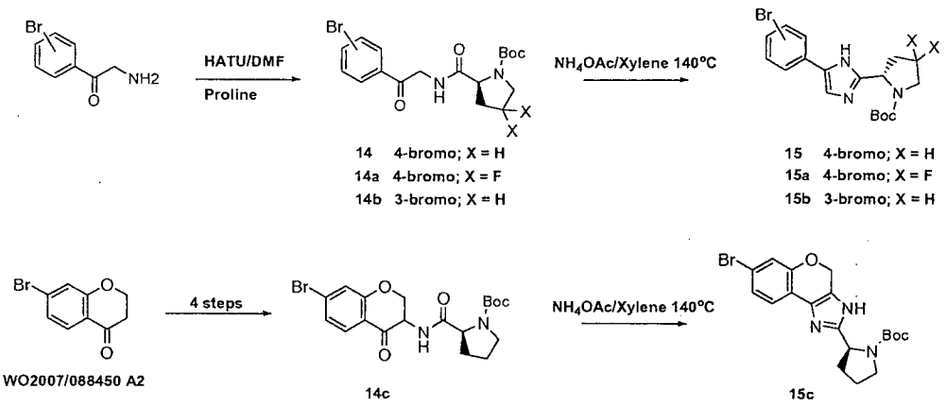
The crude α-keto azides were dissolved in CH_3OH (350 mL) and tin (II) chloride dihydrate (13.2 g, 69.6 mmol) added and the reaction mixture was stirred for 3.5 hours at 65 °C, concentrated by rotory evaporation, and dried under high vacuum for 18 hours.

The crude α-amino ketones were taken up in DMF (300 mL), Hunig's base (24.41 g, 189 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (4.07 g, 18.89 mmol), and HATU (7.18 g, 18.89 mmol) was added in one portion with vigorous stirring. After 8 hours the reaction was concentrated to 1/3 volume *in vacuo*, and partitioned between EtOAc (1 L) and 0.1N HCl (150 mL). The tin salts were removed by filtration through diatomaceous earth (Celite®), and the organic layer was washed with brine and concentrated. The crude product was charged (CH_2Cl_2) to a 40M Biotage® silica gel cartridge (divided into two runs). Gradient elution from 15% to 100% B over 1.5 L (A = Hexanes; B = Ethyl Acetate) to give Examples 13a.1 and 13b.1 (3.8 g, 35.7% combined yield) each as a mixture of diastereomers. Example 13a.1: RT = 1.58/1.51 min (condition 5). LCMS: Anal. Calcd. for $C_{21}H_{27}BrN_2O_4$: 451.12; found: 450.87 (M+H).

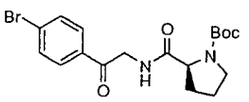
Ammonium acetate (4.4 g, 73.1 mmol) was added to a solution of the amides 13a.1 and 13b.1 (3.3 g, 7.31 mmol) in xylene (75 mL) and stirred in a pressure vessel heated at 140 °C for 4 hours. After being cooled, the reaction mixture was diluted with EtOAc (500 mL), washed with sat'd $NaHCO_3$, brine, and the organic phase was concentrated. The crude product was charged (CH_2Cl_2) to a 40S Biotage® silica gel cartridge. Gradient elution from 15% to 100% B over 750 mL (A = CH_2Cl_2; B = EtOAc) gave 2.49 g of a mixture that was subjected to a second chromatography; 40S Biotage® silica gel cartridge, elution 5% - 80% B over 1L (A = 1:1 Hex/CH_2Cl_2; B = 10% CH_3OH/EtOAc) and provided a mixture of Examples 13a.2 and 13b.2, 1.1 g (34.8%). A sample of the product was applied to semi-prep normal phase HPLC (Chiralcel OD Column, 20x250mm, 10um; 98:2 Heptane/EtOH @ 10 mL/min; UV 220/254 nm) and collect Example 13a.2 eluting at 35-36 min. ^1H NMR (500 MHz, CD_3OD) δ 7.44 (s, 1H), 7.28 (dd, J = 7.9, 2.1 Hz, 1H), 7.09 (d, J = 8.2 HZ, 1H), 4.73-4.69 (m, 1H), 3.91 (s, 2H), 3.64-3.61 (m, 1H), 3.48-3.44 (m, 1H), 3.09 (t, J = 4.6 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H), 2.31-2.11 (m, 1H), 2.01-1.88 (m, 3H), 1.46/1.48 (s, 9H). RT = 1.7 minutes (condition 1). HRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_2$: 432.1281; found: 432.1268 (M+H).

Example 13b.1		RT = 1.59 minutes (condition 5); LCMS: Anal. Calcd. for $C_{21}H_{27}BrN_2O_4$: 451.12; found: 450.98 (M+H).
Example 13b.2		RT = 1.7 minutes (condition 1). LCMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_2$: 432; found: 432 (M+H).

Synthetic route 8.

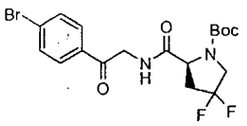
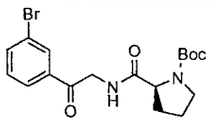


Example 14

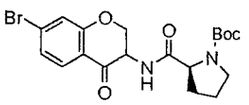


14

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 DMF (105 mL) and stirred at ambient condition for 55 minutes. DMF 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 Example 14, (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). RT = 1.70 min (condition 1); LCMS: Anal. Calcd. for $C_{18}H_{23}BrN_2NaO_4$: 433.07; found 433.09 $[M+Na]^+$.

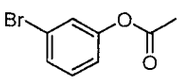
Example 14a		RT = 1.59 minutes (condition 4); LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_2O_4$: 446.06; found: 445.43 (M-H)-.
Example 14b		LCMS: Anal. Calcd. for $C_{18}H_{23}BrN_2O_4$: (M+Na)+ = 433.08; found: 433.12

Example 14c



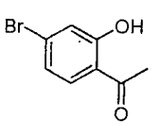
14c

Example 14c; step 1:



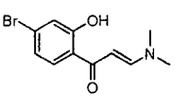
Acetyl chloride (10.2 mL, 144 mmol) was added in a dropwise manner over 1 h to a cold (ice bath) solution of 3-bromophenol (25 g,144 mmol) and pyridine (10.8 mL, 144 mmol) in dichloromethane (100 mL), and the reaction was stirred 18 hr at room temperature. Water (150 mL) was added and the organic layer was extracted with dichloromethane. The combined organic layers were washed with 2.5N $NaHSO_4$, 3N NaOH, water, brine, and dried over Na_2SO_4, and filtered. Concentration gave the 3-bromophenyl acetate as a pink liquid (28 g, 96%). GC-MS data: 214 (M^+); ^1H NMR (DMSO-d_6): 7.37-7.39 (d, 1H), 7.26-7.30 (m, 2H), 7.04-7.07(t, 1H), 2.30 (s, 3H).

Example 14c; step 2:



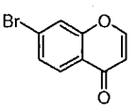
3-Bromophenyl acetate (36 g, 167 mmol) and anhydrous $AlCl_3$ (33.5g, 251 mmol) were heated at 140-150 °C for 2 hrs. After cooling, 5% HCl soln (100ml) was added and the mixture was heated (steam bath) until solid materials dissolved. A brown oil separated and was extracted into dichloromethane. To the extract was added 5N NaOH (300 mL) and enough water to dissolve the resulting precipitate. The aqueous layer was separated, acidified (pH 2.0), and extracted with ethyl acetate. The extract was dried over Na_2SO_4, filtered, and concentrated to give 1-(4-bromo-2-hydroxyphenyl)ethanone the crystals (35.8 g, 99%). GC-MS (214 M^+); ^1H NMR (DMSO-d_6) 11.99 (s, 1H, OH), 7.77-7.80 (d, 1H), 7.20 (s, 1H), 7.13-7.15 (dd, 1H), 2.6 (s, 3H).

Example 14c; step 3:



To 1-(4-bromo-2-hydroxyphenyl)ethanone (35.8g, 167 mmol) in dry benzene (800 mL) was added N,N-dimethylformamide dimethylacetal (44 mL, 333 mmol) and the solution was heated at reflux for 4 hrs and concentrated to dryness. The resulting residue was dissolved in dichloromethane (300 mL) and filtered over SiO_2. The organic layer was concentrated to afford (E)-1-(4-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one as a bright yellow solid (31.9 g, 71%). LCMS 270 (M+H); ^1H NMR (DMSO-d6) 14.96 (s, 1H), 7.86-7.94 (m, 2H), 6.96-7.02 (dd, 2H), 5.92-5.96 (d, 1H), 3.32 (s, 3H), 3.20 (s, 3H).

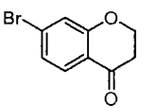
Example 14c; step 4:



Conc. HCl (100 mL) was added to a solution of (E)-1-(4-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one (31.9 g, 118 mmol) in dichloromethane (900 mL) and the reaction mixture was heated at reflux 40 min with vigorous stirring. After being cooled to room temperature, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 3M potassium carbonate soln, water, and dried over Na_2SO_4. Filtration and concentration gave 7-bromo-4H-chromen-4-one as a pale

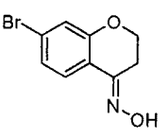
yellow solid. LCMS 224.9 (M+H); ^{1}H NMR (DMSO-d6) 8.29-8.31 (d, 1H), 7.92-7.99 (m, 2H), 7.64-7.66 (dd, 1H), 6.37-6.39 (d, 1H).

Example 14c; step 5:



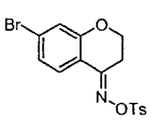
A solution of 7-bromo-4H-chromen-4-one (26 g, 116 mmol) in dry THF (500 mL) under nitrogen for 1 hr, cooled to -80 °C, and 173 mL of diisobutylaluminium hydride (2M in Toluene) was added over 30 minutes. The reaction was stirred at the same temperature for 30 min, quenched with a SiO_2 (52g) / water (52mL) suspension, and allowed to warm to 0 °C. The solution was filtered, the SiO_2 washed with EtOAc, and the combined filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$ (400 mL), washed with 1N NaOH (300 mL), dried over Na_2SO_4 and concentrated. Purification by chromatography on SiO_2 (60-120 mesh) EtOAc/Pet ether (gradient elution 0-15%) afforded 7-bromochroman-4-one 18.1 g (69%) a pale yellow solid. LCMS 229.0 (M+2H); ^{1}H NMR (DMSO-d6) 7.64-7.67 (d, 1H), 7.32 (s, 1H), 7.22-7.25(d, 1H), 4.53-4.57 (t, 2H), 2.76-2.80 (t, 2H).

Example 14c; step 6:



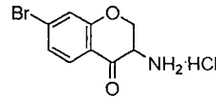
NaOAc (3.78 g, 46.2 mmol) in H_2O (30 mL) was added to a soln of 7-bromo 4-chromanone (3.5 g, 15.4 mmol) and hydroxyl-amine hydrochloride (1.75 g, 23.1 mmol) in EtOH (70 ml). The reaction was heated at reflux for 2 h, cooled to room temperature, and concentrated. The residue was diluted with H_2O and a precipitate was filtered to give 7-bromochroman-4-one oxime obtained as the needle like crystals 3.5g (98%). LCMS 244 (M+2H) RT = 1.7 min (Condition 2); ^{1}H NMR (DMSO-d_6) 11.37 (s, OH, 1H), 7.76-7.70 (d, 1H), 7.09-7.13 (d, 2H), 4.16- 4.20 (t, 2H), 2.79-2.83 (t, 2H).

Example 14c; step 7:

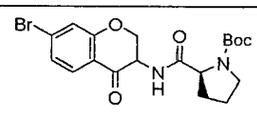


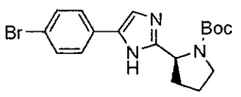
p-Toluenesulfonic anhydride (5 g, 16 mmol) was added to a solution of 7-bromochroman-4-one oxime (3.5g, 14.46 mmol) and triethylamine (2.4ml, 17.35 mmol) in dichloromethane (125 ml). The mixture was stirred for 3 h at room temperature and washed with water, brine, and dried (Na_2SO_4). Filtration and concentration under reduced pressure to afforded 7-bromochroman-4-one-O-p-toluenesulfoxime 5.5 g (96 %) as an off-white solid which was used without further purification. LCMS 398 (M+2H) RT = 1.92 min (Condition 1). ^{1}H NMR (DMSO-d6) 7.89-7.91 (d, 2H), 7.56-7.58 (d, 1H), 7.48-7.50 (d, 2H), 7.22 (s, 1H), 7.16-7.18 (d, 1H), 4.20.4.23 (t, 2H), 2.97-3.00 (t, 2H), 2.40 (s, 1H).

Example 14c; step 8:



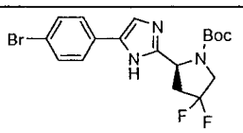
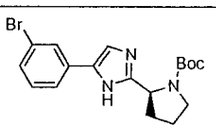
A solution of potassium ethoxide (1.27 g, 15.11 mmol) in ethanol (35 ml) was added to a solution of 7-bromochroman-4-one-O-p-toluenesulfoxime (5.7 g, 14.3 mmol) in toluene (60 ml) and the mixture was stirred for 15 h at room temperature. A precipitate (potassium tosylate) was removed by filtration and washed with diethyl ether. To the combined filtrates was added 3N HCl (20 ml) in methanol and the solution was stirred 2 h at room temperature to form the HCl salt. After removal of the solvent, the residue was triturated with diethyl ether. The resulting solid was filtered, washed with ether, and dried to afford 7-bromo-3-amino-chroman-4-one hydrochloride 2.8 g, (80 %) as off-white power. LCMS 244 (M+2H) RT = 3.77 (Condition 2); ^{1}H NMR (DMSO-d_6) 8.79 (bs, 2H), 7.71-7.74 (d, 1H), 7.45 (s, 1H), 7.34-7.37 (d, 1H), 4.67-4.80 (m, 2H), 4.43-4.51 (t, 1H).

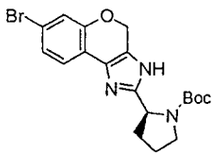
Example 14c (Prepared as described in Example 14, and derived from product of step 8)		RT = 1.76 minutes (condition 2); LCMS: Anal. Calcd. for $C_{19}H_{24}BrN_2O_5$: 439.09; found: 439 (M+H)



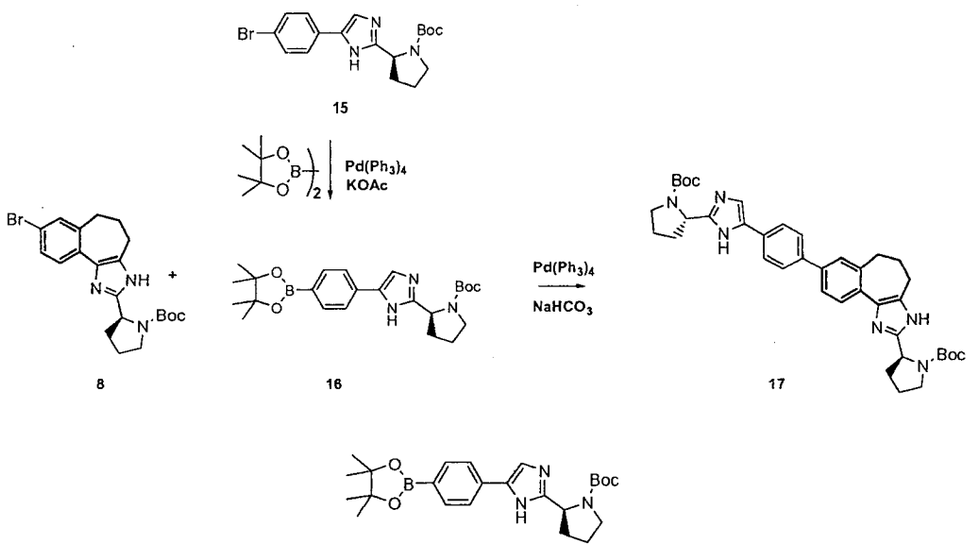
15

A mixture Example 14, (S)-tert-butyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-pyrrolidine-1-carboxylate (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140 °C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with an additional ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of Example 15, (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). RT = 1.71 min (condition 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for $C_{18}H_{23}BrN_3O_2$: 392.0974; found 392.0959 [M+H].

Example 15a (Derived from Example 14a)		RT = 1.59 minutes (condition 4); LRMS: Anal. Calcd. for $C_{18}H_{20}BrF_2N_3O_2$: 428.27; found: 428.02 (M+H).
Example 15b (Derived from Example 14b)		LRMS Anal. Calcd. for $C_{18}H_{22}BrN_3O_2$: 392.10; found: 391.96 (M+H).

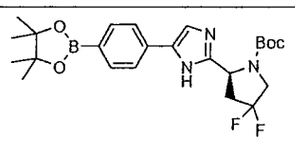
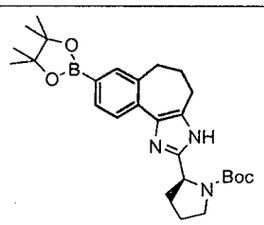
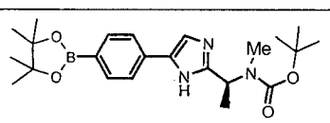
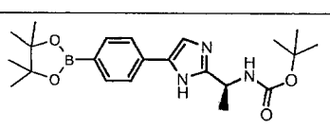
Example 15c (Derived from Example 14c)		RT = 1.6 min (condition 1); LCMS: Anal. Calcd. for $C_{19}H_{22}BrN_3O_3$: 420.33; found 422.2 (M+2H).

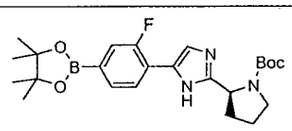
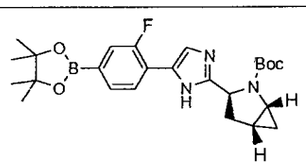
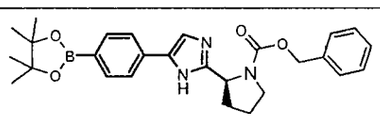
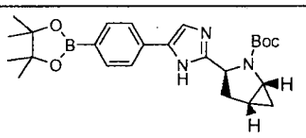
Synthetic route 9.

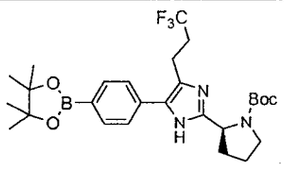
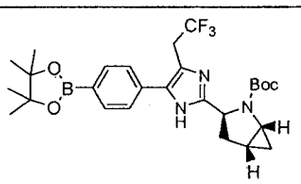
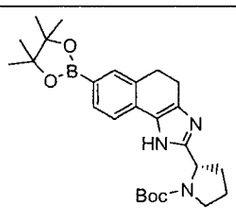
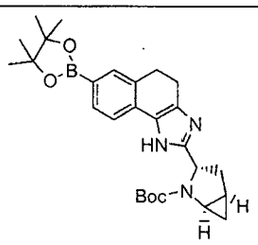


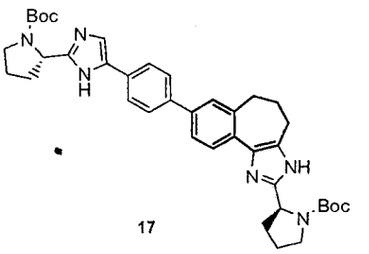
Pd(Ph_3P)$_4$ (469 mg, 0.406 mmol) was added to a screw cap pressure tube containing a mixture of Example 15, (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (4 g, 10.22 mmol), bis(pinacolato)diboron (5.4 g, 21.35 mmol), potassium acetate (2.6 g, 26.21 mmol) and 1,4-dioxane (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 CH_2Cl_2 (150 mL) and an aqueous medium (50 mL water + 10 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/CH_2Cl_2) to provide Example 16, (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 Example 16 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). RT = 1.64 min (condition 1); LC/MS: Anal. Calcd. for [M+H] $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

Example 16a (Derived from Example 15a)		RT = 1.62 minutes (condition 3); LCMS: Anal. Calcd. for $C_{34}H_{32}BF_2N_3O_4$: 475.34; found: 474.78 (M-H).
Example 16b (Derived from Example 8)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{38}BN_3O_4$: 497.3; found: 479 (M+H).
Example 16c (Derived from Example 10b).		RT = 1.83 minutes (condition 1); LCMS: Anal. Calcd. for $C_{23}H_{34}BN_3O_4$ 427; found: 427 (M+H).
Example 16d (Derived from Example 10b.1)		RT = 1.84 minutes (condition 1); LCMS: Anal. Calcd. for

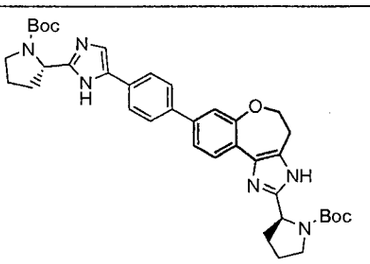
		$C_{22}H_{32}BN_3O_4$ 413; found: 414 (M+H).
Example 16e (Derived from Example 10b.5)		RT = 2.62 minutes (condition 2); LRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.26; found: 458.23 (M+H).
Example 16e.1 (Derived from Example 10b.6)		RT = 2.46 minutes (condition 2); LRMS: Anal. Calcd. for $C_{25}H_{34}BFN_3O_4$ 470.26; found: 470.19 (M+H).
Example 16f (Derived from Example 10b.4)		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{27}H_{32}BN_3O_4$ 473; found: 474 (M+H).
Example 16g (Derived from Example 10b.7)		RT = 1.59 minutes (condition 1); LCMS: Anal. Calcd. for $C_{25}H_{35}BN_3O_4$ 452.27; found: 452.23 (M+H).

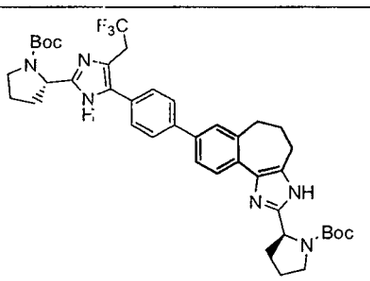
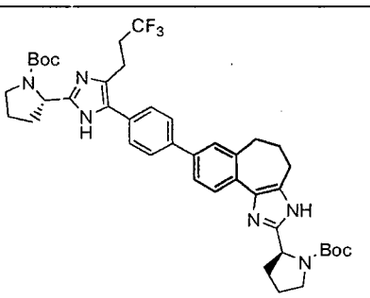
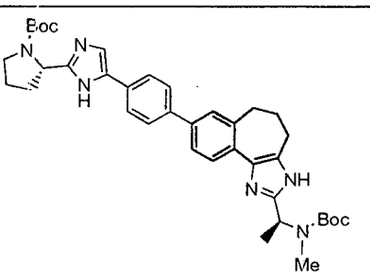
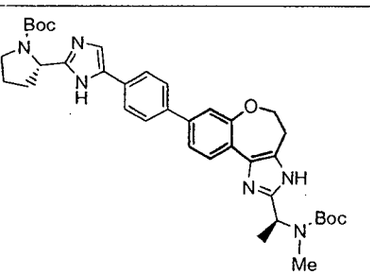
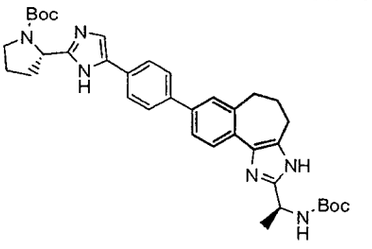
Example 16h (Derived from Example 8c)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{38}BF_3N_3O_4$ 536.29; found: 536.37 (M+H).
Example 16i (Derived from Example 10b.3)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{36}BF_3N_3O_4$ 534.27; found: 534.21 $(M+H)^+$.
Example 16j (Derived from Example 10a.3)		RT = 2.46 minutes (condition 2); LRMS: Anal. Calcd. for $C_{26}H_{37}BN_3O_4$ 466.29; found: 466.27 $M+H)^+$.
Example 16k (Derived from Example 10a.5)		RT = 2.48 minutes (condition 2); LRMS: Anal. Calcd. for $C_{27}H_{37}BN_3O_4$ 478.29; found: 478.27 $(M+H)^+$.

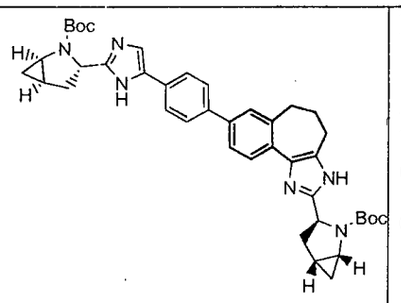
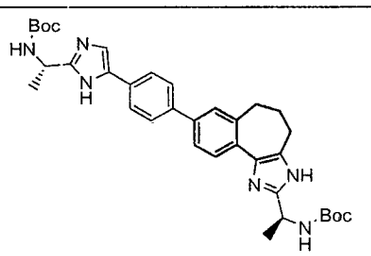
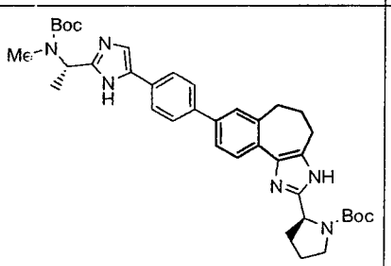
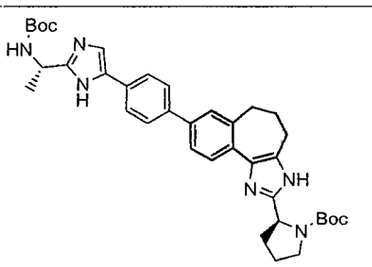
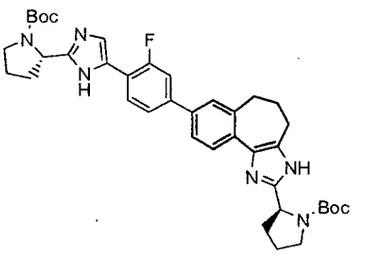


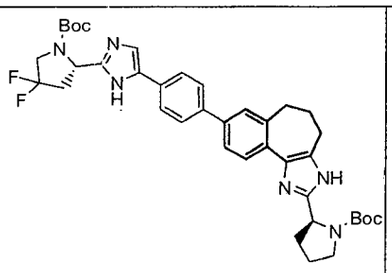
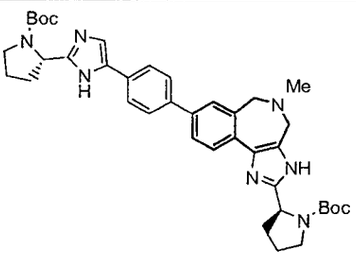
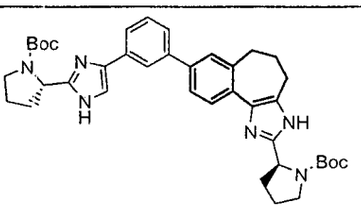
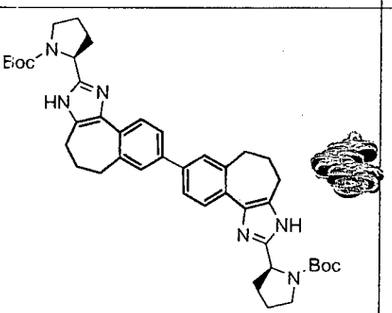
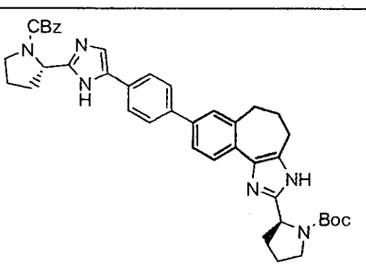
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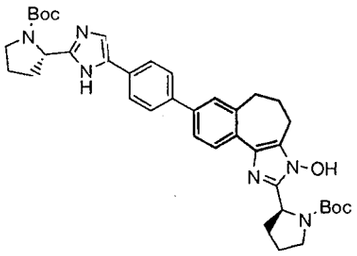
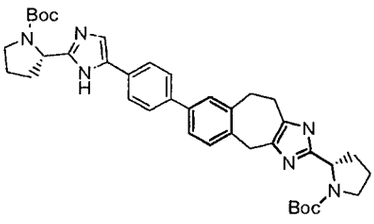
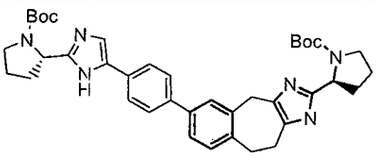
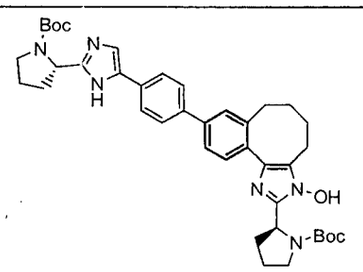
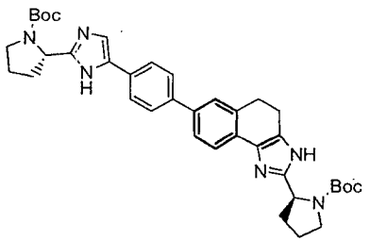
Example 8, (950 mg, 2.19 mmol); Example 16, (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (965 mg, 2.2 mmol), and $NaHCO_3$ (462 mg, 5.5 mmol) were dissolved in 1,2-dimethoxyethane (25 mL) and water (4 mL) was added. The reaction mixture was evacuated and flushed with nitrogen (3x), $Pd(Ph_3P)_4$ (127 mg, 0.11 mmol) was added, and the mixture heated (oil bath at 80°C) in a capped 100 mL pressure vessel for 8 hours. Additional catalyst (35 mg) was added and heating continued for 16 hours. After being cooled, the solution was partitioned in EtOAc/water and the organic layer washed with brine. The crude product was applied (CH_2Cl_2) to a 40 (S) Biotage® silica gel column, and gradient eluted from 20-100% B (A = CH_2Cl_2; B = EtOAc) over 1 L gave Example 17, 680 mg (49%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.05 (br s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.53-7.45 (m, 3H), 4.86-4.70 (m, 2H), 3.57-3.51 (m, 2H), 3.17 - 3.16 (m, 2H), 2.89-2.85 (m, 4H), 2.27-2.18 (m, 2H), 1.99-1.83 (m, 8H), 1.40/1.16 (s, 9H). RT = 1.7 minutes (condition 1). LRMS: Anal. Calcd. for $C_{39}H_{48}N_6O_4$: 665.38; found: 665.39 (M+H). HRMS: Anal. Calcd. for $C_{39}H_{48}N_6O_4$: 665.3815; found: 665.33845 (M+H).

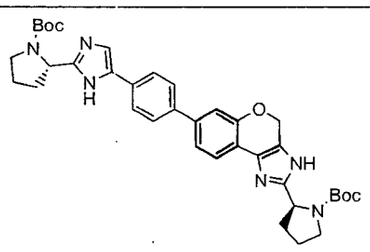
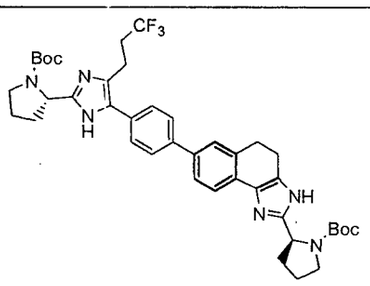
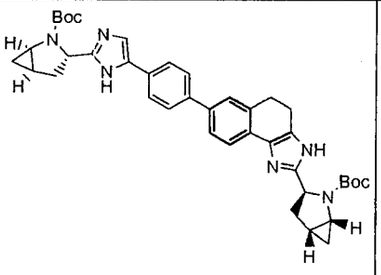
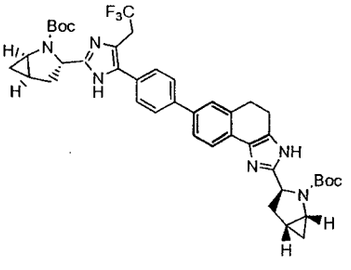
Example 17a (Derived from Example 16 and Example 8b)		RT = 2.38 minutes (Condition 2) LCMS: Anal. Calcd. for $C_{38}H_{46}N_6O_5$: 666.80; found: 665.2 (M-H).

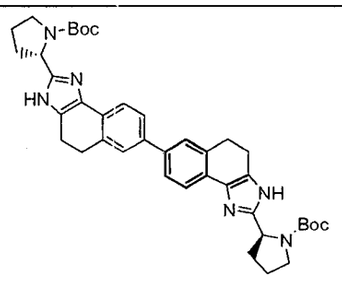
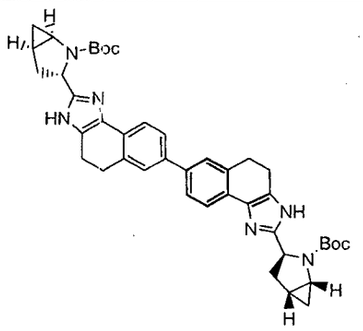
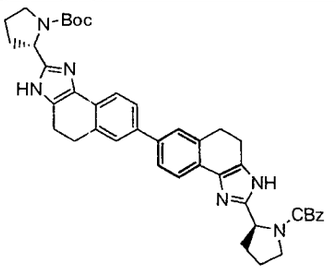
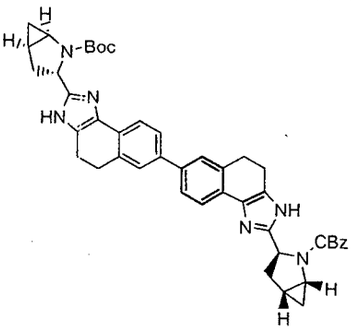
Example 17a.1 (Derived from Example 16b and Example 10b.2)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_6O_4$: 747.38; found: 747.33 (M+H).
Example 17a.2 (Derived from Example 16b and Example 8c)		RT = 1.7 minutes (condition 1); HRMS: Anal. Calcd. for $C_{42}H_{52}F_3N_6O_4$: 761.3997; found: 761.4005 (M+H).
Example 17b (Derived from Example 16 and Example 10)		RT = 1.8 minutes (condition 1); LRMS: Anal. Calcd. for $C_{38}H_{48}N_6O_4$: 675.37; found: 675.35 (M+Na).
Example 17b.1 (Derived from Example 16 and Example 10a.1)		RT = 1.65 minutes (Condition 1) LCMS: Anal. Calcd. for $C_{37}H_{46}N_6O_5$: 654.82; found: 655.4 (M+H).
Example 17c (Derived from Example 16 and Example 10a)		RT = 1.8 minutes (condition 1); LRMS: Anal. Calcd. for $C_{37}H_{46}N_6O_4$: 639.37; found: 639.32 (M+H).

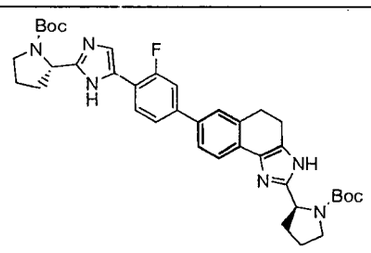
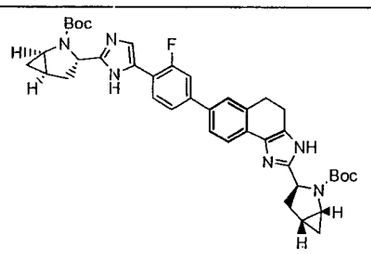
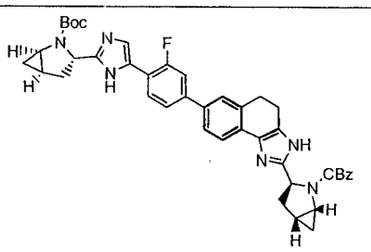
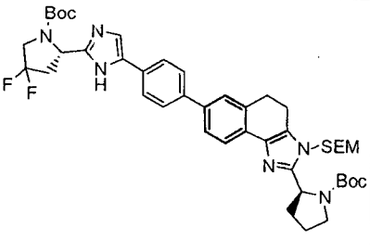
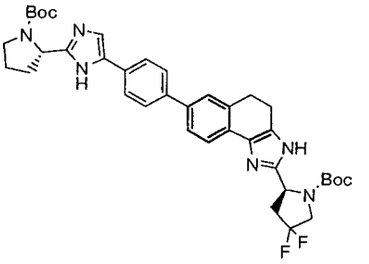
Example 17c.1 (Derived from Example 16g and Example 10a.2)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. for $C_{41}H_{49}N_6O_4$: 689.38; found: 689.43 (M+H).
Example 17d (Derived from Example 16d and Example 10a)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$: 613.34; found: 613.28 (M+H).
Example 17e (Derived from Example 16c and Example 8		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{38}H_{48}N_6O_4$: 653.38; found: 653.50 (M+H).
Example 17f (Derived from Example 16d and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{37}H_{46}N_6O_4$: 639.37; found: 639.50 (M+H).
Example 17g (Derived from Example 16e and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{47}FN_6O_4$: 683.37; found: 683.18 (M+H).

Example 17h (Derived from Example 16a and Example 8)		RT = 2.31 minutes (condition 2); LRMS: Anal. Calcd. for $C_{39}H_{47}F_2N_6O_4$: 701.35; found: 701.69 (M+H).
Example 17i (Derived from Example 16 and Example 8a)		RT = 2.02 minutes (condition 2); HRMS: Anal. Calcd. for $C_{39}H_{50}N_7O_4$: 680.3924; found: 680.3957 (M+H).
Example 17j (Derived from Example 16b and Example 15b)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{48}N_6O_4$: 665.38; found: 665.37 (M+H).
Example 17k (Derived from Example 16b and Example 8)		RT = 1.8 minutes (condition 1); LRMS: Anal. Calcd. for $C_{42}H_{52}N_6O_4$: 705.41; found: 705.40 (M+H).
Example 17m (Derived from Example 16f and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{42}H_{46}N_6O_4$ 699.37; found: 699.47 (M+H).

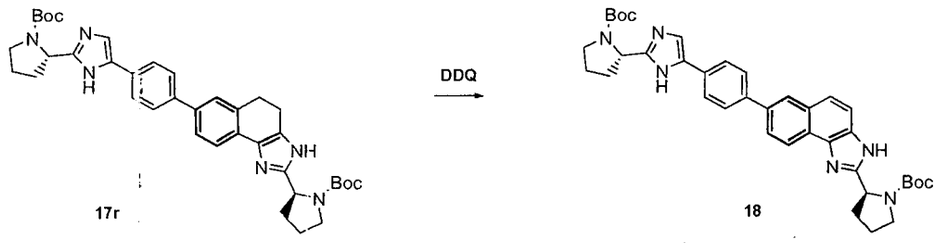
Example 17n (Derived from Example 16 and Example 7)		RT = 2.41 minutes (condition 2); LRMS: Anal. Calcd. for $C_{39}H_{49}N_6O_5$ 681.38; found: 681.49 (M+H).
Example 17o (Derived from Example 16 and Example 13a.2)		RT = 1.7 minutes (condition 1) ; HRMS: Anal. Calcd. for $C_{39}H_{38}N_6O_4$ 665.3810; found: 655.3789 (M+H).
Example 17p (Derived from Example 16 and Example 13b.2)		RT = 1.7 minutes (condition 1) ; LCMS: Anal. Calcd. for $C_{39}H_{38}N_6O_4$ 665; found: 655 (M+H).
Example 17q (Derived from Example 16 and Example 7c)		RT = 2.43 minutes (condition 2) ; LRMS: Anal. Calcd. for $C_{40}H_{51}N_6O_5$ 695.39; found: 695.55 (M+H).
Example 17r (Derived from Example 16 and Example 10a.3)		RT = 2.25 minutes (condition 2); LRMS: Anal. Calcd. for $C_{38}H_{47}N_6O_4$ 651.37; found: 651.33 (M+H).

Example 17r.a (Derived from Example 16 and Example 15c)		RT = 2.05 minutes (Condition 2) LCMS: Anal. Calcd. for $C_{37}H_{44}N_6O_5$: 652.78; found: 653.4 (M+H).
Example 17r.1 (Derived from Example 16h and Example 10a.3)		RT = 1.73 minutes (condition 1); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_6O_4$ 747.38; found: 747.46 (M+H).
Example 17r.2 (Derived from Example 16g and Example 10a.5)		RT = 2.17 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{47}N_6O_4$ 675.37; found: 675.39 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{47}N_6O_4$ 675.3653; found: 675.3680 (M+H).
Example 17r.3 (Derived from Example 16i and Example 10a.5)		RT = 1.72 minutes (condition 1). HRMS: Anal. Calcd. for $C_{42}H_{48}F_3N_6O_4$ 757.3684; found: 757.3684 (M+H).

Example 17r.4 (Derived from Example 16j and Example 10a.3)		RT = 2.21 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{49}N_6O_4$ 677.38; found: 677.36 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{49}N_6O_4$ 677.3810; found: 677.3803 (M+H).
Example 17r.5 (Derived from Example 16k and Example 10a.5)		RT = 2.25 minutes (condition 2); LRMS: Anal. Calcd. for $C_{42}H_{49}N_6O_4$ 701.38; found: 701.36 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{49}N_6O_4$ 701.3810; found: 701.3798 (M+H).
Example 17r.6 (Derived from Example 16j and Example 11a)		RT = 2.21 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{47}N_6O_4$ 711.37; found: 711.52 (M+H).
Example 17r.7 (Derived from Example 16k and Example 11b)		RT = 2.06 minutes (condition 2); LRMS: Anal. Calcd. for $C_{45}H_{47}N_6O_4$ 735.37; found: 735.38 (M+H).

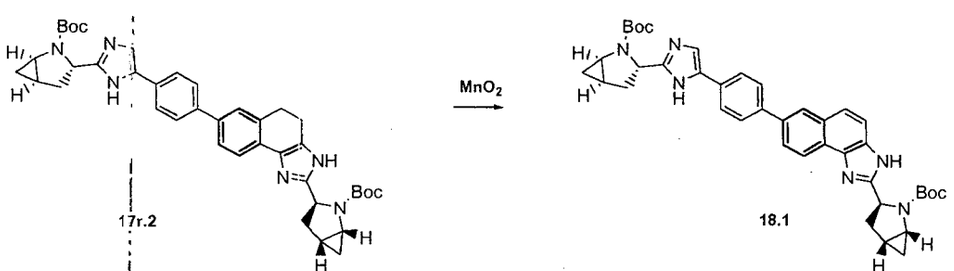
Example 17s (Derived from Example 16e and Example 10a.3)		RT = 2.31 minutes (condition 2); LRMS: Anal. Calcd. for $C_{38}H_{46}FN_6O_4$ 669.36; found: 669.60 (M+H).
Example 17t.1 (Derived from Example 16e.1 and Example 10a.5)		RT = 2.22 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{46}FN_6O_4$ 693.36; found: 693.36 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{46}FN_6O_4$ 693.3559; found: 693.3584 (M+H).
Example 17s.2 (Derived from Example 16e.1 and Example 11b)		RT = 2.2 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{44}FN_6O_4$ 727.34; found: 727.35 (M+H).
Example 17t (Derived from Example 16a and Example 11)		RT = 2.71 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{59}F_2N_6O_5Si$ 817.42; found: 817.71 (M+H).
Example 17t.1 (Derived from Example 16 and Example 10a.4)		RT = 2.25 minutes (condition 2); HRMS: Anal. Calcd. for $C_{38}H_{45}F_2N_6O_4$ 687.3465; found: 687.3497 (M+H).

Synthetic route 10.



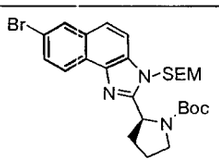
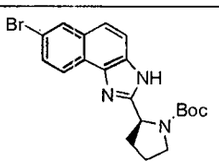
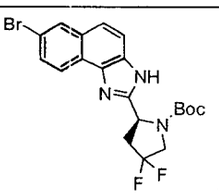
DDQ (116 mg, 0.51 mmol) was added to a solution of Example 17r (S)-tert-butyl 2-(7-(4-(5-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-2-yl)phyenyl)-4,5-dihydro-1H-naphtho[1,2d]imidazol-2-yl)pyrrolidine-1-carboxylate (332 mg, 0.51 mmol) in benzene (5 mL) under nitrogen atmosphere and the dark brown mixture was heated at reflux for 2 hours. The solvent was removed *in vacuo* and the residue was charged (CH_2Cl_2) to a 25 (M) Biotage® silica gel column. Segment 1; Gradient eluted from 50-100% B over 720 mL (A = CH_2Cl_2; B = 20% CH_3OH in CH_2Cl_2) Segment 2; Gradient eluted from 0-50% B over 720 mL (A = CH_2Cl_2; B = CH_3OH) gave Example 18, 261 mg (79%). ^1H NMR (500 MHz, DMSO-d_6) δ 8.46 (br s, 1H), 8.31 (s, 1H), 7.95-7.55 (m, 8H), 5.1-4.8 (rotomers, 2H), 3.67 (br.s , 1H), 3.57 (br.s , 1H), 3.48-3.47 (m, 1H), 3.39 - 3.38 (m, 1H), 2.42-1.89 (m, 8H), 1.42/1.18 (s, 9H). RT = 2.24 minutes (condition 2). LRMS: Anal. Calcd. for C38H44N6O4: 649.35; found: 649.65 (M+H).

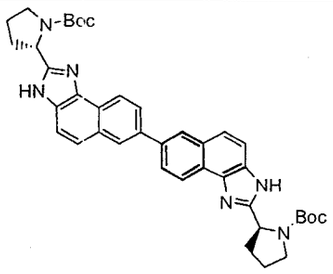
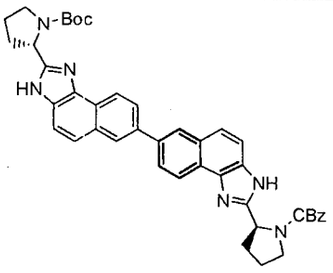
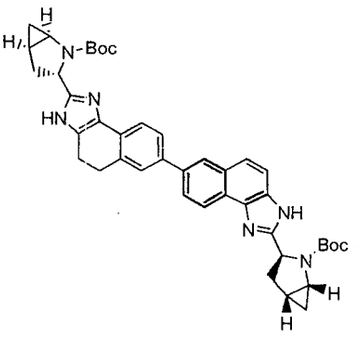
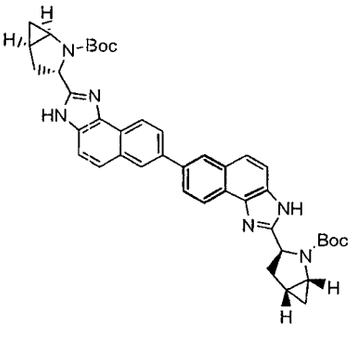
Synthetic route 10a.

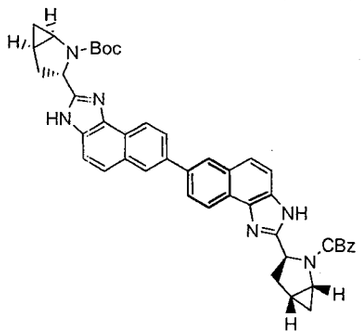
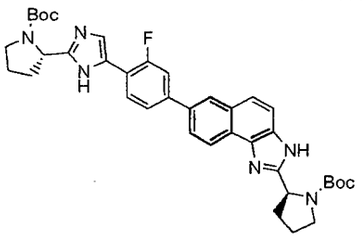
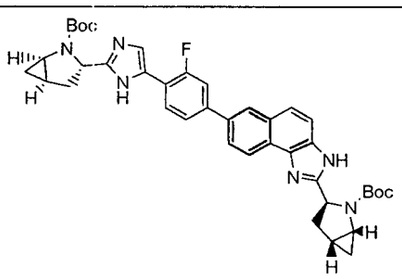
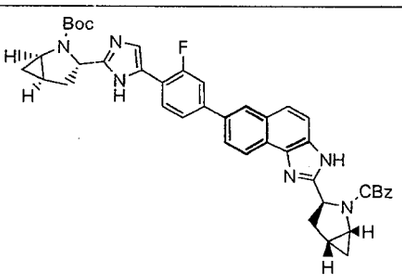


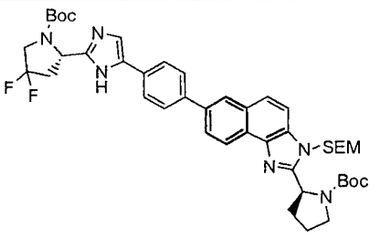
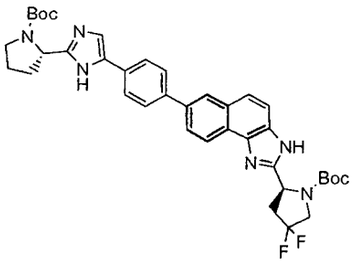
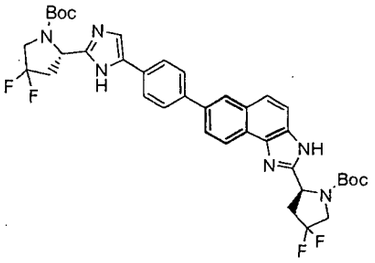
Activated MnO_2 (77 mg, 0.889 mmol) was added in one portion to a stirred solution of Example 17r.2 (200 mg, 0.296 mmol) in dry CH_2Cl_2 (2 mL), and the suspension was stirred for 4h. Additional MnO_2 (300 mg) was added and the

mixture stirred 16h. This sequence was repeated until LCMS revealed no remaining starting material. The reaction mixture was filtered through diatomaceous earth (Celite®), concentrated, and dried under high vacuum for 1h to give Example 18.1 (185.8 mg, 92 %) as a yellowish-orange solid. LCMS: RT = 2.24 minutes, Calcd. for $C_{40}H_{45}N_6O_4$ 673.35; found: 673.36 (M+H). HRMS: Calcd for $C_{40}H_{45}N_6O_4$ 673.3497; found: 673.3525 (M+H).

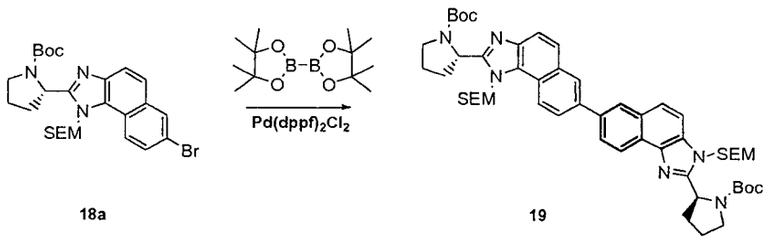
Example 18a (Derived from Example 11)		RT = 3.5 minutes (condition 2); LCMS: Anal. Calcd. for $C_{26}H_{37}BrN_3O_3Si$ 546.18; found: 546.21 (M+H).
Example 18b (Derived from Example 10a.3)		RT = 2.74 minutes (condition 2); LCMS: Anal. Calcd. for $C_{20}H_{23}BrN_3O_2$ 416.08; found: 416.08 (M+H).
Example 18b.1 (Derived from Example 10a.4)		RT = 2.62 minutes (condition 2); LCMS: Anal. Calcd. for $C_{20}H_{21}BrF_2N_3O_2$ 454.08 and 452.08; found: 454.01 and 454.01 (M+H).

Example 18b.2 (Derived from Example 17r.4)		RT = 2.28 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{45}N_6O_4$ 673.35; found: 673.36 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{45}N_6O_4$ 673.3497; found: 673.3498 (M+H).
Example 18b.3 (Derived from Example 17r.6)		RT = 2.30 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{43}N_6O_4$ 707.34; found: 707.52 (M+H).
Example 18b.4 (Derived from Example 17r.7)		Example not characterized.
Example 18b.5 (Derived from Example 17r.5)		RT = 2.32 minutes (condition 2); LRMS: Anal. Calcd. for $C_{42}H_{45}N_6O_4$ 697.35; found: 697.36 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{45}N_6O_4$ 697.3497; found:

		697.3488 (M+H).
Example 18b.3 (Derived from Example 17r.1)		RT = 2.13 minutes (condition 2); LRMS: Anal. Calcd. for $C_{45}H_{43}N_6O_4$ 731.34; found: 731.32 (M+H).
Example 18c (Derived from Example 17s)		RT = 2.3 minutes (condition 2). HRMS: Anal. Calcd. for $C_{38}H_{44}FN_6O_4$ 667.3403; found: 667.3419 (M+H).
Example 18c.1 (Derived from Example 17s.1)		RT = 2.29 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{44}FN_6O_4$ 691.34; found: 691.33 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{44}FN_6O_4$ 691.3403; found: 691.3420 (M+H).
Example 18c.2 (Derived from Example 17s.2)		RT = 2.05 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{42}FN_6O_4$ 725.32; found: 725.25 (M+H).

Example 18d (Derived from Example 17t)		RT = 2.87 minutes (condition 2); HRMS: Anal. Calcd. for $C_{44}H_{57}F_2N_6O_4Si$ 815.4122; found: 815.4149 (M+H).
Example 18e (Derived from Example 17t.1)		RT = 2.34 minutes (condition 2); HRMS: Anal. Calcd. for $C_{38}H_{43}F_2N_6O_4$ 685.3308; found: 685.3342 (M+H).
Example 18f (Derived from Examples 16a and 18b.1 according to the procedure described for Example 17)		RT = 2.34 minutes (condition 2); HRMS: Anal. Calcd. for $C_{38}H_{41}F_4N_6O_4$ 721.3120; found: 721.3128 (M+H).

Synthetic route 11

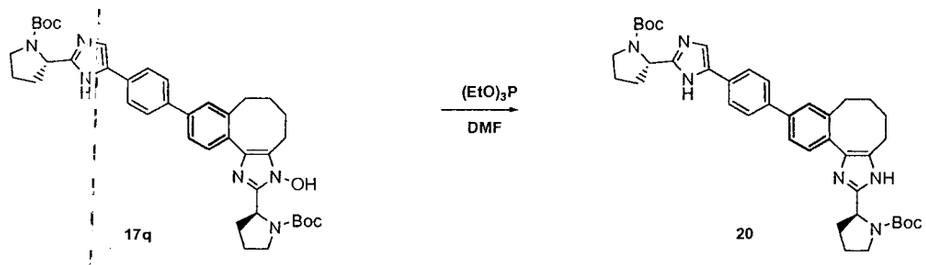


18a 19

[1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(ii)complex with dichloromethane (11.2 mg, 0.014 mmol) was added to a stirred solution of Example 18a (150 mg, 0.274 mmol), bis-pinacol diborane (34.8 mg, 0.137 mmol), dppf (7.61 mg, 0.014 mmol), and K_2CO_3 (114 mg, 0.823 mmol) in DMSO (2.5 mL) under argon atmosphere in a screw top pressure vessel. The solution was flushed thoroughly with argon, sealed, and immersed in an oil bath preheated at 80 °C and stirred 18 hours.

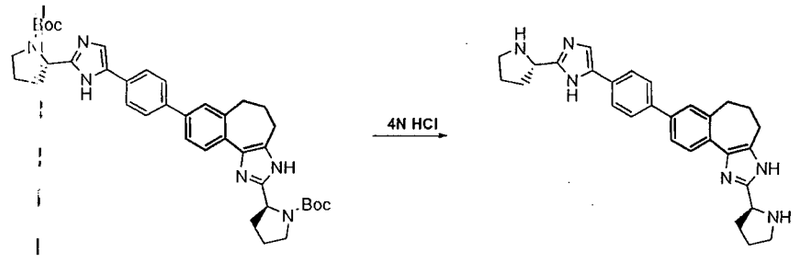
The mixture was cooled, diluted with EtOAc and washed with sat'd $NaHCO_3$ solution, brine, and dried (Na_2SO_4) and filtered. Solvent was removed *in vacuo* and the residue was charged (CH_2Cl_2) to a 25 (M) Biotage® silica gel column: Segment 1. 10% B for 75 mL; Segment 2. Gradient eluted from 10-100% B over 1.8 L; (A = Hexanes; B = EtOAc) gave Example 19, 88.7 mg (33%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56-8.54 (m, 2H), 8.48 (s, 2H), 8.12-8.10 (m, 2H), 7.95-7.91 (m, 4H), 5.83-5.76 (m, 4H), 5.30-5.22 (m, 2H), 3.72-3.61 (m, 4H), 3.53 (t, J = 7.3 Hz, 4H), 2.44-2.13 (m, 4H) 2.11-2.08 (m, 2H), 2.0-1.94 (m, 2H), 1.38/1.08 (s, 18H), 0.91-0.81 (m, 4H), -0.06 (s, 18H). RT = 3.2 minutes (condition 2); HRMS: Anal. Calcd. for $C_{52}H_{73}N_6O_6Si_2$ 933.5125; found: 933.5132 (M+H).

Synthetic route 12



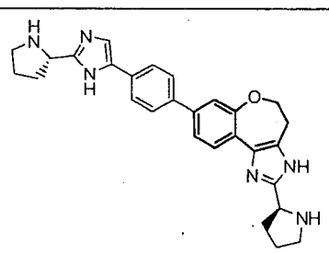
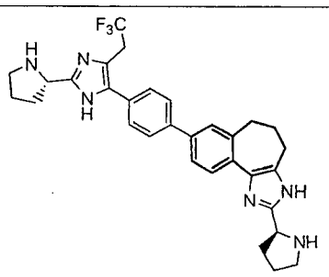
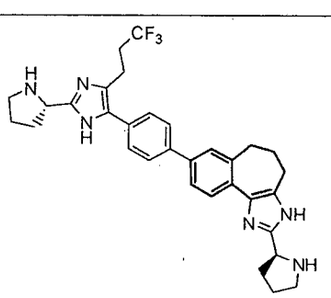
Triethylphosphite (0.257 mL, 1.48 mmol) was added to Example 17q, (340 mg, 0.489 mmol) in DMF (5 mL) and stirred at 80°C for 16 hours. Additional triethylphosphite (0.3 mL and 0.6 mL) was added at 8 hours intervals until LCMS indicated the reaction was complete. The solvent was removed *in vacuo* and the residue was charged (CH_2Cl_2) to a 25 (M) Biotage® silica gel column. Segment 1. 0% B for 300 mL; Segment 2. Gradient eluted from 0-50% B over 1440 mL; Segment 3. Gradient eluted 50-100% B over 600 mL (A = CH_2Cl_2; B = 20% CH_3OH in CH_2Cl_2) gave Example 20, 286 mg (82%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84-7.80 (m, 8H), 4.87-4.68 (m, 2H), 3.55-3.54 (m, 2H), 3.40-3.30 (m, 6H), 2.82-2.76 (m, 2H), 2.25-1.82 (m, 8H), 1.63-1.57 (m, 2H), 1.42/1.18 (s, 9H). RT = 2.32 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{51}N_6O_4$ 679.40; found: 679.57 $(M+H)^+$.

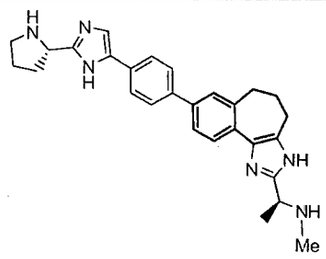
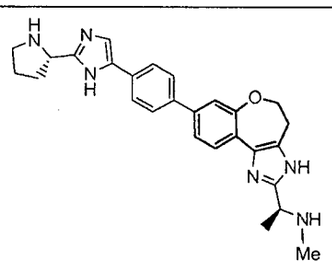
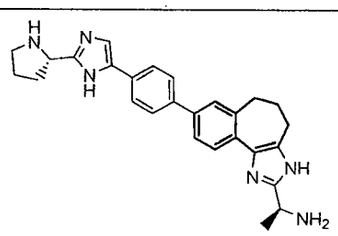
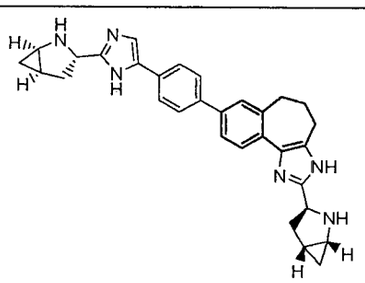
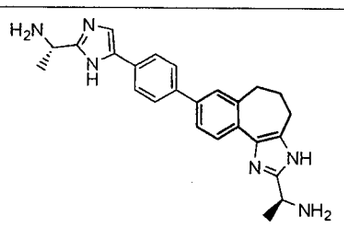
Synthetic route 13

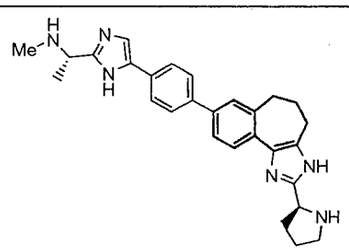
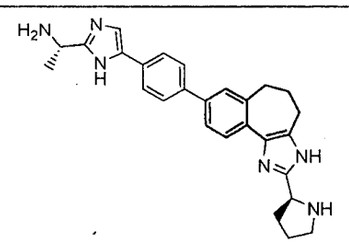
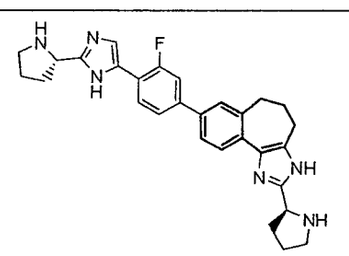
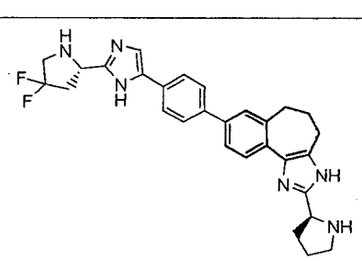
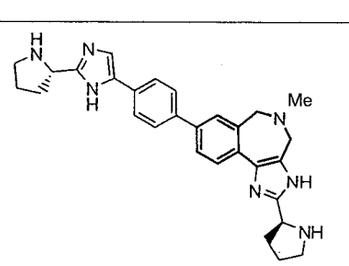


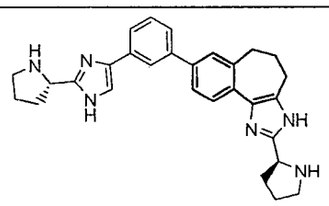
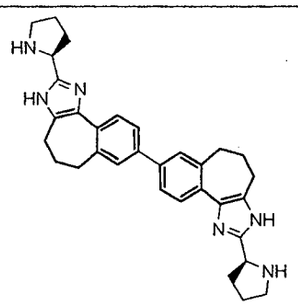
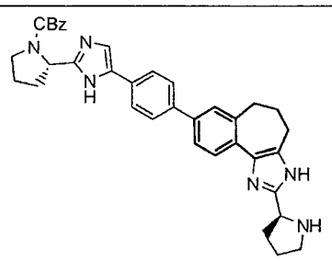
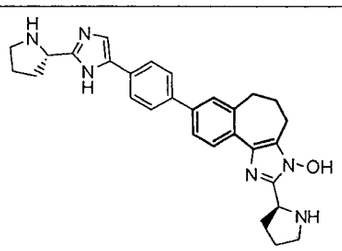
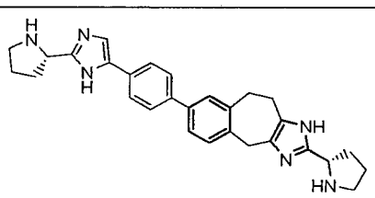
17 21

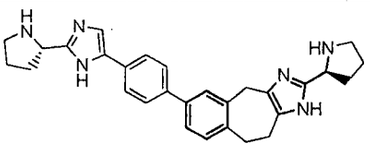
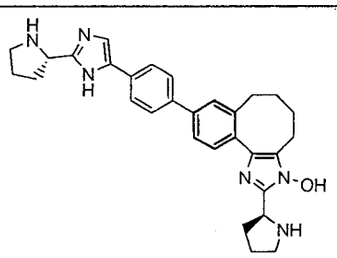
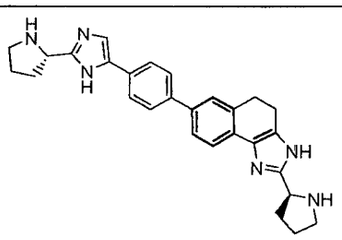
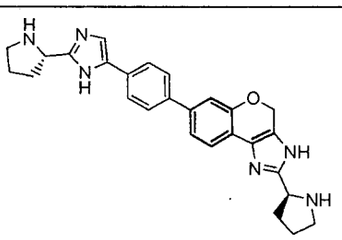
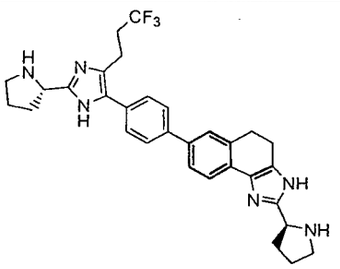
Example 17, (411 mg, 0.62 mmol) was dissolved in CH_3OH (20 mL) and HCl/Dioxane (100 mL of 4N) was added and the reaction was stirred 4 hr. The solvents were removed *in vacuo*, and the tetra HCl salt was exposed to high vacuum for 18 hours to give Example 21, 350 mg (94%) as an HCl salt which was used without further purification. RT = 1.3 minutes (condition 1). LCMS: Anal. Calcd. for $C_{29}H_{33}N_6$: 465; found: 465 (M+H).

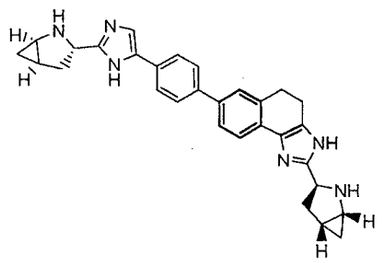
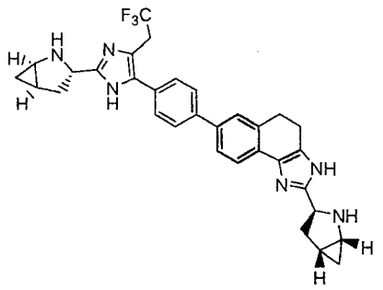
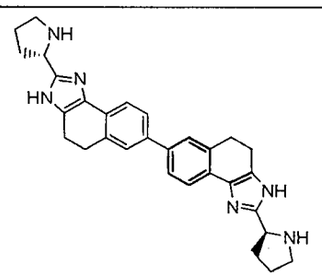
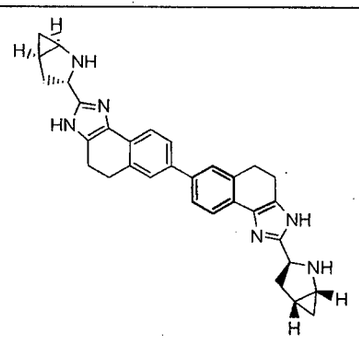
Example 21a (Derived from Example 17a)		RT = 2.99 minutes (condition 2); LCMS: Anal. Calcd. For $C_{37}H_{46}N_6O_5$: 466.57; found: 467.2.2 (M+H).
Example 21a.1 (Derived from Example 17a.1)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{31}H_{34}F_3N_6$ 547.28; found: 547.19 (M+H).
Example 21a.2 (Derived from Example 17a.2)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{32}H_{36}F_3N_6$: 561.29; found: 561.36 (M+H).

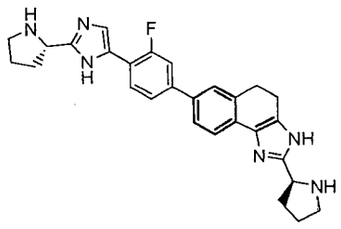
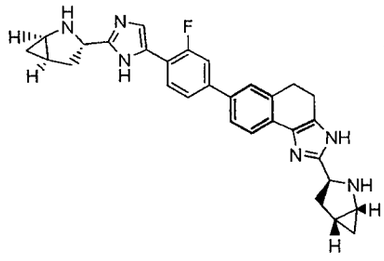
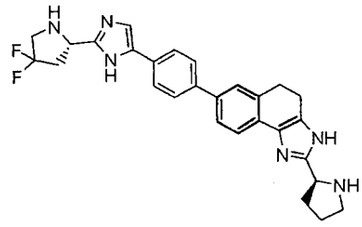
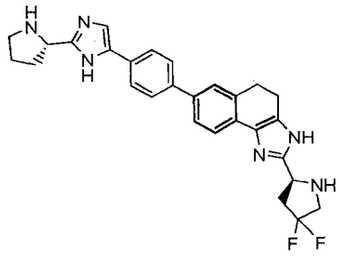
Example 21b (Derived from Example 17b)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{28}H_{32}N_6$ 452; found: 452 (M+H).
Example 21b.1 (Derived from Example 17b.1)		RT = 1.2 minutes (condition 2); LCMS: Anal. Calcd. for $C_{37}H_{46}N_6O_5$: 454.25; found: 455.2 (M+H).
Example 21c (Derived from Example 17c)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{30}N_6$ 438; found: 438 (M+H).
Example 21c.1 (Derived from Example 17c.1)		RT = 1.2 minutes (condition 1); LCMS: Anal. Calcd. for $C_{31}H_{33}N_6$ 489.28; found: 489.28 (M+H).
Example 21d (Derived from Example 17d)		RT = 1.2 minutes (condition 1); LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 412 (M+H).

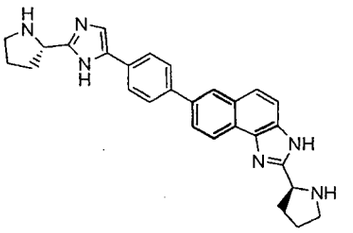
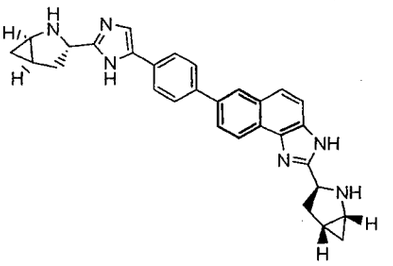
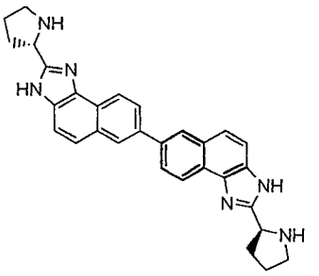
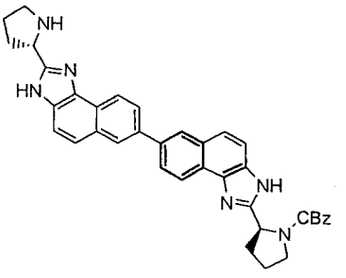
Example 21e (Derived from Example 17e)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{28}H_{32}N_6$ 452; found: 452 (M+H).
Example 21f (Derived from Example 17f)		RT = 1.2 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{30}N_6$ 438; found: 438 (M+H).
Example 21g (Derived from Example 17g)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{29}H_{31}FN_6$ 483; found: 483 (M+H).
Example 21h (Derived from Example 17h)		RT = 1.7 minutes (condition 2); LCMS: Anal. Calcd. for $C_{29}H_{31}F_2N_6$ 501.25; found: 501.51 (M+H).
Example 21i (Derived from Example 17i)		RT = 1.5 minutes (condition 2); LRMS: Anal. Calcd. for $C_{29}H_{34}N_7$ 480.28; found: 480.26 (M+H).

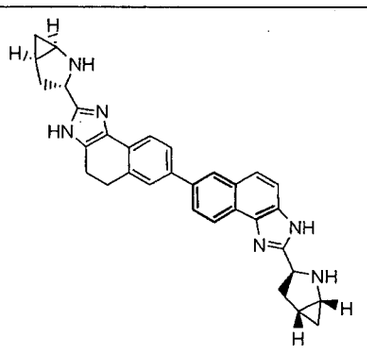
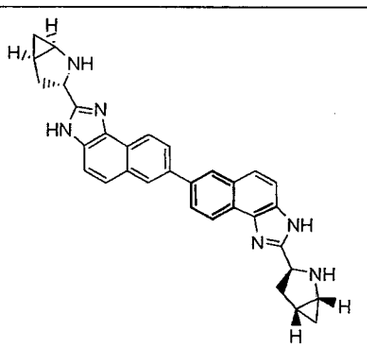
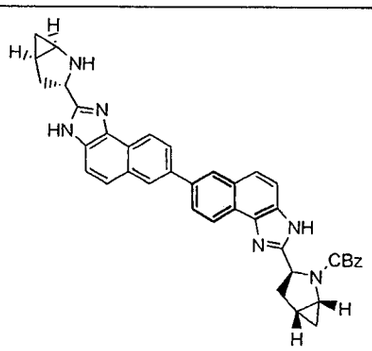
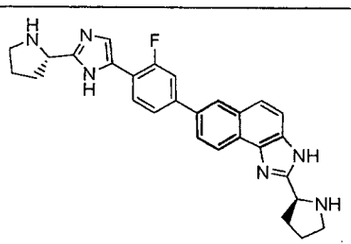
Example 21j (Derived from Example 17j)		RT = 1.3 minutes (condition 1); LRMS: Anal. Calcd. for $C_{29}H_{32}N_6$ 464; found: 464 (M+H).
Example 21k (Derived from Example 17k)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{32}H_{36}N_6$ 505; found: 505 (M+H).
Example 21m (Derived from Example 17m)		RT = 1.5 minutes (condition 1); LRMS: Anal. Calcd. for $C_{37}H_{38}N_6O_2$ 598; found: 598 (M+H).
Example 21n (Derived from Example 17n)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{29}H_{33}N_6O$ 481.26; found: 481.37 (M+H).
Example 21o (Derived from Example 17o)		RT = 2.1 minutes (condition 1) LCMS: Anal. Calcd. for $C_{29}H_{32}N_6$ 464; found: 464 (M+H).

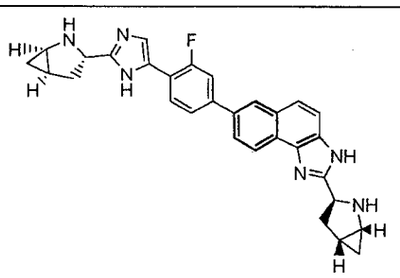
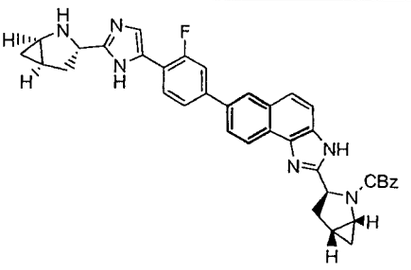
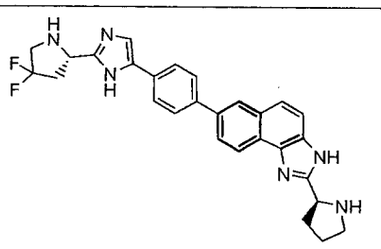
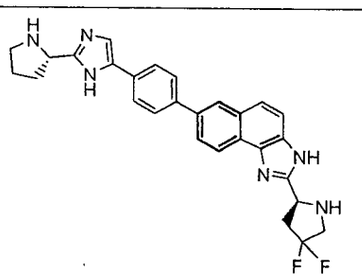
Example 21p (Derived from Example 17p)		RT = 2.0 minutes (condition 1) LCMS: Anal. Calcd. for $C_{29}H_{32}N_6$ 464; found: 464 (M+H).
Example 21q (Derived from Example 17q)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{35}N_6O$ 495.28; found: 495.37 (M+H).
Example 21r (Derived from Example 17r)		RT = 1.5 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{30}N_6$ 451.26; found: 451.33 $(M+H)^+$.
Example 21r.a (Derived from Example 17r.a)		RT = 1.1 minutes (condition 1); LCMS: Anal. Calcd. for $C_{37}H_{44}N_6O_5$: 452.18; found: 453.2 (M+H).
Example 21r.1 (Derived from Example 17r.1)		RT = 1.4 minutes (condition 1) LCMS: Anal. Calcd. for $C_{31}H_{34}F_3N_6$ 547.28; found: 547.26 $(M+H)^+$.

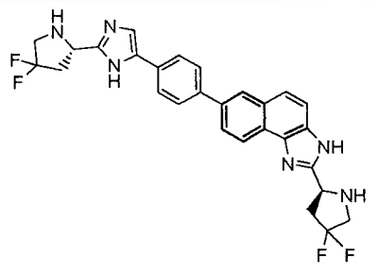
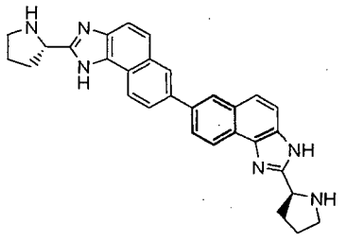
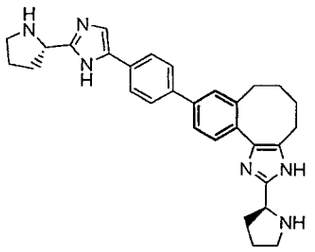
Example 21r.2 (Derived from Example 17r.2)		RT = 1.46 min, (condition 2), LCMS: Anal. Calcd for $C_{30}H_{31}N_6$ (M+H) 475.26; found: 475.25. HRMS: Anal. Calcd for $C_{30}H_{31}N_6$ 475.2605; found: 475.2616 (M+H).
Example 21r.3 (Derived from Example 17r.3)		RT = 1.4 minutes (condition 1) LCMS: Anal. Calcd. for $C_{32}H_{32}F_3N_6$ 557.26; found: 557.22 (M+H).
Example 21r.4 (Derived from Example 17r.4)		RT = 1.43 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{33}N_6$ 477.28; found: 477.22 (M+H). HRMS: Calcd for $C_{30}H_{33}N_6$ 477.2761; found 477.2765 (M+H).
Example 21r.5 (Derived from Example 17r.5)		RT = 1.56 minutes (condition 2) LCMS: Anal. Calcd. for $C_{32}H_{33}N_6$ 501.28; found: 501.29 (M+H). HRMS: Calcd for $C_{32}H_{33}N_6$ 501.2761;

		found 501.2761 (M+H).
Example 21s (Derived from Example 17s)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{30}FN_6$ 469.25; found: 469.47 $(M+H)^+$.
Example 21s.1 (Derived from Example 17s.1)		RT = 1.62 min, (condition 2), LCMS: Anal. Calcd for $C_{30}H_{30}FN_6$ 493.25; found: 493.28 (M+H). HRMS: Calcd for $C_{30}H_{30}FN_6$ 493.2511; found 493.2520 (M+H).
Example 21t (Derived from Example 17t)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{29}F_2N_6$ 487.23; found: 487.51 (M+H).
Example 21t.1 (Derived from Example 17t.1)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{29}F_2N_6$ 487.24; found: 487.51 (M+H).

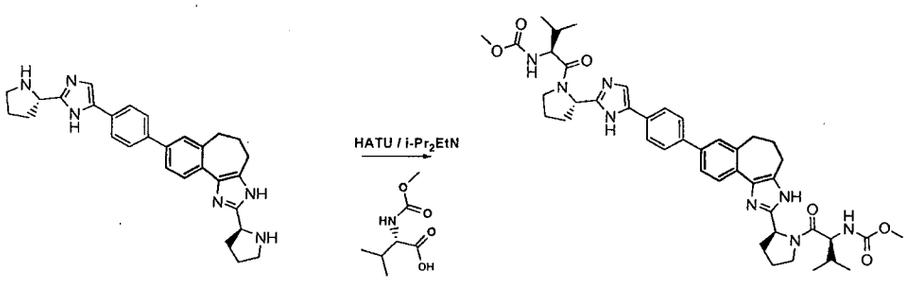
Example 21u (Derived from Example 18)		RT = 1.6 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{29}N_6$ 449.25; found: 449.46 (M+H).
Example 21u.1 (Derived from Example 18.1)		RT = 1.61 min, (condition 2), LCMS: Anal. Calcd for $C_{30}H_{29}N_6$ 473.36; found: 473.28 (M+H). HRMS: Anal. Calcd. for $C_{30}H_{29}N_6$ 473.2448; found: 473.2457 (M+H).
Example 21u.2 (Derived from Example 18b.2)		See Example 21x below for characterization.
Example 21u.3 (Derived from Example 18b.3)		RT = 2.10 min, (condition 2), LCMS: Anal. Calcd for $C_{38}H_{35}N_6O_2$ 607.46; found: 607.46 (M+H).

Example 21u.4 (Derived from Example 18b.4)		Example not characterized.
Example 21u.5 (Derived from Example 18b.5)		RT = 1.82 minutes (condition 2); LRMS: Anal. Calcd. for $C_{32}H_{29}N_6$ 497.25; found: 497.29 (M+H). HRMS: Calcd for $C_{32}H_{29}N_6$ 497.2448; found 497.2448 (M+H).
Example 21u.6 (Derived from Example 18b.6)		RT = 1.91 min (condition 2); LCMS: Anal. Calcd. for $C_{40}H_{35}N_6O_2$ 631.28; found: 631.27 (M+H).
Example 21v (Derived from Example 18c)		RT = 1.8 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{28}FN_6$ 467.24; found: 467.43 (M+H).

Example 21v.1 (Derived from Example 18c.1)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{28}FN_6$ 491.24; found: 491.25 (M+H). HRMS: Calcd. for $C_{30}H_{28}FN_6$ 491.2354; found 491.2364 (M+H).
Example 21v.2 (Derived from Example 18c.2)		RT = 1.76 minutes (condition 2) LCMS: Anal. Calcd. for $C_{38}H_{34}FN_6O_2$ 625.27; found: 625.19 (M+H).
Example 21w (Derived from Example 18d)		RT = 1.9 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{27}F_2N_6$ 485.23; found: 485.46 (M+H).
Example 21w.1 (Derived from Example 18e)		RT = 1.8 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{27}F_2N_6$ 485.23; found: 485.30 (M+H).

Example 21w.2 (Derived from Example 18f)		RT = 2.3 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{25}F_4N_6$ 521.21; found: 521.28 (M+H).
Example 21x (Derived from Example 19) NOTE: Same as Example 21u.2		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{29}N_6$ 473.24; found: 473.27 (M+H).
Example 21x.1 (Derived from Example 20)		RT = 1.6 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{35}N_6$ 479.29; found: 479.39 (M+H).

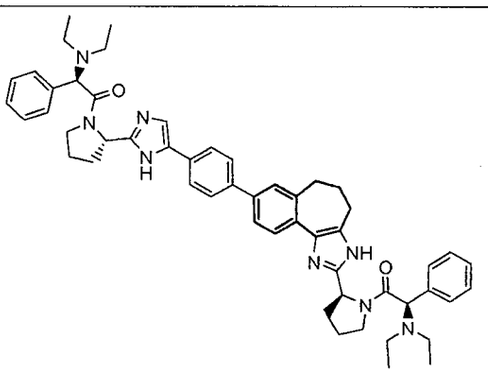
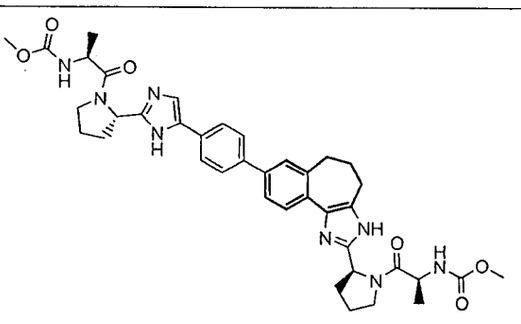
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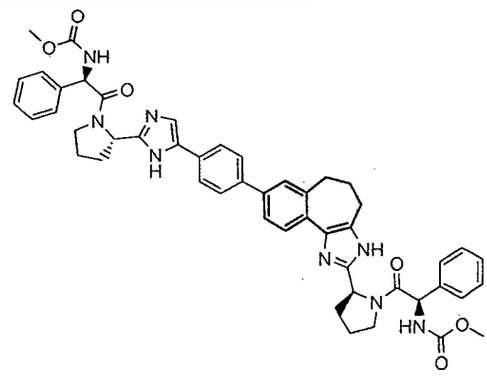
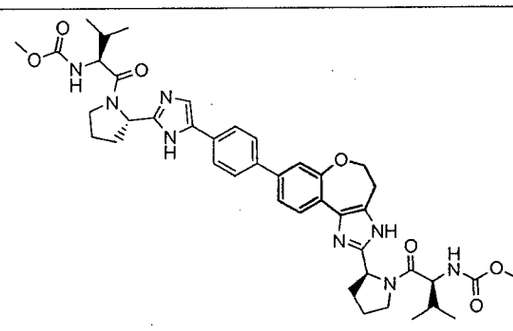


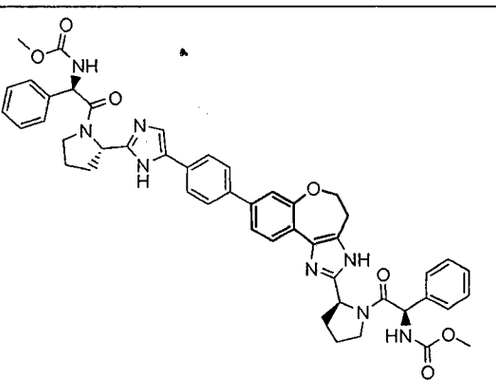
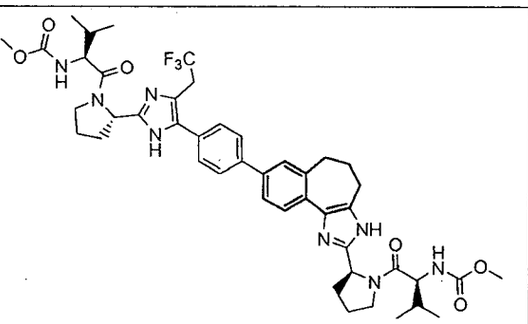
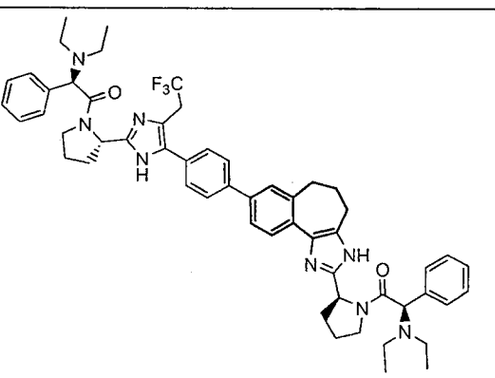
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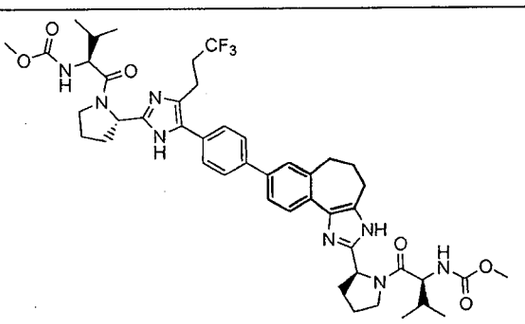
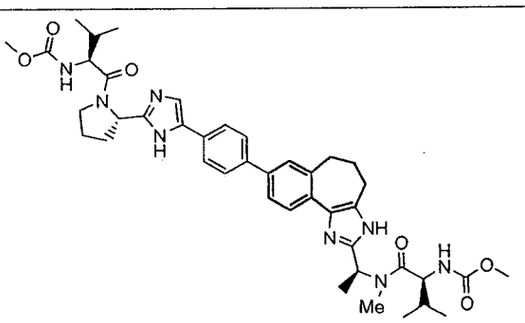
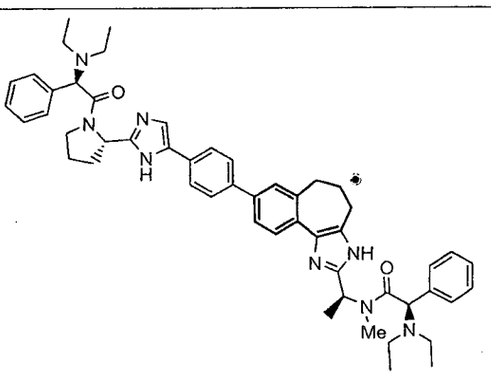
HATU (88 mg, 0.33 mmol) was added and rapidly stirred solution of Example 21, (87.5 mg, 0.145 mmol), Cap-51: N-methoxycarbonyl-L-valine (63.3 mg, 0.36 mmol), and Hunig's base (0.23 mL, 1.25 mmol) in DMF (3.5 mL). The reaction mixture was stirred 16 hours before being diluted with CH_3OH (1 vol) and directly subjected to semi prep HPLC (4 injections at 2 mL each; Dynamax 60A prep C8 column; 25% - 100% B over 30 min; Flow Rate = 20 mL/min; Wavelength = 220 nm; Solvent A = 0.1% TFA in 10%methanol/90%H2O; Solvent B = 0.1% TFA in

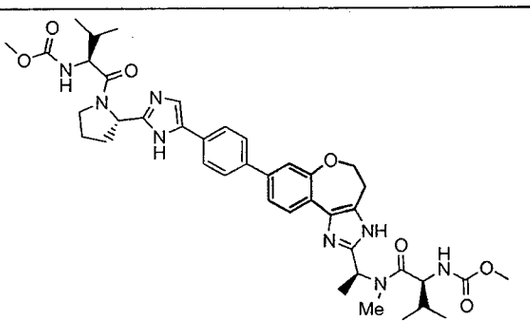
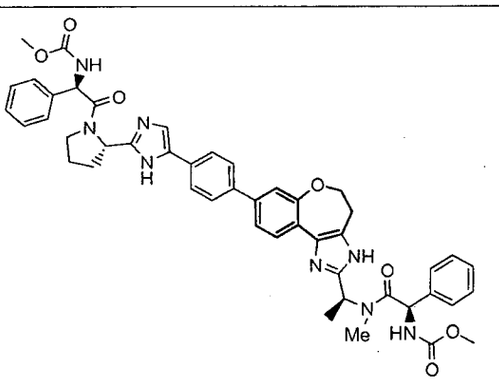
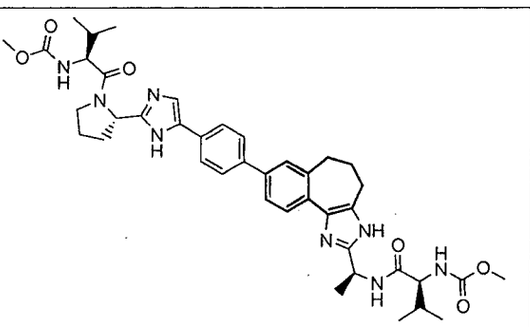
90%methanol/10% H2O) to give Example 22, (TFA salt). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04-8.02 (m, 1H), 7.78-7.58 (m, 4H), 7.49-7.41(m, 3H), 7.30-7.24 (m, 2H), 5.09-5.01 (m, 2H), 4.1-4.03 (m, 2H), 3.81-3.79 (m, 4H), 3.54 (s, 6H), 2.92-2.84 (m, 4H), 2.17-2.09 (m, 4H), 2.00-1.87 (m, 8H), 0.79-0.81 (m, 12H). RT = 1.57 minutes (condition 1). LRMS: Anal. Calcd. for $C_{43}H_{55}N_8O_6$: 779.42; found: 779.48 (M+H). HRMS: Anal. Calcd. for $C_{43}H_{55}N_8O_6$: 779.4245; found: 779.4249 (M+H).

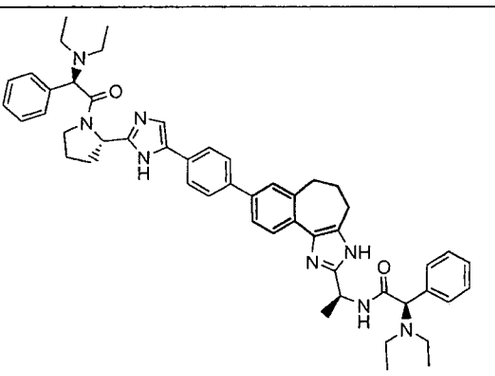
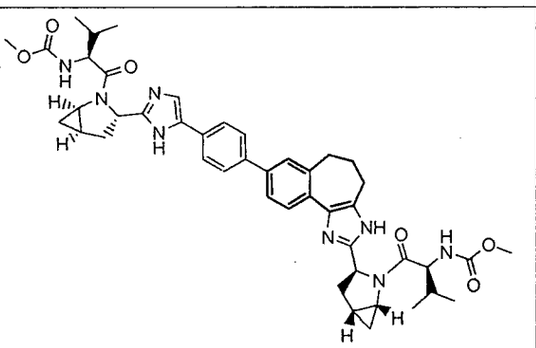
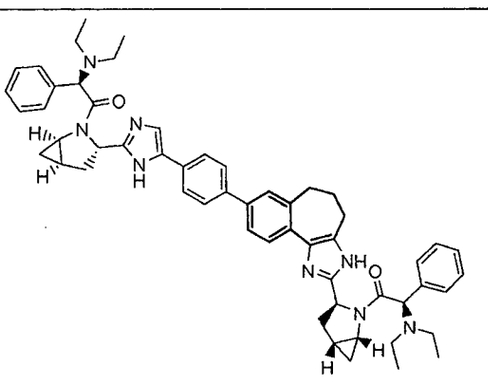
Example 22.1 (Derived from Example 21 and Cap-2)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for $C_{53}H_{62}N_8O_2$ 843.51; found: 843.89 (M+H). HRMS: Anal. Calcd. for $C_{53}H_{62}N_8O_2$ 843.5047; found: 843.5099 (M+H).
Example 22.2 (Derived from Example 21 and Cap-52)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{46}N_8O_6$ 723.36; found: 723.39 (M+H). HRMS: Anal. Calcd. for $C_{39}H_{46}N_8O_6$

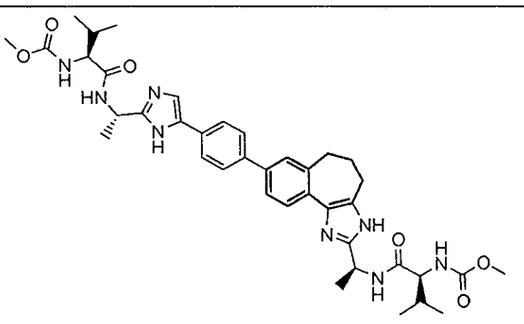
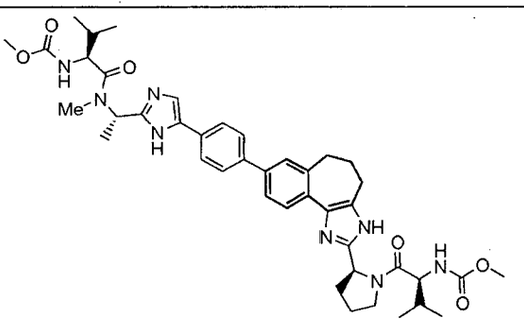
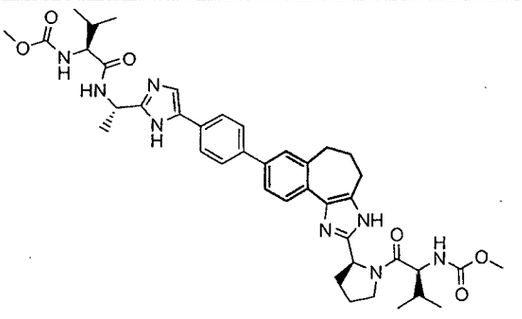
		723.3619; found: 723.3643 (M+H).
Example 22.3 (Derived from Example 21 and Cap-4)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{49}H_{50}N_8O_6$ 723.39; found: 723.40 (M+H). HRMS: Anal. Calcd. for $C_{49}H_{50}N_8O_6$ 847.3932; found: 847.3953 (M+H).
Example 22a (Derived from Example 21a and Cap-51)		RT = 2.0 minutes (condition 4); LRMS: Anal. Calcd. for $C_{42}H_{53}N_8O_7$ 781.41; found: 781.33 (M+H).

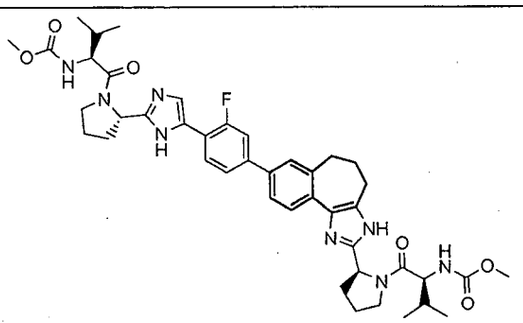
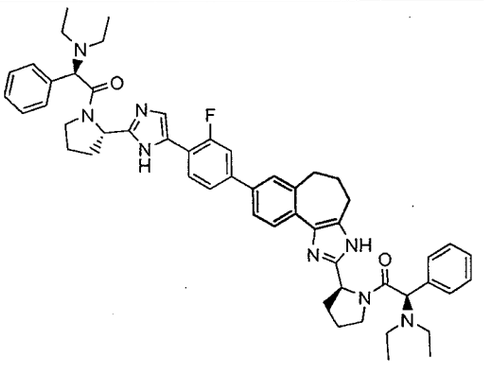
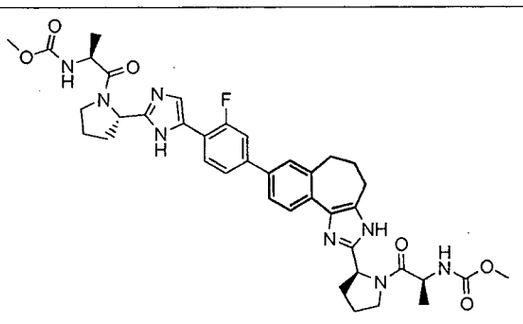
Example 22a.1 (Derived from Example 21a and Cap-4)		RT = 2.2 minutes (condition 4); LRMS: Anal. Calcd. for $C_{48}H_{49}N_8O_7$ 849.37; found: 849.25 (M+H).
Example 22a.2 (Derived from Example 21a.1 and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{45}H_{56}F_3N_8O_6$ 861.4281; found: 861.4269 (M+H).
Example 22a.3 (Derived from Example 21a.1 and Cap-2)		RT = 1.4 minutes (condition 1); HRMS: Anal. Calcd. for $C_{55}H_{64}F_3N_8O_2$ 925.5099; found: 925.5096 (M+H).

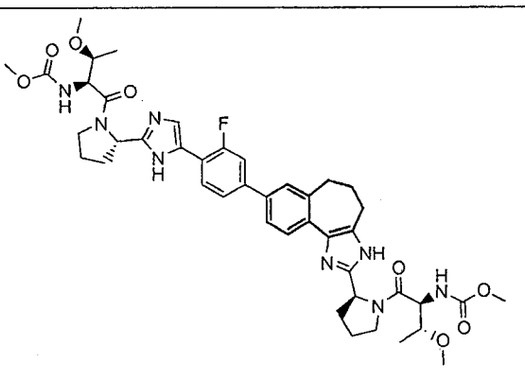
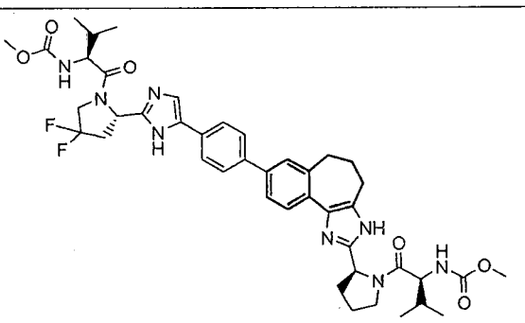
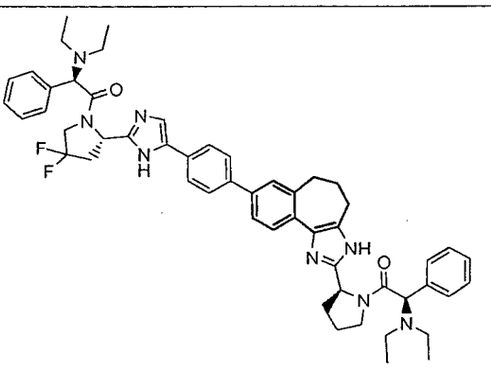
Example 22a.4 (Derived from Example 21a.2 and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{46}H_{57}F_3N_8O_6$ 875.4426; found: 875.4406 (M+H).
Example 22b (Derived from Example 21b and Cap-51)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. for $C_{42}H_{54}N_8O_6$ 767.37; found: 767.42 (M+H).
Example 22b.1 (Derived from Example 21b and Cap-2)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for $C_{52}H_{62}N_8O_2$ 831.50; found: 831.63 (M+H).

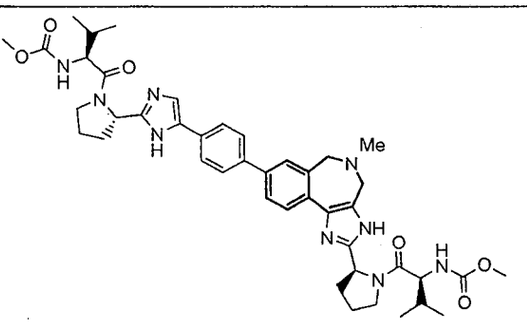
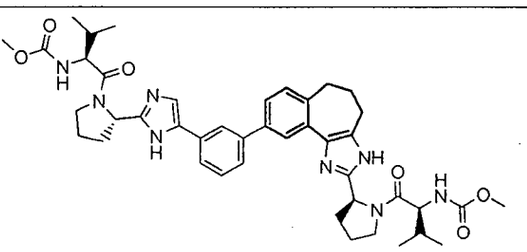
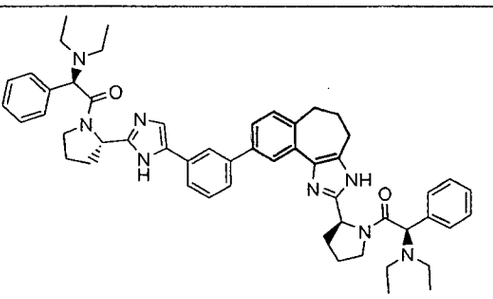
Example 22b.2 (Derived from Example 21b.1 and Cap-51)		RT = 2.1 minutes (condition 4); LRMS: Anal. Calcd. for $C_{41}H_{53}N_8O_7$ 769.40; found: 769.21 (M+H).
Example 22b.3 (Derived from Example 21b.1 and Cap-4)		RT = 2.2 minutes (condition 4); LRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 837.37; found: 837.19 (M+H).
Example 22c (Derived from Example 21c and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{41}H_{52}N_8O_6$ 753.4083; found: 753.4085 (M+H).

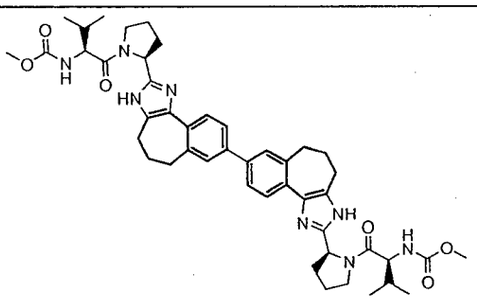
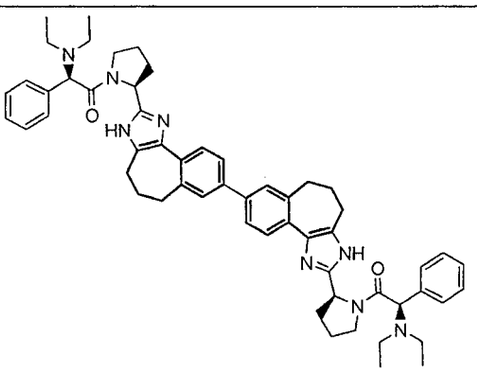
Example 22c.1 (Derived from Example 21c and Cap-2)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for $C_{51}H_{60}N_8O_2$ 817.49; found: 817.62 (M+H).
Example 22c.2 (Derived from Example 21c.1 and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{45}H_{55}N_8O_6$ 803.4239; found: 803.4236 (M+H).
Example 22c.3 (Derived from Example 21c.1 and Cap-2)		RT = 1.3 minutes (condition 1); HRMS: Anal. Calcd. for $C_{55}H_{63}N_8O_2$ 867.5068; found: 867.5058 (M+H).

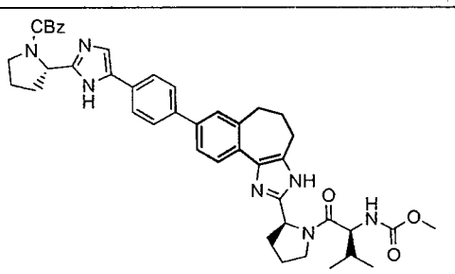
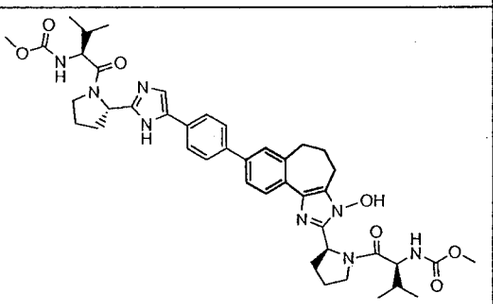
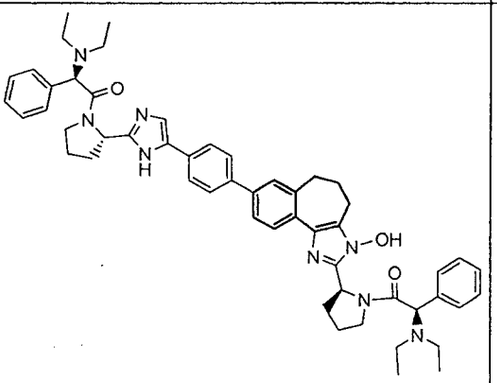
Example 22d (Derived from Example 21d and Cap-51)		RT = minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{50}N_8O_6$ 727.39; found: 727.32 (M+H).
Example 22e (Derived from Example 21e and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{42}H_{54}N_8O_6$ 767.4239; found: 767.4240 (M+H).
Example 22f (Derived from Example 21f and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{41}H_{52}N_8O_6$ 753.41; found: 753.54 (M+H).

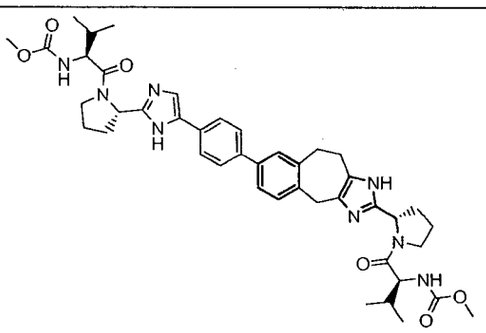
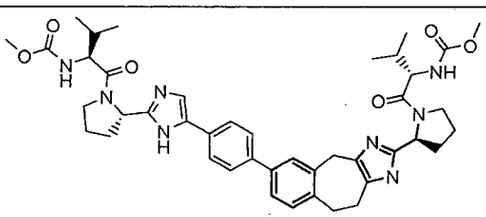
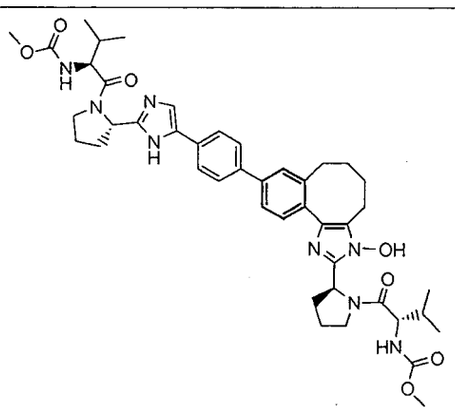
Example 22g (Derived from Example 21g and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{53}FN_8O_6$ 797.41; found: 797.21 (M+H).
Example 22g.1 (Derived from Example 21g and Cap-2)		RT = 1.4 minutes (condition 1); HRMS: Anal. Calcd. for $C_{53}H_{61}FN_8O_2$ 861.50; found: 861.31 (M+H).
Example 22g.2 (Derived from Example 21g and Cap-52)		RT = 1.4 minutes (condition 1); HRMS: Anal. Calcd. for $C_{39}H_{45}FN_8O_6$ 741.35; found: 741.19 (M+H).

Example 22g.3 (Derived from Example 21g and Cap-86)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{53}FN_8O_6$ 829.41; found: 829.25 (M+H).
Example 22h (Derived from Example 21h and Cap-51)		RT = 2.05 minutes (condition 2); LCMS: Anal. Calcd. for $C_{43}H_{52}F_2N_8O_6$ 815.41; found: 815.79 (M+H). HRMS: Anal. Calcd. for $C_{43}H_{52}F_2N_8O_6$ 815.4056; found: 815.4032 (M+H).
Example 22h.1 (Derived from Example 21h and Cap-2)		RT= 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{53}H_{60}F_2N_8O_2$ 879.49; found: 879.86 (M+H). HRMS: Anal. Calcd. for

		$C_{53}H_{60}F_2N_8O_2$ 879.4886; found: 879.4855 (M+H).
Example 22i (Derived from Example 21i and Cap-51)		RT = 1.8 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{56}N_9O$ 794.44; found: 794.41 (M+H). HRMS: Anal. Calcd. for $C_{43}H_{56}N_9O$ 794.4354; found: 794.4365 (M+H).
Example 22j (Derived from Example 21j and Cap-51)		RT= 1.6 minutes (condition 1); LCMS: Anal. Calcd. for $C_{43}H_{54}N_8O_6$ 779.42; found: 779.39 (M+H).
Example 22j.1 (Derived from Example 21j and Cap-2)		RT= 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{53}H_{62}N_8O_2$ 843.51; found:

		843.48 (M+H). HRMS: Anal. Calcd. for $C_{53}H_{62}N_8O_{43}$ 843.5074; found: 843.5079 (M+H).
Example 22k (Derived from Example 21k and Cap-51)		RT= 1.7 minutes (condition 1); LCMS: Anal. Calcd. for $C_{46}H_{58}N_8O_6$ 819.46; found: 819.50 (M+H). HRMS: Anal. Calcd. for $C_{46}H_{58}N_8O_6$ 819.4558; found: 819.4547 (M+H).
Example 22k.1 (Derived from Example 21k and Cap-2)		RT= 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{56}H_{66}N_8O_2$ 883.54; found: 883.56 (M+H). HRMS: Anal. Calcd. for $C_{56}H_{66}N_8O_2$ 883.5387; found: 883.5353 (M+H).

Example 22m (Derived from Example 21m and Cap-51)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. for $C_{44}H_{49}N_7O_5$ 756.39; found: 756.55 (M+H).
Example 22n (Derived from Example 21n and Cap-51)		RT = 2.1 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{55}N_8O_7$ 795.41; found: 795.53 (M+H). HRMS: Anal. Calcd. for $C_{43}H_{55}N_8O_7$ 795.4188; found: 795.4188 (M+H).
Example 22n.1 (Derived from Example 21n and Cap-2)		RT= 1.9 minutes (condition 2); LRMS: Anal. Calcd. for $C_{53}H_{63}N_8O_3$ 859.49; found: 859.59 (M+H). HRMS: Anal. Calcd. for $C_{53}H_{63}N_8O_3$ 859.5018; found: 859.5015 (M+H).

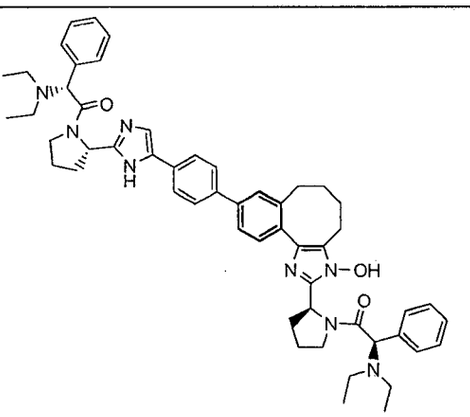
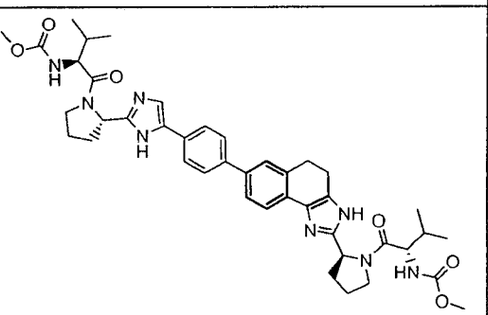
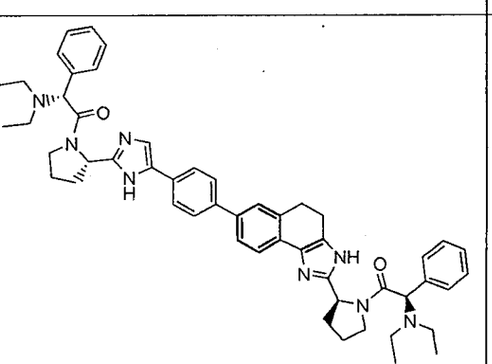
Example 22o (Derived from Example 21o and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{54}N_8O_5$ 779.4239; found: 779.4242 (M+H).
Example 22p (Derived from Example 21p and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{54}N_8O_5$ 779.4239; found: 779.4243 (M+H).
Example 22q (Derived from Example 21q and Cap-51)		RT = 2.2 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_7$ 809.43; found: 809.53 (M+H). HRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_7$ 809.4345; found: 809.4345 $(M+H)^+$.

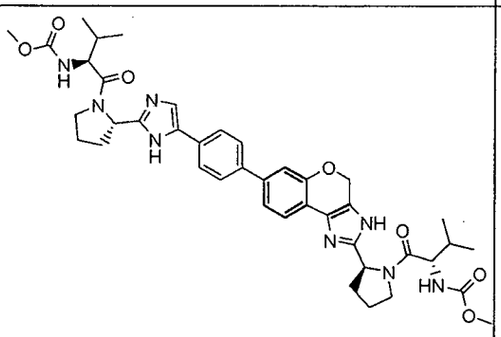
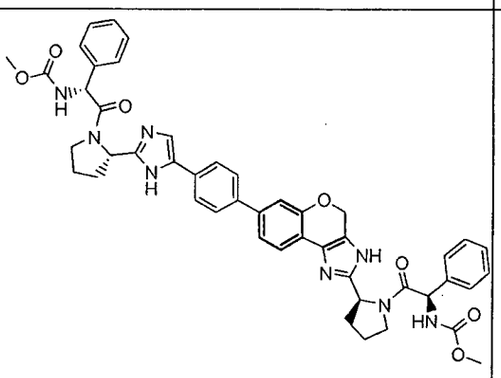
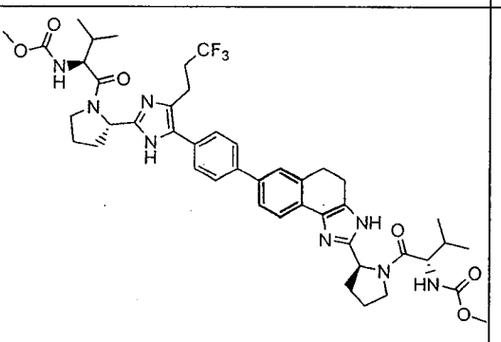
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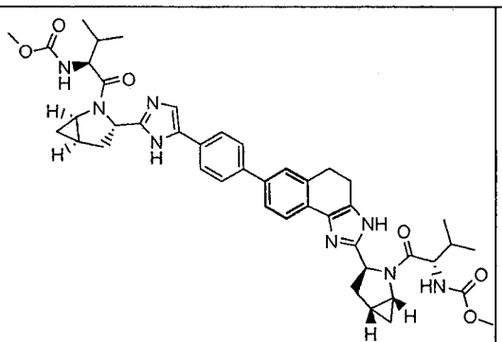
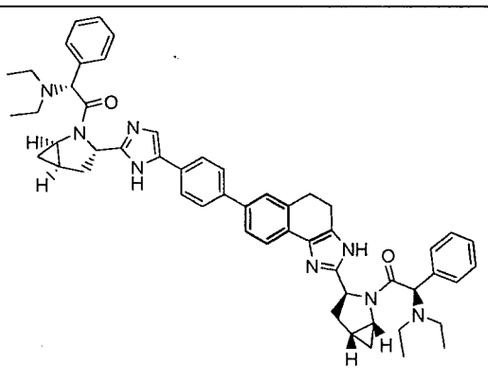
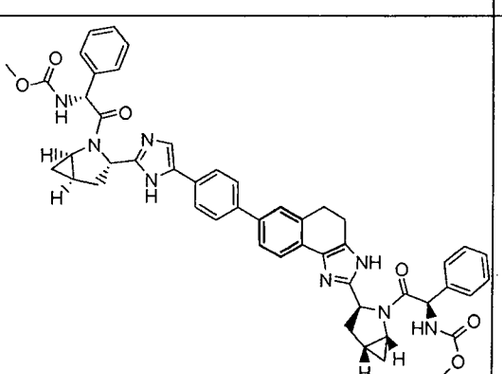
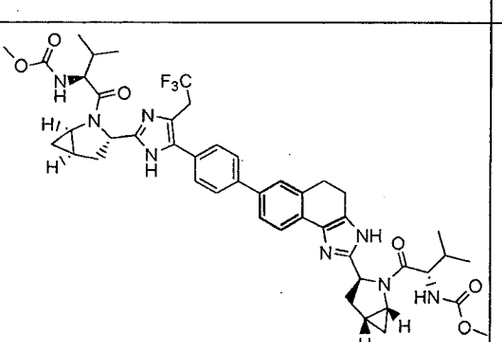
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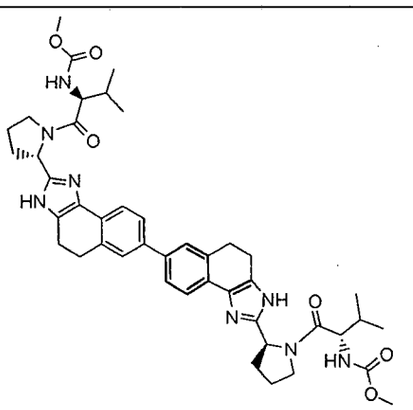
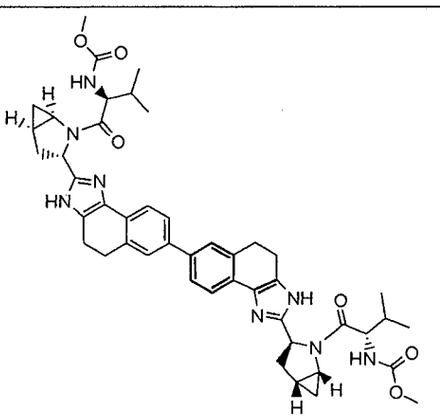
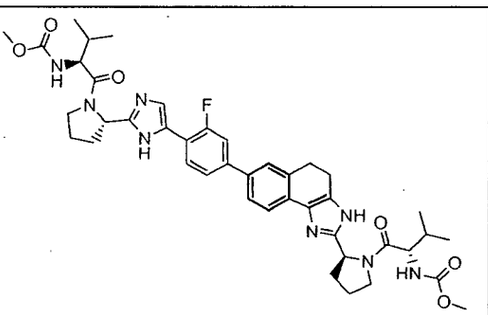
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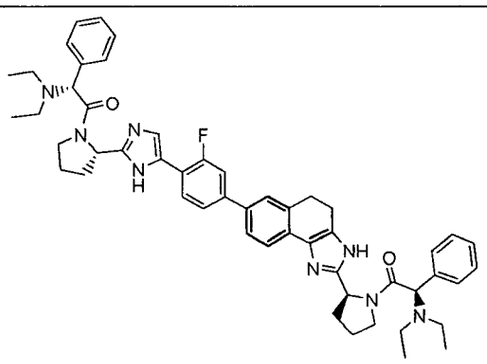
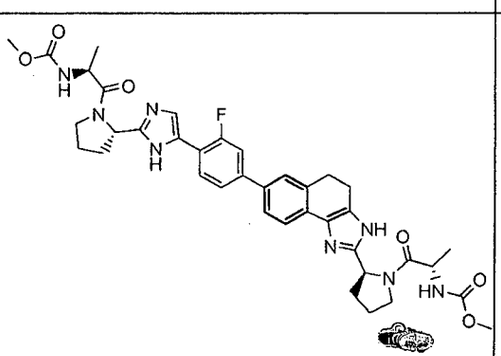
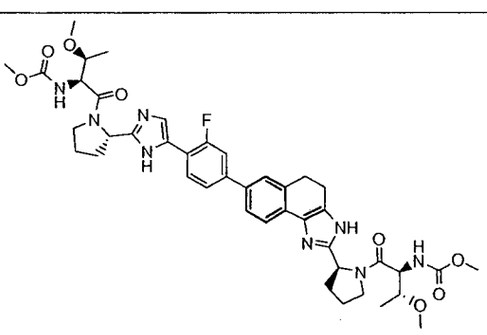
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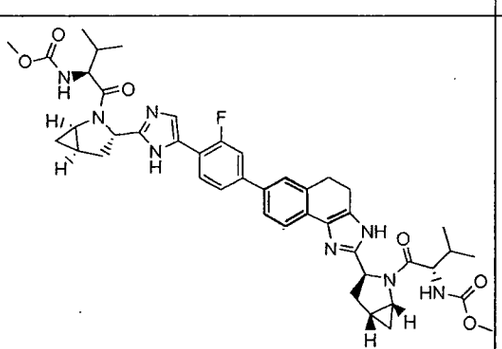
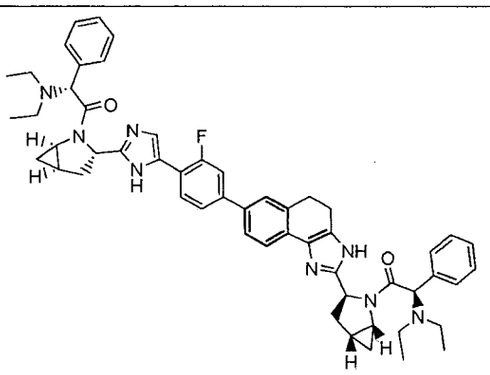
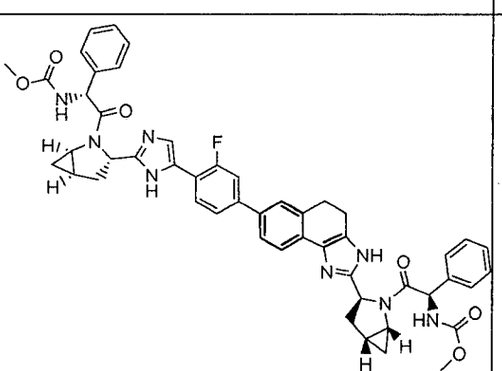
Example 22q.1 (Derived from Example 21q and Cap-2)		RT = 1.9 minutes (condition 2); LRMS: Anal. Calcd. for $C_{54}H_{65}N_8O_3$ 873.51; found: 873.60 (M+H). HRMS: Anal. Calcd. for $C_{54}H_{65}N_8O_3$ 873.5174; found: 873.5171 (M+H).
Example 22r (Derived from Example 21r and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{53}N_8O_6$ 765.41; found: 765.51 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{53}N_8O_6$ 765.4083; found: 765.4088 (M+H).
Example 22r.a (Derived from Example 21r and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{61}N_8O_2$ 829.49; found: 829.65 (M+H). HRMS: Anal.

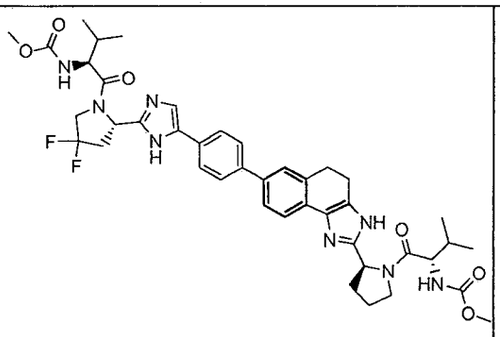
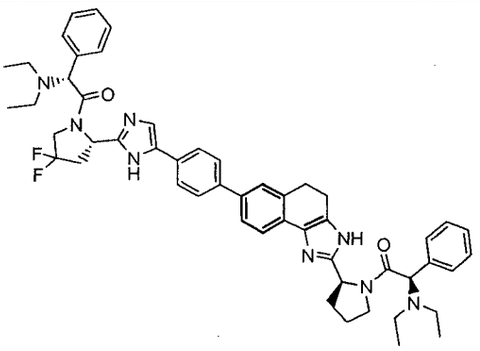
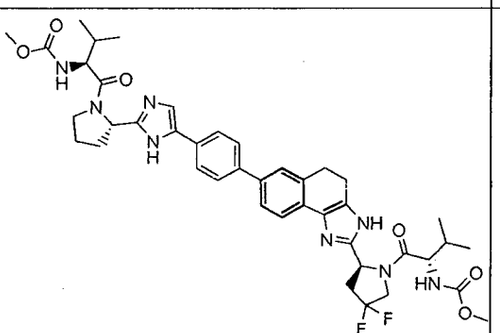
		Calcd. for $C_{52}H_{61}N_8O_2$ 829.4912; found: 829.4917 (M+H).
Example 22r.b (Derived from Example 21r.a and Cap-51)		RT = 2.1 minutes (condition 4); LCMS: Anal. Calcd. for $C_{41}H_{51}N_8O_7$ 767.67; found: 767.17 (M+H).
Example 22r.c (Derived from Example 21r.a and Cap-4)		RT = 2.2 minutes (condition 4); LCMS: Anal. Calcd. for $C_{47}H_{47}N_8O_7$ 835.35; found: parent not obs. (M+H).
Example 22r.1 (Derived from Example 21r.1 and Cap-51)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{45}H_{56}N_8O_6$ 861.43; found: 861.61 (M+H).

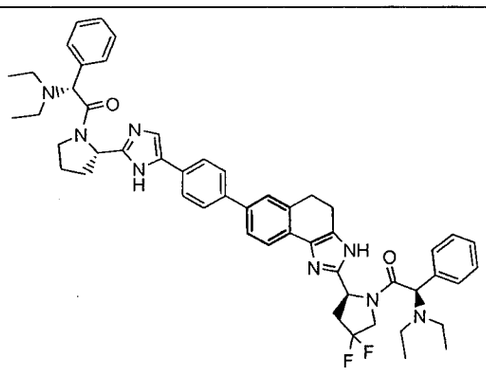
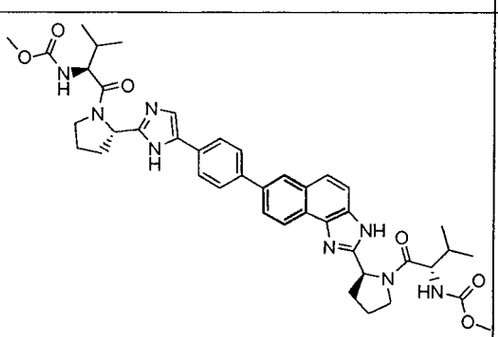
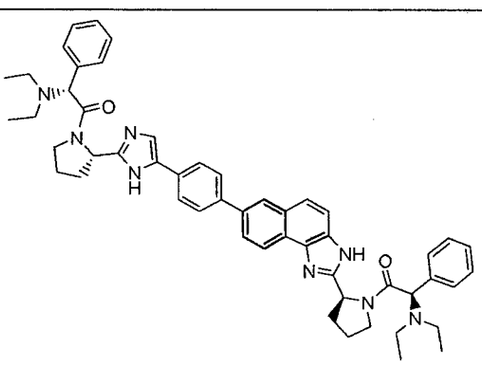
Example 22r.2 (Derived from Example 21r.2 and Cap-51)		RT = 1.95 min (condition 2). HRMS: Calcd for $C_{44}H_{53}N_8O_6$ 789.4083; found: 789.4098 (M+H).
Example 22r.2a (Derived from Example 21r.2 and Cap-2)		RT = 1.70 min (condition 2). HRMS: Calcd for $C_{54}H_{61}N_8O_2$ 853.4912; found: 853.4925 (M+H).
Example 22r.2b (Derived from Example 21r.2 and Cap-4)		RT = 1.85 min (condition 2); LCMS: Anal. Calcd for $C_{50}H_{49}N_8O_6$ 857.38; found: 857.41 (M+H).
Example 22r.3 (Derived from Example 21r.3 and Cap-51)		RT = 1.6 minutes (condition 1). HRMS: Anal. Calcd. for $C_{46}H_{54}F_3N_8O_6$ 871.4113; found: 871.4114 (M+H).

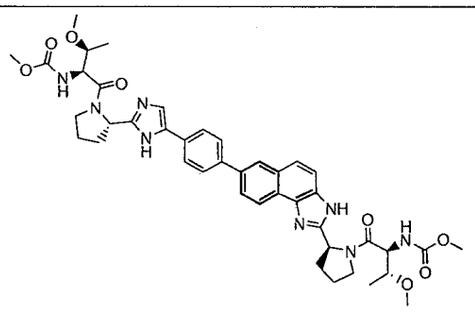
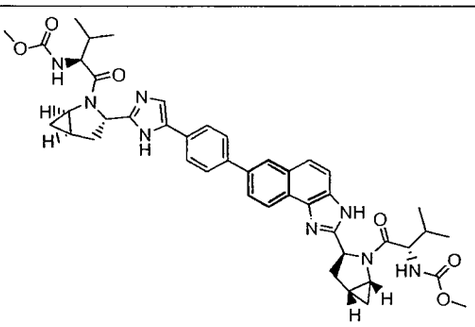
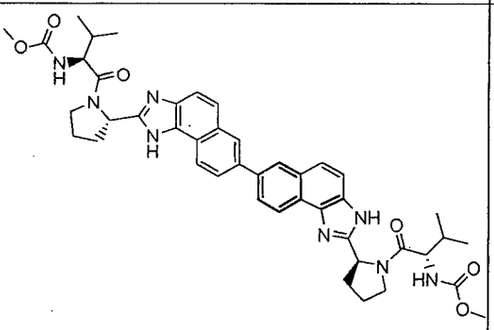
Example 22r.4 (Derived from Example 21r.4 and Cap-51)		RT = 1.97 min (condition 2). HRMS: Calcd for $C_{44}H_{55}N_8O_6$ 791.4239; found: 791.4329 (M+H).
Example 22r.5 (Derived from Example 21r.5 and Cap-51)		RT = 2.02 min (condition 2); LCMS: Anal. Calcd for $C_{46}H_{55}N_8O_6$ 815.42; found: 815.52 (M+H). HRMS: Calcd for $C_{46}H_{55}N_8O_6$ 815.4239; found: 813.4239 (M+H).
Example 22s (Derived from Example 21s and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{52}FN_8O_6$ 783.39; found: 783.64 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{52}FN_8O_6$ 783.3988; found:

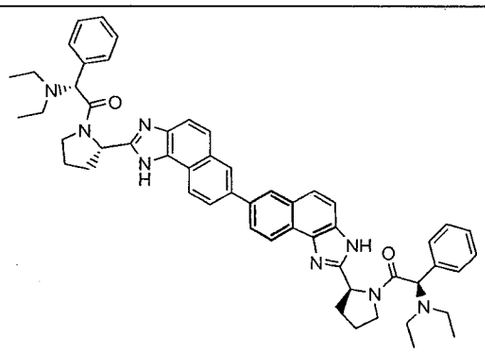
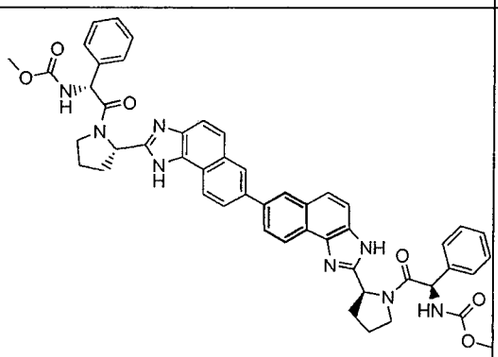
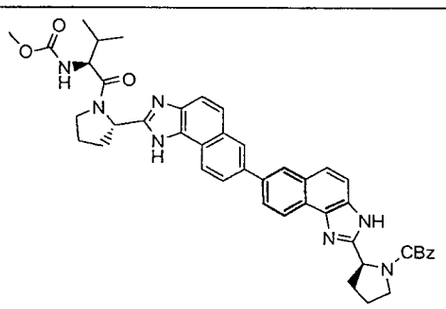
		783.3972 (M+H).
Example 22s.a (Derived from Example 21s and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{60}FN_8O_2$ 847.47; found: 847.76 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{60}FN_8O_2$ 847.4818; found: 847.4804 (M+H).
Example 22s.b (Derived from Example 21s and Cap-52)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{38}H_{43}FN8O_6$ 727.34; found: 727.70 (M+H). HRMS: Anal. Calcd. for $C_{38}H_{43}FN_8O_6$ 727.3362; found: 727.3378 (M+H).
Example 22s.c (Derived from Example 21s and Cap-86)		RT = 1.9 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}FN_8O_8$ 815.39; found: 815.73 (M+H).

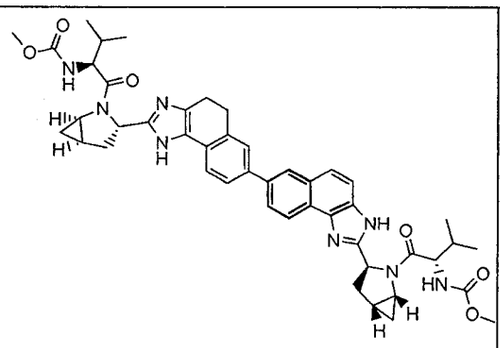
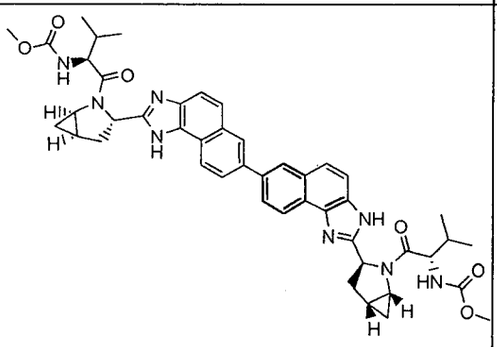
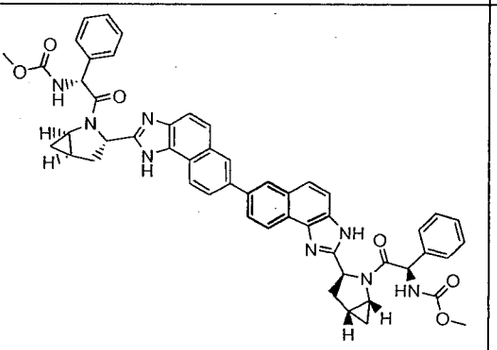
		HRMS: Anal. Calcd. for $C_{42}H_{51}FN_8O_8$ 815.3887; found: 815.3916 (M+H).
Example 22s.1 (Derived from Example 21s.1 and Cap-51)		RT = 2.00 min, (condition 2). HRMS: Calcd for $C_{44}H_{52}FN_8O_6$ 807.3988; found: 807.4008 (M+H).
Example 22s.1a (Derived from Example 21s.1 and Cap-2)		RT =1.74 min, (condition 2). HRMS: Calcd for $C_{54}H_{60}FN_8O_2$ 871.4818; found: 871.4830 (M+H)..
Example 22s.1b (Derived from Example 21s.1 and Cap-4)		RT = 2.02 min (condition 2); LCMS: Anal. Calcd for $C_{50}H_{48}FN_8O_6$ 875.37; found: 875.53 (M+H).

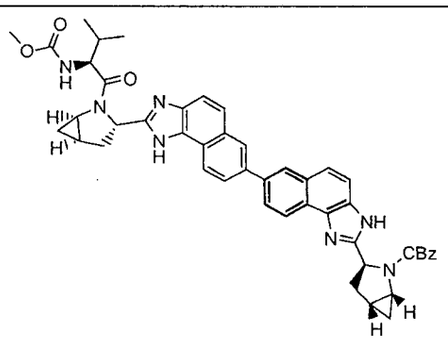
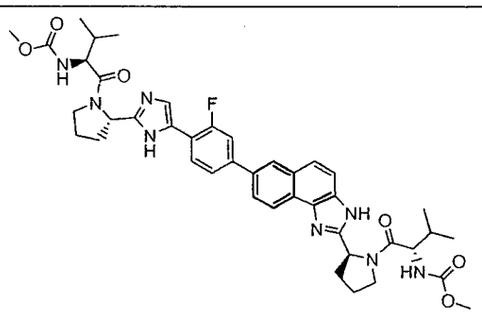
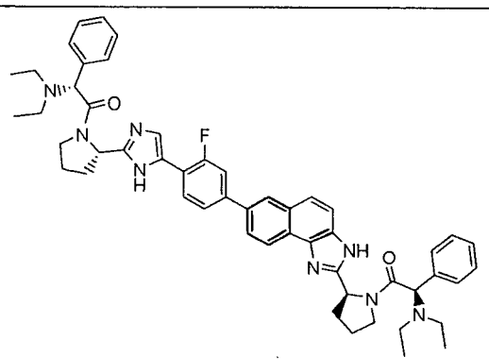
Example 22t (Derived from Example 21t and Cap-51)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}F_2N_8O_6$ 801.39; found: 801.73 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{51}F_2N_8O_6$ 801.3900; found: 801.3874 (M+H).
Example 22t.a (Derived from Example 21t and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.47; found: 865.86 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.4729; found: 865.4706 (M+H).
Example 22t.1 (Derived from Example 21t.1 and Cap-51)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{50}F_2N_8O_6$ 801.39; found: 801.45 (M+H). HRMS: Anal.

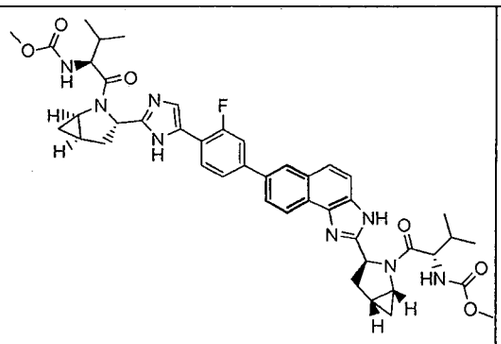
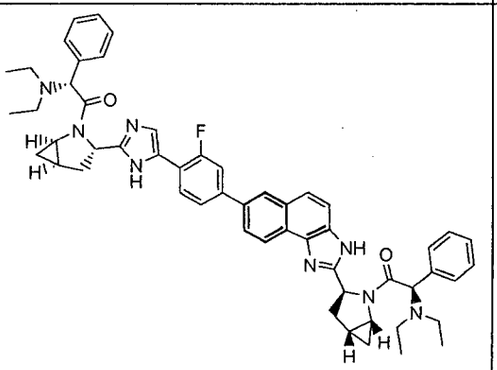
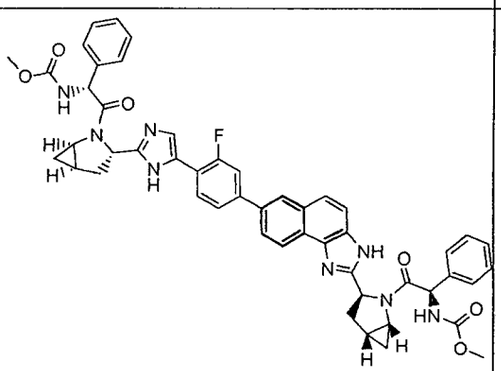
		Calcd. for $C_{42}H_{50}F_2N_8O_6$ 801.3894; found: 801.3923 (M+H).
Example 22t.1a (Derived from Example 21t.1 and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.47; found: 865.54 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.4724; found: 865.4735 (M+H).
Example 22u (Derived from Example 21u and Cap-51)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}N_8O_6$ 763.39; found: 763.75 (M+H).
Example 22u.a (Derived from Example 21u and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{59}N_8O_2$ 827.48; found: 827.75 (M+H). HRMS: Anal. Calcd. for

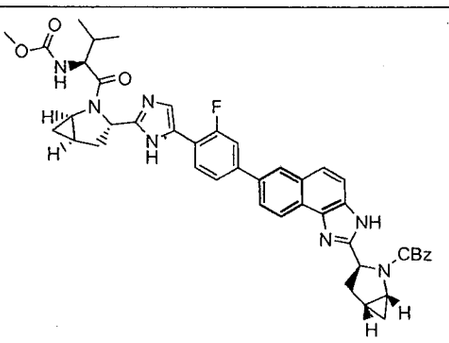
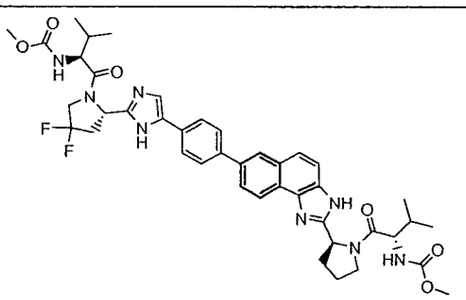
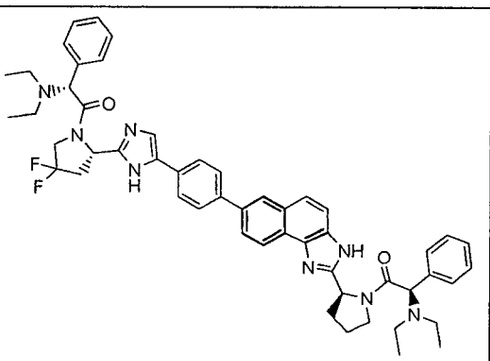
		$C_{52}H_{59}N_8O_2$ 827.4756; found: 827.4762 (M+H).
Example 22u.b (Derived from Example 21u and Cap-86)		RT = 1.9 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}N_8O_8$ 795.38; found: 795.72 (M+H).
Example 22u.1 (Derived from Example 21u.1 and Cap-51)		RT = 2.00 min, (condition 2), LCMS: Anal. Calcd for $C_{44}H_{51}N_8O_6$ 787.39; found: 787.39 (M+H). HRMS: Calcd for $C_{44}H_{51}N_8O_6$ 787.3926; found: 787.3944 (M+H).
Example 22u.2 (Derived from Example 21x and Cap-51)		RT = 2.0 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_6$ 787.39; found: 787.58 (M+H). HRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_6$ 787.3926; found:

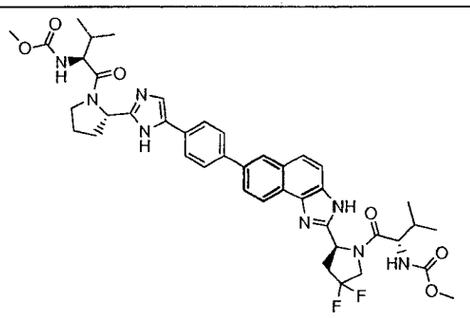
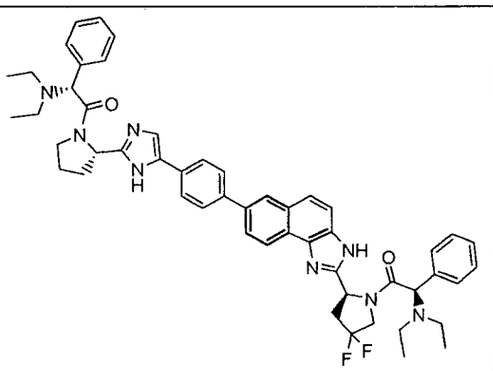
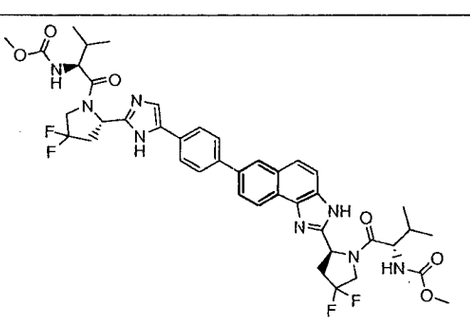
		787.3921 (M+H).
Example 22u.2a (Derived from Example 21x and Cap-2)		RT = 1.86 min, (condition 2), LCMS: Anal. Calcd for $C_{54}H_{59}N_8O_2$ 851.48; found: 851.44 (M+H). HRMS: Calcd for $C_{54}H_{59}N_8O_2$ 851.4755; found: 851.4756 (M+H).
Example 22u.2b (Derived from Example 21x and Cap-4)		RT = 2.14 min, (condition 2), LCMS: Anal. Calcd for $C_{50}H_{47}N_8O_6$ 855.36; found: 855.58 (M+H). HRMS: Calcd for $C_{50}H_{47}N_8O_6$ 855.3613; found: 855.3611 (M+H).
Example 22u.3 (Derived from Example 21u.3 and Cap-51)		RT = 2.18 min, (condition 2), LCMS: Anal. Calcd for $C_{45}H_{46}N_7O_5$ 764.36; found: 764.57 (M+H).

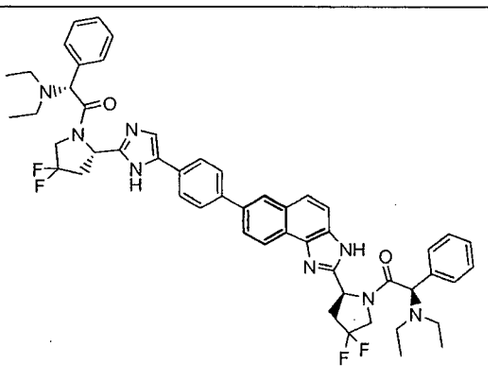
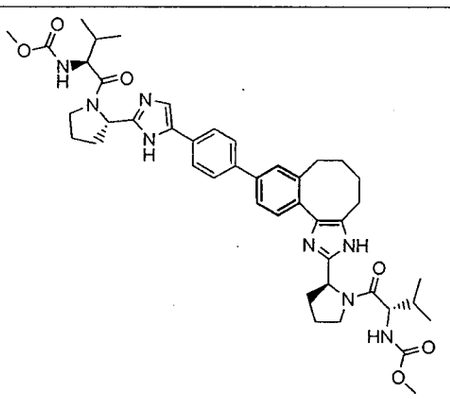
Example 22u.4 (Derived from Example 21u.4 and Cap-51)		RT = 2.08 min (condition 2); LCMS: Anal. Calcd for $C_{46}H_{53}N_8O_6$ 813.41; found: 813.35 (M+H). HRMS: Calcd for $C_{46}H_{53}N_8O_6$ 813.4083; found: 813.4087 (M+H).
Example 22u.5 (Derived from Example 21u.5 and Cap-51)		RT = 2.14 min, (condition 2), LCMS: Anal. Calcd for $C_{46}H_{51}N_8O_6$ 811.39; found: 811.39 (M+H). HRMS: Calcd for $C_{46}H_{51}N_8O_6$ 811.3926; found: 811.3945 (M+H).
Example 22u.5a (Derived from Example 21u.5 and Cap-4)		RT = 2.02 min (condition 2); LCMS: Anal. Calcd for $C_{52}H_{47}N_8O_6$ 879.36; found: 879.53 (M+H).

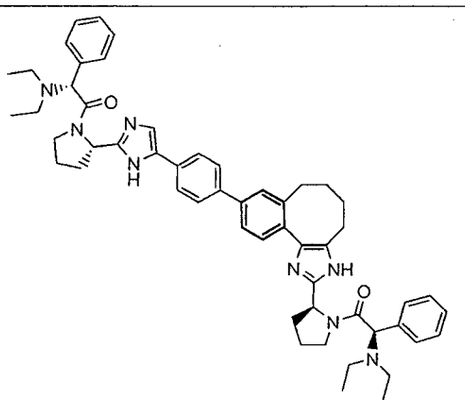
Example 22u.6 (Derived from Example 21u.6 and Cap-51)		RT = 2.02 min; (condition 2); LCMS: Anal. Calcd for $C_{47}H_{46}N_7O_5$ 788.41; found: 788.36 (M+H).
Example 22v (Derived from Example 21v and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{50}FN_8O_6$ 781.38; found: 781.85 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{50}FN_8O_6$ 781.3832; found: 781.3850 (M+H).
Example 22v.a (Derived from Example 21v and Cap-2)		RT = 1.7 minutes (condition 2). HRMS: Anal. Calcd. for $C_{52}H_{58}FN_8O_2$ 845.4661; found: 845.4655 (M+H).

Example 22v.1 (Derived from Example 21v.1 and Cap-51)		RT =2.05 min, (condition 2), Calcd for $C_{44}H_{50}FN_8O_6$ 805.38; found: 805.35 (M+H). HRMS: Calcd for $C_{44}H_{50}FN_8O_6$ 805.3832; found: 805.3850 (M+H).
Example 22v.1a (Derived from Example 21v.1 and Cap-2)		RT = 1.38 min, (condition 2). HRMS: Calcd for $C_{54}H_{58}FN_8O_2$ 869.4678 found: 869.4661 (M+H).
Example 22v.1b (Derived from Example 21v.1 and Cap-4)		RT = 1.94 min (condition 2); Anal. Calcd for $C_{50}H_{47}FN_8O_6$ 873.35; found: 873.33 (M+H).

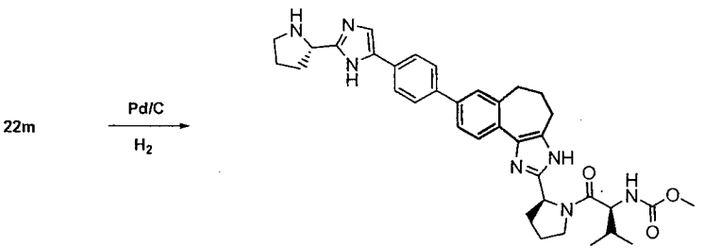
Example 22v.1c (Derived from Example 21v.2 and Cap-51)		RT = 1.88 minutes (condition 2); LCMS: Anal. Calcd. for $C_{45}H_{45}FN_7O_5$ 782.35; found: 782.22 (M+H).
Example 22w (Derived from Example 21w and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.37; found: 799.81 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.3738; found: 799.3759 (M+H).
Example 22w.a (Derived from Example 21w and Cap-2)		RT = 1.7 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.47; found: 863.64 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4567; found: 863.4561 (M+H).

Example 22w.1 (Derived from Example 21w.1 and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.37; found: 799.41 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.3738; found: 799.3761 (M+H).
Example 22w.1a (Derived from Example 21w.1 and Cap-2)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.46; found: 863.50 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4567; found: 863.4575 (M+H).
Example 22w.2 (Derived from Example 21w.2 and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{47}F_4N_8O_6$ 835.36; found: 835.61 (M+H). HRMS: Anal.

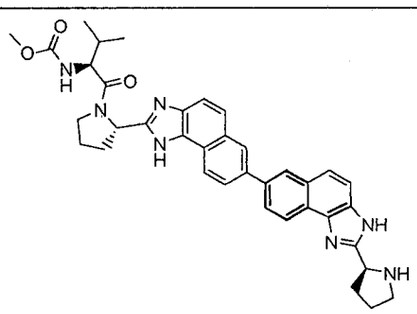
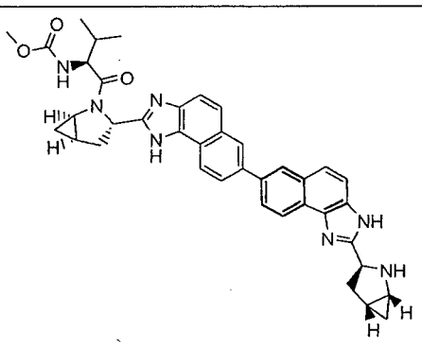
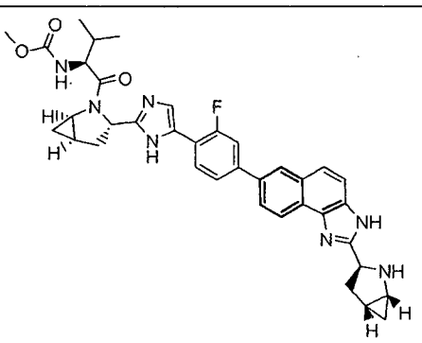
		Calcd. for $C_{42}H_{47}F_4N_8O_6$ 835.3549; found: 835.3547 (M+H).
Example 22w.2a (Derived from Example 21w.2 and Cap-2)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_2$ 899.44; found: 899.66 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_2$ 899.4379; found: 899.4375 (M+H).
Example 22x.1 (Derived from Example 21x.1 and Cap-51)		RT = 2.1 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_6$ 793.43; found: 793.48 (M+H). HRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_6$ 793.4396; found: 793.4396 (M+H).

Example 22x.1a (Derived from Example 21x.1 and Cap-2)		RT = 1.8 minutes (condition 2); LRMS: Anal. Calcd. for $C_{54}H_{65}N_8O_2$ 857.52; found: 857.61 (M+H). HRMS: Anal. Calcd. for $C_{54}H_{65}N_8O_2$ 857.5225; found: 857.5219 (M+H).

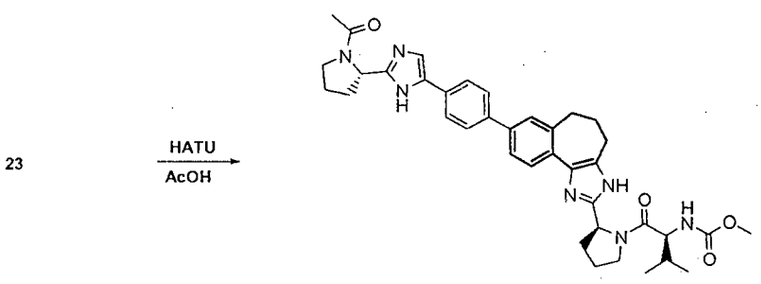
Synthetic route 15 (Unsymmetrical Cap Analogs)



A solution of Example 22m, (149 mg, 0.197 mmol) and K_2CO_3 (27 mg) in CH_3OH (5 mL) and water (0.3 mL) was flushed with nitrogen and 10% palladium/carbon (30 mg) added. The reaction was flushed with hydrogen and stirred 6 h, filtered through diatomaceous earth (Celite®), and the filtrate concentrated and dried under high vacuum to give Example 23, 122 mg (100%) RT = 1.5 minutes (condition 1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 7.6 Hz, 2H), 7.50-7.40 (m, 3H), 7.28 (d, J = 8.6 Hz, 1H), 5.04 (br. s, 1H), 4.18 (t, J = 7.0 Hz, 1H), 4.09 (t, J = 8.2 Hz, 1H), 3.82 (br. s, 2H), 3.55 (s, 3H), 3.01-2.85 (m, 6H), 2.16-1.71 (m, 10H), 0.9-0.87 (m, 7H). LRMS: Anal. Calcd. for $C_{36}H_{43}N_7O_3$ 622.35; found: 622.44 (M+H).

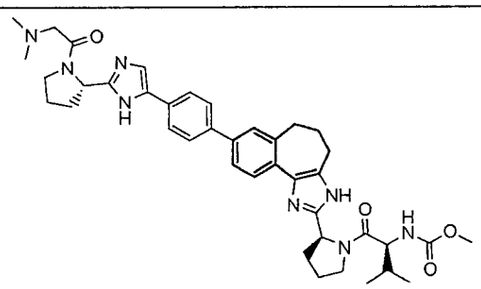
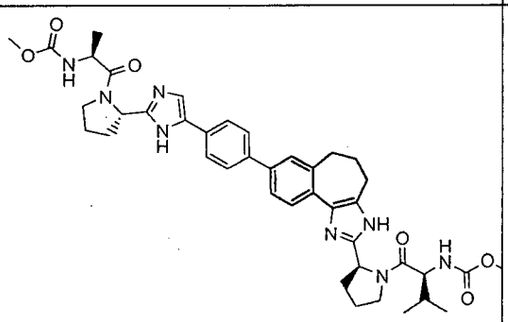
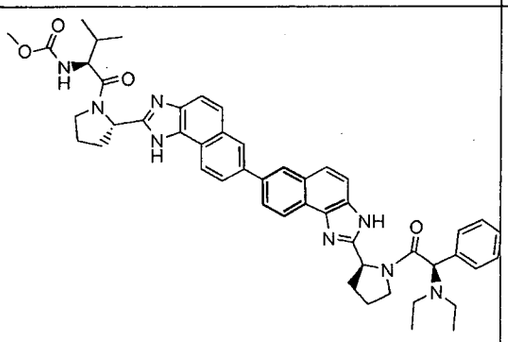
Example 23.1 (Derived from Example 22u.3)		RT = 1.90 minutes (condition 2), LCMS: Calcd for $C_{37}H_{40}N_7O_3$ 630.32; found: 630.41 (M+H).
Example 23.2 (Derived from Example 22u.6)		RT = 1.75 minutes (condition 2), LCMS: Calcd for $C_{39}H_{40}N_7O_3$ 654.32; found: 654.35 (M+H).
Example 23.3 (Derived from Example 22v.1c)		RT = 1.57 minutes (condition 2), LCMS: Calcd for $C_{37}H_{39}FN_7O_3$ 648.31; found: 648.21 (M+H).

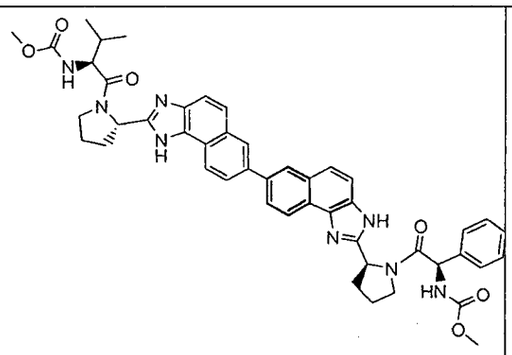
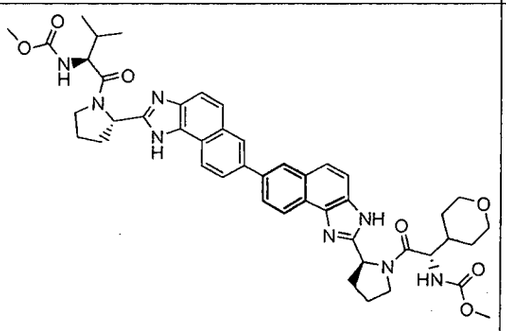
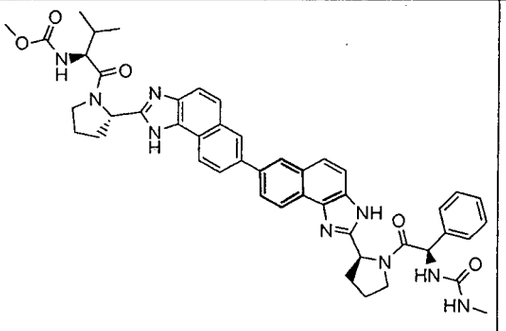
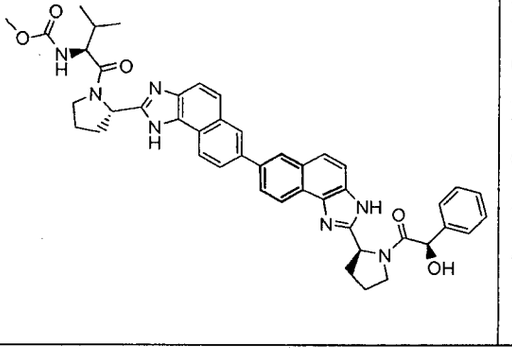
Synthetic route 16 (Unsymmetrical Cap Analogs)

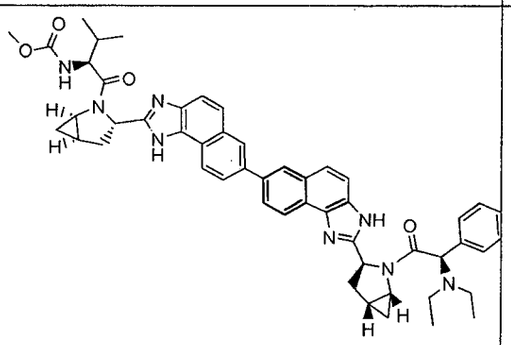
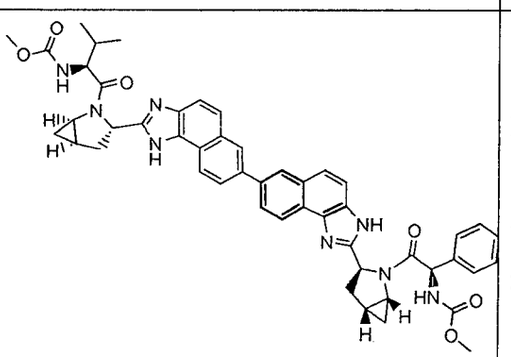
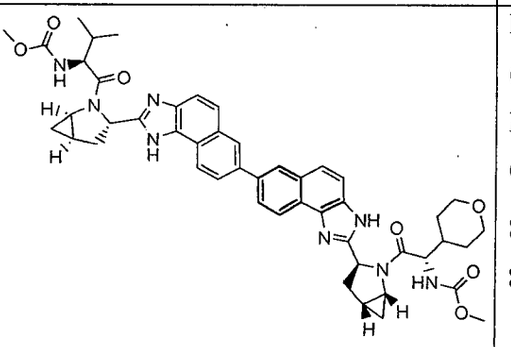
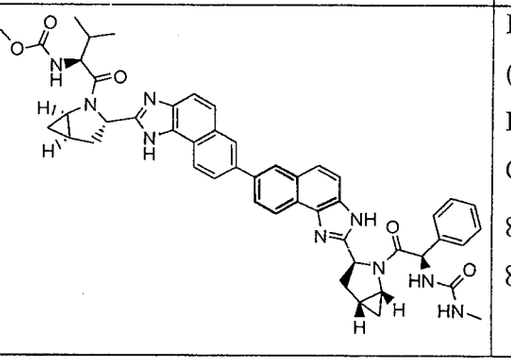


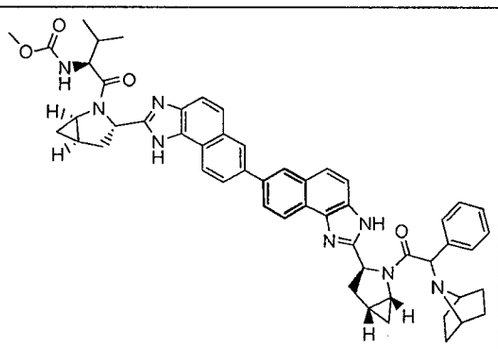
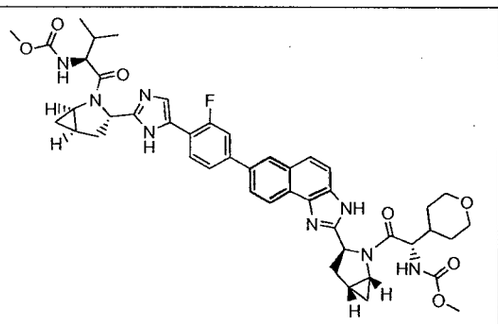
Capping was performed on Example 23 as described in synthetic route 14 to prepare Example 22. Except only 1 equivalent of HATU and 4 equivalents Hunig's base

were used to prepare Example 24: RT = 1.5 minutes (condition 1); LCMS: Anal. Calcd. for $C_{38}H_{45}N_7O_4$ 664.36; found: 664.48 (M+H).

Example 24.a (Derived from Example 23 and N,N-dimethyl glycine)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_4$ 707.40; found: 707.53 (M+H).
Example 24.b (Derived from Example 23 and Cap-52)		RT = 1.5 minutes (condition 1); LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_6$ 751.39; found: 751.33 (M+H).
Example 24.1 (Derived from Example 23.1 and Cap-2)		RT = 1.95 min, (condition 2), LCMS: Calcd for $C_{49}H_{55}N_8O_4$ 819.43; found: 819.65 (M+H).

Example 24.1a (Derived from Example 23.1 and Cap-4)		RT = 2.10 (condition 2), LCMS: Calcd for $C_{47}H_{49}N_8O_8$ 821.38; found: 821.61 (M+H).
Example 24.1b (Derived from Example 23.1 and Cap-170)		RT = 1.98 min (condition 2), LCMS: Calcd for $C_{46}H_{53}N_8O_7$ 829.40; found: 829.61 (M+H).
Example 24.1c (Derived from Example 23.1 and Cap-45a)		RT = 2.14 min (condition 2), LCMS: Calcd for $C_{48}H_{52}N_9O_5$ 834.41; found: 834.60 (M+H).
Example 24.1d (Derived from Example 23.1 and R-Mandelic acid)		RT = 2.02 min, (condition 2), LCMS: Calcd for $C_{45}H_{46}N_7O_5$ 764.36; found: 764.57 (M+H).

Example 24.2 (Derived from Example 23.2 and Cap-2)		RT = 1.80 min; (condition 2); LCMS: Calcd for $C_{51}H_{55}N_8O_4$ 843.43; found: 843.48 (M+H).
Example 24.2a (Derived from Example 23.2 and Cap-4)		RT = 1.99 min; (condition 2); LCMS: Calcd for $C_{49}H_{49}N_8O_6$ 845.38; found: 845.32 (M+H).
Example 24.2b (Derived from Example 23.2 and Cap-170)		RT = 1.85 min (condition 2); LCMS: Calcd for $C_{48}H_{53}N_8O_7$ 853.40; found: 853.51 (M+H).
Example 24.2c (Derived from Example 23.2 and Cap-45a)		RT = 2.02 min, (condition 2), LCMS: Calcd for $C_{50}H_{52}N_9O_5$ 858.41; found: 858.36 (M+H).

Example 24.2d (Derived from Example 23.2 and Cap-77)		RT = 1.81 min; (condition 2); LCMS: Calcd for $C_{53}H_{55}N_8O_4$ 867.43; found: 867.47 (M+H).
Example 24.3 (Derived from Example 23.3 and Cap-170)		RT = 1.68 min; (condition 2); LCMS: Calcd for $C_{46}H_{52}FN_8O_7$ 847.40; found: 847.32 (M+H).

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.

HCV 1b-377-neo replicon cells were used to test the currently described compound series as well as cells resistant to compound A containing a Y2065H mutation in NS5A (described in application PCT/US2006/022197). The compounds tested were determined to have more than 10-fold less inhibitory activity on cells containing the mutation than wild-type cells indicating a related mechanism of action between the two compound series. Thus, the compounds of the present disclosure can be effective to inhibit the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/O4014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype.

It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC50 values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment compounds of the present disclosure are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC50 ranges against HCV 1b are as follows: A = >100 nM; B = 1-99 nM; C = 101-999 pM; and D = 1-100 pM.

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

Table 2

Example	*Activity or Range*
22	5 pM
22.1	D
22.2	D
22.3	D
22a.1	D
22a.2	D
22a.3	10 pM
22a.4	D
22b	D
22b.1	D
22b.2	D
22b.3	D
22c	D
22c.1	D
22c.3	D
22d	D
22e	3 pM
22f	D
22g	1 pM

22g.1	D
22g.2	20 pM
22g.3	D
22h	D
22h.1	D
22i	130 pM
22j	14 nM
22j.1	B
22k	D
22k.1	D
22m	D
22n	D
22n.1	D
22o	C
22p	160 pM
22q	D
22q.1	D
22r	D
22r.a	D
22r.b	D
22r.1	D
22r.2	D
22r.2a	D
22r.2b	D
22r.3	3 pM
22r.4	D
22r.5	D
22s	D
22s.a	D
22s.c	20 pM
22s.1	D
22s.1a	D

22s.1b	D
22t	1 pM
22t.a	D
22t.1	D
22t.1a	D
22u	D
22u.a	10 pM
22u.b	D
22u.1	D
22u.2	D
22u.2a	D
22u.2b	20 pM
22u.4	D
22u.5	D
22u.5a	D
22v	D
22v.a	C
22v.1	D
22v.1a	D
22v.1b	D
22w	D
22w.a	120 pM
22w.1	D
22w.1a	D
22w.2	D
22w.2a	D
22x.1	D
22x.1a	D
24	320 pM
24.a	D
24.b	D
24.1	D

24.1a	D
24.1b	D
24.1c	D
24.1d	D
24.2	D
24.2a	D
24.2b	D
24.2c	D
24.2d	D
24.3	

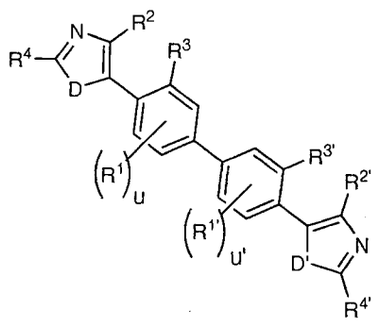
It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects 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

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

D and D' are each independently selected from NR^5, O, and S; wherein each R^5 is independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, hydroxy, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl;

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

R^2 is selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

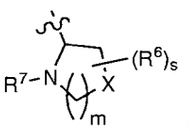
R^3 is selected from hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; or

R^2 and R^3, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy,

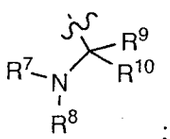
haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, oxo, and spirocycle;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, oxo, and spirocycle;

R^4 and $R^{4'}$ are each independently selected from



and



; wherein

each m is independently 0, 1, or 2;

each s is independently 0, 1, 2, 3, or 4;

each X is independently selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$; provided that when n is 0, X is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and -NR^aR^b, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each R^7 is independently selected from hydrogen and R^{11}-C(O)-, and R^{11}-C(S)-;

R^8 is selected from hydrogen and alkyl;

R^9 and R^{10} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

R^9 and R^{10}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^z, O, and S; wherein R^z is selected from hydrogen and alkyl; and

each R^{11} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy,

arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein D and D' are each NR^5.

3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently selected from hydrogen and hydroxy.

4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein u and u' are each 0.

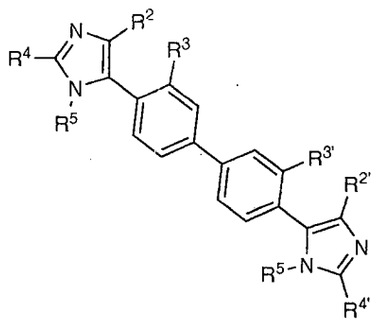
5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and haloalkyl.

6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen and halo.

7. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3, together with the carbon atoms to which they are attached, form a six- or seven-membered carbocyclic ring.

8. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered ring optionally containing one heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups.

9. A compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

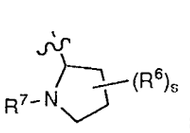
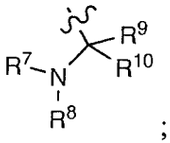
R^2 is selected from hydrogen and haloalkyl; and

R^3 is selected from hydrogen and halo; or

R^2 and R^3, together with the carbon atoms to which they are attached, form a five- or six-membered aromatic or non-aromatic ring carbocyclic ring;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered aromatic or non-aromatic ring optionally containing one heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups;

R^4 and $R^{4'}$ are each independently selected from

 and  ; wherein

each s is 0 or 2;

each R^6 is independently selected from alkyl and halo, wherein the alkyl forms a fused three-membered ring with an adjacent carbon atom;

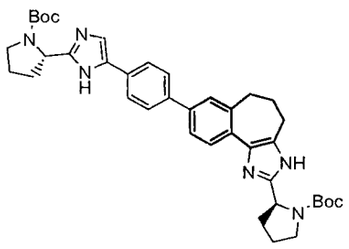
each R^7 is independently selected from hydrogen and R^{11}-C(O)-;

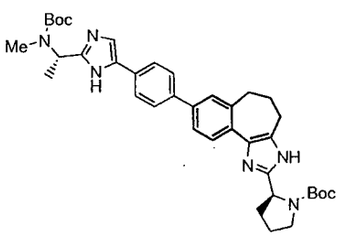
R^8 is selected from hydrogen and alkyl;

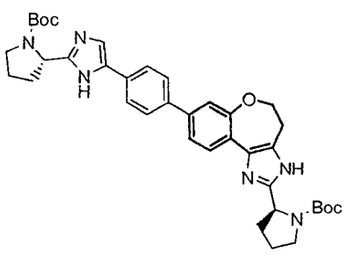
R^9 and R^{10} are each independently selected from hydrogen and alkyl; and

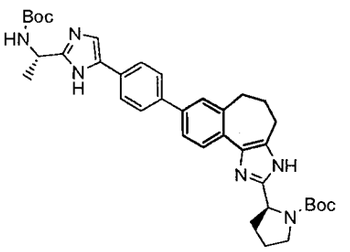
each R^{11} is independently selected from alkyl, arylalkoxy, arylalkyl, and (NR^cR^d)alkyl.

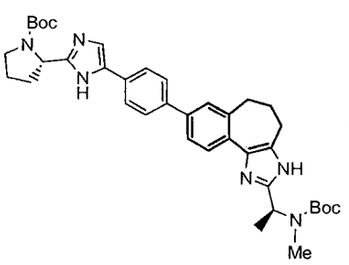
10. A compound selected from:

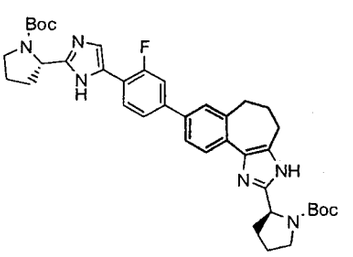


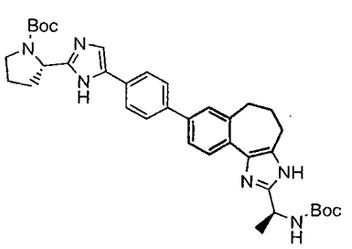


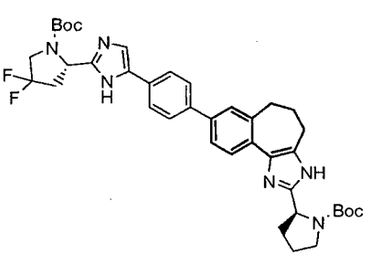


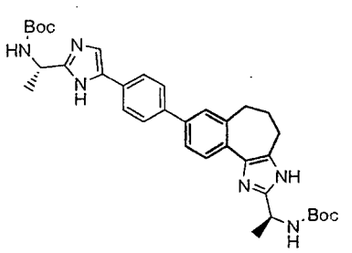


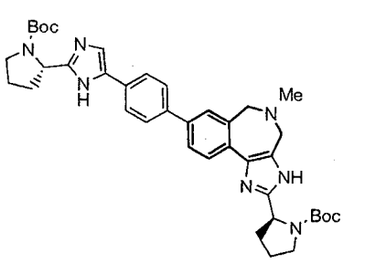


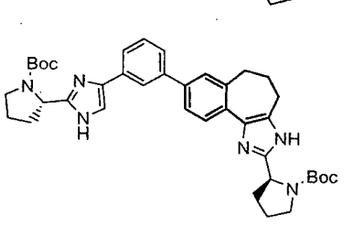




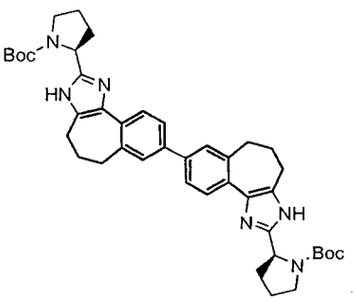


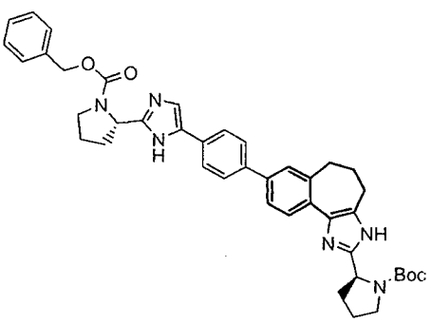


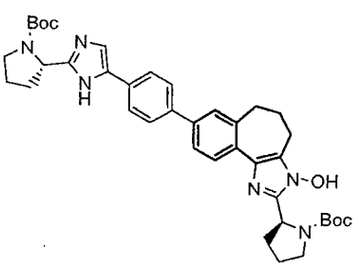


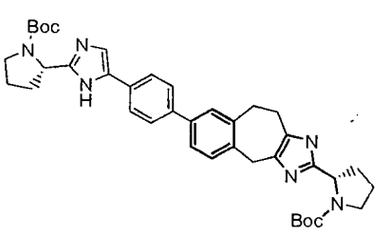


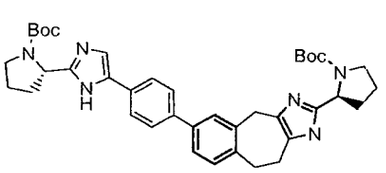


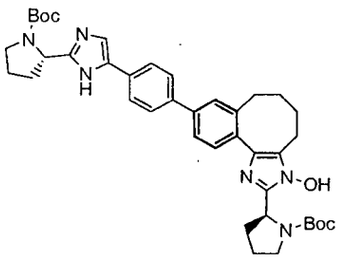


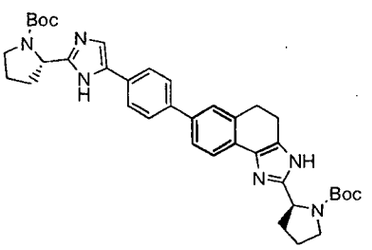


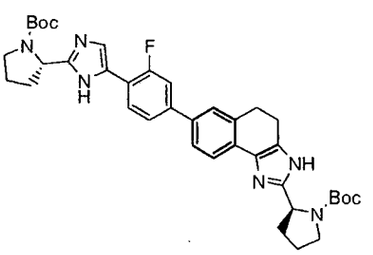


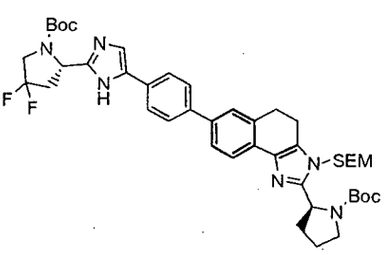


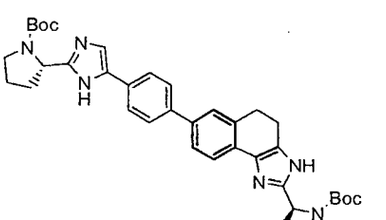


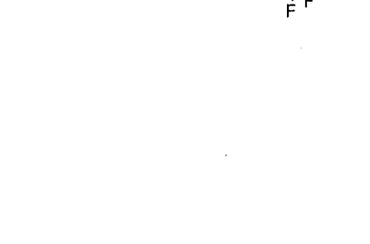


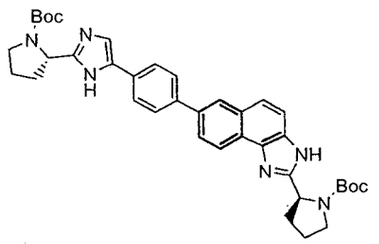


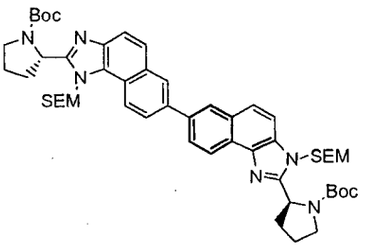


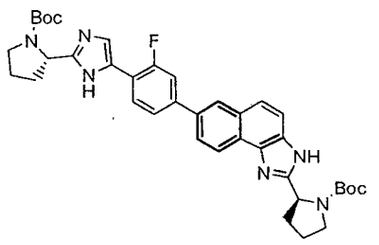


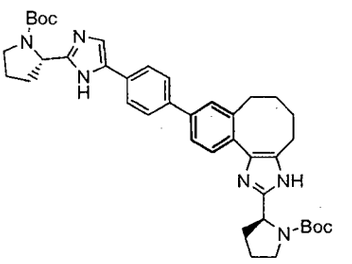


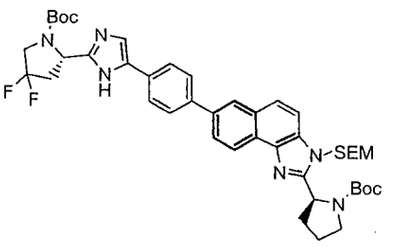


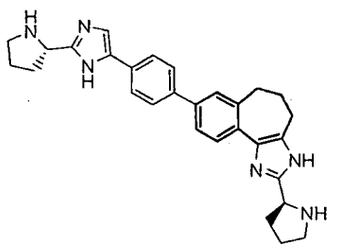


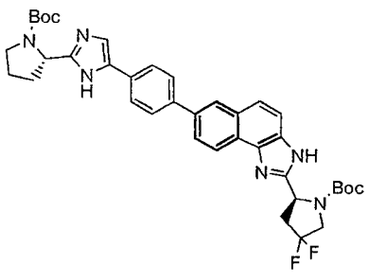


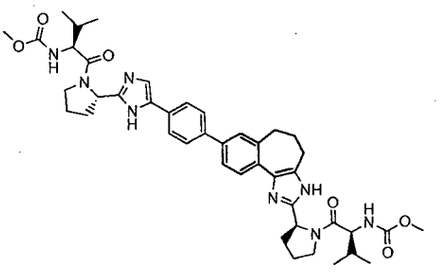


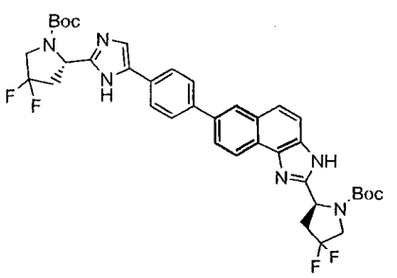


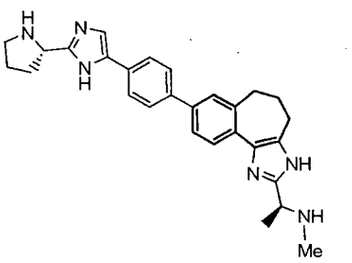


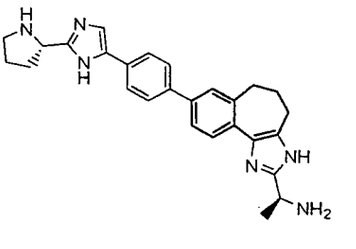


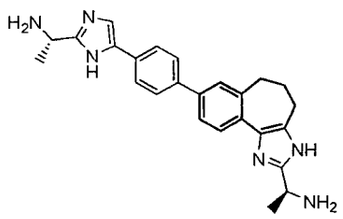


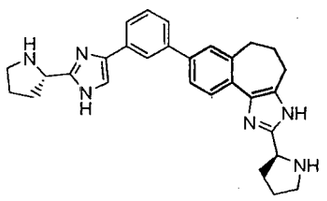


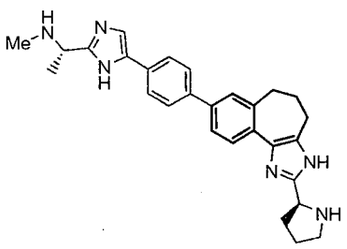


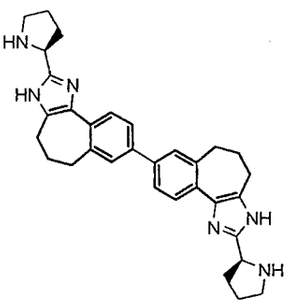


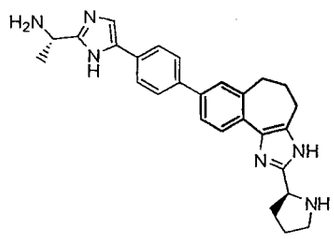


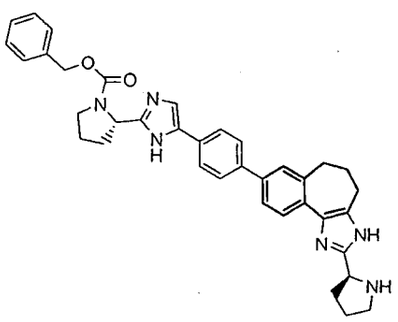


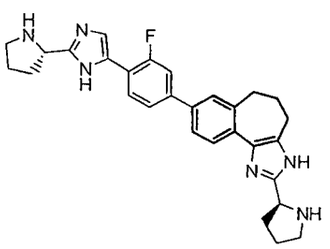


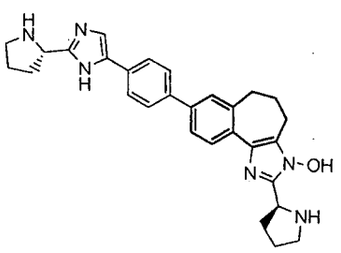


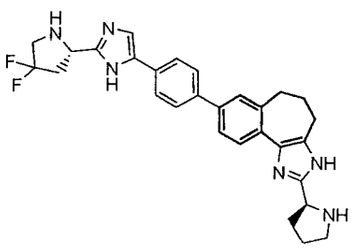


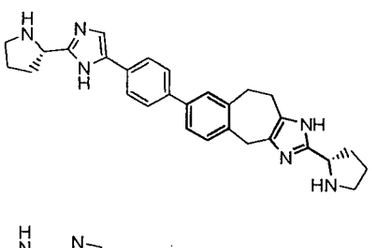


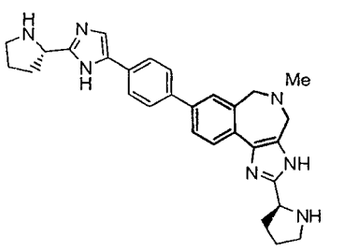


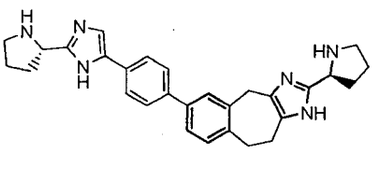


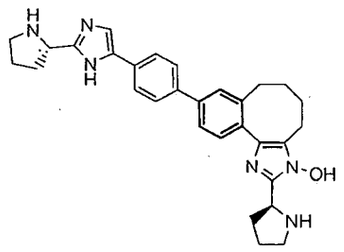


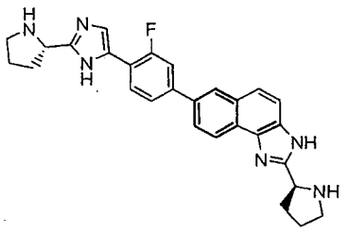


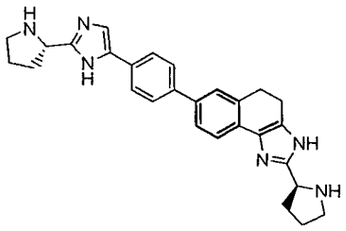


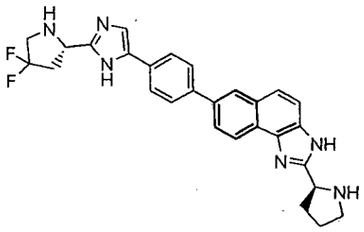


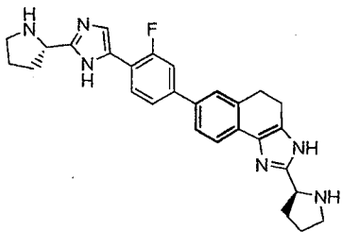


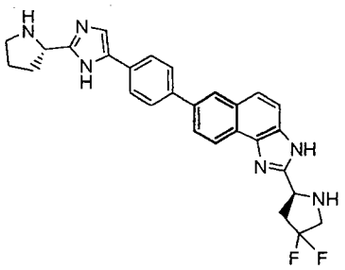


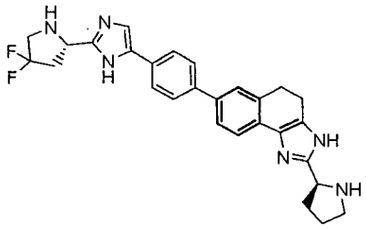


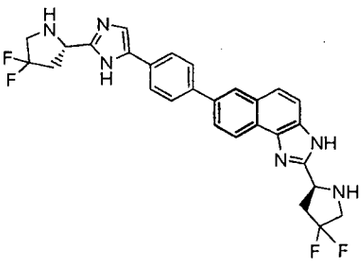


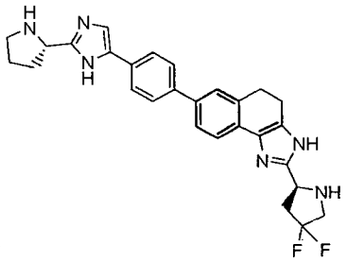


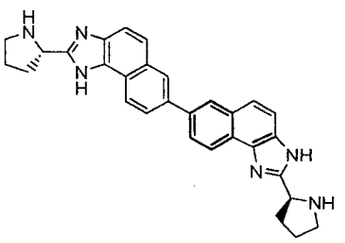


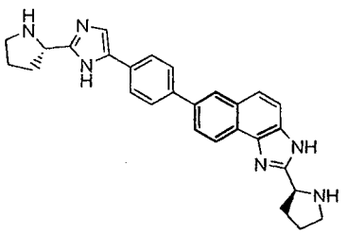




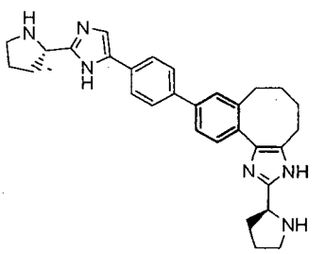


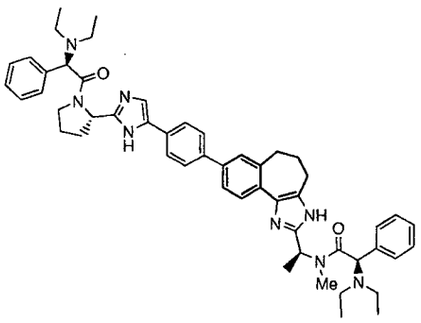


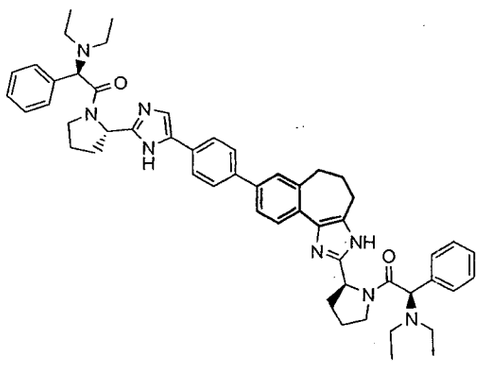


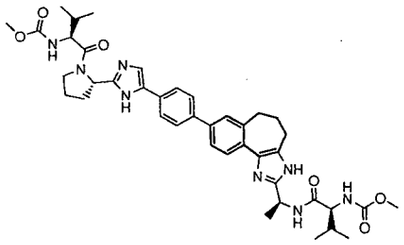


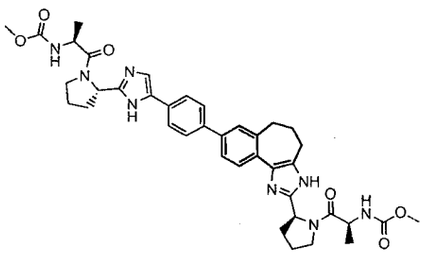


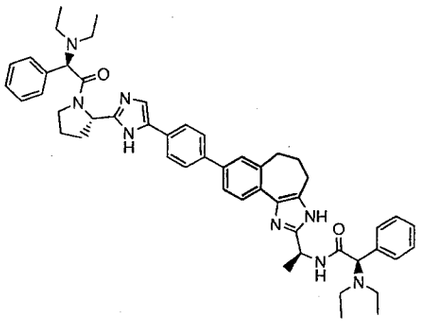


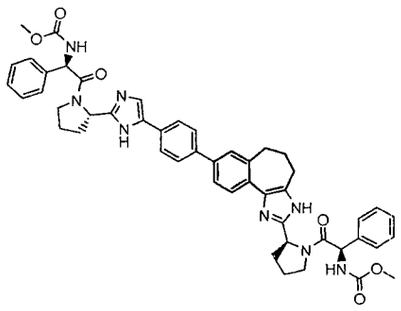


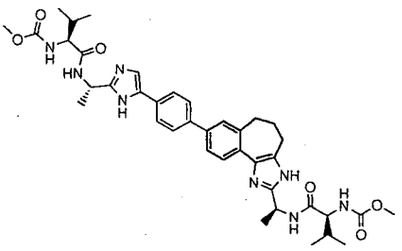


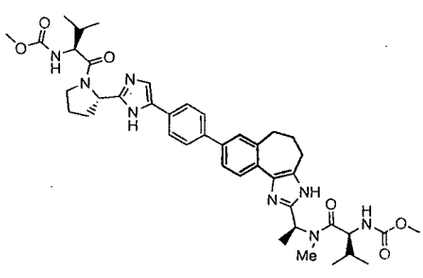


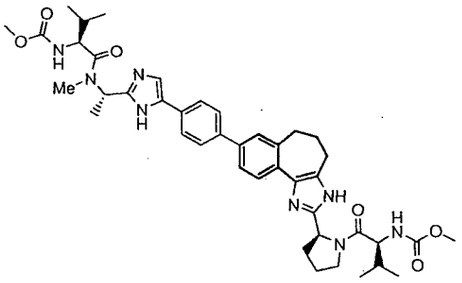


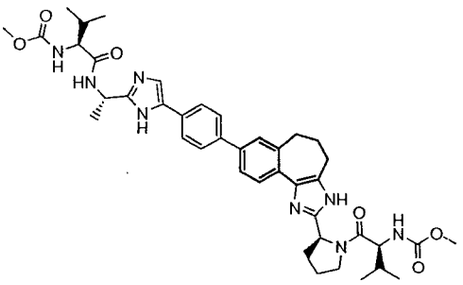


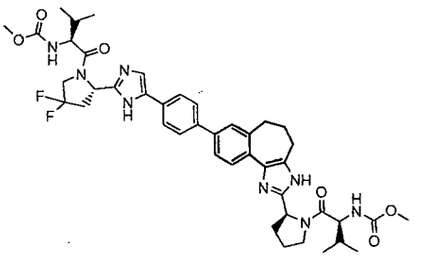


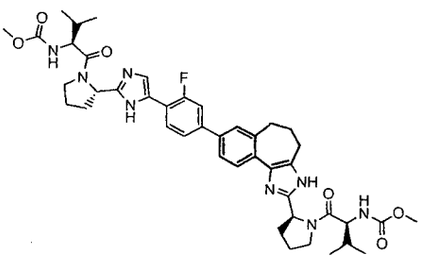


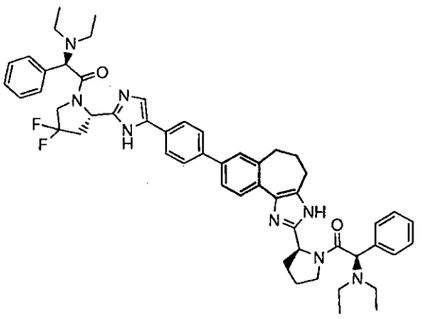


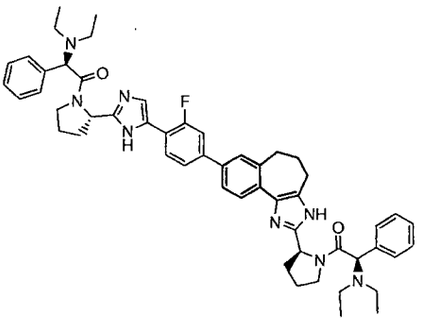


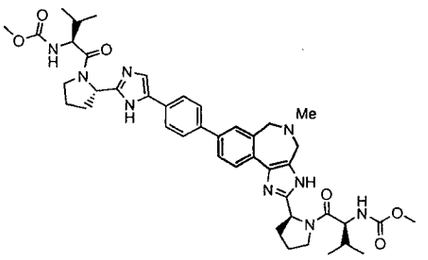


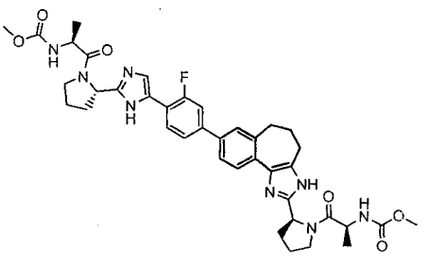


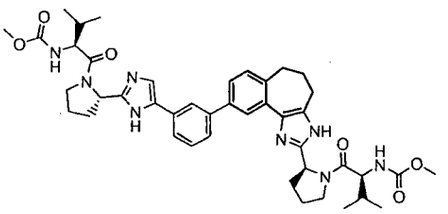


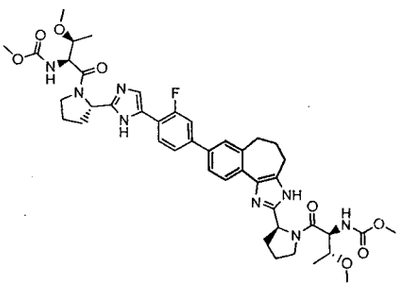


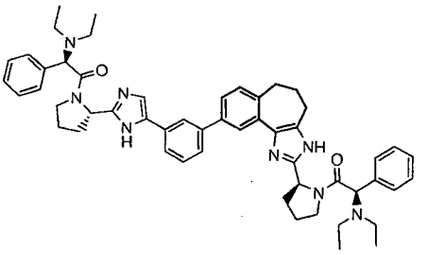


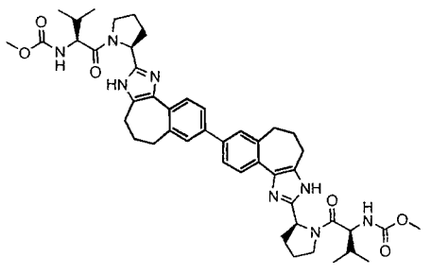


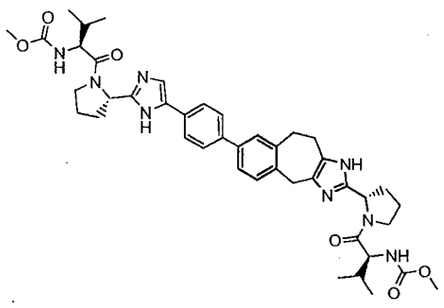


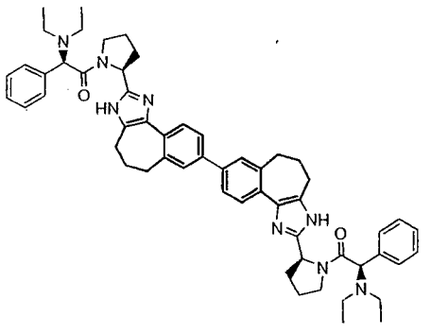


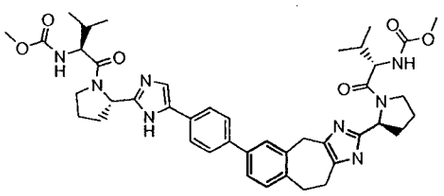


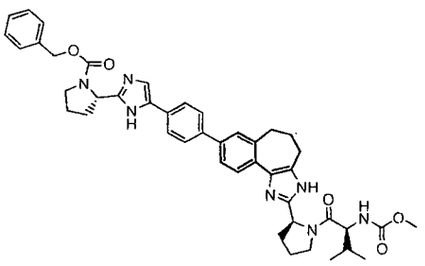


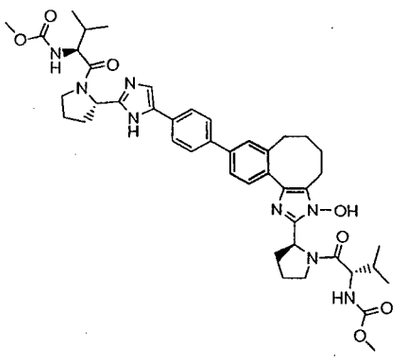


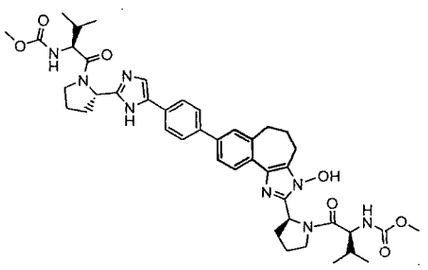


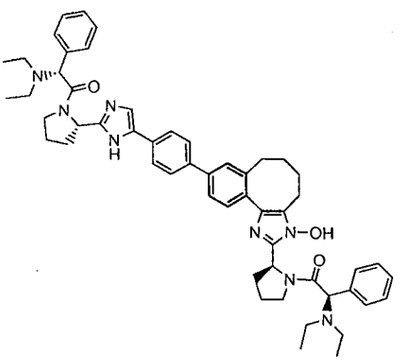


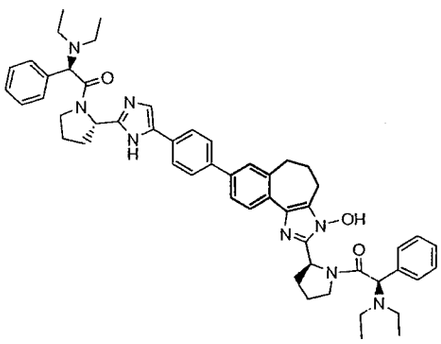


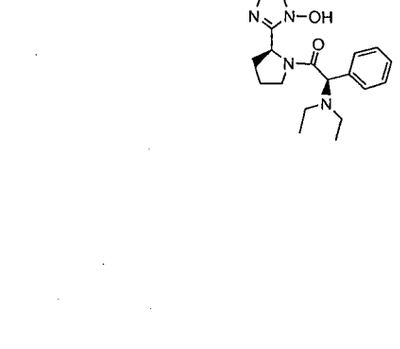


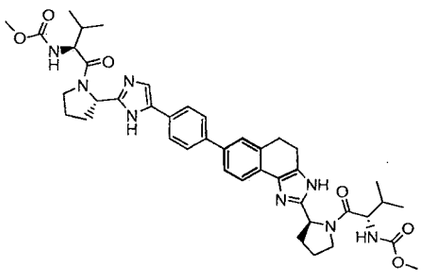


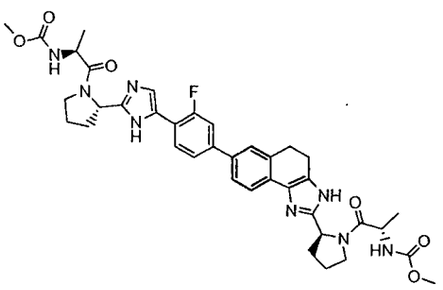


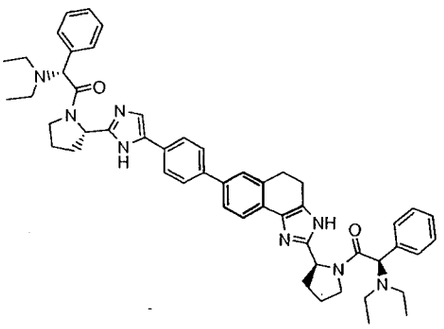


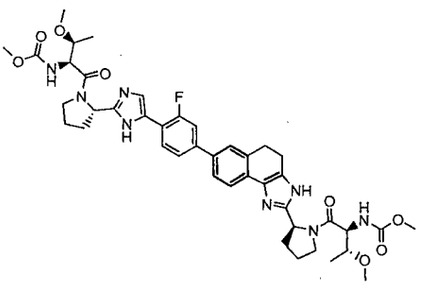


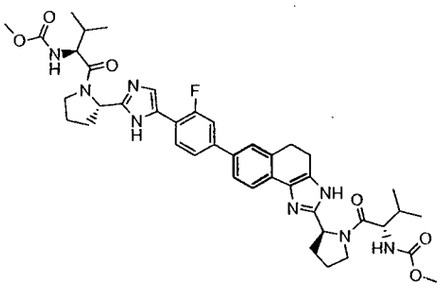


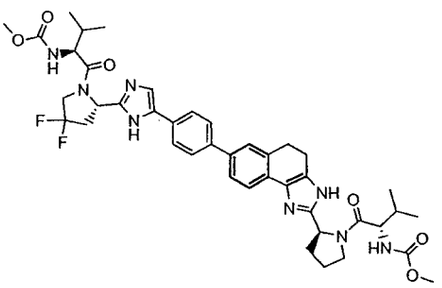


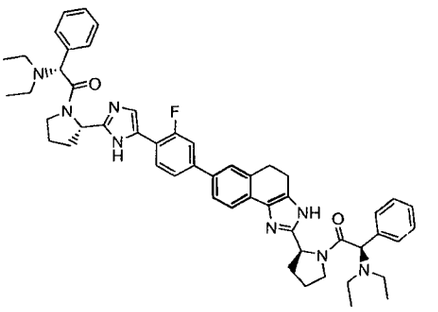


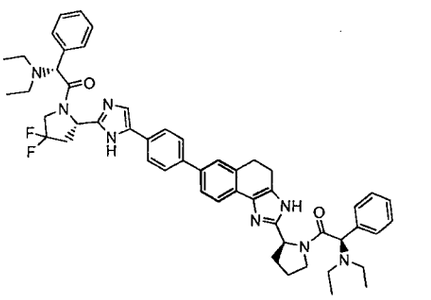


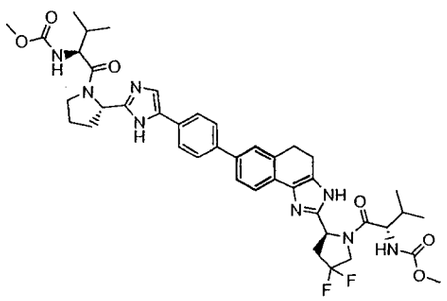


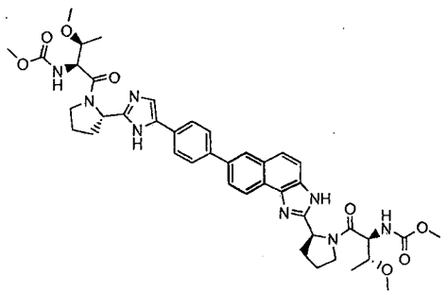


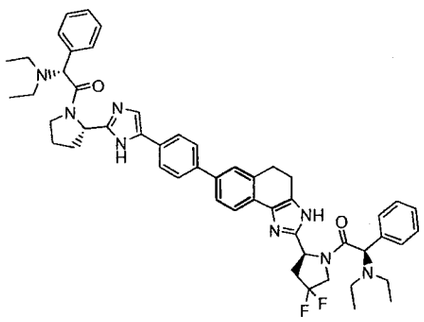


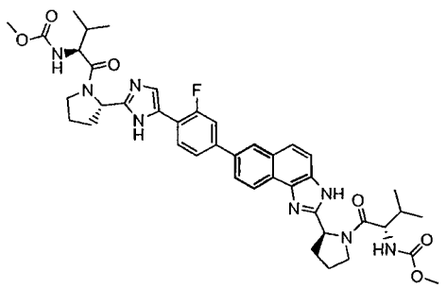


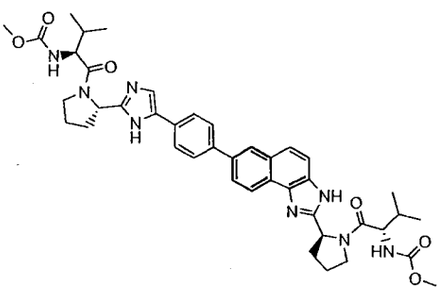


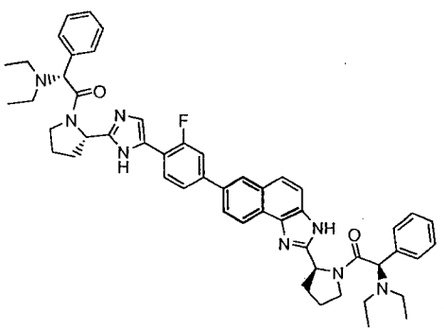


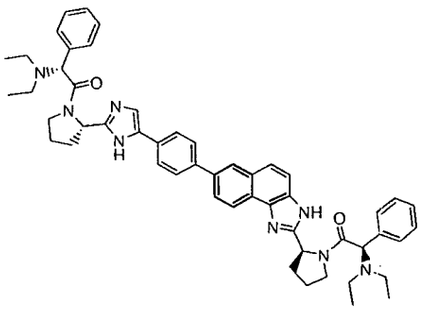


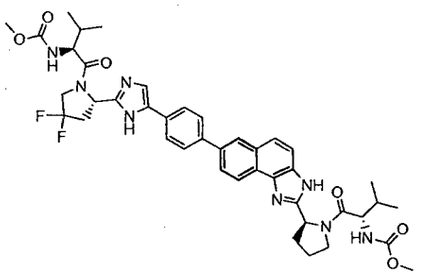


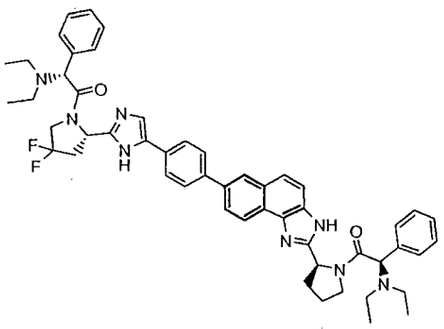


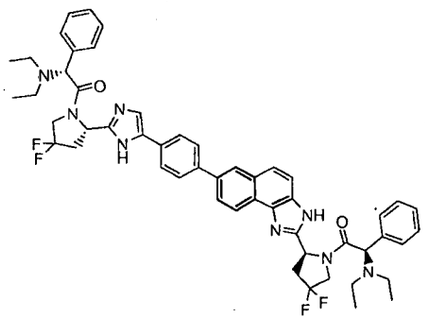


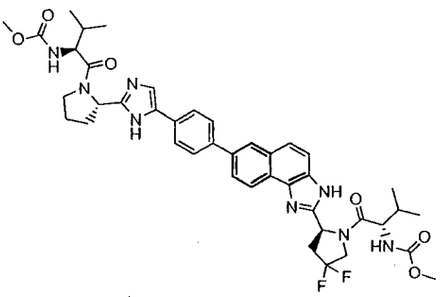


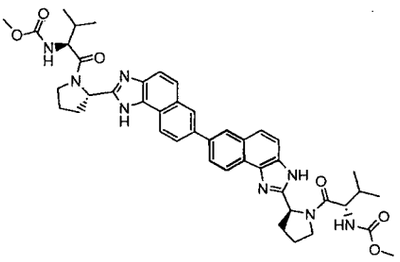


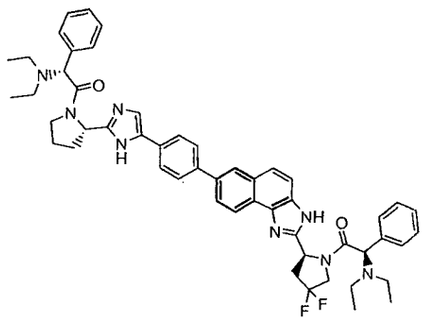


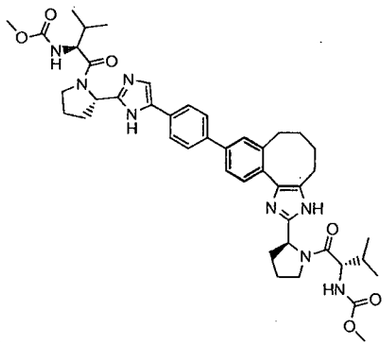


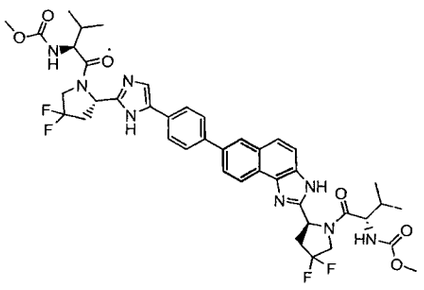


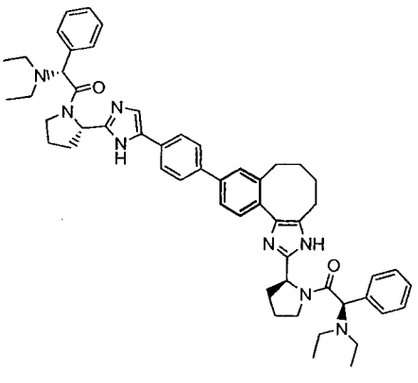


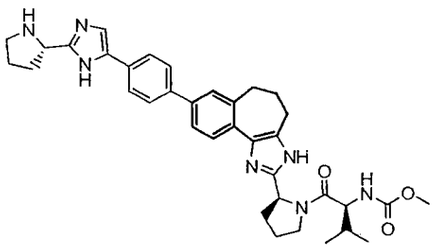


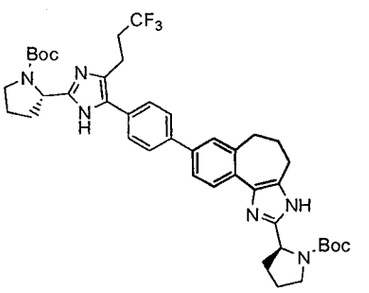


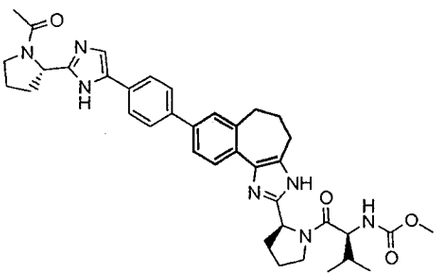


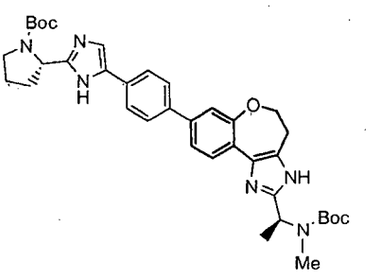


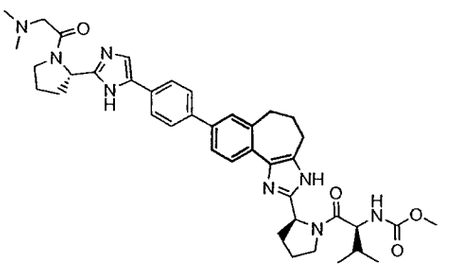


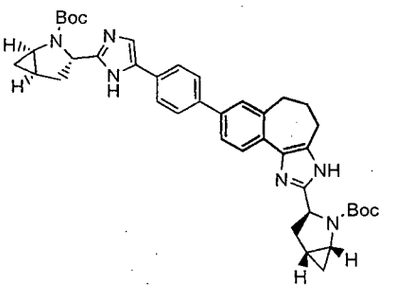


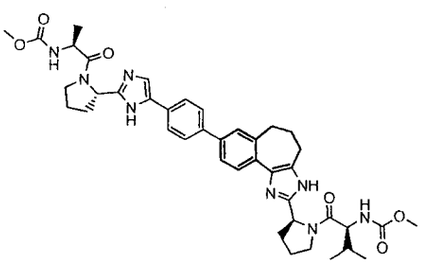


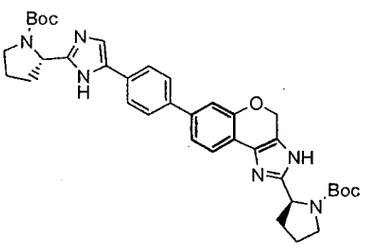


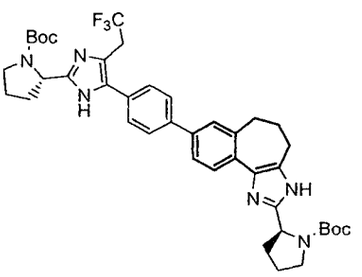


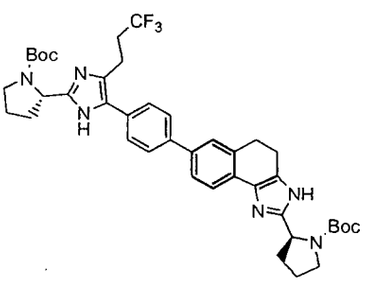


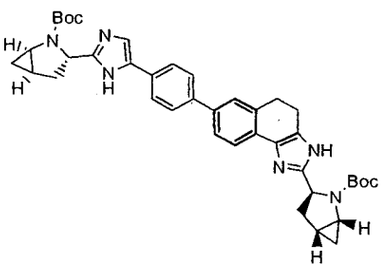


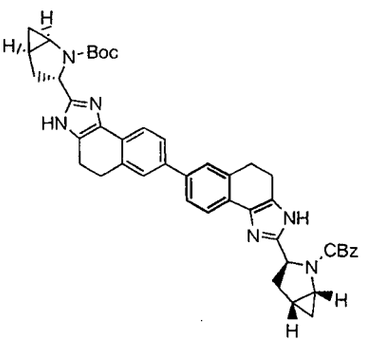


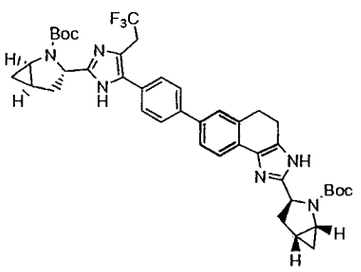


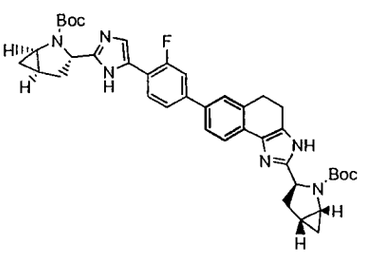


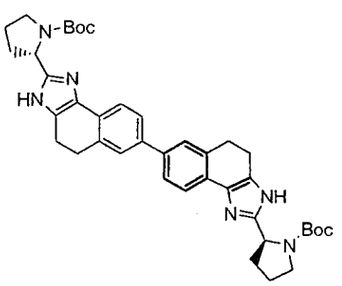


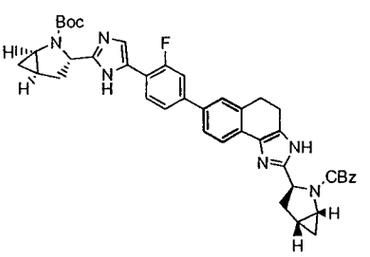


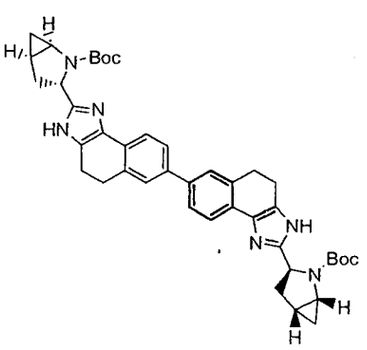


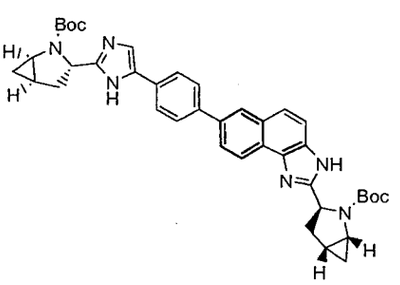


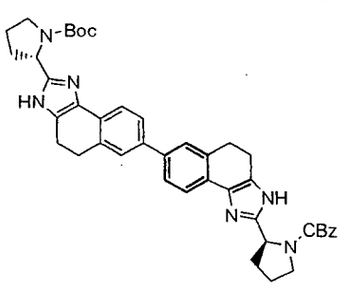


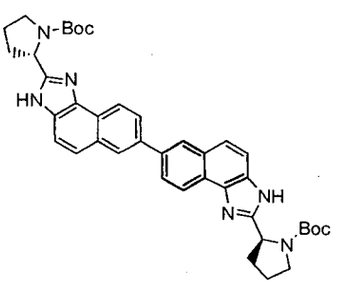




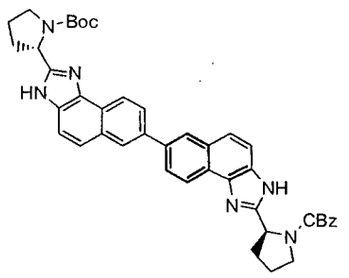


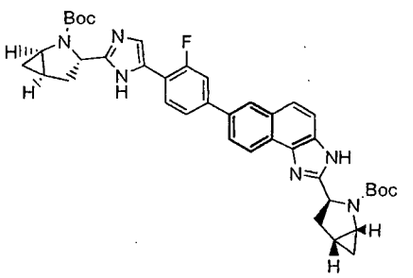


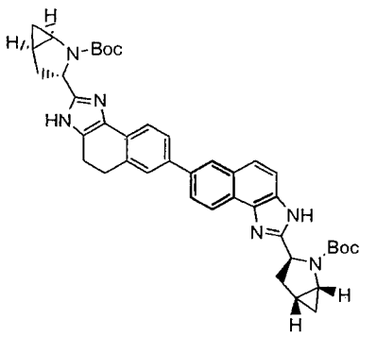


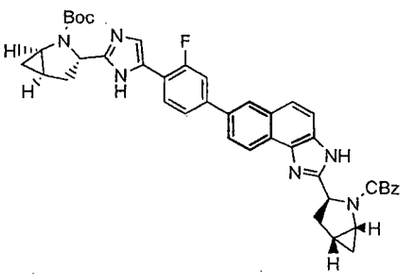


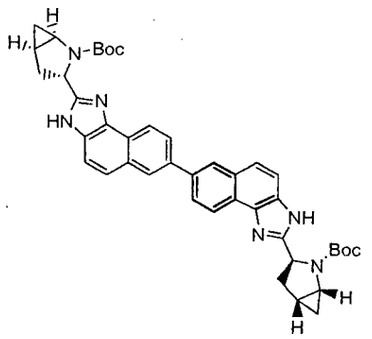
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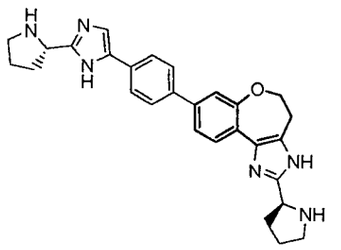


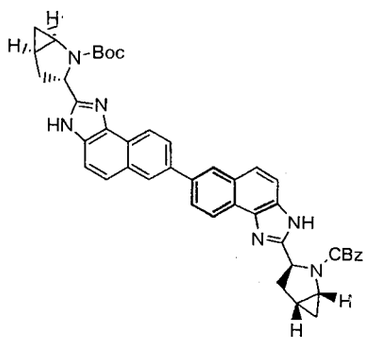


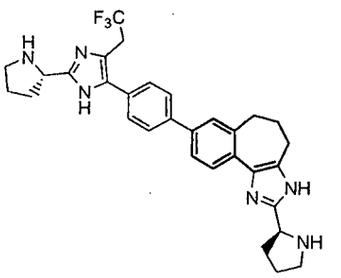


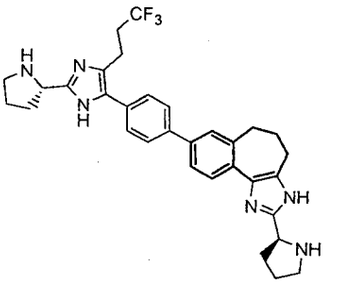


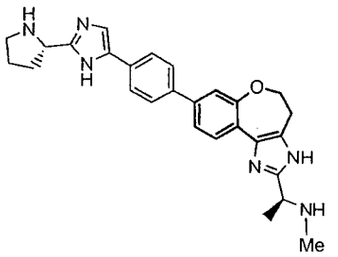


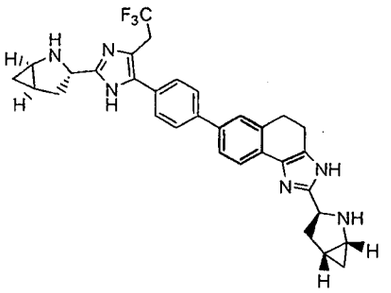


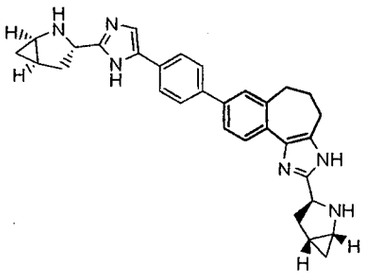


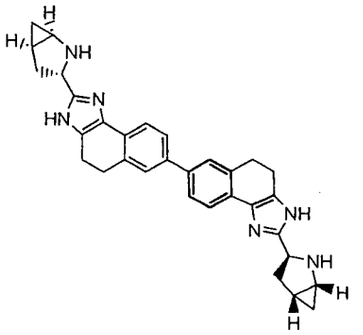


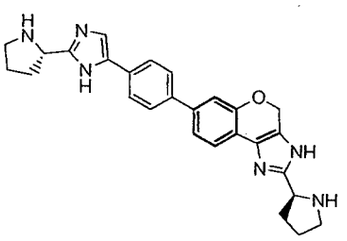


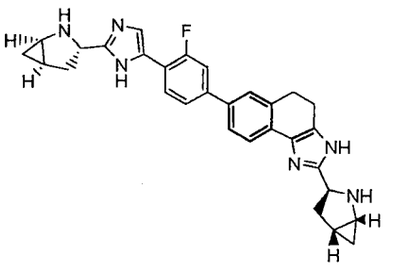


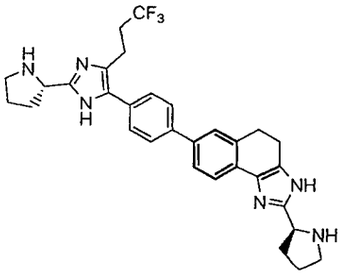


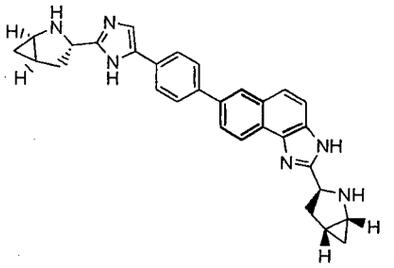


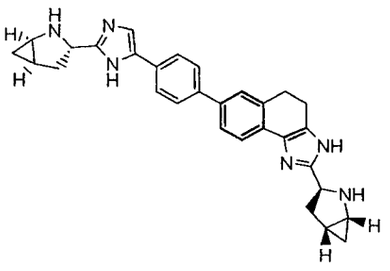


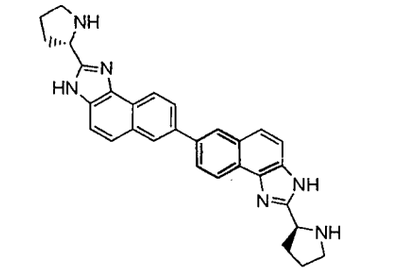


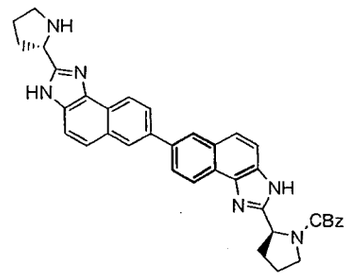


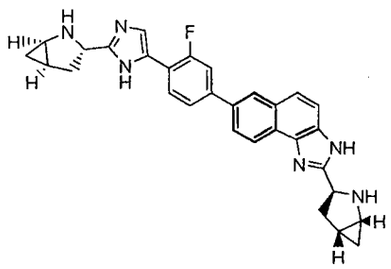


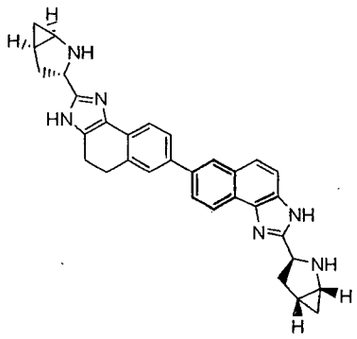


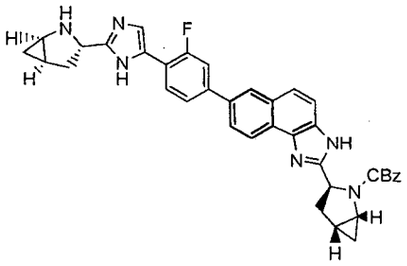


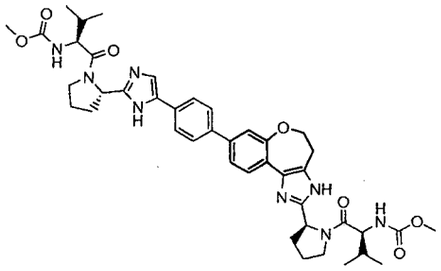


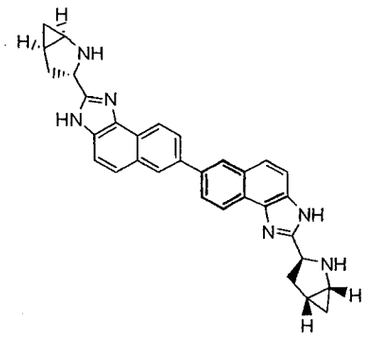


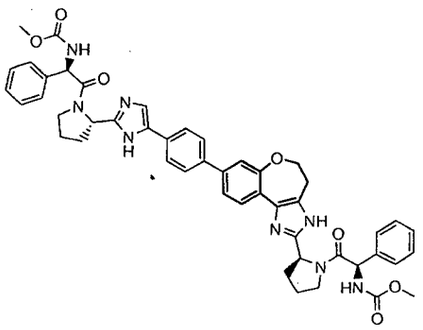


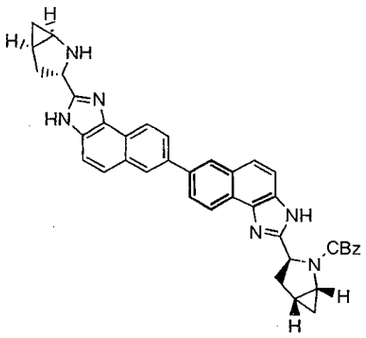


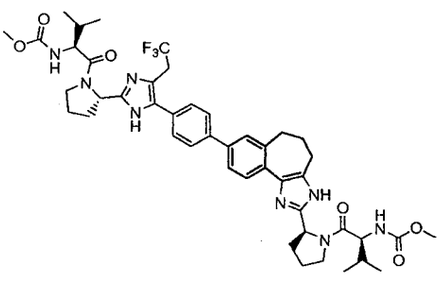


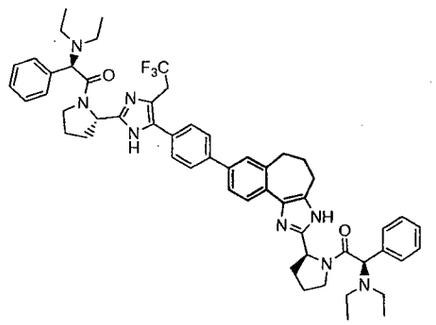


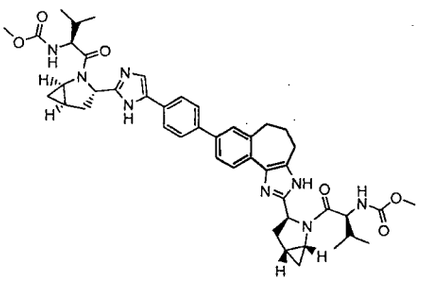


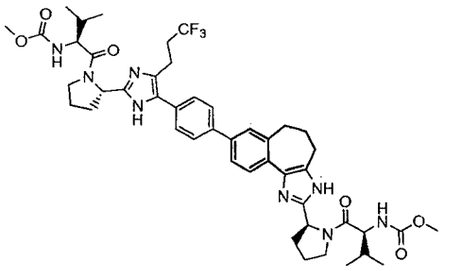


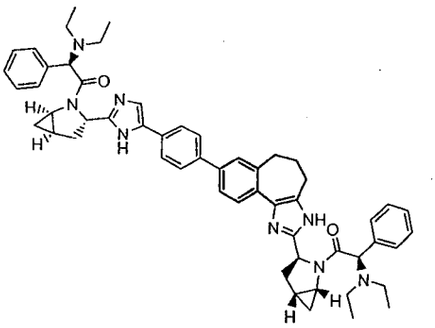


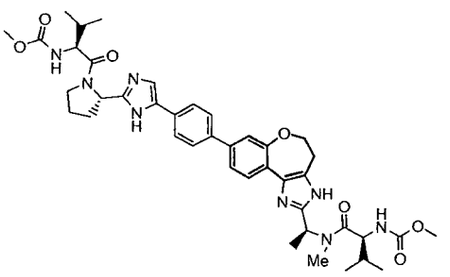


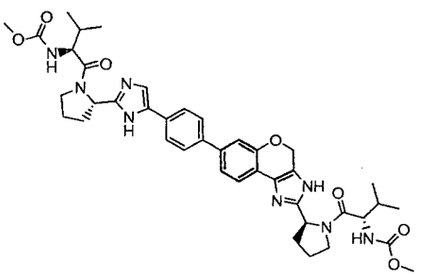


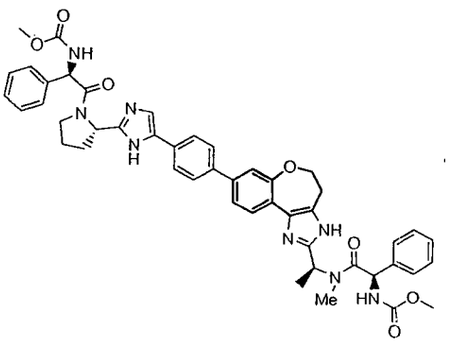


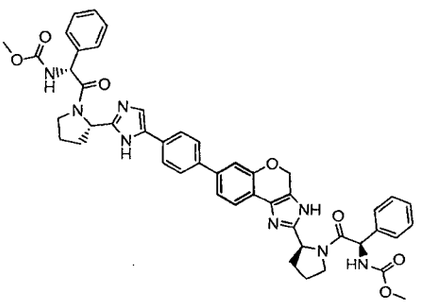


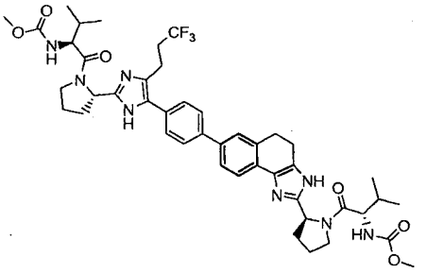


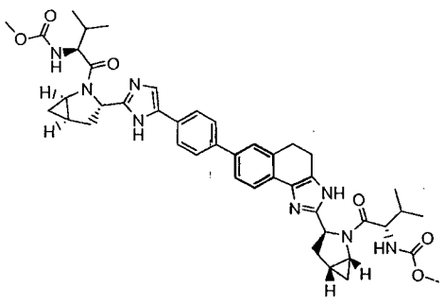


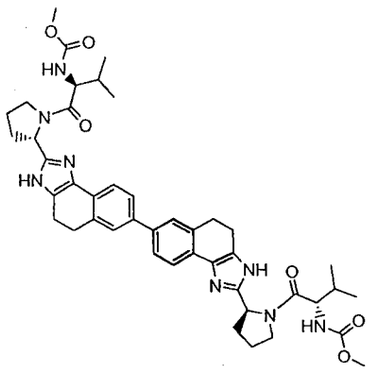


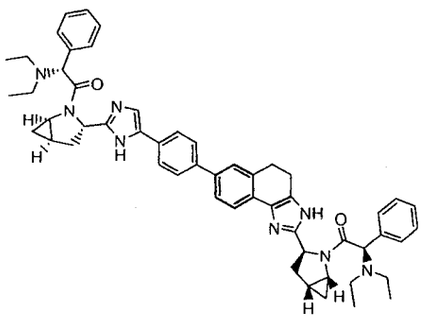


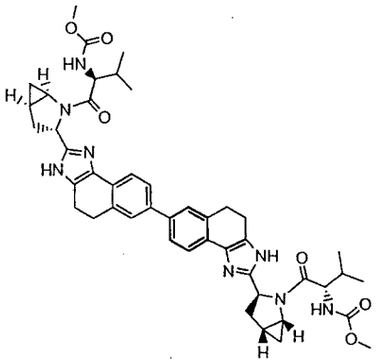


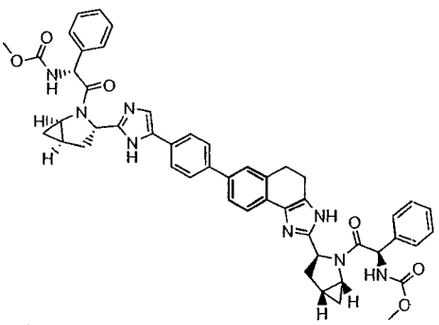


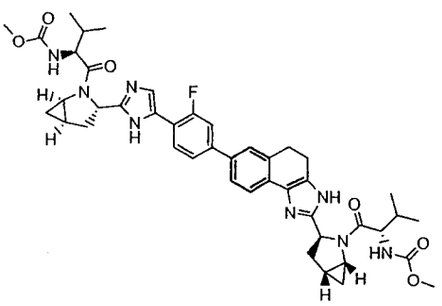


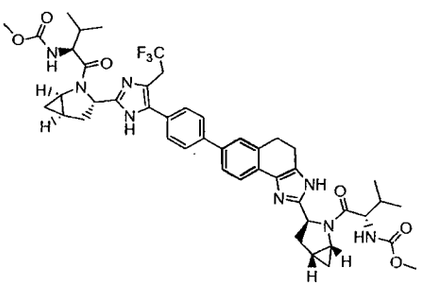


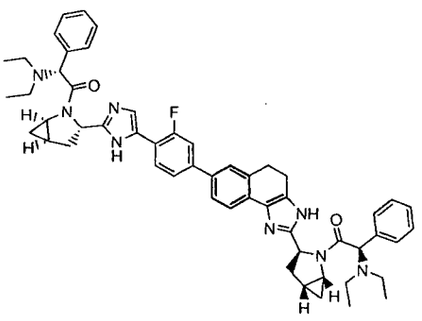


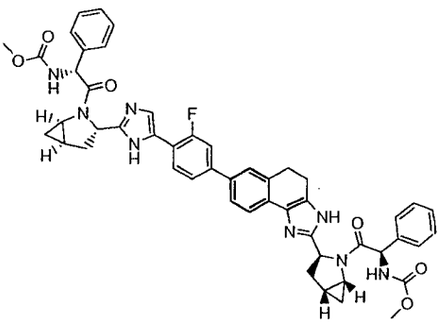


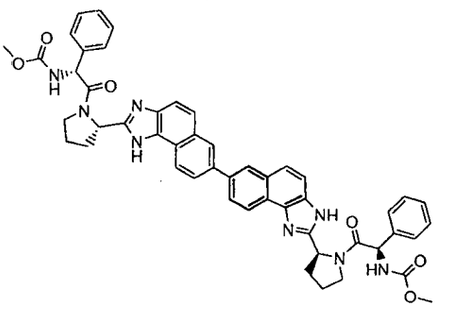


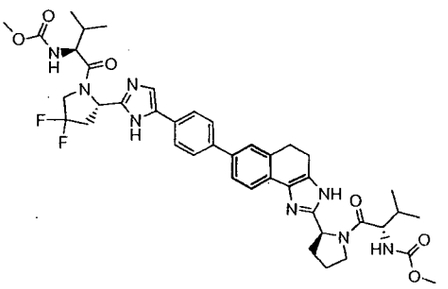


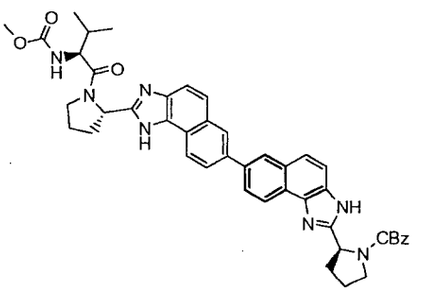


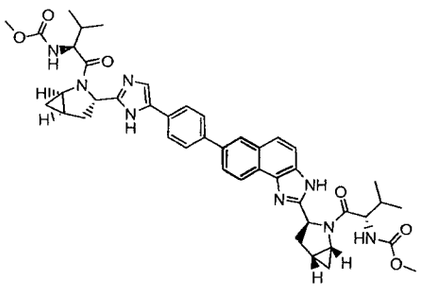


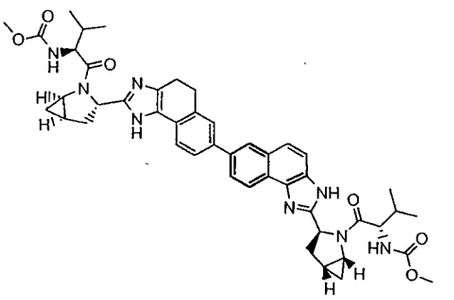


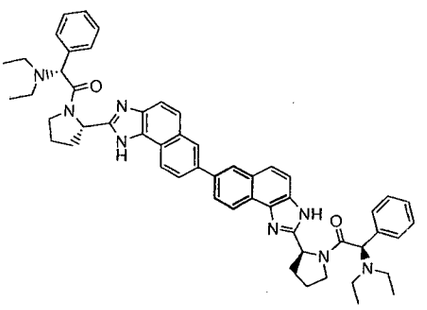


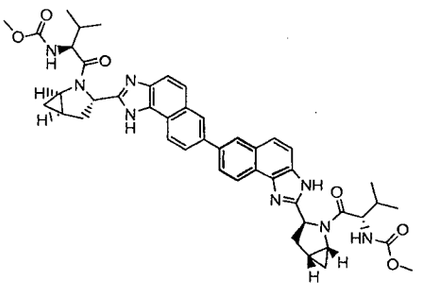


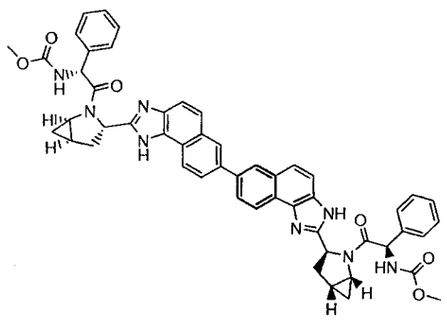


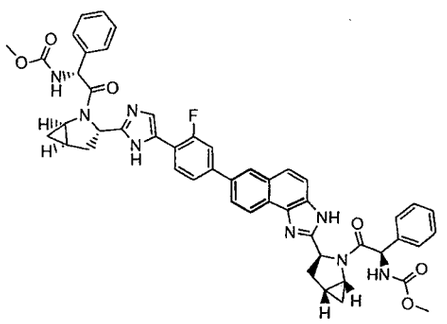


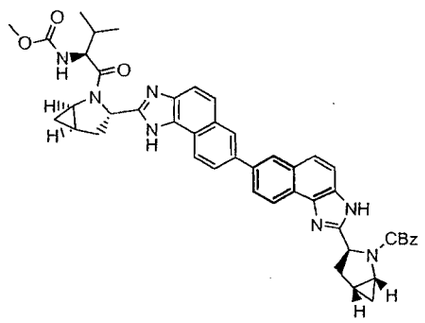


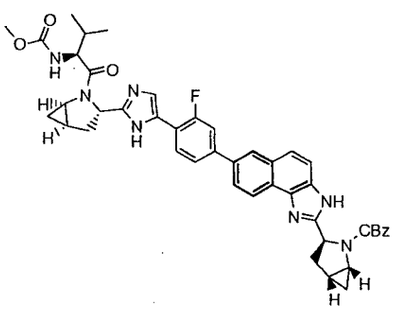


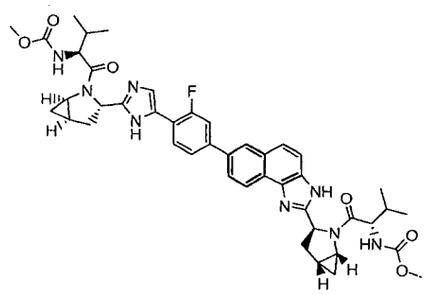


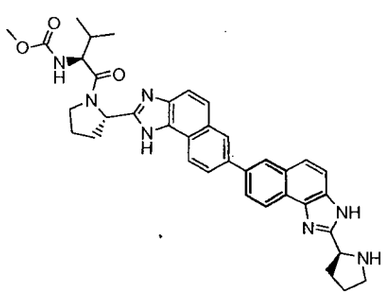


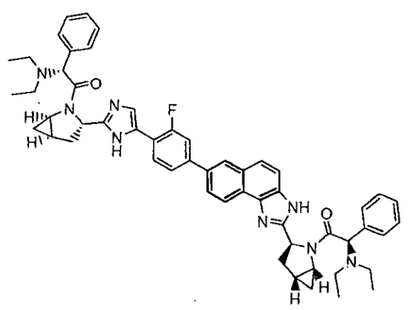


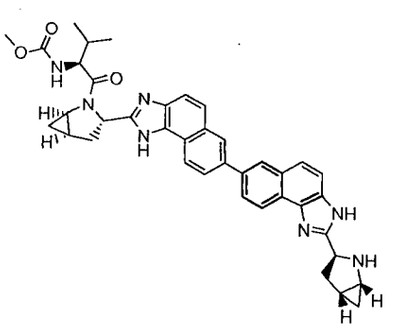




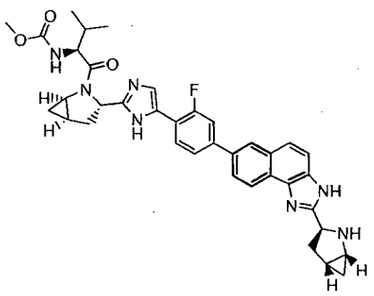


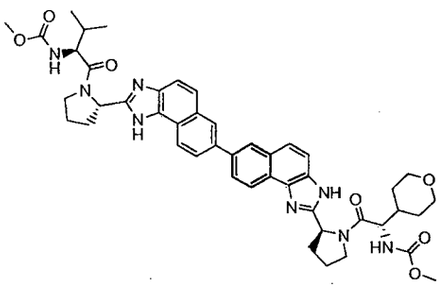


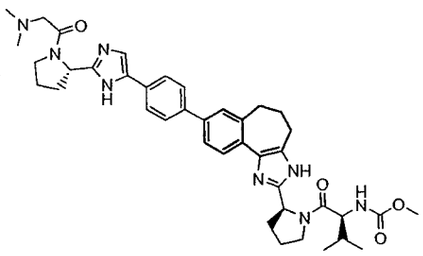


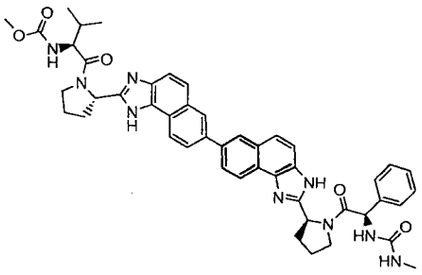


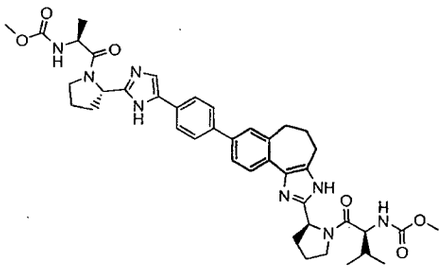
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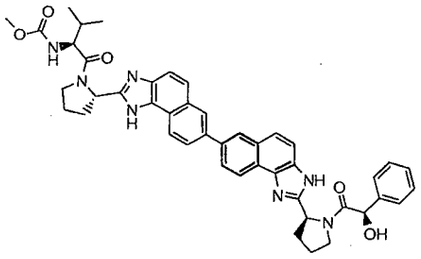




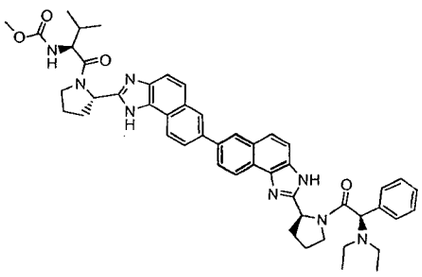


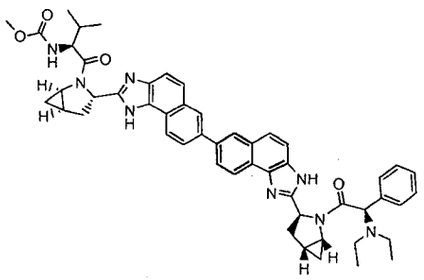




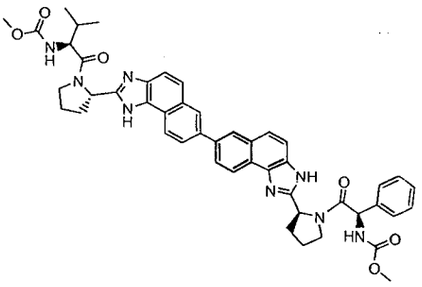


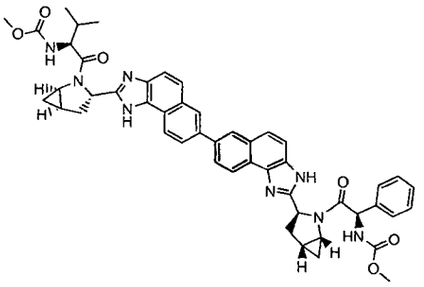
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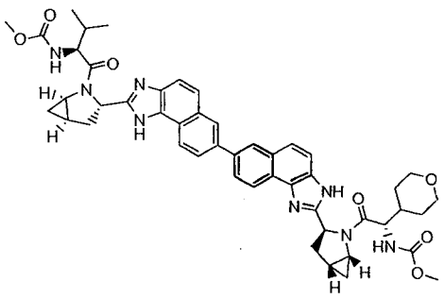


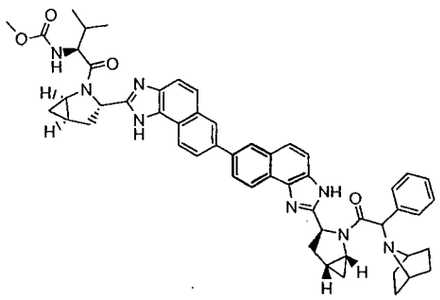


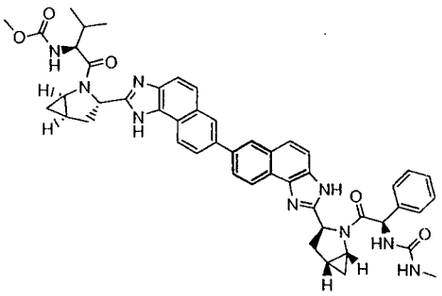
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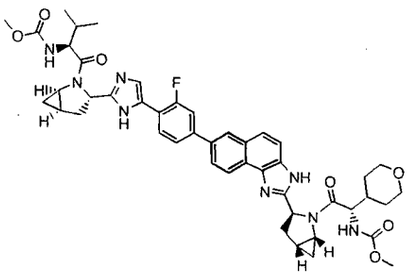












;

and

or a pharmaceutically acceptable salt thereof.

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

12. The composition of claim 11 further comprising one or two additional compounds having anti-HCV activity.

13. The composition of claim 12 wherein at least one of the additional compounds is an interferon or a ribavirin.

14. The composition of claim 13 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

15. The composition of claim 14 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.

16. The composition of claim 15 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.

17. 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.

18. The method of claim 17 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.

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

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

21. The method of claim 18 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.

22. The method of claim 18 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.

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INHIBIDORES DEL VIRUS DE LA HEPATITIS C

Descripción de la Invención

La presente invención 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 los 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.

En la actualidad, la terapia más eficaz contra el VHC emplea una combinación de interferón alfa y ribavirina, conduciendo a una eficacia sustancial en el 40% de los pacientes. Los resultados clínicos recientes demuestran que el interferón alfa pegilado es superior al interferón alfa no modificado como monoterapia. No obstante, incluso con pautas terapéuticas experimentales que conllevan combinaciones de interferón alfa pegilado y ribavirina, una fracción sustancial de pacientes no experimenta una reducción

sostenida en la carga viral. Así, existe una clara y antigua necesidad de desarrollar compuestos terapéuticos eficaces para el tratamiento de la infección por VHC.

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 enextremosulados 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. Se han caracterizado al menos seis genotipos principales y se han descrito más de 50 subtipos. Los genotipos principales del VHC se diferencian en su distribución en todo el mundo y la significación clínica de la heterogeneidad genética del VHC sigue siendo difícil de conseguir a pesar de numerosos estudios del efecto positivo de genotipos sobre la patogénesis y tratamiento.

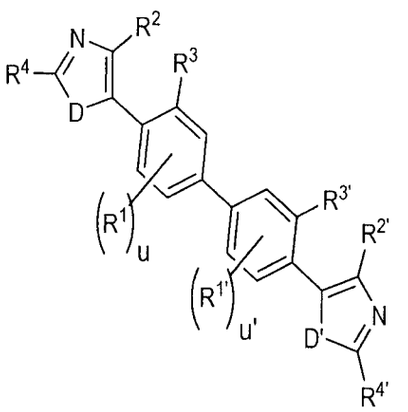
El genoma del ARN del VHC es de aproximadamente 9500 nucleótidos y tiene un marco de lectura abierto (ORF) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En células infectadas, esta poliproteína se

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 descripción 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 como cofactor para la NS3 proteasa y posiblemente ayudando en la localización de membrana de NS3 y otros componentes de replicasa viral. La compleja formación de la proteína NS3 con NS4A parece necesaria para los sucesos de procesamiento, potenciando la eficacia proteolítica en todos los sitios. La proteína NS3 también presenta actividades nucleósido trifosfatasa y ARN helicasa. NS5B (también denominada en la presente descripción polimerasa del VHC) es una ARN polimerasa dependiente de ARN que está implicada en la replicación del VHC.

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 son eficaces para inhibir la función de la proteína NS5A. La proteína NS5A del VHC se describe, por ejemplo, en Tan, S.-L., Katzel, M.G. *Virology* 2001, *284*, 1-12; y en Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

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



(I),

o una de sus sales farmacéuticamente aceptables, en la que

u y u' son independientemente 0, 1, 2 ó 3;

D y D' se seleccionan cada uno independientemente de NR^5, O, y S; seleccionándose cada R^5 independientemente de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, hidroxi, (NR^aR^b)carbonilo y trialquilsililalcoxialquilo;

cada R^1 y $R^{1'}$ se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo,

hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo;

R^2 se selecciona de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo y (NR^aR^b)carbonilo; y

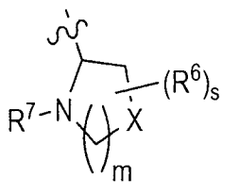
R^3 se selecciona de hidrógeno, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo; o

R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; estando el anillo de cinco a ocho miembros opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo, (NR^aR^b)carbonilo, oxo y espirociclo;

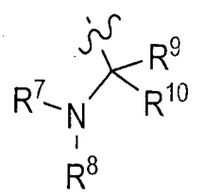
$R^{2'}$ y $R^{3'}$, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos seleccionados independientemente de nitrógeno, oxígeno, y azufre; estando el anillo de cinco a ocho miembros

opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo, (NR^aR^b)carbonilo, oxo y espirociclo;

cada uno de R^4 y $R^{4'}$ se selecciona independientemente de



y



;

en las que

cada m es independientemente 0, 1 ó 2;

cada s es independientemente 0, 1, 2, 3 ó 4;

cada X se selecciona independientemente de O, S, S(O), SO_2, CH_2, CHR^6 y $C(R^6)_2$; con la condición de que cuando n es 0, X se selecciona de CH_2, CHR^6 y $C(R^6)_2$;

cada R^6 se selecciona independientemente de alcoxi, alquilo, arilo, halo, haloalquilo, hidroxi y $-NR^aR^b$, pudiendo formar el alquilo opcionalmente un anillo de tres a seis miembros condensado con un átomo de carbono adyacente, estando el anillo de tres a seis miembros opcionalmente sustituido con uno o dos grupos alquilo;

cada R^7 se selecciona independientemente de hidrógeno y R^{11}-C(O)-, y

R^{11}-C(S)-;

R^8 se selecciona de hidrógeno y alquilo;

cada uno de R^9 y R^{10} se selecciona independientemente de hidrógeno, alquenilo, alcoxialquilo, alquilo, haloalquilo y (NR^aR^b)alquilo; o,

R^9 y R^{10}, junto con el átomo de carbono al que están unidos, forman un anillo saturado de cinco o seis miembros que opcionalmente contiene uno o dos heteroátomos seleccionados de NR^z, O, y S; seleccionándose R^z de hidrógeno y alquilo; y

cada R^{11} se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alcoxicarbonilalquilo, alquilo, alquilcarbonilalquilo, arilo, arilalquenilo, arilalcoxi, arilalquilo, ariloxialquilo, cicloalquilo, (cicloalquil)alquenilo, (cicloalquil)alquilo, cicloalquiloxialquilo, haloalquilo, heterociclilo, heterociclilalquenilo, heterociclilalcoxi, heterociclilalquilo, heterocicliloxialquilo, hidroxialquilo, -NR^cR^d, (NR^cR^d)alquenilo, (NR^cR^d)alquilo y (NR^cR^d)carbonilo.

En una primera modalidad del primer aspecto la presente invención proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que D y D' son cada uno NR^5. En una segunda modalidad del primer aspecto, cada R^5 se selecciona independientemente de hidrógeno e hidroxi.

En una tercera modalidad del primer aspecto la presente invención proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que u y u' son cada uno 0.

En una cuarta modalidad del primer aspecto la presente invención proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que R^2 se selecciona de hidrógeno y haloalquilo.

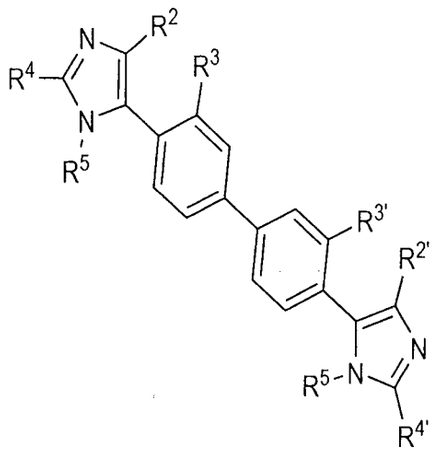
En una quinta modalidad del primer aspecto la presente invención proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que R^3 se selecciona de hidrógeno y halo.

En una sexta modalidad del primer aspecto la presente invención proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo carbocíclico de seis o siete miembros.

En una séptima modalidad del primer aspecto la presente invención proporciona un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, en la que $R^{2'}$ y $R^{3'}$, junto con los átomos de carbono a los que están unidos, forman un anillo de seis a ocho miembros que opcionalmente contiene un heteroátomo seleccionado de oxígeno, nitrógeno y azufre; estando el anillo opcionalmente sustituido con uno o dos grupos alquilo.

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



(II),

o una de sus sales farmacéuticamente aceptables, en la que

R^2 se selecciona de hidrógeno y haloalquilo; y

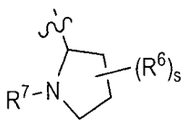
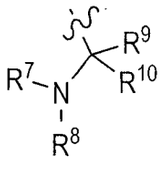
R^3 se selecciona de hidrógeno y halo; o

R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo carbocíclico aromático o no aromático de cinco o seis miembros;

$R^{2'}$ y $R^{3'}$, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de seis a ocho miembros que opcionalmente contiene un heteroátomo seleccionado de oxígeno, nitrógeno y azufre; estando el anillo opcionalmente sustituido con uno o dos grupos alquilo;

cada uno de R^4 y $R^{4'}$ se selecciona independientemente de

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y ; en las que

cada s es 0 ó 2;

cada R^6 se selecciona independientemente de alquilo y halo, formando el alquilo un anillo condensado de tres miembros con un átomo de carbono adyacente;

cada R^7 se selecciona independientemente de hidrógeno y R^{11}-C(O)-;

R^8 se selecciona de hidrógeno y alquilo;

cada uno de R^9 y R^{10} se selecciona independientemente de hidrógeno y alquilo; y

cada R^{11} se selecciona independientemente de alquilo, arilalcoxi, arilalquilo y (NR^cR^d)alquilo.

En un tercer aspecto la presente invención 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 modalidad del tercer aspecto la composición comprende uno o dos compuestos adicionales que tienen actividad anti-VHC. En una segunda modalidad al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

En una cuarta modalidad la presente invención 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 anti-VHC, seleccionándose al menos uno de los compuestos adicionales de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una reapuesta de linfocitos T cooperador tipo I, ARN interferente, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta modalidad la presente invención 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 anti-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 VVHC, proteína NS5A de VHC y IMPDH para el tratamiento de una infección por VHC.

En un cuarto aspecto la presente invención proporciona u 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 modalidad del cuarto aspecto el procedimiento comprende además administrar uno o dos compuestos adicionales que tienen actividad anti-VHC antes, después o de forma simultánea con el compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables. En una segunda modalidad al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

En una cuarta modalidad del cuarto aspecto la presente invención 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 anti-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 tipo I, ARN interferente, ARN antisentido, Imiqimod,

ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta modalidad del cuarto aspecto la presente invención 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 anti-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, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, salida de VVHC, proteína NS5A de VHC y IMPDH para el tratamiento de una infección por VHC.

Otras modalidades de la presente invención pueden comprender combinaciones adecuadas de dos o más de las modalidades y/o aspectos revelados en la presente descripción.

Otras modalidades y aspectos de la invención serán evidentes de acuerdo con la descripción proporcionada a continuación.

Los compuestos de la presente invención también

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existen como tautómeros; por tanto la presente invención también incluye formas tautoméricas.

La descripción de la presente invención 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 invención son aquellos que son adecuados para uso como agentes farmacéuticos.

Se pretende que la definición de cualquier sustituyente o variable (por ejemplo, R^1, R^2, R^5, R^6, etc.) en una posición particular en una molécula sea independiente de sus definiciones dondequiera que esté en la molécula. Por ejemplo, cuando u es 2, cada uno de los dos grupos R^1 puede ser el mismo o diferente.

Todas las patentes, solicitudes de patente y referencia bibliográficas citadas en esta descripción descriptiva se incorporan a la presente por referencia en su totalidad. En el caso de inconsistencias, prevalecerá la presente invención, incluyendo definiciones.

Tal como se usa en la presente descripción 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.

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A no ser que se indique de otro modo, todos los grupos arilo, cicloalquilo y heterociclilo de la presente invención 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 "alquenilo," tal como se usa en la presente descripción, se refiere a un grupo de cadena lineal o ramificada de dos a seis átomos de carbono que contiene al menos un doble enlace carbono-carbono.

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

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

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

El término "alcoxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alcoxi.

El término "alcoxialquilcarbonilo," tal como se usa en la presente descripción, se refiere a un grupo

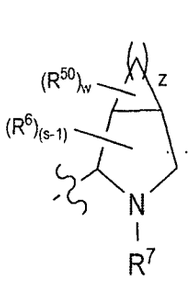
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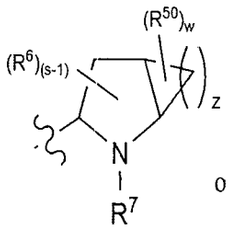
alcoxialquilo unido al resto molecular principal a través de un grupo carbonilo.

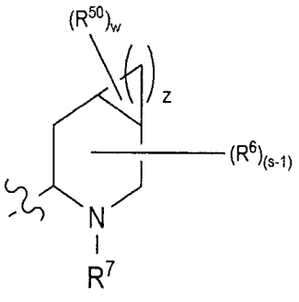
El término "alcoxicarbonilo," tal como se usa en la presente descripción, se refiere a un grupo alcoxi unido al resto molecular principal a través de un grupo carbonilo.

El término "alcoxicarbonilalquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alcoxicarbonilo.

El término "alquilo," tal como se usa en la presente descripción, 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 invención, cuando m es 1 ó 2; X es CHR^6, y R^6 es alquilo, cada alquilo puede formar opcionalmente un anillo condensado de tres a seis miembros con un átomo de carbono adyacente proporcionando las estructuras mostradas a continuación:



,


o


;

en las que z es 1, 2, 3 ó 4, w es 0, 1 ó 2, y R^{50} es alquilo. Cuando w es 2, los dos grupos alquilo R^{50} pueden ser iguales o distintos.

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

El término "alquilcarbonilalquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alquilcarbonilo.

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

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

El término "alquilsulfonilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo unido al resto molecular principal a través de un grupo sulfonilo.

El término "arilo," tal como se usa en la presente descripción, 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 invención 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 invención 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 "arilalquenilo," tal como se usa en la presente descripción, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos arilo.

El término "arilalcoxi," tal como se usa en la presente descripción, se refiere a un grupo arilo unido al

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resto molecular principal a través de un grupo alcoxi.

El término "arilalcoxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos arilalcoxi.

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

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

El término "arilalquilo," tal como se usa en la presente descripción, 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 y $-NR^xR^y$.

El término "arilalquilcarbonilo," tal como se usa en la presente descripción, se refiere a un grupo arilalquilo

unido al resto molecular principal a través de un grupo carbonilo.

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

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

El término "ariloxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos ariloxi.

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

El término "arilsulfonilo," tal como se usa en la presente descripción, se refiere a un grupo arilo unido al resto molecular principal a través de un grupo sulfonilo.

Los términos "Extremo" y "extremo" tal como se usan en la presente descripción, se refieren al grupo que está colocado en el átomo de nitrógeno del anillo que contiene nitrógeno terminal, es decir, los anillos pirrolidona del compuesto de Fórmula (I). Se sobreentiende que "Extremo" o "extremo" pueden hacer referencia al reaccionante usado para unir el grupo al anillo que contiene nitrógeno terminal o al fragmento en el producto final, es decir, "Extremo-51" o "El

fragmento Extremo-51 encontrado en el Ejemplo 5".

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

El término "carboxi," tal como se usa en la presente descripción, se refiere a $-CO_2H$.

El término "ciano," tal como se usa en la presente descripción, se refiere a -CN.

El término "cicloalquilo," tal como se usa en la presente descripción, se refiere a un sistema de anillo hidrocarbonato saturado monocíclico que tiene de tres a siete átomos y ningún heteroátomo. Ejemplos representativos de grupos cicloalquilo incluyen, aunque sin quedar limitados a los mismos, ciclopropilo, ciclopentilo y ciclohexilo. Los grupos cicloalquilo de la presente invención 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)alquenilo," tal como se usa en la presente descripción, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos cicloalquilo.

El término "(cicloalquil)alquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos cicloalquilo. La parte alquilo del (cicloalquil)alquilo está además opcionalmente sustituida con uno o dos grupos seleccionados independientemente de hidroxi y $-NR^cR^d$.

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

El término "cicloalquiloxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos cicloalquiloxi.

El término "cicloalquilsulfonilo," tal como se usa en la presente descripción, se refiere a un grupo cicloalquilo unido al resto molecular principal a través de un grupo sulfonilo.

El término "formilo," tal como se usa en la presente descripción, se refiere a -CHO.

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

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

El término "haloalcoxicarbonilo," tal como se usa

en la presente descripción, se refiere a un grupo haloalcoxi unido al resto molecular principal a través de un grupo carbonilo.

El término "haloalquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos, tres o cuatro átomos de halógeno.

El término "heterociclilo," tal como se usa en la presente descripción, 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]oc-2-tilo y 2-azabiciclo[2.2.2]oc-3-tilo. Los grupos heterociclilo de la presente invención 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,

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indolinilo, indolilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, piperazinilo, piperidinilo, pirazolilo, piridinilo, pirrolidinilo, pirrolopiridinilo, pirrolilo, tiazolilo, tienilo, tiomorfolinilo, 7-azabiciclo[2.2.1]hept-7-ilo, 2-azabiciclo[2.2.2]oc-2-tilo, y 2-azabiciclo[2.2.2]oc-3-tilo. Los grupos heterociclilo de la presente invención 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 "heterociclilalquenilo," tal como se usa en la presente descripción, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos heterociclilo.

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

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

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

El término "heterociclilcarbonilo," tal como se usa en la presente descripción, se refiere a un grupo heterociclilo

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unido al resto molecular principal a través de un grupo carbonilo.

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

El término "heterocicliloxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos heterocicliloxi.

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

El término "hidroxi," tal como se usa en la presente descripción, se refiere a -OH.

El término "hidroxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos hidroxi.

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

El término "nitro," tal como se usa en la presente descripción, se refiere a $-NO_2$.

El término "$-NR^aR^b$," tal como se usa en la presente

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descripción, se refiere a dos grupos, R^a y R^b, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^a y R^b se seleccionan independientemente de hidrógeno, alquenilo y alquilo.

El término "(NR^aR^b)alquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^aR^b$.

El término "(NR^aR^b)carbonilo," tal como se usa en la presente descripción, se refiere a un grupo $-NR^aR^b$ unido al resto molecular principal a través de un grupo carbonilo.

El término "$-NR^cR^d$," tal como se usa en la presente descripción, 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, 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

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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 descripción, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos $-NR^cR^d$.

El término "(NR^cR^d)alquilo," tal como se usa en la presente descripción, 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, arilalcoxialquilcarbonilo, carboxi, heterociclilo, heterociclilcarbonilo, hidroxi y (NR^eR^f)carbonilo; estando el heterociclilo además opcionalmente sustituido con uno, dos,

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tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "(NR^cR^d)carbonilo," tal como se usa en la presente descripción, se refiere a un grupo $-NR^cR^d$ unido al resto molecular principal a través de un grupo carbonilo.

El término "$-NR^eR^f$," tal como se usa en la presente descripción, 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, (ciclolalquil)alquilo no sustituido, heterociclilo no sustituido, heterociclilalquilo no sustituido, (NR^xR^y)alquilo y (NR^xR^y)carbonilo.

El término "(NR^eR^f)alquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^eR^f$.

El término "(NR^eR^f)alquilcarbonilo," tal como se usa en la presente descripción, se refiere a un grupo (NR^eR^f)alquilo unido al resto molecular principal a través de un grupo carbonilo.

El término "(NR^eR^f)carbonilo," tal como se usa en la presente descripción, se refiere a un grupo $-NR^eR^f$ unido al resto molecular principal a través de un grupo carbonilo.

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El término "(NR^eR^f)sulfonilo," tal como se usa en la presente descripción, se refiere a un grupo $-NR^eR^f$ unido al resto molecular principal a través de un grupo sulfonilo.

El término "$-NR^xR^y$," tal como se usa en la presente descripción, 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.

El término "(NR^xR^y)alquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^xR^y$.

El término "(NR^xR^y)carbonilo," tal como se usa en la presente descripción, se refiere a un grupo $-NR^xR^y$ unido al resto molecular principal a través de un grupo carbonilo.

El término "oxo," tal como se usa en la presente descripción, se refiere a =O.

El término "sulfonilo," tal como se usa en la presente descripción, se refiere a $-SO_2-$.

El término "trialquilsililo," tal como se usa en la presente descripción, se refiere a $-SiR_3$, siendo R alquilo. Los grupos R pueden ser iguales o distintos.

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El término "trialquilsililalquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos trialquilsililo.

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

El término "trialquilsililalcoxialquilo," tal como se usa en la presente descripción, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos trialquilsililalcoxi.

En los compuestos de la presente invención 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 extremoacidad 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 invención 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 invención incluye cada uno de los isómeros conformacionales de estos compuestos y sus mezclas.

La expresión "compuestos de la presente invención" 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.

Los compuestos de la presente invención pueden existir como sales farmacéuticamente aceptables. La expresión "sal farmacéuticamente aceptable," tal como se usa en la presente descripción, representa sales o formas híbridas de los compuestos de la presente invención 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, dibromhidrato, diclorhidrato, diyodhidrato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formiato, fumarato, bromhidrato, clorhidrato, yodhidrato, 2-hidroxietanosulfonato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, 2-naftalenosulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fósfato, 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.

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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 pueden administrar cantidades terapéuticamente eficaces de un compuesto de fórmula (I), así como sus sales farmacéuticamente aceptables, en forma de compuestos químicos en bruto, es posible presentar el ingrediente activo como una composición farmacéutica. Por consiguiente, la invención proporciona además composiciones farmacéuticas que incluyen cantidades terapéuticamente eficaces de compuestos de fórmula

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(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 descripción, 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 al 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 invención se proporciona también 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 descripción, se refiere a los compuestos,

materiales, composiciones y/o formas de dosificación 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 dosis unitaria que contienen una cantidad predeterminada de ingrediente activo por dosis unitaria. 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 invención. De forma típica, las composiciones farmacéuticas de esta invención se administrarán de aproximadamente 1 a aproximadamente 5 veces por día o, como alternativa, como una infusión continua. La 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 de dosificación 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 dosis unitaria preferidas son aquellas que contienen una dosis diaria o subdosis, tal como se ha explicado en la presente descripción, 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 invención comprenden una combinación de un compuesto de la presente invención 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 o 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 de dosificación 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 briqueteando, añadiendo un lubricante y disgregante y prensando en comprimidos. Una mezcla de polvo se preparar 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 briquetas 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 invención también se pueden combinar con un vehículo inerte fluido y comprimirse en comprimidos directamente sin llevarlos a las etapas de granulación o briqueteado. Se puede disponer un revestimiento protector opaco o transparente consistente en una extremoa de goma laca, una extremoa de azúcar o material polimérico y un revestimiento final de cera. Se pueden añadir colorantes a estos revestimientos para distinguir las diferentes dosis unitarias.

Los fluidos orales tales como soluciones, jarabes o

elixires se pueden preparar en forma de dosis unitaria 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 dosis unitaria para administración oral se pueden microenextremosular. 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 unilamelares pequeñas, vesículas unilamelares grandes y vesículas multilamelares. Los liposomas se pueden formar a partir de una diversidad de fosfolípidos 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 portadores 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, polihidroxietilaspartamidefenol o polietilenoxidepolilisina sustituida con restos palitoilo. 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 extremorolactona, poli(ácido hidroxi butírico), poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de bloque de hidrogeles reticulados o anfipáticos.

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 vehículos 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 genera 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 sales 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 dosis unitaria 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 mamíferos.

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 invención 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 invención. Los compuestos de la invención se pueden administrar con otros compuestos con actividad anti-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		Inhibidor de ciclofilina	Novartis
Zadaxina		Inmunomodulador	Sciclone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista de TLR9	Coley

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Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
Batabulina (T67)	Anticanceroso	Inhibidor de β-tubulina	Tularik Inc., South San Francisco, CA
ISIS 14803	Antivírico	Antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antivírico	Antivírico	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antivírico	Inhibidor de VHC	Achillion / Gilead
Compuestos de pirazolopirimidina y sales del documento WO-2005047288 26 de mayo de 2005	Antivírico	Inhibidores de VHC	Arrow Therapeutics Ltd.
Levovirina	Antivírico	Inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antivírico	Inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antivírico	anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Israel

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Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
Telaprevir (VX-950, LY-570310)	Antivírico	Inhibidor de serina proteasa de NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
VHC-796	Antivírico	Inhibidor de replicasa de NS5B	Wyeth / Viropharma
NM-283	Antivírico	Inhibidor de replicasa de NS5B	Idenix / Novartis
GL-59728	Antivírico	Inhibidor de replicasa de NS5B	Gene Labs / Novartis
GL-60667	Antivírico	Inhibidor de replicasa de NS5B	Gene Labs / Novartis
2'C MeA	Antivírico	Inhibidor de replicasa de NS5B	Gilead
PSI 6130	Antivírico	Inhibidor de replicasa de NS5B	Roche
R1626	Antivírico	Inhibidor de replicasa de NS5B	Roche
2'C Metil adenosina	Antivírico	Inhibidor de replicasa de NS5B	Merck
JTK-003	Antivírico	Inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Levovirina	Antivírico	ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirina	Antivírico	ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Viramidina	Antivírico	Profármaco de Ribavirina	Ribapharm Inc., Costa Mesa, CA

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Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
Heptazima	Antivírico	ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antivírico	Inhibidor de serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
SCH 503034	Antivírico	Inhibidor de serina proteasa	Schering Plough
Zadazim	Modulador inmunitario	Modulador inmunitario	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Inmunomodulador	Modulador inmunitario	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Inmunosupresor	Inmunosupresor de IgG de VHC	F. Hoffmann-La Roche LTD, Basilea, Suiza
Civacir	Inmunosupresor	Inmunosupresor de IgG de VHC	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferón	albúmina IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferón	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferón	IFN-ω	Intarcia Therapeutics

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Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
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
Intron A y Zadaxina	Interferón	IFN-α2b/α1-timosina	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferón	IFN-α2b/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferón	INF-γ	InterMune Inc., Brisbane, CA
Interferón-β	Interferón	Interferón-β-1a	Serono
Multiferon	Interferón	IFN de acción prolongada	Viragen/Valentis
Wellferon	Interferón	IFN-αn1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferón	IFN-α natural	Viragen Inc., Plantation, FL

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Nombre comercial	*Clase fisiológica*	*Tipo de Inhibidor o Diana*	*Empresa suministradora*
Pegasys	Interferón	IFN-α2a PEGilado	F. Hoffmann-La Roche LTD, Basilea, Suiza
Pegasys y Ceplene	Interferón	IFN-α2a PEGilado/ Modulador inmunitario	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
PEG-Intron / Ribavirin	Interferón	IFN-α2b PEGilado /ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Protector hepático	antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Protector hepático	inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antivírico	Inhibidor de serina proteasa	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antivírico	Inhibidor de replicasa de NS5B	Genelabs
ANA-971	Antivírico	agonista de TLR-7	Anadys

Los compuestos de la presente invención 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 invención son útiles para establecer o determinar el sitio de unión de otros compuestos antivíricos, por ejemplo, por inhibición competitiva.

Los compuestos de esta invención 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 invención 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 (*in vivo*) o procedimientos que se producen *in vitro*.

Las abreviaturas usadas en la presente solicitud, incluyendo en particular en los esquemas de reacción ilustrativos y ejemplos siguientes, son bien conocidas por

los expertos en la técnica. Algunas de las abreviaturas usadas son las siguientes: TFA para ácido trifluoracético; Ph para fenilo; tBu o t-Bu para terc-butilo; DMSO para dimetil sulfóxido; DMF para N,N-dimetilformamida; EtOH para etanol; Boc o BOC para terc-butoxicarbonilo; THF para tetrahidrofurano; Et_2O para éter dietílico; Et para etilo; MeOH para metanol; EtOAc y EtOAC para acetato de etilo; TA para temperatura ambiente; t_R para tiempo de retención; h o hr para horas; sat. para saturado; PCC para cloroformiato de piridinio; TBDPS para terc-butildifenilsililo; DMAP para 4-dimetilaminopiridina; TBAF para fluoruro de tetrabutilamonio; Et_3N o TEA para trietilamina; min para minutos; OAc para acetato; Cbz para carbobenciloxi; SEM para 2-trimetilsililetoximetoxi; AIBN para azobisisoburitronitrilo; HATU para hexafluorfosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio; DDQ para 2,3-dicloro-5,6-diciano-1,4-benzoquinona; dppf para 1,1'-bis(difenilfosfino)ferroceno; e iPr_2NEt o DIPEA o DIEA para diisopropilamina.

Los compuestos y procedimientos de la presente invención se comprenderán mejor en relación con los siguientes esquemas de reacción de síntesis que ilustran los procedimientos por medio de los cuales se pueden preparar los compuestos de la presente invención. 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.

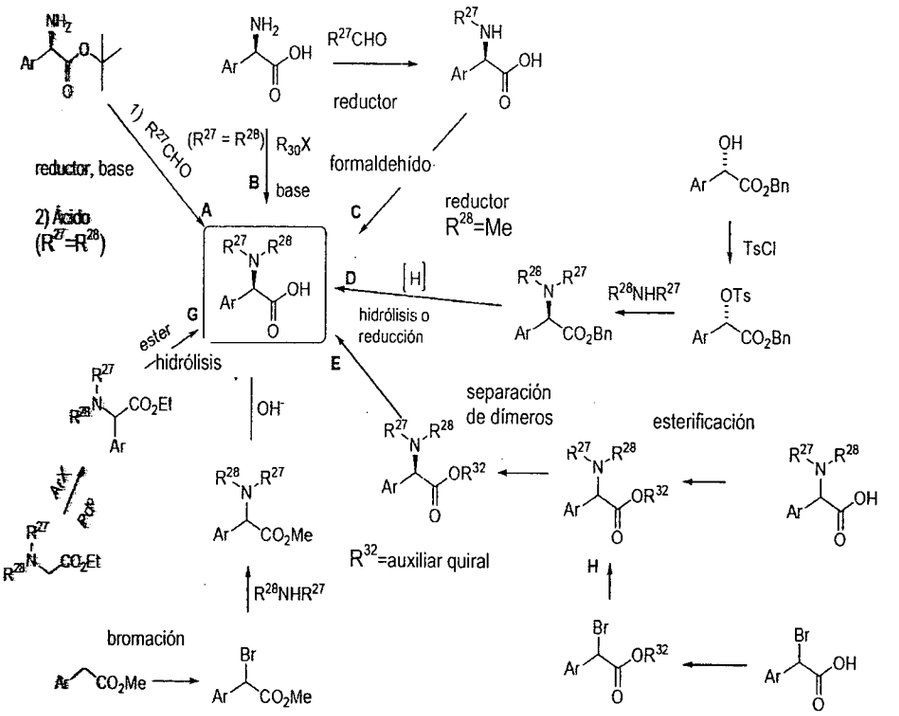
Esquema de reacción 1: Derivados de fenilglicina sustituidos

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 trifluoracético. 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 intersecciona 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.

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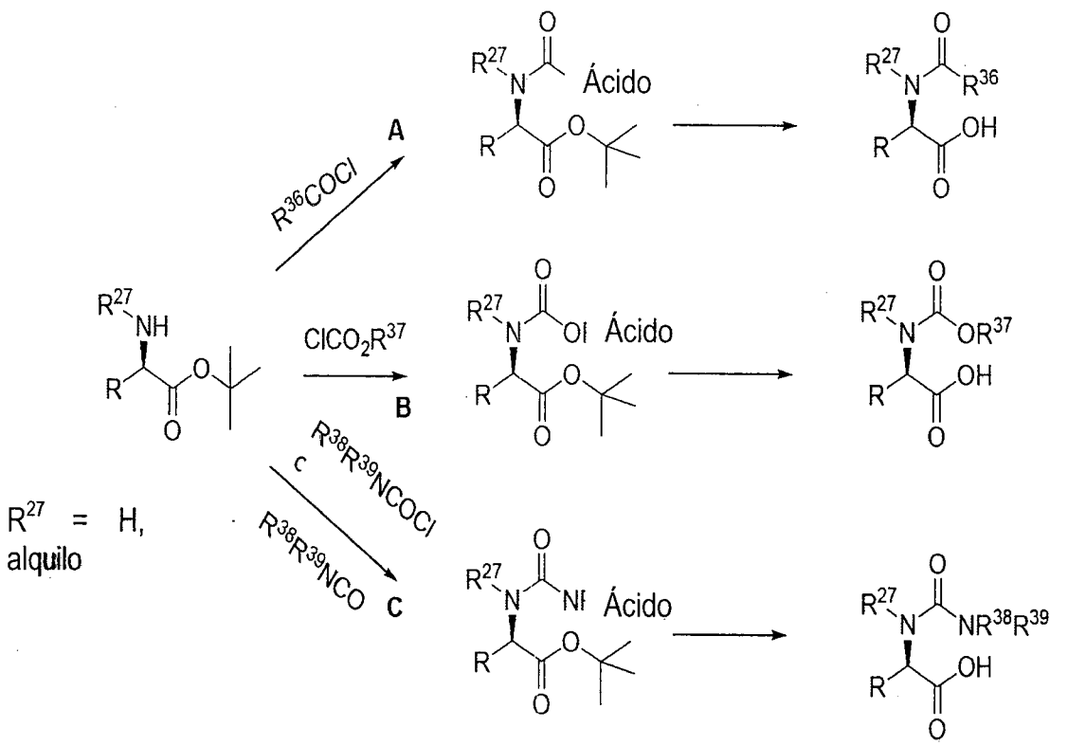


Esquema de reacción 2: Derivados de aminoácido acilados

En otra modalidad de la presente invención, 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 fácilmente retirable 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 carbamoilo 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-

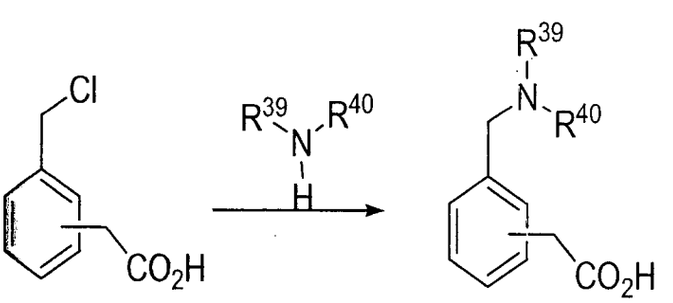
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butílico con base fuerte tal como HCl o ácido trifluoracético).



Esquema de reacción 3

Los ácidos fenilacéticos sustituidos con amino se pueden preparar por tratamiento de un ácido clorometilfenilacético con un exceso de una amina.



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 LC Shimadzu LC acoplado con un sistema de MS Waters Micromass

ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. Las condiciones de LC empleadas en determinar el tiempo de retención (t_R) fueron:

Síntesis de extremos comunes

Condiciones adicionales de LC aplicables a la presente sección, a no ser que se indiquen de otro modo.

Cond.-MS-W1

Columna = XTERRA 3,0 X 50 mm S7

Inicio % 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%

Cond.-MS-W2

Columna = XTERRA 3,0 X 50 mm S7

Inicio % 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%

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Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Cond.-MS-W5

Columna = XTERRA 3,0 X 50 mm S7

Inicio % 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%

Cond.-D1

Columna = XTERRA C18 3,0 X 50 mm S7

Inicio % 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%

Cond.-D2

Columna = Phenomenex-Luna 4,6 X 50 mm S10

Inicio % 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%

Cond.-M3

Columna = XTERRA C18 3,0 X 50 mm S7

Inicio % 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%

Condición I

Columna = Phenomenex-Luna 3,0X 50 mm S10

Inicio % 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%

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Disolvente B = TFA al 0,1% en metanol al 90%/H_2O al 10%

Condición II

Columna = Phenomenex-Luna 4,6X50 mm S10

Inicio % 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 = PHC XTERRA C18 3,0 x 50mm S7

Inicio % de B = 0

Final % de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

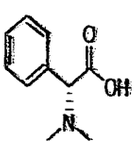
Caudal = 4 ml/min

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%

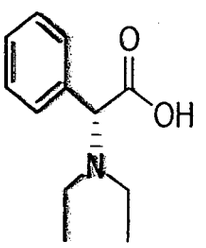
Extremo-I



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Se añadió una suspensión de Pd al 10%/C (2,0g) en metanol (10 ml) a una mezcla de (R)-2-fenilglicina (10g, 66,2 mmol), formaldehído (33 ml de 37% en peso en agua), HCL 1N (30 ml) y metanol (30 ml) y se expuso a H_2 (60 psi) 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 *Extremo*-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); LC (Cond. I): TR = 0,25; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180,10; encontrado 180,17; HRMS: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180,1025; encontrado 180,1017.

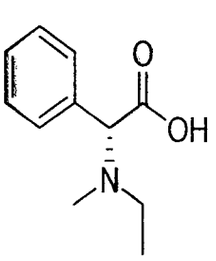
Extremo-2



Se añadió $NaBH_3CN$ (6,22g, 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 añadió 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 *Extremo*-2 como un sólido blanco brillante en dos tandas (tanda-1: 4,16 g; tanda-2: 2,19 g). RMN de ^{1}H (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). LC (Cond. I): TR = 0,43 min; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208,13; encontrado 208,26

Extremo-3



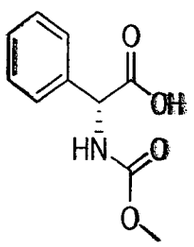
Se añadió secuencialmente acetaldehído (5,0 ml, 89,1 mmol) y una suspensión de Pd al 10%/C (720 mg) en

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 en un balón 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 (2,846g). 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). LC (Cond. I): TR = 0,39 min; >95 % de índice de homogeneidad; LC/MS: 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 (1,492g, 6,918 mmol), formaldehído (20 ml de 37% en peso en agua), HCl 1N (20 ml) y metanol (23 ml). La mezcla de reacción se agitó en un balón 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 *Extremo-3* como un sólido blanco (985 mg). RMN de ^1H (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). LC (Cond. I): TR = 0,39 min; >95 % de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,12; encontrado 194,18; HRMS: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,1180; encontrado 194,1181.

Extremo-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,

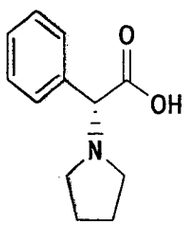
se filtró y se lavó con hexanos (100 ml) proporcionando 2-(metoxicarbonilamino)-2-fenilacetato de (R)-terc-butilo como un sólido blanco (7,7 g). RMN de ^{1}H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): 7,98 (d, J = 8,0, 1H), 7,37-7,29 (m, 5H), 5,09 (d, J = 8, 1H), 3,56 (s, 3H), 1,33 (s, 9H). LC (Cond. I): TR = 1,53 min; ~90 % de índice de homogeneidad; LC/MS: 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 *Extremo*-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 ^{1}H (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). LC (Cond. I): TR = 1,01 min; >95 % de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210,08; encontrado 210,17; HRMS: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210,0766;

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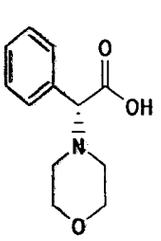
encontrado 210,0756.

Extremo-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 *Extremo-5* como una espuma blanca semiviscosa (1,0 g). RMN de ^1H (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); TR = 0,30 min (Cond. I); >98% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206,12; encontrado 206,25.

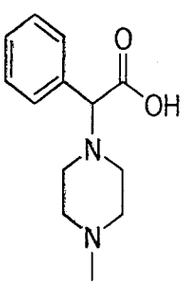
Extremo-6



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La sal TFA de *Extremo*-6 se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el procedimiento de preparación de *Extremo*-5. RMN de ^1H (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); TR = 0,32 min (Cond. I); >98%; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222,11; encontrado 222,20; HRMS: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222,1130; encontrado 222,1121.

Extremo-7



Extremo-7a: enantiómero 1
Extremo-7b: enantiómero 2

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 el 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). TR = 3,00 (Cond. III); >90% de índice de homogeneidad; LC/MS: 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 ^1H ($CDCl_3$, 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). TR = 2,10 (Cond. III); >98% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325,19; encontrado 325,20.

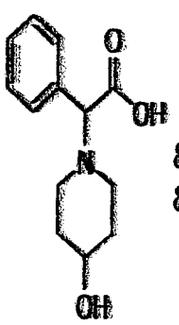
Se añadió una solución en metanol (10 ml) de cualquiera de los enantiómeros de 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo (1,0 g, 3,1 mmol) a una suspensión de Pd al 10%/C (120 mg) en metanol (5,0 ml). La mezcla de reacción se expuso a un balón de hidrógeno con un control cuidadoso durante <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 *Extremo*-7, contaminado con ácido fenilacético como una espuma castaña (867,6 mg; la masa es superior al rendimiento teórico). El producto se usó en la etapa siguiente sin purificación adicional. RMN de ^1H (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),

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2,19 (s, 3H); TR = 0,31 (Cond. II); >90% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235,14; encontrado 235,15; HRMS: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235,1447; encontrado 235,1440.

La síntesis de *Extremo*-8 y *Extremo*-9 se llevó a cabo de acuerdo con la síntesis de *Extremo*-7 usando aminas apropiadas para la etapa de desplazamiento de SN_2 (es decir, 4-hidroxipiperidina para *Extremo*-8 y (S)-3-fluoropirrolidina para *Extremo*-9) y condiciones modificadas para la separación de los intermedios estereoisoméricos respectivos, como se describe más adelante.

Extremo-8



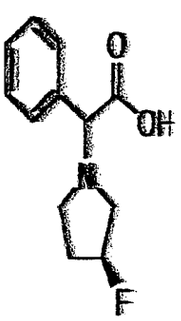
8a: enantiómero 1
8b: enantiómero 2

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 L, 10 µm) eluyendo con 80:20 de heptano/etanol a 10 ml/min, controlada

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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 *Extremo*-7 proporcionando *Extremo*-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). TR = 0,28 (Cond. III); >98% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236,13; encontrado 236,07; HRMS: Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236,1287; encontrado 236,1281.

Extremo-9



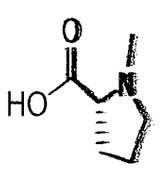
9a: diastereómero 1
9b: diastereómero 2

La separación diastomérica 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 TEA, 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

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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 *Extremo*-7 para preparar Extremos 9a y 9b. *Extremo*-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). TR = 0,42 (Cond. I); >95% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224,11; encontrado 224,14; *Extremo*-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), 1,97 (s, 1H), 2,95-2,43 (m, 4H), 2,19-1,78 (m, 2H). TR = 0,44 (Cond. I); LC/MS: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224,11; encontrado 224,14.

Extremo-10

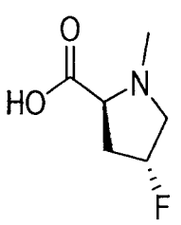


A una solución de D-prolina (2,0 g, 17 mmol) y formaldehído (2,0 ml de 37% en peso en H_2O) en metanol (15 ml) se añadió una suspensión de Pd al 10%/C (500 mg) en

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metanol (5 ml). La mezcla se agitó en un balón de hidrógeno durante 23 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío proporcionando *Extremo*-10 como un sólido blanquecino (2,15 g). RMN de ^{1}H (DMSO-d_6, δ = 2,5, 500 MHz) 3,42 (m, 1H), 3,37 (dd, J = 9,4, 6,1, 1H), 2,85-2,78 (m, 1H), 2,66 (s, 3H), 2,21-2,13 (m, 1H), 1,93-1,84 (m, 2H), 1,75-1,66 (m, 1H). TR = 0,28 (Cond. II); >98% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130,09; encontrado 129,96.

Extremo-11

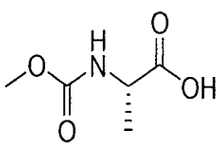


Una mezcla de ácido (2S,4R)-4-fluoropirrolidin-2-carboxílico (0,50 g, 3,8 mmol), formaldehído (0,5 ml de 37% en peso en H_2O), HCl 12 N (0,25 ml) y Pd al 10%/C (50 mg) en metanol (20 ml) se agitó en un balón de hidrógeno durante 19 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El residuo se recristalizó en isopropanol proporcionando la sal HCl de *Extremo*-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

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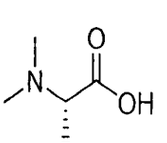
(m, 1H). TR = 0,28 (Cond. II); >98% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 143,08; encontrado 148,06.

Extremo-12 (igual que el Extremo 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 *Extremo*-12 como un aceite incoloro. RMN de ^1H (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).

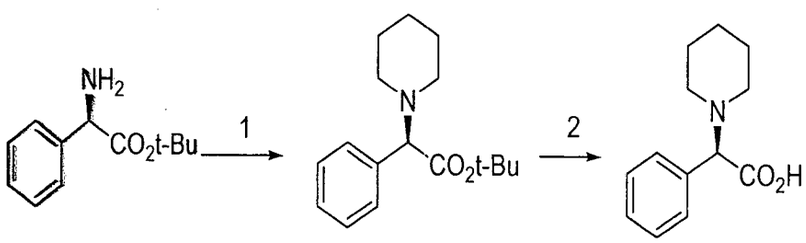
Extremo-13



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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 (50 psi) 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 *Extremo-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).

Extremo-14



EXTREMO-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 acético ácido (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

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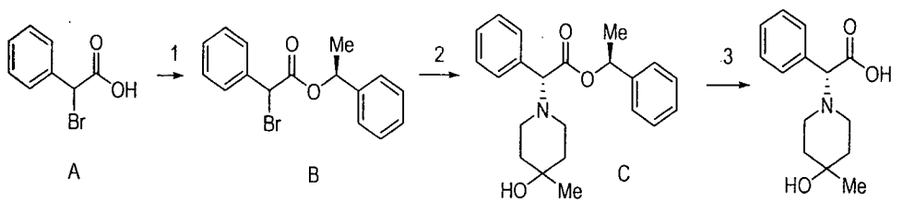
seguidamente y el residuo se repartió con NaOH acuoso al 10% y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta sequedad proporcionando un aceite transparente. Este material se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0,1% de TFA) dando el éster intermedio (2,70 g, 56%) como un aceite transparente. RMN de ^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). LC/MS: 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, 2,88mmol) en diclorometano (10 ml) se añadió TFA (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se concentró hasta sequedad dando un aceite amarillo claro. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0,1% de TFA). Las fracciones apropiadas se reunieron y se concentraron hasta sequedad a vacío. El residuo se disolvió entonces en una cantidad mínima de metanol y se aplicó en cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos se aclararon con metanol (40 ml) y luego eluyó el compuesto deseado usando amoníaco 2M en metanol (50 ml). Las fracciones que contenían producto se reunieron y

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concentraron y el residuo se suspendió en agua. La liofilización de esta solución proporcionó el compuesto del epígrafe (0,492 g, 78%) como un sólido amarillo claro. RMN de ^1H (DMSO-d_6) 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). LC/MS: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

Extremo-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 ^1H (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),

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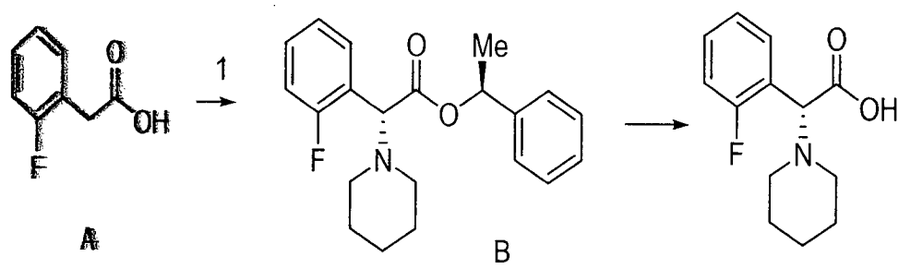
1,51 (d, J = 6,6 Hz, 1,5H).

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). LCMS: 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). LCMS: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$.

Etapa 3: ácido (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0,185 g, 0,52 mmol) en diclorometano (3 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0,1% de TFA) dando el compuesto del epígrafe (como sal TFA) como un sólido azulado pálido (0,128 g, 98%). LCMS: Anal. Calculado para $C_{14}H_{19}NO_3$: 249; encontrado: 250 $(M+H)^+$.

Extremo-16



A B

(R)-EXTREMO-16

Etapa 1: 2-(2-fluorofenil)acetato de (S)-1-feniletilo: Una mezcla de ácido 2-fluorofenilacético (5,45 g, 35,4 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)

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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

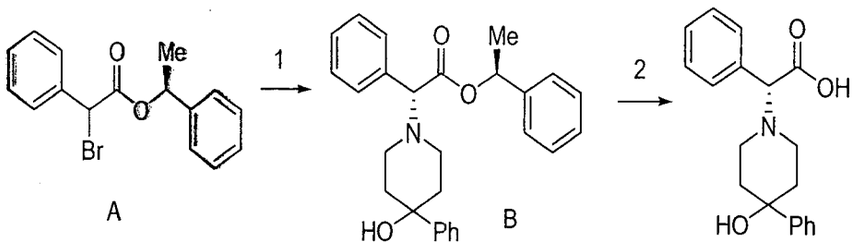
se concentraron a vacío. Al residuo se añadió piperidina (5,73 ml, 58,1 mmol) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles se concentraron entonces a vacío y el residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-30% de éter dietílico-hexano) proporcionando 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 diastereoisomérica (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 (c, 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. 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 (balón 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

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epígrafe como un sólido incoloro (0,503 g, 98%). RMN de ^1H (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). LCMS: Anal. Calculado para $C_{13}H_{16}FNO_2$: 237; encontrado: 238 $(M+H)^+$.

Extremo-17



(R)-EXTREMO-17

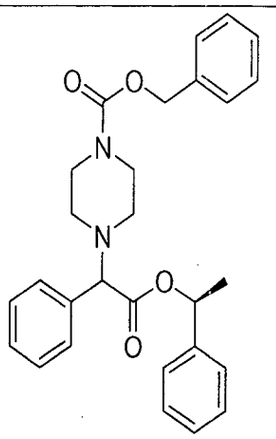
Etapa 1: (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1,50 g, 4,70 mmol) en THF (25 ml) se añadió trietilamina (1,31 ml, 9,42 mmol), seguido por yoduro de tetrabutilamonio (0,347 g, 0,94 mmol). La mezcla de reacción 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 ^1H. La separación

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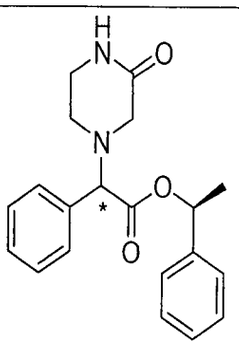
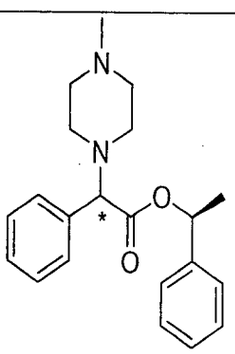
de esos isómeros se llevó a cabo usando cromatografía de fluido supercrítico (Chiralcel OJ-H, 30 x 250mm; 20% etanol en CO_2 a 35 °C), dando primero el isómero (R) del compuesto del epígrafe (0,534 g, 27%) como un aceite amarillo y luego el isómero (S) correspondiente (0,271 g, 14%), también como un aceite amarillo. Isómero (S,R): RMN de ^1H (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. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$; Isómero (S,S): RMN de ^1H (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. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$.

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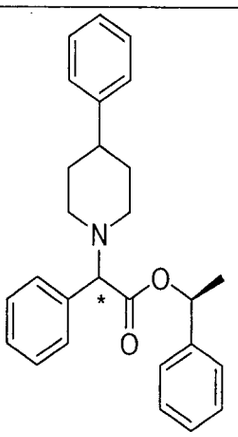
Los ésteres siguientes se prepararon de una forma similar.

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). LCMS: 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).

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		LCMS: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458,22; Encontrado: 459,44 $(M+H)^+$.
Intermedio -17b		Diastereómero 1: TR = 11,76 min (Condición II); LCMS: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338,16 Encontrado: 339,39 $(M+H)^+$; Diastereómero 2: TR = 10,05 min (Condición II); LCMS: 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); LCMS: 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); LCMS: Análisis

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		calculado para: $C_{21}H_{26}N_2O_2$ 338,20 Encontrado: 339,45 $(M+H)^+$.
Intermedio -17d		Diastereómero 1: TR = 7,19 min (Condición I); LCMS: Análisis calculado para: $C_{27}H_{29}NO_2$ 399,22 Encontrado: 400,48 $(M+H)^+$; Diastereómero 2: TR = 9,76 min (Condición I); LCMS: 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: 150 bar

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: 150 bar

Caudal: 2,0 ml/min.

UV controlado a 220 nm

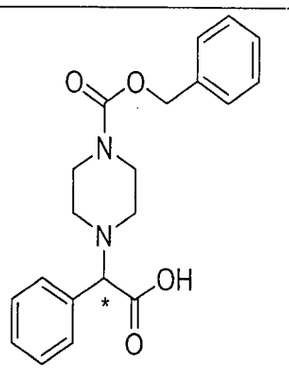
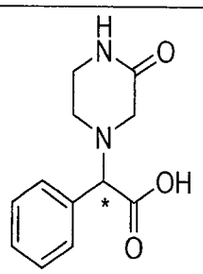
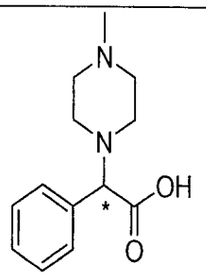
Inyección: 1,0 mg/ml de metanol

Extremo-17, Etapa 2: ácido (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0,350 g, 0,84 mmol) en diclorometano (5 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0,1% de TFA) dando el compuesto del epígrafe (como sal TFA) como un sólido blanco (0,230 g, 88%). LCMS: Anal. Calculado para $C_{19}H_{21}NO_3$: 311,15; encontrado: 312 $(M+H)^+$.

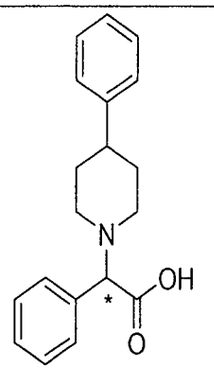
Los siguientes ácidos carboxílicos se prepararon

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en forma ópticamente pura de una forma similar:

Extremo-17a		TR = 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). LCMS: Análisis calculado para: $C_{20}H_{22}N_2O_4$ 354,16; Encontrado: 355,38 $(M+H)^+$.
Extremo-17b		TR = 0,27 (Condición III); LCMS: Análisis calculado para: $C_{12}H_{14}N_2O_3$ 234,10; Encontrado: 235,22 $(M+H)^+$.
Extremo-17c		TR = 0,48 (Condición II); LCMS: Análisis calculado para: $C_{13}H_{18}N_2O_2$ 234,14; Encontrado: 235,31 $(M+H)^+$.

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Extremo-17d		TR = 2,21 (Condición I); LCMS: Análisis calculado para: $C_{19}H_{21}NO_2$ 295,16; Encontrado: 296,33 $(M+H)^+$.

Condiciones LCMS para determinar el tiempo de retención

Condición I

Columna: Phenomenex-Luna 4,6 X 50 mm S10

Inicio % 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

Inicio % 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%

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Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0,1%

Condición III

Columna: Phenomenex 10µ 3,0 X 50 mm

Inicio % de B = 0

Final % de B = 100

Tiempo de gradiente = 2 min

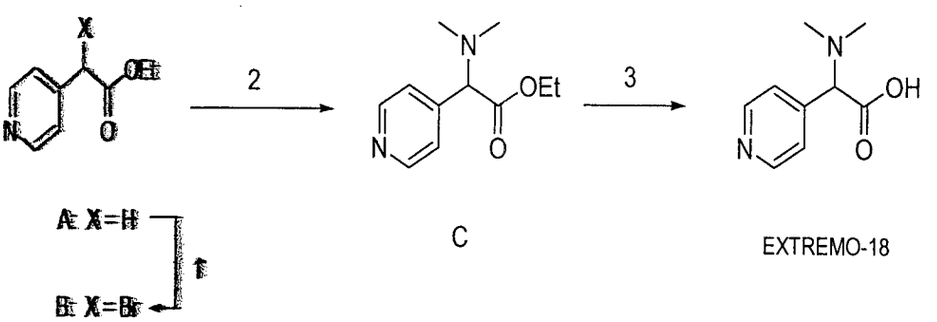
Caudal = 4 ml/min

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%

Extremo-18



Etapa 1: 2-(4-piridil)-2-bromoacetato de (R,S)-Etilo: A una solución de 4-piridilacetato de etilo (1,00 g, 6,05 mmol) en THF seco (150 ml) a 0 °C en argon 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

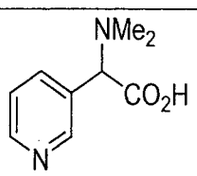
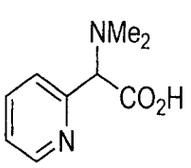
lavó (salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío. El aceite amarillo resultante se purificó inmediatamente por cromatografía ultrarrápida (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (1,40 g, 95%) como un aceite amarillo algo estable. RMN de ^1H (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). LCMS: 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 extremoa fina) los volátiles se eliminaron a vacío y el residuo se purificó por cromatografía ultrarrápida (columna Biotage, 40+M SiO_2; 50%-100% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe (0,539 g, 31%) como un aceite amarillo claro. RMN de ^1H (400 MHz, $CDCl_3$) 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. Calculado para $C_{11}H_{16}N_2O_2$: 208; encontrado: 209 $(M+H)^+$.

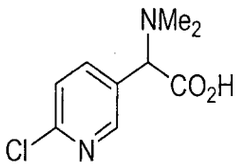
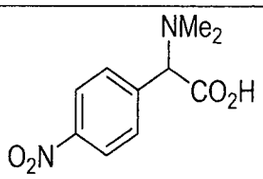
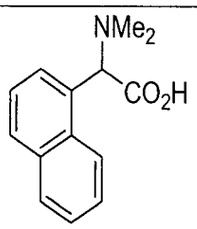
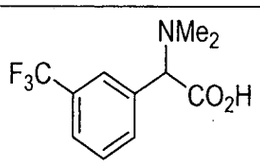
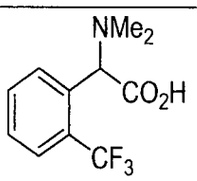
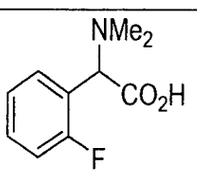
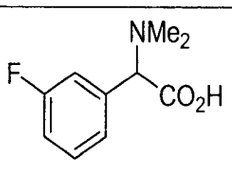
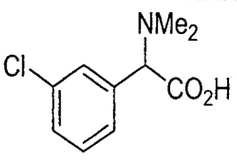
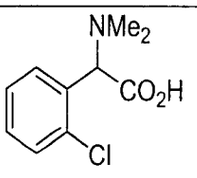
Etapa 3: ácido (R,S)-2-(4-piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-

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 ^1H (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).

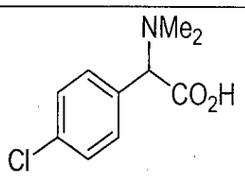
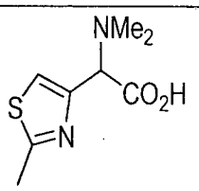
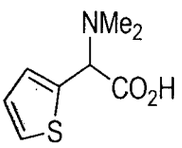
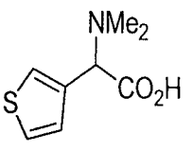
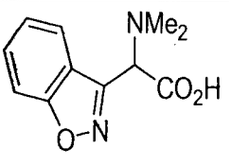
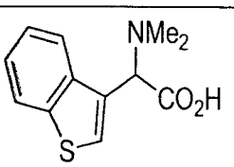
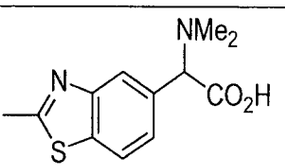
Los siguientes ejemplos se prepararon de una forma similar usando el procedimiento descrito antes;

Extremo-19		LCMS: Anal. Calculado para $C_9H_{12}N_2O_2$: 180; encontrado: 181 $(M+H)^+$.
Extremo-20		LCMS: sin ionización. RMN de ^1H (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).

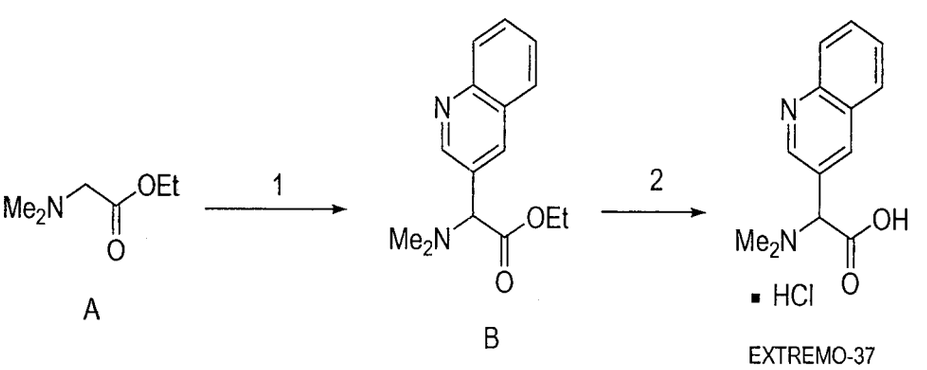
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Extremo-21		LCMS: Anal. Calculado para $C_9H_{11}ClN_2O_2$: 214, 216; encontrado: 215, 217 $(M+H)^+$.
Extremo-22		LCMS: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-23		LCMS: Anal. Calculado para $C_{14}H_{15}NO_2$: 229; encontrado: 230 $(M+H)^+$.
Extremo-24		LCMS: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Extremo-25		LCMS: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Extremo-26		LCMS: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.
Extremo-27		LCMS: Anal. Calculado para $C_{10}H_{12}FNO_2$: 247; encontrado: 248 $(M+H)^+$.
Extremo-28		LCMS: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Extremo-29		LCMS: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.

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

Extremo-37



A B EXTREMO-37

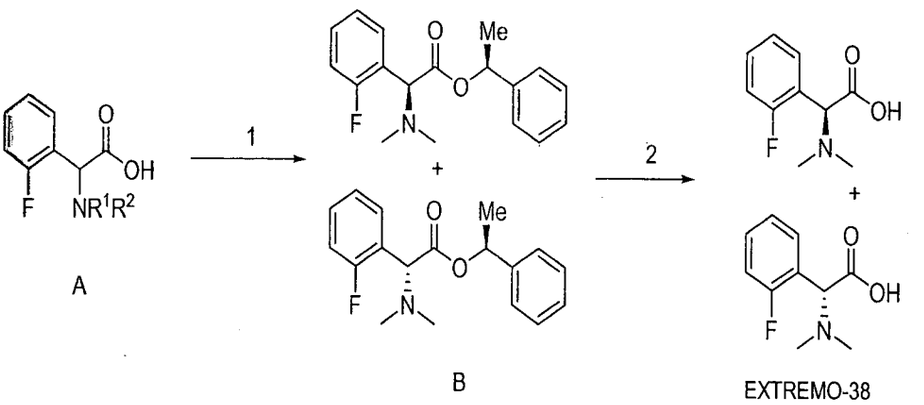
Etapa 1: 2-(quinolin-3-il)-2-(N,N-dimetilamino)-acetato de (R,S)-etilo: Una mezcla de N,N-dimetilaminoacetato de etilo (0,462 g, 3,54 mmol), K_3PO_4 (1,90 g, 8,95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0,090 g, 0,176 mmol) y tolueno (10 ml) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. La mezcla de reacción se calentó entonces a 100 °C durante 12 horas, después de lo cual se enfrió hasta temperatura ambiente y se vertió en H_2O. La mezcla se extrajo con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó primero por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) y luego por cromatografía ultrarrápida (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (0,128 g, 17%) como un aceite naranja. RMN de ^1H (400 MHz, $CDCl_3$) 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. 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

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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. LCMS: Anal. Calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.

Extremo-38



Etapa 1: 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo) y 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-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 diastereoisomérica pura resultante se separó entonces por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0,1% de TFA) dando primero (R)-2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-1-fenetilo (0,501 g, 13%) y luego (S)-2-(dimetilamino)-2-(2-fluorofenil)-acetato de (S)-1-fenetilo (0,727 g. 18%), ambas como sus sales TFA. isómero (S,R): RMN de ^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). LCMS: 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). LCMS: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$.

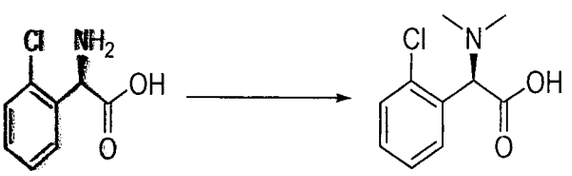
Etapa 2: ácido (R)-2-(dimetilamino)-2-(2-fluorofenil)acético: Una mezcla de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo), sal TFA (1,25 g, 3,01 mmol) y 20% de $Pd(OH)_2/C$ (0,125 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (balón 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

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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). LCMS: 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.

Extremo-39



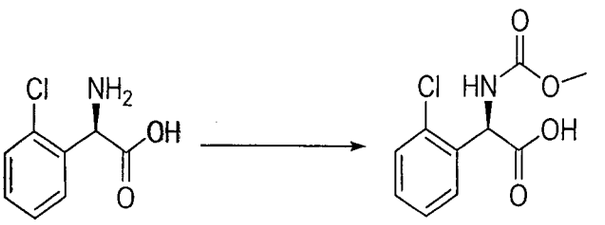
EXTREMO-39

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 (balón de H_2) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. El residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0,1% de TFA) dando la sal TFA del compuesto del epígrafe ácido (R)-2-(dimetilamino)-2-(2-clorofenil)acético como un aceite incoloro (0,290 g, 55%). RMN de ^1H (400 MHz, CD_3OD) δ 7,59-7,65 (m, 2H), 7,45-7,53 (m, 2H), 5,40 (s, 1H), 2,87 (s, 6H). LCMS: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213;

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encontrado: 214 $(M+H)^+$.

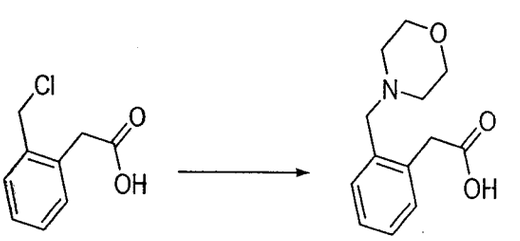
Extremo-40



EXTREMO-40

A una solución enfriada en hielo de (R)-(2-clorofenil)glicina (1,00 g, 5,38 mmol) y NaOH (0,862 g, 21,6 mmol) en H_2O (5,5 ml) se 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). LCMS: Anal. Calculado para $C_{10}H_{10}ClNO_4$: 243; encontrado: 244 $(M+H)^+$.

Extremo-41

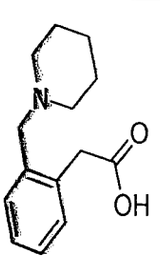
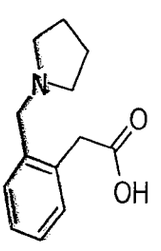


EXTREMO-41

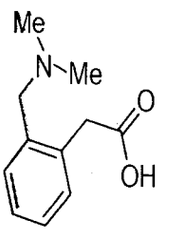
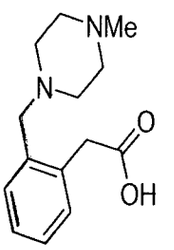
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A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2,00 g, 10,8 mmol) en THF (20 ml) se añadió morfolina (1,89 g, 21,7 mmol) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó entonces con acetato 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). LCMS: Anal. Calculado para $C_{13}H_{17}NO_3$: 235; encontrado: 236 $(M+H)^+$.

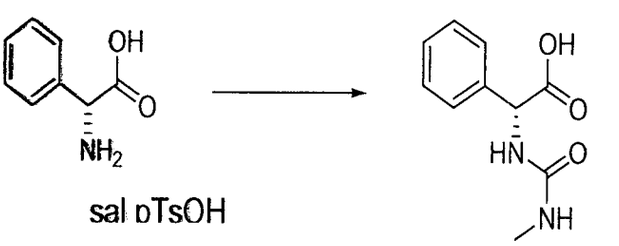
Los siguientes ejemplos se prepararon de igual modo usando el procedimiento descrito para *Extremo*-41:

Extremo-42		LCMS: Anal. Calculado para $C_{14}H_{19}NO_2$: 233; encontrado: 234 $(M+H)^+$.
Extremo-43		LCMS: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

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Extremo-44		LCMS: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 194 $(M+H)^+$.
Extremo-45		LCMS: Anal. Calculado para $C_{14}H_{20}N_2O_2$: 248; encontrado: 249 $(M+H)^+$.

Extremo-45a



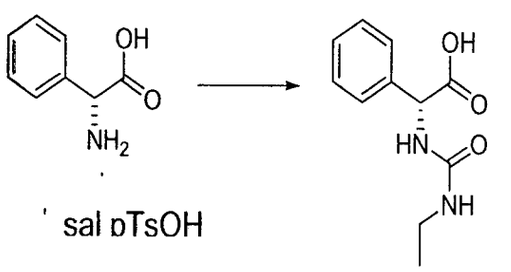
EXTREMO-45a

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

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purificación adicional. RMN de ^1H (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. 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 time, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, TR = 1,38 min, 90% de índice de homogeneidad.

Extremo-46



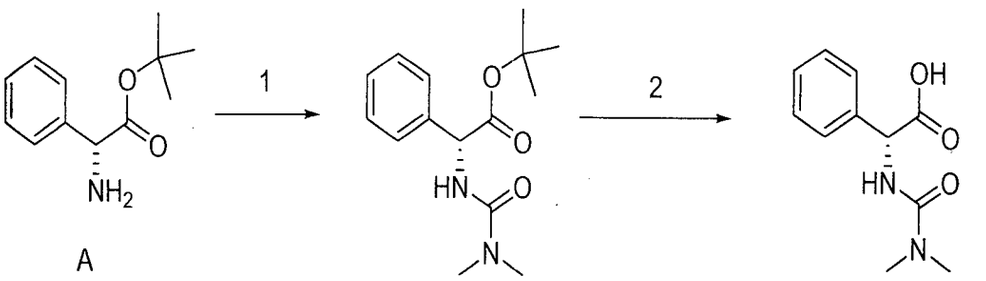
EXTREMO-46

El producto deseado se preparó de acuerdo con el procedimiento descrito para *Extremo*-45a. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 0,96 (t, *J*=7,17 Hz, 3H) 2,94 - 3,05 (m, 2H) 5,17 (d, *J*=7,93 Hz, 1H) 6,05 (t, *J*=5,19 Hz, 1H) 6,60 (d, *J*=7,63 Hz, 1H) 7,26 - 7,38 (m, 5H) 12,68 (s, 1H). LCMS: 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, TR = 0,87 min, 90% de índice de homogeneidad.

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Extremo-47



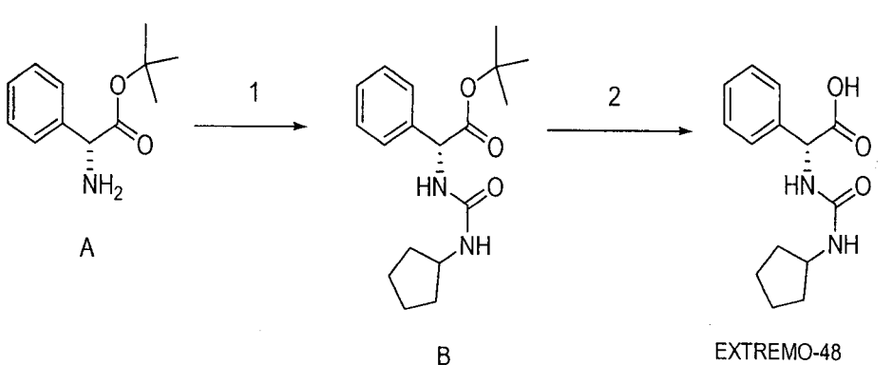
A B EXTREMO-47

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 dimetilcarbamoilo (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). LCMS: 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, TR = 2,26 min, 97% de índice de homogeneidad.

Etapa 2: ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-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 ^1H (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. 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, TR = 0,75 min, 93% de índice de homogeneidad.

Extremo-48



A B EXTREMO-48

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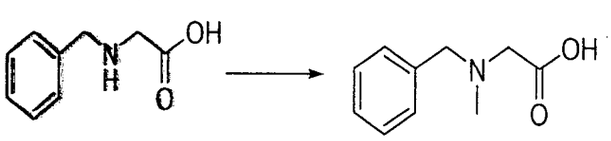
Etapa 1: 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo: A una solución agitada de clorhidrato del ácido (R)-2-amino-2-fenilacético (1,0 g, 4,10 mmol) y base de Hunig (1,0 ml, 6,15 mmol) en DMF (15 ml) se añadió isocianato de ciclopentilo (0,46 ml, 4,10 mmol) gota a gota y durante 10 minutos. 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). LCMS: 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, TR = 2,82 min, 96% de índice de homogeneidad.

Etapa 2: Ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-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

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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 ^{1}H (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. 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, TR = 1,24 min, 100% de índice de homogeneidad.

Extremo-49

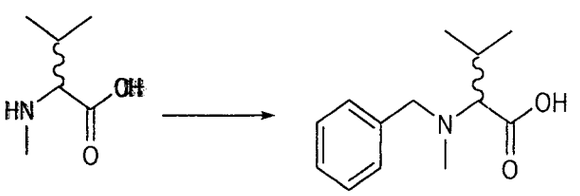


EXTREMO-49

A una solución agitada de 2-(bencilamino)acético ácido (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). LCMS: Análisis calculado para: $C_{10}H_{13}NO_2$ 179,09; Encontrado: 180,20 $(M+H)^+$.

Extremo-50



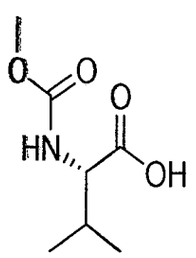
EXTREMO-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico(0,50 g, 3,81 mmol) en agua (30 ml) se 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

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TFA, B = 10% de agua, 90 % de metanol, 0,1% de TFA) proporcionando ácido 2-(bencil(metil)amino)-3-metilbutanoico, sal TFA (126 mg, 19%) como una cera incolora. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0,98 (d, 3H) 1,07 (d, 3H) 2,33 - 2,48 (m, 1H) 2,54 - 2,78 (m, 3H) 3,69 (s, 1H) 4,24 (s, 2H) 7,29 - 7,65 (m, 5H). LCMS: Análisis calculado para: $C_{13}H_{19}NO_2$ 221,14; Encontrado: 222,28 $(M+H)^+$.

Extremo-51

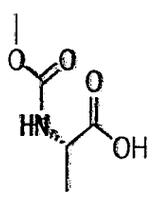


Se añadió Na_2CO_3 (1,83g, 17,2 mmol) a una solución de NaOH (33 ml de 1M/H_2O, 33 mmol) de L-valina (3,9 g, 33,29 mmol) y la solución resultante se enfrió con baño de hielo-agua. Se añadió gota a gota durante 15 minutos cloroformiato de metilo (2,8 ml, 36,1 mmol), se retiró el baño de enfriamiento y 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 *Extremo-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),

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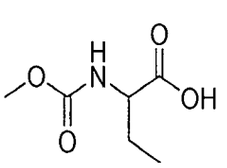
7,33 (d, J = 8,6, 1H), 3,84 (dd, J = 8,4, 6,0, 1H), 3,54 (s, 3H), 2,03 (m, 1H), 0,87 (m, 6H). HRMS: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176,0923; encontrado 176,0922

Extremo-52 (Igual que el Extremo-12)

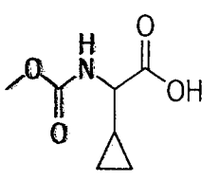
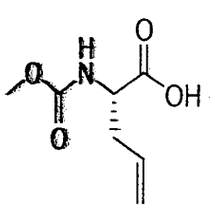
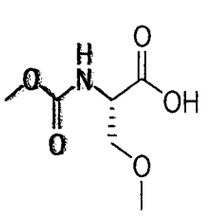


Extremo-52 se sintetizó a partir de L-alanina de acuerdo con el procedimiento descrito para la síntesis de *Extremo*-51. Con fines caracterizadores, se purificó una porción del material bruto por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando *Extremo*-52 como un aceite incoloro viscoso. 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).

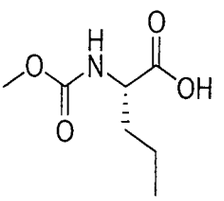
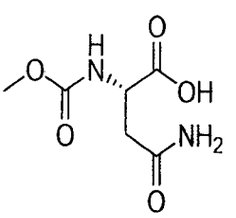
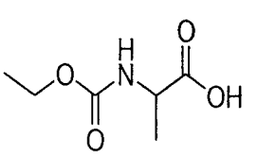
Extremo-53 a -64 se prepararon a partir de materiales partida apropiados de acuerdo con el procedimiento descrito para la síntesis de *Extremo*-51, con las modificaciones indicadas sin las hubiera.

Extremo	Estructura	Datos
Extremo-53*a*: (R) *Extremo*-53*b*: (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

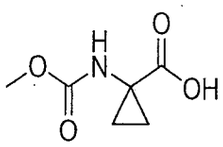
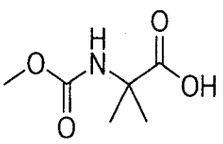
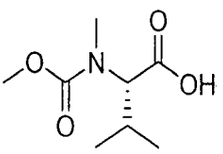
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		(d, J = 7,3, 3H). TR = 0,77 minutos (Cond. II); LC/MS: Anal. Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184,06; encontrado 184,07. HRMS Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184,0586; encontrado 184,0592.
Extremo-54a: (R) *Extremo-54b*: (S)		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). HRMS Calculado para $[M+H]^+$ $C_7H_{12}NO_4$: 174,0766; encontrado 174,0771
Extremo-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).
Extremo-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).

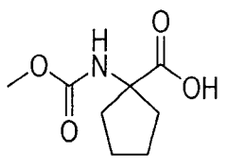
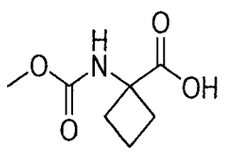
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Ejemplo 57		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 12,50 (s, 1H), 8,02 (d, J = 7,7, 0,08H), 7,40 (d, J = 7,9, 0,76H), 7,19 (d, J = 8,2, 0,07H), 7,07 (d, J = 6,7, 0,09H), 4,21-4,12 (m, 0,08H), 4,06-3,97 (m, 0,07H), 3,96-3,80 (m, 0,85H), 3,53 (s, 3H), 1,69-1,51 (m, 2H), 1,39-1,26 (m, 2H), 0,85 (t, J = 7,4, 3H). LC (Cond. II): TR = 1,39 LC/MS: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176,09; encontrado 176,06.
Ejemplo 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). TR = 0,16 min (Cond. II); LC/MS: Anal. Calculado para $[M+H]^+$ $C_6H_{11}N_2O_5$: 191,07; encontrado 191,14.
Ejemplo 59a: (R) Ejemplo 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). HRMS: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162,0766; encontrado 162,0771.

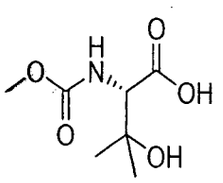
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Extremo-60		El material bruto se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando un aceite viscoso incoloro que cristalizó en un blancoa viscoso que cristalizó en un sólido blanco al exponerse a alto vacío. RMN de ^1H (DMSO-d_6, 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). HRMS: Anal. Calculado para $[M+H]^+$ $C_6H_{10}NO_4$: 160,0610; encontrado 160,0604.
Extremo-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). HRMS: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162,0766; encontrado 162,0765.
Extremo-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). LC/MS: Anal. Calculado para $[M-H]^-$ $C_8H_{14}NO_4$: 188,09; encontrado 188,05.

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Extremo-63		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para elprocedimiento 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). LC/MS: Anal. Calculado para $[M+H]^+$ $C_8H_{14}NO_4$: 188,09; encontrado 188,19.
Extremo-64		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para elprocedimiento 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).

Extremo-65



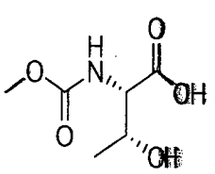
Se añadió cloroformiato de metilo (0,65 ml, 8,39 mmol) gota a gota durante 5 minutos a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0,449 g, 4,23 mmol), NaOH (8,2 ml de

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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 *Extremo*-65 como una espuma semiviscosa blanca (1,236 g). RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 6,94 (d, J = 8,5, 0,9 H), 6,53 (s ancho, 1H), 3,89 (d, J = 8,8, 1H), 2,94 (s, 3H), 1,15 (s, 3H), 1,13 (s, 3H).

Extremo-66 y -67 se prepararon a partir de materiales de partida disponible comercialmente empleando el procedimiento descrito para la síntesis de *Extremo*-65.

Extremo-66

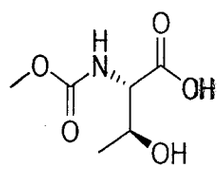


RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 12,58 (s ancho, 1H), 7,07 (d, J = 8,3, 0,13H), 6,81 (d, J = 8,8, 0,67H), 4,10-4,02 (m, 1,15H), 3,91 (dd, J = 9,1, 3,5, 0,85H), 3,56 (s, 3H), 1,09 (d, J = 6,2, 3H). [Nota: solo se indican

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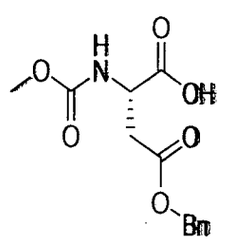
las señales dominantes de NH]

Extremo-67



RMN de ^1H (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]

Extremo-68

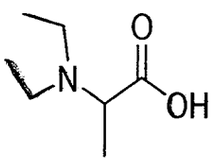


Se añadió cloroformiato de metilo (0,38 ml, 4,9 mmol) gota a gota a una mezcla de NaOH 1N (ac) (9,0 ml, 9,0 mmol), $NaHCO_3$ 1M (ac) (9,0 ml, 9,0 mol), éster β-bencílico del ácido L-aspártico (1,0 g, 4,5 mmol) y dioxano (9 ml). La mezcla de reacción se agitó en condiciones ambientales durante 3 hr, y 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

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proporcionando *Extremo*-68 como un aceite amarillo claro (1,37 g; la masa es superior al rendimiento teórico, y el producto se usó sin purificación adicional). RMN de ^{1}H (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). LC (Cond. II): TR = 1,90 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282,10; encontrado 282,12.

Extremo-69a y -69b



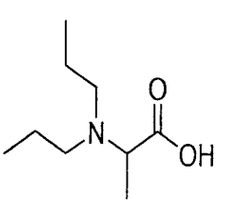
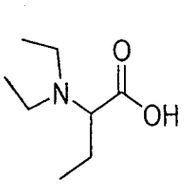
Extremo-69a: enantiómero (R)
Extremo-69b: enantiómero (S)

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

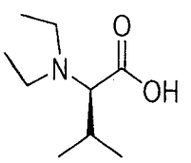
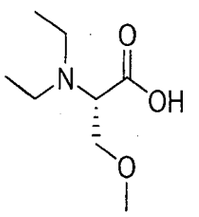
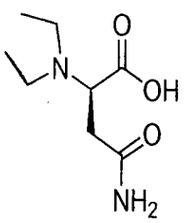
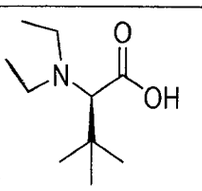
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Dowex ® 50WX8-100 (la columna se lavó con agua y el compuesto eluyó con NH_4OH diluido, preparado mezclando 18 ml de NH_4OH y 282 ml de agua) proporcionando *Extremo*-69 (2,0 g) como un sólido higroscópico blando blanquecino. RMN de ^1H (DMSO-d_6, 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).

Extremo-70 a -74x se prepararon de acuerdo con el procedimiento descrito para la síntesis de *Extremo*-69 empleando materiales de partida apropiados.

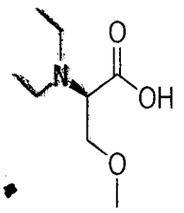
Extremo-70a: (R) *Extremo-70b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 3,42 (q, J = 7,1, 1H), 2,68-2,60 (m, 4H), 1,53-1,44 (m, 4H), 1,19 (d, J = 7,3, 3H), 0,85 (t, J = 7,5, 6H). LC/MS: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174,15; encontrado 174,13.
Extremo-71a: (R) *Extremo-71b*: (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). LC/MS: Anal. Calculado para $[M+H]^+$ $C_8H_{18}NO_2$: 160,13; encontrado 160,06.

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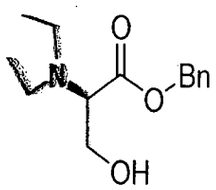
Extremo-72		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 400 MHz): δ 2,77-2,66 (m, 3H), 2,39-2,31 (m, 2H), 1,94-1,85 (m, 1H), 0,98 (t, *J* = 7,1, 6H), 0,91 (d, *J* = 6,5, 3H), 0,85 (d, *J* = 6,5, 3H). LC/MS: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174,15; encontrado 174,15.
Extremo-73		RMN de ^1H (DMSO-d_6, 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).
Extremo-74		RMN de ^1H (DMSO-d_6, δ = 2,5 ppm, 500 MHz): δ 7,54 (s, 1H), 6,89 (s, 1H), 3,81 (t, *J* = 6,6, k,1H), 2,82-2,71 (m, 4H), 2,63 (dd, *J* = 15,6, 7,0, 1H), 2,36 (dd, *J* = 15,4, 6,3, 1H), 1,09 (t, *J* = 7,2, 6H). TR = 0,125 minutos (Cond. II); LC/MS: Anal. Calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189,12; encontrado 189,13.
Extremo-74x		LC/MS: Anal. Calculado para $[M+H]^+$ $C_{10}H_{22}NO_2$: 188,17; encontrado 188,21

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Extremo-75



Extremo-75, etapa a



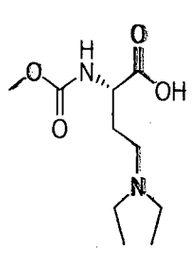
Se añadió $NaBH_3CN$ (1,6 g, 25,5 mmol) a una solución enfriada (baño de hielo/agua) en agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2,0 g, 8,6 mmol). Se añadió acetaldehído (1,5 mL, 12,5 mmol) gota a gota durante 5 min, se retiró el baño de enfriamiento, y la mezcla de reacción se agitó en condiciones 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 ^1H (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). LC/MS (Cond. II): TR = 1,38 min; LC/MS: Anal. Calculado para $[M+H]^+ C_{14}H_{22}NO_3$: 252,16; encontrado 252,19.

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Extremo-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 *Extremo*-75, contaminado con ácido (R)-2-(dietilamino)-3-hidroxipropanoico, como un semisólido amarillo (100 mg). El producto se usó como tal sin purificación adicional.

Extremo-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,

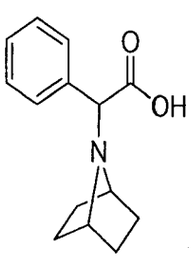
se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 3,5 hr. Se añadió más acetaldehído (2,7 ml, 48,1 mmol) y la reacción se agitó durante 20,5 hr. Se eliminó a vacío la mayoría del componente MeOH, y la mezcla restante se trató con HCl concentrado hasta 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 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

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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 *Extremo*-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). LC/MS: Anal. Calculado para $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233,15; encontrado 233,24.

Extremo-77a y -77b



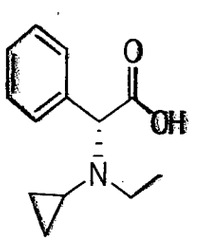
Extremo-77a: enantiómero 1
Extremo-77b: enantiómero 2

La síntesis de *Extremo*-77 se llevó a cabo de acuerdo con el procedimiento descrito para *Extremo*-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

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sometieron a hidrogenación de acuerdo con la preparación de *Extremo*-7 proporcionando *Extremo*-77: RMN de ^{1}H (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). LC (Cond. I): TR = 0,67 min; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232,13; encontrado 232,18. HRMS: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232,1338; encontrado 232,1340.

Extremo-78

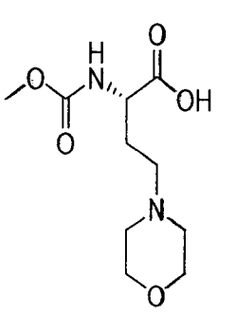


Se añadió $NaCNBH_3$ (0,5828 g, 9,27 mmol) a una mezcla de la sal HCl de ácido (*R*)-2-(etilamino)-2-fenilacético (un intermedio en la síntesis de *Extremo*-3; 0,9923 mg, 4,60 mmol) y (1-etoxiciclopropoxi)trimetilsilano (1,640 g, 9,40 mmol) en MeOH (10 ml), y se calentó la mezcla semiheterogénea a 50 °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

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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 *Extremo*-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). LC (Cond. I): TR = 0,64 min; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220,13; encontrado 220,21. HRMS: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220,1338; encontrado 220,1343.

Extremo-79



Se burbujeó ozono a través de una solución enfriada (-78 °C) en CH_2Cl_2 (5,0 ml) de *Extremo*-55 (369 mg, 2,13 mmol) durante aproximadamente 50 min hasta que la mezcla de reacción alcanzaba 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

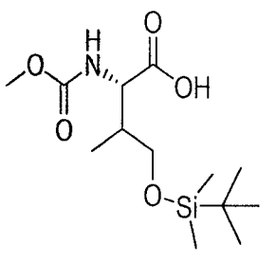
continuó agitando durante otros 30 min, y luego se eliminó el componente volátil a vacío proporcionando un aceite viscoso incoloro.

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 *Extremo*-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 *Extremo*-79 impuro como un aceite viscoso marrón, que se usó para la etapa siguiente sin purificación adicional.

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Extremo-80a y -80b



Extremo-80a: diastereómero S/S
Extremo-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). LC (Cond. I): TR = 0,90 min; LC/MS: 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*-

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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). LC (Cond. I): TR = 2,16 min; LC/MS: 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

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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 ^{1}H). 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 ^{1}H (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). LC (Cond. I): TR = 2,19 min; LC/MS: 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

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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 disolvente), 1,58 (m, 1H), 0,88 (d, J = 6,8, 3H). LC (Cond. I): TR = 2,00 min; LC/MS: 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). LC (Cond. I): TR = 1,92 min; LC/MS: 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 DIBAL estaban basadas 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 ^1H (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). LC (Cond. I): TR = 1,98 min;

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LC/MS: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378,15; encontrado 378,42. Isómero (3S,4R)-lactona: RMN de ^1H (DMSO-d_6, 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. I): TR = 2,03 min; LC/MS: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378,15; encontrado 378,49.

Se añadieron TBDMS-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

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(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). LC (Cond. 1, donde el tiempo de ejecución de prolongó hasta 4 min): TR = 3,26 min; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578,31; encontrado 578,40. Isómero (2S,3R)-silil éter: RMN de ^{1}H (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 balón 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 balón se recargó con H_2 cuando fue necesario. La mezcla de reacción se diluyó con CH_2Cl_2 y se filtró a través de una almohadilla de tierra de diatomeas (Celite-545®), y se lavó la almohadilla 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

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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). LC/MS: 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

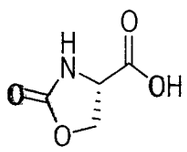
408

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 *Extremo*-80a como un sólido blanquecino. Se elaboró ácido (2S,3R)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico de forma similar a *Extremo*-80b. *Extremo*-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). LC/MS: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328,16; encontrado 328,46. *Extremo*-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). LC/MS: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328,16; encontrado 328,53. Los productos brutos se utilizaron sin

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purificación adicional.

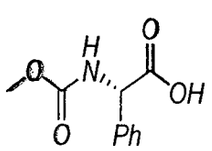
Extremo-81



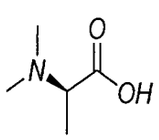
Se prepararon de acuerdo con el protocolo descrito por Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Extremo-82 a Extremo-85

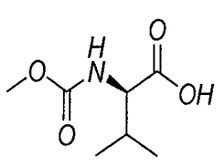
Extremo-82 a *Extremo*-85 se sintetizaron a partir de los materiales de partida apropiados de acuerdo con el procedimiento descrito para *Extremo*-51 o *Extremo*-13. Las muestras presentaron perfiles espectrales similares a los de sus enantiómeros (es decir, *Extremo*-4, *Extremo*-13, *Extremo*-51 y *Extremo*-52, respectivamente).



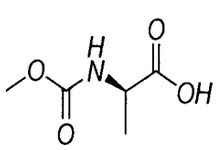
EXTREMO-82



EXTREMO-83

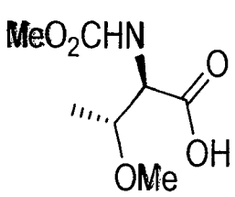


EXTREMO-84



EXTREMO-85

Extremo-86

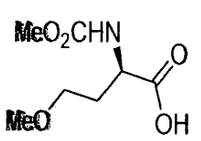


A una mezcla de O-metil-L-treonina (3,0 g, 22,55 mmol), NaOH (0,902 g, 22,55 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (1,74 ml, 22,55 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 12 h y se acidificó hasta pH 1 usando HCl

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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). LCMS: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 190 $(M-H)^-$.

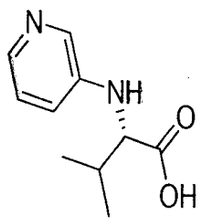
Extremo-87



A una mezcla de L-homoserina (2,0 g, 9,79 mmol), Na_2CO_3 (2,08 g, 19,59 mmol) en H_2O (15 ml) se 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). LCMS: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 192 $(M+H)^+$.

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Extremo-88

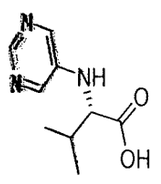


Se calentó una mezcla de L-valina (1,0 g, 8,54 mmol), 3-bromopiridina (1,8 ml, 18,7 mmol), K_2CO_3 (2,45 g, 17,7 mmol) y CuI (169 mg, 0,887 mmol) en DMSO (10 ml) a 100°C durante 12h. La mezcla de reacción se enfrió hasta ta, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánica 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 una almohadilla de resina de intercambio catiónico (Strata) (aproximadamente 25 g). Se lavó la almohadilla 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),

412

0,91 (d, J = 6,6 Hz, 3H). LCMS: Anal. Calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

Extremo-89

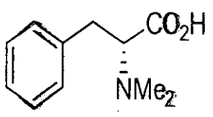


Se calentó a 100°C durante 12 horas una mezcla de L-valina (1,0 g, 8,54 mmol), 5-bromopirimidina (4,03 g, 17,0 mmol), K_2CO_3 (2,40 g, 17,4 mmol) y CuI (179 mg, 0,94 mmol) en DMSO (10 ml). La mezcla de reacción se enfrió hasta TA, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las 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 una almohadilla de resina de intercambio catiónico (Strata) (aproximadamente 25g). La almohadilla 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

913

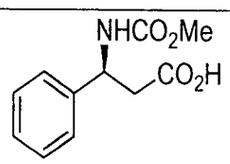
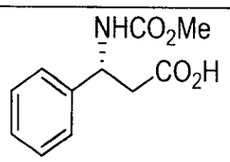
se usó como tal en las posteriores reacciones. LCMS: Anal. Calculado para $C_9H_{13}N_3O_2$: 195; encontrado: 196 $(M+H)^+$.

Extremo-90

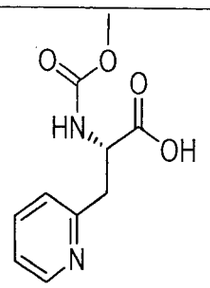
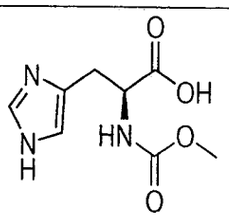
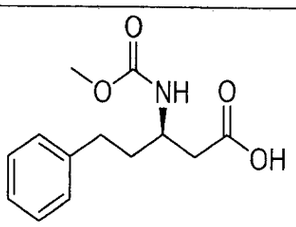
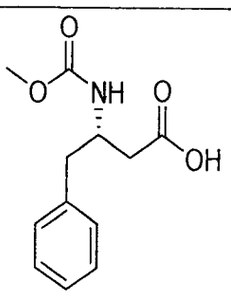
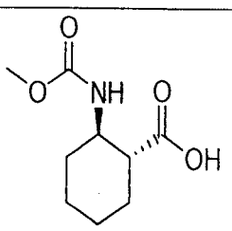
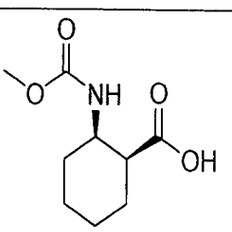


Se preparó *Extremo*-90 de acuerdo con el procedimiento descrito para la preparación de *Extremo*-1. El material bruto se usó como tal en las etapas posteriores. LCMS: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

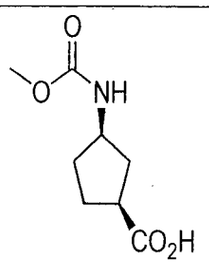
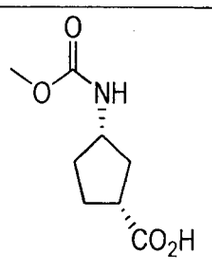
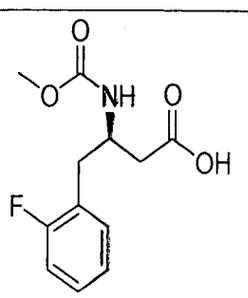
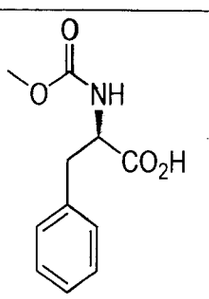
Los siguientes extremos se prepararon de acuerdo con el procedimiento del usado para la preparación del extremo 51, a menos que se indique de otro modo:

Extremo	Estructura	LCMS
Extremo-91		LCMS: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Extremo-92		LCMS: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.

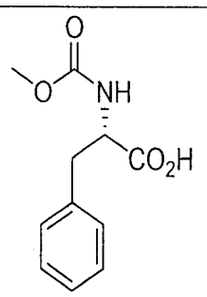
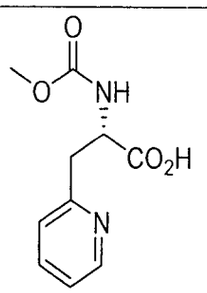
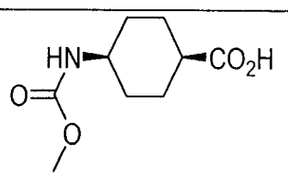
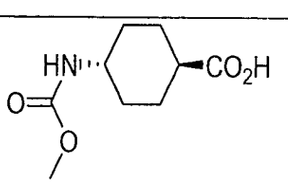
414

Extremo-93		LCMS: Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$. Anal.
Extremo-94		LCMS: Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$. Anal.
Extremo-95		LCMS: Calculado para $C_{13}H_{17}NO_4$: 251; encontrado: 250 $(M-H)^-$. Anal.
Extremo-96		LCMS: Calculado para $C_{12}H_{15}NO_4$: 237; encontrado: 236 $(M-H)^-$. Anal.
Extremo-97		LCMS: Calculado para $C_9H_{15}NO_4$: 201; encontrado: 200 $(M-H)^-$. Anal.
Extremo-98		LCMS: Calculado para $C_9H_{15}NO_4$: 201; encontrado: 202 $(M+H)^+$. Anal.

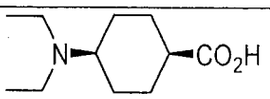
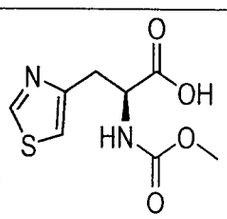
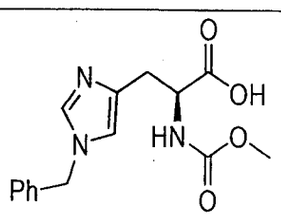
915

Extremo-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).
Extremo-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).
Extremo-100		LCMS: Anal. Calculado para $C_{12}H_{14}NO_4F$: 255; encontrado: 256 $(M+H)^+$.
Extremo-101		LCMS: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.

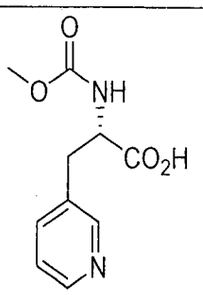
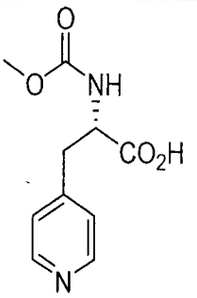
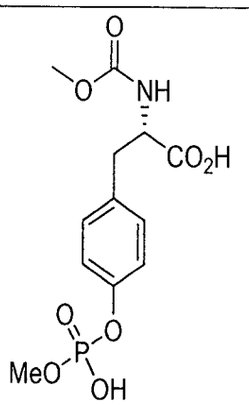
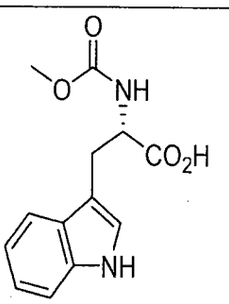
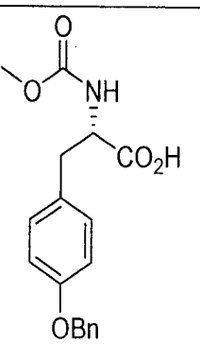
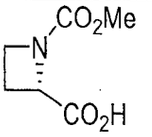
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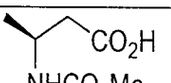
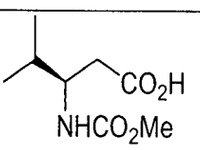
Extremo-102		LCMS: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$
Extremo-103		LCMS: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-104		RMN de ^1H (400 MHz, CD_3OD) δ 3,60 (s, 3H), 3,50 - 3,53 (m, 1H), 2,66 - 2,69 y 2,44 - 2,49 (m, 1H), 1,91 - 2,01 (m, 2H), 1,62 - 1,74 (m, 4H), 1,51 - 1,62 (m, 2H).
Extremo-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

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		(m, 2H).
Extremo-106	 Se preparó a partir de ácido cis-4-aminociclohexanocarboxílico y acetaldehído empleando u procedimiento similar descrito para la síntesis de Extremo-2. La sal HCl bruta se hizo pasar a través de un lavado con MCX ($MeOH/H_2O/CH_2Cl_2$; elución con NH_3 2N /MeOH) proporcionando un aceite que se disolvió en CH_3CN/H_2O y se liofilizó proporcionando un sólido color castaño.	RMN de ^1H (400 MHz, CD_3OD) 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 (t, *J* = 7,3 Hz, 6H).
Extremo-107		LCMS: Anal. Calculado para $C_8H_{10}N_2O_4S$: 230; encontrado: 231 $(M+H)^+$.
Extremo-108		LCMS: Anal. Calculado para $C_{15}H_{17}N_3O_4$: 303; encontrado: 304 $(M+H)^+$.

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Extremo-109		LCMS: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-110		LCMS: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-111		LCMS: Anal. Calculado para $C_{12}H_{16}NO_8P$: 333; encontrado: 334 $(M+H)^+$.
Extremo-112		LCMS: Anal. Calculado para $C_{13}H_{14}N_2O_4$: 262; encontrado: 263 $(M+H)^+$.
Extremo-113		LCMS: Anal. Calculado para $C_{18}H_{19}NO_5$: 329; encontrado: 330 $(M+H)^+$.
Extremo-114		RMN de ^1H (400 MHz, $CDCl_3$) δ 4,82

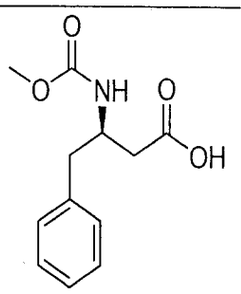
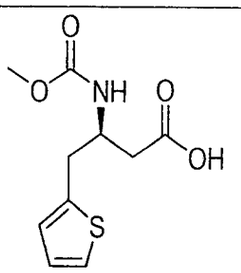
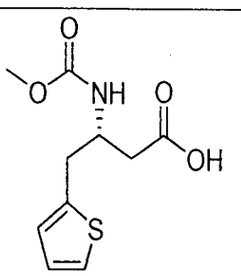
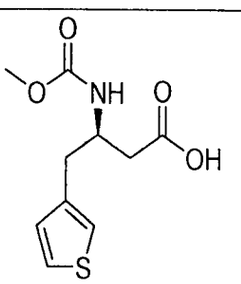
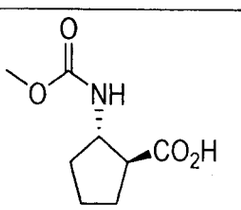
		- 4,84 (m, 1H), 4,00 - 4,05 (m, 2H), 3,77 (s, 3H), 2,56 (s ancho, 2H)
Extremo-115		RMN de ^{1}H (400 MHz, $CDCl_3$) δ 5,13 (s ancho, 1H), 4,13 (s ancho, 1H), 3,69 (s, 3H), 2,61 (d, *J* = 5,0 Hz, 2H), 1,28 (d, *J* = 9,1 Hz, 3H).
Extremo-116		RMN de ^{1}H (400 MHz, $CDCl_3$) δ 5,10 (d, *J* = 8,6 Hz, 1H), 3,74 - 3,83 (m, 1H), 3,69 (s, 3H), 2,54 - 2,61 (m, 2H), 1,88 (sept, *J* = 7,0 Hz, 1H), 0,95 (d, *J* = 7,0 Hz, 6H).

Extremo-117 a Extremo-123

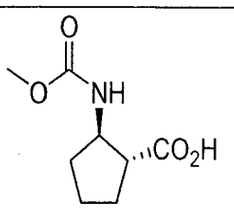
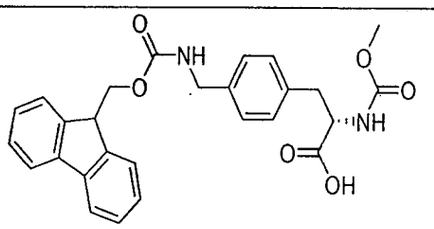
Para la preparación de los extremos *Extremo*-117 a *Extremo*-123 los Boc aminoácidos se obtuvieron de suministradores comerciales y se desprotegieron por tratamiento con TFA al 25% en CH_2Cl_2. Después de completarse la reacción que se juzgó por LCMS se eliminaron los disolventes a vacío y se carbamoiló la sal TFA

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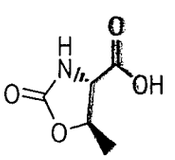
correspondiente del aminoácido con cloroformiato de metilo de acuerdo con el procedimiento descrito para el *Extremo*-51.

Extremo	Estructura	LCMS
Extremo-117		LCMS: Anal. Calculado para $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$.
Extremo-118		LCMS: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-119		LCMS: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-120		LCMS: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-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 -

421

		2,10 (m, 3H), 1,64 - 1,76 (m, 2H), 1,44 - 1,53 (m, 1H).
Extremo-122		El perfil de RMN de ^1H es similar al de su enantiómero, Extremo-121.
Extremo-123		LCMS: Anal. Calculado para $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$.

Extremo-124

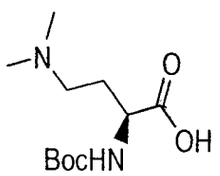


Se carbamoiló la sal clorhidrato de éster terc-butílico de L-treonina de acuerdo con el procedimiento para *Extremo*-51. La mezcla de reacción bruta se acidificó con HCl 1N hasta pH~1 y la mezcla se extrajo con EtOAc (2X50 ml). Las fases orgánicas reunidas se concentraron a vacío dando un aceite incoloro que solidificó en reposo. La extremoa 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 LCMS se

422

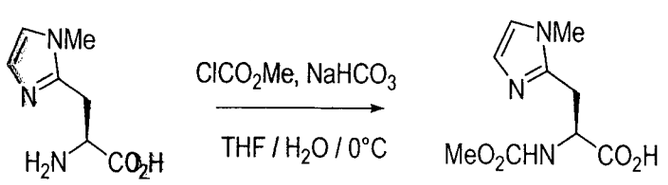
mostró que era el producto deseado. Ambas tandas se reunieron dando 0,52 g de un sólido. RMN de ^1H (400 MHz, CD_3OD) δ 4,60 (m, 1H), 4,04 (d, J = 5,0 Hz, 1H), 1,49 (d, J = 6,3 Hz, 3H). LCMS: Anal. Calculado para $C_5H_7NO_4$: 145; encontrado: 146 $(M+H)^+$.

Extremo-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 con un balón 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. LCMS: Anal. Calculado para $C_{11}H_{22}N_2O_4$: 246; encontrado: 247 $(M+H)^+$.

Extremo-126



cj-25 EXTREMO-126

423

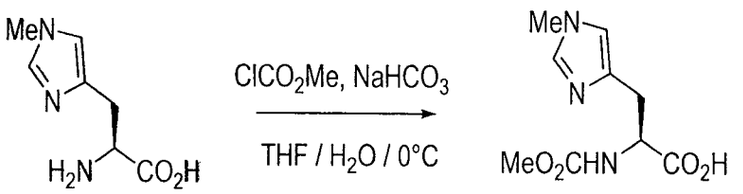
Este procedimiento es una modificación del que se usó para preparar *Extremo*-51. A una suspensión de 3-metil-L-histidina (0,80 g, 4,70 mmol) en THF (10mL) y H_2O (10 ml) a 0°C se añadió $NaHCO_3$ (0,88 g, 10,5 mmol). La mezcla resultante se trató con $ClCO_2Me$ (0,40 ml, 5,20 mmol) y se dejó agitar la mezcla a 0°C. Después de agitar durante aproximadamente. 2h la LCMS 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 LCMS 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 LCMS mostró que no quedaba éster. Seguidamente la mezcla se acidificó con HCl 6N y los disolventes se eliminaron a vacío. La LCMS 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 =

424

9,0, 15,6 Hz, 1H). LCMS: Análisis calculado para $C_9H_{13}N_3O_4$: 227,09; encontrado: 228,09 $(M+H)^+$.

Extremo-127



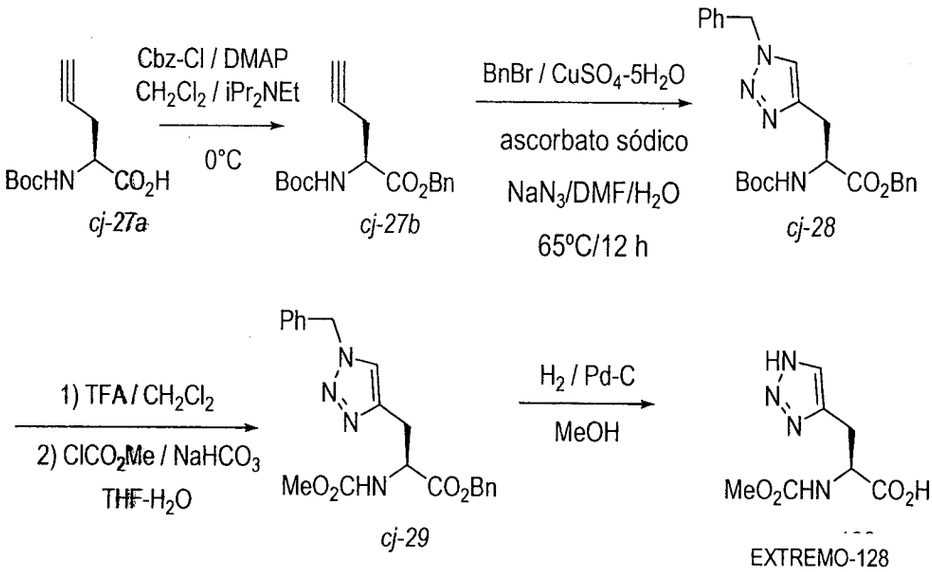
cj-26 EXTREMO-127

Extremo-127 se preparó de acuerdo con el procedimiento para *Extremo*-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 LCMS 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).

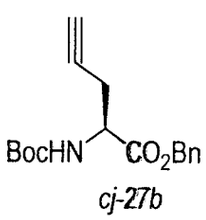
LCMS: Anal. Calculado para $C_9H_{13}N_3O_4$: 227,09; encontrado: 228 $(M+H)^+$.

925

Extremo-128



Etapa 1. Preparación de 2-(terc-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b).



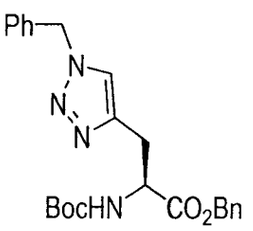
cj-27b

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

476

Hz, 1H), 1,44 (s, 9H). LCMS: 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

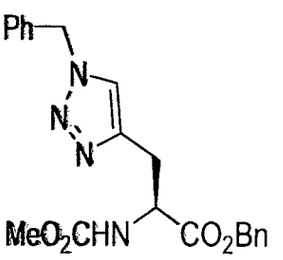
A una mezcla de 2-(terc-butoxicarbonilamino)pent-4-noato de (S)-bencilo (0,50 g, 1,65 mmol), ascorbato sódico (0,036 g, 0,18 mmol), $CuSO_4$-$5H_2O$ (0,022 g, 0,09 mmol) y NaN_3 (0,13 g, 2,1 mmol) en DMF-H_2O (5 ml, 4:1) a ta se añadió BnBr (0,24 ml, 2,02 mmol) y la mezcla se calentó hasta 65°C. Después de 5 horas, la LCMS indicó baja conversión. Se añadió una porción adicional de NaN_3 (100 mg) y se continuó calentando durante 12 horas. La reacción se vertió en EtOAc y H_2O y se agitó. Las 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

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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).

LCMS: 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).



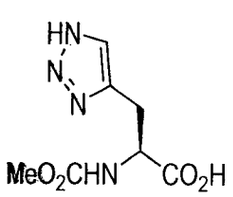
cj-29

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 extremoas orgánicas se separaron y se extrajo la extremoa acuosa 2x con EtOAc. Las

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extremoas 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). LCMS: 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 (*Extremo*-128).



Cap-128

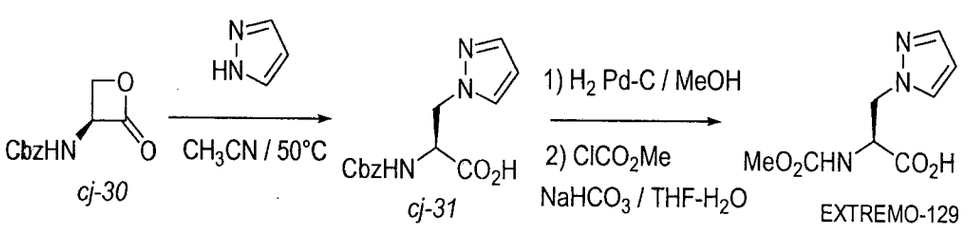
Se sometió 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (502 mg, 1,11 mmol) a hidrogenación en presencia de Pd-C (82 mg) en MeOH (5 ml) a presión atmosférica durante 12h. La mezcla se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Se obtuvo ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico como una goma incolora (266 mg,

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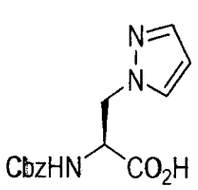
111%) que estaba contaminada con aproximadamente 10% del éster metílico. El material se usó sin purificación adicional.

RMN de ^1H (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). LCMS: Anal. Calculado para $C_7H_{10}N_4O_4$: 214; encontrado: 215 $(M+H)^+$.

Extremo-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

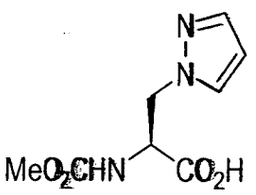
430

a vacío y luego se trituró con una pequeña cantidad de CH_3CN (aproximadamente 4 ml) proporcionando una segunda tanda (43,5 mg). Rendimiento total 370,4 mg (44%).

p.f. 165,5 - 168°C. p.f. lit 168,5 - 169,5 Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105.

RMN de ^1H (400 MHz, CD_3OD) 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. Calculado para $C_{14}H_{15}N_3O_4$: 289; encontrado: 290 $(M+H)^+$.

Etapa 2. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (*Extremo-129*).



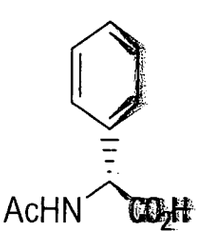
EXTREMO-129

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 ^1H (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). LCMS: Anal. Calculado para $C_9H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.

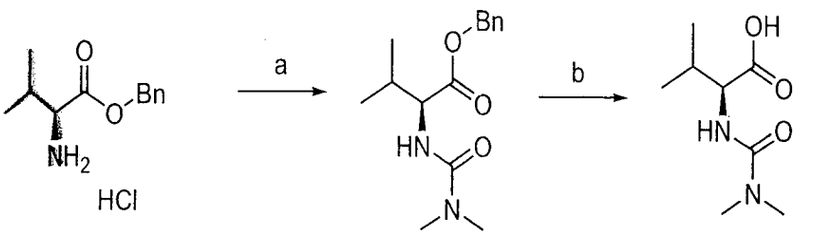
Extremo 130



Extremo 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.

Extremo-131

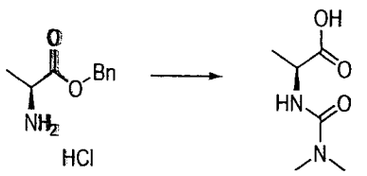


Etapa a: Se añadió cloruro de dimetilcarbamoilo (0,92 ml, 10 mmol) lentamente a una solución de clorhidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2,44 g; 10 mmol) y base de Hunig (3,67 ml, 21 mmol) en THF (50 ml). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16 horas) y se concentró a presión reducida. El residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El aceite amarillo resultante se purificó por cromatografía ultrarrápida, eluyendo con acetato de etilo:hexanos (1:1). Las fracciones recogidas se concentraron a vacío proporcionando 2,35 g (85%) de aceite transparente. RMN de. ^1H (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): TR = 1,76 min; MS: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279,17; encontrado 279,03.

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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 *Extremo-131* como espuma blanca, que se usó sin purificación posterior. RMN de ^1H (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): TR = 0,33 min; MS: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189,12; encontrado 189,04.

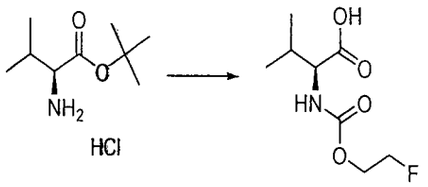
Extremo-132



Extremo-132 se preparó a partir de clorhidrato de 2-aminopropanoato de (S)-bencilo de acuerdo con el procedimiento descrito para *Extremo-131*. RMN de ^1H (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). LC (Cond. 1): TR = 0,15 min; MS: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161,09; encontrado 161,00.

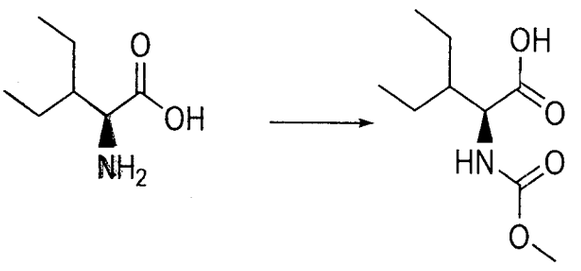
434

Extremo-133



Extremo-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 *Extremo-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).

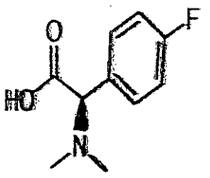
Extremo-134



Extremo-134 se preparó a partir de (S)-dietil alanina y cloroformiato de metilo de acuerdo con el procedimiento descrito para *Extremo-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). LC (Cond. 2): TR = 0,66 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$: 204,12; encontrado 204,02.

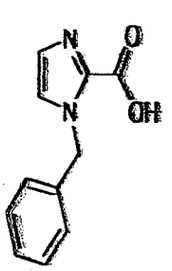
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Extremo-135



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 con balón en paladio al 10% sobre carbón (60 mg) durante 16 h a 25°C. La mezcla se filtró a través de Celite proporcionando la sal HCl de *Extremo-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); TR = 0,19 min (Cond.-MS-W5); índice de homogeneidad del 95%; LRMS: Análisis calculado para $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198,09; encontrado: 198,10.

Extremo-136

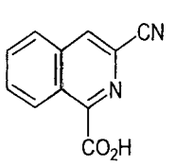


A una suspensión enfriada (-50 °C) de 1-bencil-1*H*-imidazol (1,58 g, 10,0 mmol) en éter dietílico anhidro (50 ml) en nitrógeno se añadió n-butil litio (2,5 M en hexanos, 4,0 ml, 10,0 mmol) gota a gota. Después de agitar durante 20

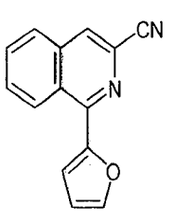
436

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 *Extremo-136* como un sólido blanco (817 mg, 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); TR = 0,51 min (Cond.-MS-W5); índice de homogeneidad del 95%; LRMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203,08; encontrado: 203,11.

Extremo-137



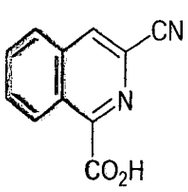
Extremo-137, etapa a



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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 *Extremo-137, etapa a* como un sólido blanco que se usó como tal (230 mg, 105%). TR = 1,95 min (Cond.-MS-W2); índice de homogeneidad del 90%; LRMS: Análisis calculado para $[M+H]^+$ $C_{14}H_8N_2O$: 221,07; encontrado: 221,12.

Extremo-137

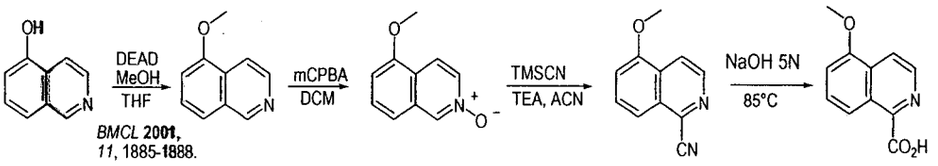


A una suspensión de *Extremo 137, etapa a*, (110 mg, 0,50 mmol) y periodato sódico (438 mg, 2,05 mmol) en tetracloruro de carbono (1 ml), acetonitrilo (1 ml) y agua (1,5 ml) se añadió tricloruro de rutenio hidratado (2 mg,

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 *Extremo-137* (55 mg, 55%) como un sólido de color grisáceo. TR = 1,10 min (Cond.-MS-W2); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_8N_2O_2$: 200,08; encontrado: 200,08.

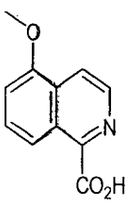
Extremos 138 a 158

Estrategia de síntesis. Procedimiento A.

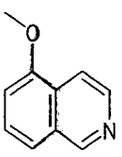


BMCL 2001, 11, 1885-1888.

Extremo-138



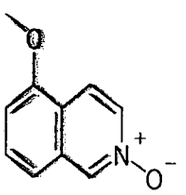
Extremo-138, etapa a



A una suspensión agitada de 5-hidroxisoquinolina (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 purificó (elución con acetato de etilo al 40%/hexanos) proporcionando *Extremo-138, etapa a* como un sólido amarillo claro (1,00 g, 45%). 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); TR = 0,66 min (Cond. D2); índice de homogeneidad del 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO$: 160,08; encontrado 160,10.

Extremo-138, etapa b

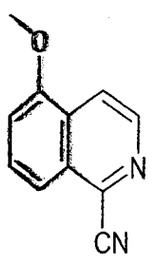


A una solución agitada de *Extremo 138, etapa a* (2,34 g, 14,7 mmol) en diclorometano anhidro (50 ml) a temperatura ambiente se añadió ácido *meta*-cloroperbenzoico (77%, 3,42 g, 19,8 mmol) en una porción. Después de agitar durante 20 horas, se añadió carbonato potásico en polvo (2,0 g) y la mezcla se agitó durante 1 hora a temperatura ambiente antes de que se filtrara y concentrara proporcionando *Extremo-138, etapa b* como un sólido amarillo pálido que era

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suficientemente puro para usarse posteriormente (2,15 g, 83,3%). RMN de ^{1}H ($CDCl_3$, 400 MHz) δ 8,73 (d, J = 1,5 Hz, 1H), 8,11 (dd, J = 7,3, 1,7 Hz, 1H), 8,04 (d, J=7,1 Hz, 1H), 7,52 (t, J = 8,1 Hz, 1H), 7,28 (d, J = 8,3 Hz, 1H), 6,91 (d, J = 7,8 Hz, 1H), 4,00 (s, 3H); TR = 0,92 min, (Cond.-D1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO_2$: 176,07; encontrado: 176,0.

Extremo-138, etapa c

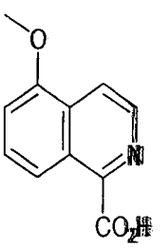


A una solución agitada de *Extremo 138, etapa b* (0,70 g, 4,00 mmol) y trietilamina (1,1 ml, 8,00 mmol) en acetonitrilo seco (20 ml) a temperatura ambiente en nitrógeno se añadió cianuro de trimetilsililo (1,60 ml, 12,00 mmol). La mezcla se calentó a 75 °C durante 20 h antes de enfriar hasta temperatura 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 acetato de etilo al 5%/hexanos) hasta acetato de etilo al 25%/hexanos proporcionando *Extremo-138, etapa c* (498,7 mg) como un sólido blanco cristalino junto con 223 mg de más *Extremo-138, etapa c* recuperado del filtrado.

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RMN de ^{1}H ($CDCl_3$, 500 MHz) δ 8,63 (d, *J* = 5,5 Hz, 1H), 8,26 (d, *J* = 5,5 Hz, 1H), 7,88 (d, *J* = 8,5 Hz, 1H), 7,69 (t, *J* = 8,0 Hz, 1H), 7,08 (d, *J* = 7,5 Hz, 1H), 4,04 (s, 3H); TR = 1,75 min, (Cond.-D1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185,07; encontrado: 185,10.

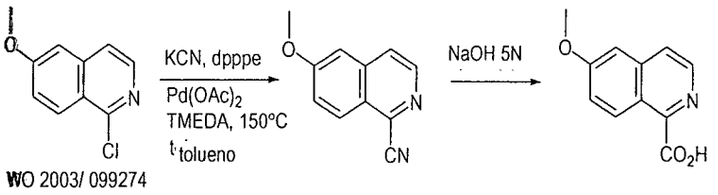
Extremo-138



Se trató *Extremo-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 1N. 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 *Extremo-138* como un sólido amarillo (0,44g, 88,9%). RMN de ^{1}H (DMSO-d_6, 400 MHz) δ 13,6 (s ancho, 1H), 8,56 (d, *J* = 6,0 Hz, 1H), 8,16 (d, *J* = 6,0 Hz, 1H), 8,06 (d, *J* = 8,8 Hz, 1H), 7,71-7,67 (m, 1H), 7,30 (d, *J* = 8,0 Hz, 1H), 4,02 (s, 3H); TR = 0,70 min (Cond.-D1); índice de homogeneidad del 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

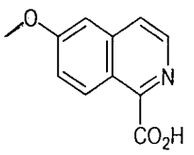
Estrategia de síntesis. Procedimiento B (derivado de *Tetrahedron Letters*, **2001**, *42*, 6707).

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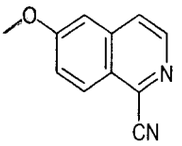


WO 2003/ 099274

Extremo-139



Extremo-139, etapa a

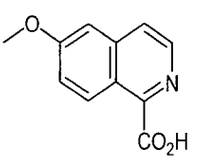


A un vial roscado de pared gruesa que contenía una suspensión desgasificada en argon de 1-cloro-6-metoxiisoquinolina (1,2 g, 6,2 mmol; preparado de acuerdo con el procedimiento del documento WO 2003/ 099274), cianuro potásico (0,40 g, 6,2 mmol), 1,5-bis(difenilfosfino)pentano (0,27 g, 0,62 mmol) y acetato de paladio (II) (70 mg, 0,31 mmol) en tolueno anhidro (6 ml) se añadió *N,N,N',N'*-tetrametiletilendiamina (0,29 ml, 2,48 mmol). El vial se selló, se calentó hasta 150 °C durante 22 h y luego se dejó enfriar hasta 25 °C. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con acetato de etilo al 5%/hexanos hasta acetato de etilo al 25%/hexanos proporcionando *Extremo-139, etapa a* como un sólido blanco (669,7 mg). RMN de ^1H

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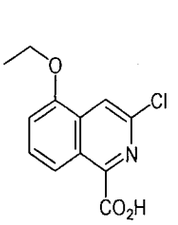
($CDCl_3$, 500 MHz) δ 8,54 (d, *J* = 6,0 Hz, 1H), 8,22 (d, *J* = 9,0 Hz, 1H), 7,76 (d, *J* = 5,5 Hz, 1H), 7,41-7,39 (m, 1H), 7,13 (d, *J* = 2,0 Hz, 1H), 3,98 (s, 3H); TR = 1,66 min (Cond.-D1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185,07; encontrado: 185,20.

Extremo-139

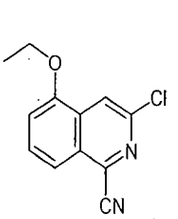


Extremo-139 se preparó a partir de la hidrólisis básica de *Extremo-139, etapa a* con NaOH 5*N* de acuerdo con el procedimiento descrito para *Extremo 138*. RMN de ^1H (400 MHz, DMSO-d_6) δ 13,63 s muy ancho, 1H), 8,60 (d, *J* = 9,3 Hz, 1H), 8,45 (d, *J* = 5,6 Hz, 1H), 7,95 (d, *J* = 5,9 Hz, 1H), 7,49 (d, *J* = 2,2 Hz, 1H), 7,44 (dd, *J* = 9,3, 2,5 Hz, 1H), 3,95 (s, 3H); TR = 0,64 min (Cond.-D1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

Extremo-140



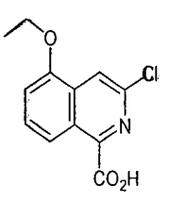
Extremo-140, etapa a



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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'-tetrametiletilenediamina (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 eluyendo con acetato de etilo al 10%/hexanos hasta acetato de etilo al 40%/hexanos proporcionando *Extremo-140, etapa a* como un sólido amarillo (160 mg, 34%). TR = 2,46 min (Cond.-MS-W2); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{12}H_9ClN_2O$: 233,05; encontrado: 233,08.

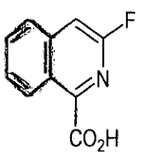
Extremo-140



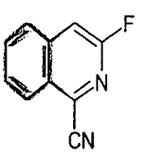
Extremo-140 se preparó por la hidrólisis ácida de

Extremo-140, etapa a con HCl 12*N* como se describe en el procedimiento para la preparación de *Extremo 141*, descrito más adelante. TR = 2,24 min (Cond.-MS-W2); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252,04; encontrado: 252,02.

Extremo-141

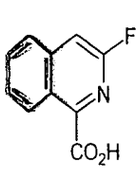


Extremo-141, etapa a



Extremo-141, etapa a se preparó a partir de 1-bromo-3-fluoroisoquinolina (preparado 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 *Extremo-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); TR = 1,60 min (Cond.-D1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_6FN_2$: 173,05; encontrado: 172,99.

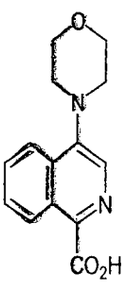
Extremo-141



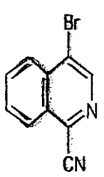
446

Se trató *Extremo-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 *Extremo-141* como un sólido blanquecino (44,1 mg, 47,8%). El filtrado se diluyó con diclorometano y se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró proporcionando más *Extremo-141* que era suficientemente puro para usarlo posteriormente (29,30 mg, 31,8%). 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); TR = 1,33 min (Cond.-D1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 191,97.

Extremo-142



Extremo-142, etapa a

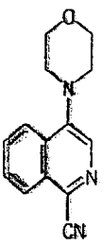


Extremo-142, etapa a se preparó a partir de N-óxido de 4-bromoisoquinolina como se describe en el procedimiento

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en dos etapas para la preparación de *Extremo-138, etapas b y c*. TR = 1,45 min (Cond.-MS-W1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_6BrN_2$: 232,97; encontrado: 233,00.

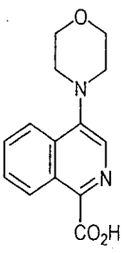
Extremo-142, etapa b



A una suspensión desgasificada en argon de *Extremo-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 y se filtró a través de tierra de diatomeas (Celite®). La purificación del residuo sobre gel de sílice, eluyendo con acetato de etilo del 10% a 70%/hexanos proporcionó *Extremo-142, etapa b* (38 mg, 32%) como un sólido amarillo, que se llevó a etapas posteriores directamente. TR = 1,26 min (Cond.-MS-W1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{14}H_{14}N_3O$: 240,11; encontrado: 240,13.

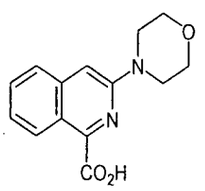
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Extremo-142

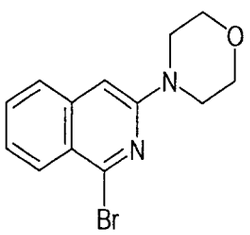


Extremo-142 se preparó a partir de *Extremo-142, etapa b* con hidróxido sódico 5*N* como se describe en el procedimiento para *Extremo 138*. TR = 0,72 min (Cond.-MS-W1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259,11; encontrado: 259,08.

Extremo-143



Extremo-143, etapa a

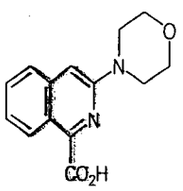


A una solución agitada de 3-amino-1-bromoisoquinolina (444 mg, 2,00 mmol) en dimetilformamida anhidra (10 ml) se añadió hidruro sódico (60%, sin lavar, 96 mg, 2,4 mmol) en una porción. La mezcla se agitó a 25 °C durante 5 min antes de añadir éter 2-bromoetílico (90%, 250 µl, 2,00 mmol). La mezcla se agitó otra vez a 25 °C durante 5 h y a 75 °C durante 72 h antes de enfriar hasta 25 °C, se

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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 eluyendo con acetato de etilo al 0% a 70%/hexanos proporcionó *Extremo-143, etapa a* como un sólido amarillo (180 mg, 31%). TR = 1,75 min (Cond.-MS-W1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293,03; encontrado: 293,04.

Extremo-143

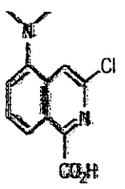


A una solución fría (-60 °C) de *Extremo-143, etapa a* (154 mg, 0,527 mmol) en tetrahidrofurano anhidro (5 ml) se añadió una solución de *n*-butil litio en hexanos (2,5 M, 0,25 ml, 0,633 mmol). Después de 10 min, se burbujeó dióxido de carbono en la mezcla de reacción durante 10 minutos antes que se inactivara con HCl 1N y se dejó calentar hasta 25°C. La mezcla se extrajo entonces con diclorometano (3 x 30 ml) y los extractos orgánicos reunidos se concentraron a vacío. La purificación del residuo por una HPLC de fase inversa (MeOH/agua/TFA) proporcionó *Extremo-143* (16 mg, 12%). TR = 1,10 min (Cond.-MS-W1); índice de homogeneidad del 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259,11; encontrado:

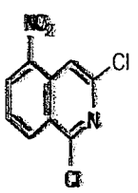
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259,08.

Extremo-144

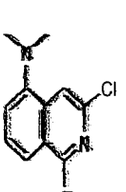


Extremo-144, etapa a



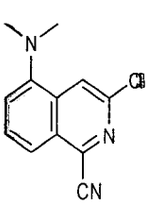
Se añadió 1,3-dicloroisoquinolina (2,75 g, 13,89 mmol) en pequeñas porciones a una solución fría (0 °C) de ácido nítrico fumante (10 ml) y ácido sulfúrico concentrado (10 ml). La mezcla se agitó a 0°C durante 0,5 horas antes de que se calentara gradualmente hasta 25°C a la que se agitó durante 16 horas. 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 *Extremo-144, etapa a* (2,73 g, 81%) como un sólido amarillo que se usó directamente. TR = 2,01 min. (Cond.-D1); índice de homogeneidad del 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242,97; encontrado: 242,92.

Extremo-144, etapa b



Se suspendió *Extremo-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 7 psi H_2 durante 1,5 h. Seguidamente se añadieron formalina (5 ml) y máx óxido de platino (30 mg) y la suspensión se volvió a someter a hidrogenación de Parr a 45 psi H_2 durante 13 h. Seguidamente se filtró 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 eluyendo con acetato de etilo al 5% en hexanos hasta acetato de etilo al 25% en hexanos proporcionando *Extremo-144, etapa b* (231 mg, 78%) como un sólido amarillo pálido. TR = 2,36 min (Cond.-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); LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241,03; encontrado: 241,02. HRMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241,0299; encontrado: 241,0296.

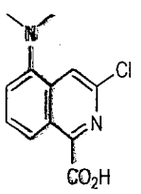
Extremo-144, etapa c



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Extremo-144, etapa c se preparó a partir de *Extremo-144, etapa b* de acuerdo con el procedimiento descrito para la preparación de *Extremo-139, etapa a*. TR = 2,19 min (Cond.-D1); índice de homogeneidad del 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232,06; encontrado: 232,03. HRMS: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232,0642; encontrado: 232,0631.

Extremo-144



Extremo-144 se preparó de acuerdo con el procedimiento descrito para *Extremo-141*. TR = 2,36 min (Cond.-D1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238,01; encontrado: 238,09.

Extremos-145 a 162

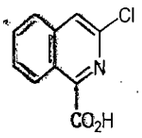
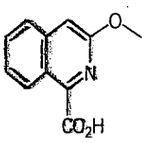
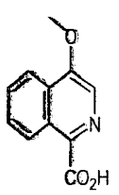
Extremos-145 a *162* se prepararon a partir de las 1-cloroisoquinolinas apropiadas de acuerdo con el procedimiento descrito para la preparación de *Extremo-138* (Procedimiento A) o *Extremo-139* (Procedimiento B) a no ser que se describa de otro modo más adelante.

Organizacion y
Digitalizacion CSA Ltda

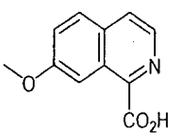
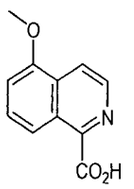
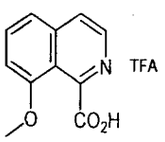
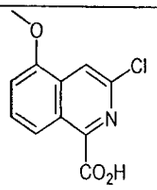
PATENTE DE INVENCION

10-98657

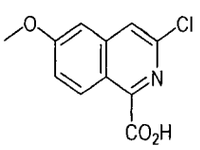
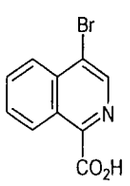
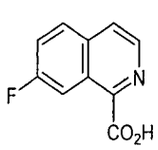
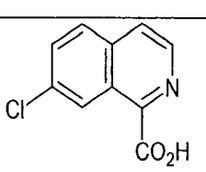
TOMO: 3/3

Extremo n°	Extremo	Procedimiento	Hidrólisis	T_r (Condición de LC); índice de homogeneidad, % ; datos MS
Extremo -145	 Preparado a partir de 1,3-dicloroisoquinolina disponible comercialmente	B	12*N* HCl	1,14 min (Cond.-MS-W1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,00.
Extremo -146	 Preparado a partir de 3-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	1,40 min (Cond.-D1); 95% ; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,06.
Extremo -147	 Preparado a partir de 1-cloro-4-hidroxiisoquinolina disponible comercialmente	B	NaOH 5N	0,87 min (Cond.-D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

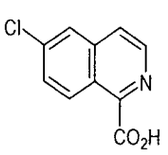
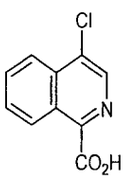
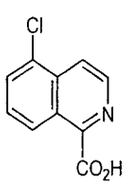
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Extremo -148	 Preparado a partir de 7-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0,70 min (Cond.-D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.
Extremo -149	 Preparado a partir de 5-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0,70 min (Cond.-D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.
Extremo -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 (Cond.-D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,04.
Extremo -151	 Preparado a partir de 5-metoxi-1,3-dicloroisoquinolina, que se	B	HCl 12N	1,78 min (Cond.-D1); 90%; LCMS: Análisis calculado para $[M+H]^+$

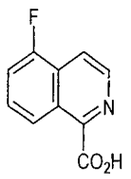
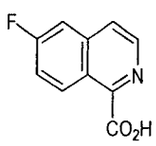
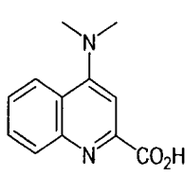
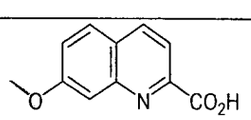
455

	puede sintetizar siguiendo el procedimiento del documento WO 2005 / 051410.			$C_{11}H_9ClNO_3$: 238,03; encontrado: 238,09.
Extremo -152	 Preparado a partir de 6-metoxi-1,3-dicloroisoquinolina disponible comercialmente	B	HCl 12N	1,65 min (Cond.-D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238,00; encontrado: 238,09.
Extremo -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 (Cond.-MS-W1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7BrNO_2$: 251,97; encontrado: 251,95.
Extremo -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 (Cond.-MS-W1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03.
Extremo -155		B	NaOH 5N	0,59 min (Cond.-MS-W1); 90%;

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	Preparado a partir de 1,7-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274			LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,00.
Extremo -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 (Cond.-MS-W1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,03.
Extremo -157	 Preparado a partir de 1,4-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 062241	B	HCl 12N	1,49 min (Cond.-D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_{17}ClNO$: 208,02; encontrado: 208,00.
Extremo -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 (Cond.-MS-W1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado:

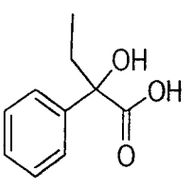
457

				208,01.
Extremo -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 (Cond.-MS-W1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03.
Extremo -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 (Cond.-MS-W1); 90%; LCMS: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03.
Extremo -161	 Preparado a partir de ácido 4-bromoquinolin-2-carboxílico y dimetilamina (DMSO, 100 °C)	--	--	0,70 min (Cond. D1); 95%; LCMS: Análisis calculado para $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217,10; encontrado: 217,06.
Extremo -162	 Preparado a partir de *m*-anisidina siguiendo el procedimiento descrito en *J. Hetero. Chem.* **1993**, 17 y	--	--	0,65 min (Cond.-M3); 95%; LCMS: Análisis calculado

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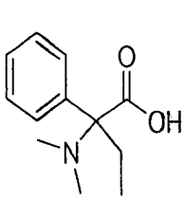
	Heterocycles, 2003, *60*, 953.			para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 203,94.

Extremo-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 *Extremo-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).

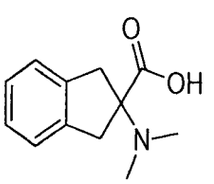
Extremo-164



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Se expuso a H_2 a 50 psi 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 *Extremo-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).

Extremo-165

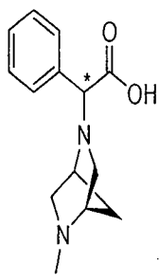


A una mezcla de ácido 2-amino-2-indanocarboxílico (258,6 mg, 1,46 mmol) y ácido fórmico (0,6 ml, 15,9 mmol) en 1,2-dicloroetano (7 ml) se añadió formaldehído (0,6 ml, 37% en agua). La mezcla se agitó a ~25 °C durante 15 min luego se calentó a 70 °C durante 8h. El componente volátil se eliminó a vacío 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 *Extremo-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). LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$:

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206,12; encontrado: 206,07.

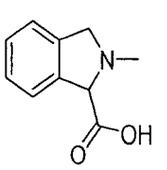
Extremo-166a y -166b



Extremo-166a: Diastereómero-1
Extremo-166b: Diastereómero-2

Extremos-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 *Extremo-7a y Extremo-7b*, con la salvedad de que se separó el éster bencílico intermedio usando una columna semiprepeparativa 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. *Extremo-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). LC/MS: Análisis calculado para $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247,14; encontrado: 247,11.

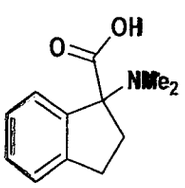
Extremo-167



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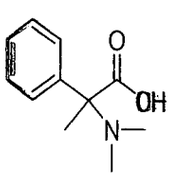
Se agitó una solución de ácido Boc-1,3-dihidro-2H-isoindol carboxílico racémico (1,0g, 3,8 mmol) en TFA al 20%/CH_2Cl_2 a ~25 °C durante 4h. Se eliminó todo el componente volátil a vacío. Se expuso una mezcla del material bruto resultante, formaldehído (15 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (10 mg) en MeOH a H_2 (40 PSI) en un frasco de Parr durante 23 h. La mezcla de reacción se filtró sobre Celite y se concentró a vacío proporcionando *Extremo-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). LC/MS: Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_2$: 178,09; encontrado: 178,65.

Extremo-168



Se preparó *Extremo-168* racémico a partir de ácido Boc-aminoindano-1-carboxílico racémico de acuerdo con el procedimiento descrito para la preparación de *Extremo-167*. El producto bruto se empleó como tal.

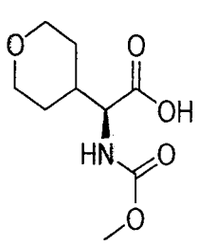
Extremo-169



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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 (55 PSI) 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 *Extremo-169* como un semisólido viscoso (2,1 g). RMN de ^1H ($CDCl_3$, 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). LC/MS: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,12; encontrado: 194,12.

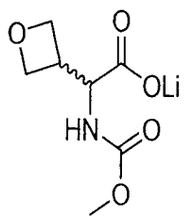
Extremo-170



Al 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 0°C 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); LC/MS: Análisis calculado para $[M+H]^+$ $C_9H_{16}NO_5$: 218,1; encontrado 218,1.

Extremo-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 a un balón 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 azufreico y 100 ml de agua) indicó la conversión completa. La reacción se filtró a través de Celite y se concentró. El residuo se purificó por Biotage® (cada con diclorometano en 25 de muestra; elución en columna 25S con diclorometano para 3CV luego 0 a 5% de MeOH / diclorometano sobre 250ml luego mantenido a 5% de MeOH / diclorometano para 250ml; fracciones de 9 ml). Las fracciones obtenidas que contenían material deseado y se concentraron hasta 120 mg (81%) de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo como un aceite incoloro. RMN de ^1H (500 MHz, CLOROFORMO-D) 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). LC/MS: 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

azufreico 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 ^{1}H (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).

EJEMPLOS

La presente invención se describirá ahora con relación a ciertas modalidades que no pretenden limitar su alcance. Por el contrario, la presente invención cubre todas las alternativas, modificaciones y equivalentes que se pueden incluir en el alcance de las reivindicaciones. Así, los siguientes ejemplos que incluyen modalidades específicas, ilustrarán una práctica de la presente invención, sobreentendiéndose que los ejemplos tienen fines ilustrativos de ciertas modalidades 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 cromatografía ultrarrápida se llevó a cabo sobre gel de sílice (SiO_2) de acuerdo con la técnica de cromatografía ultrarrápida de Still (*J. Org. Chem.* **1978**, *43*, 2923).

La valoración de la pureza y el análisis de masas de baja resolución se llevó a cabo en un sistema de LC Shimadzu acoplado con un sistema de MS Waters Micromass ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. Las condiciones de LC empleadas en la determinación del tiempo de retención (TR) fueron:

Los tiempos de retención se determinaron de acuerdo con las siguientes condiciones de LC/MS:

Condición 1

Columna = Phenomenex-Luna 3,0X 50 mm S10

Inicio % 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 2

Columna = Phenomenex-Luna 4,6X50 mm S10

Inicio % de B = 0

Final % de B = 100

Tiempo de gradiente = 3 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 3

Columna = LCMS. GEMINI C-18 4,6 × 50 mm

Inicio % de B = 0

Final % de B = 100

Tiempo de gradiente = 3 min

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Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = NH_4OAc al 0,1% en acetonitrilo al 10% /H_2O al 90%

Disolvente B = NH_4OAc al 0,1% en acetonitrilo al 90% /H_2O al 10%

Condición 4

Columna = Phenomenex-Luna 3,0 X 50 mm S10

Inicio % 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%

Condición 5

Columna = Luna C18 4,6 × 30 mm

Inicio % de B = 0

Final % de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

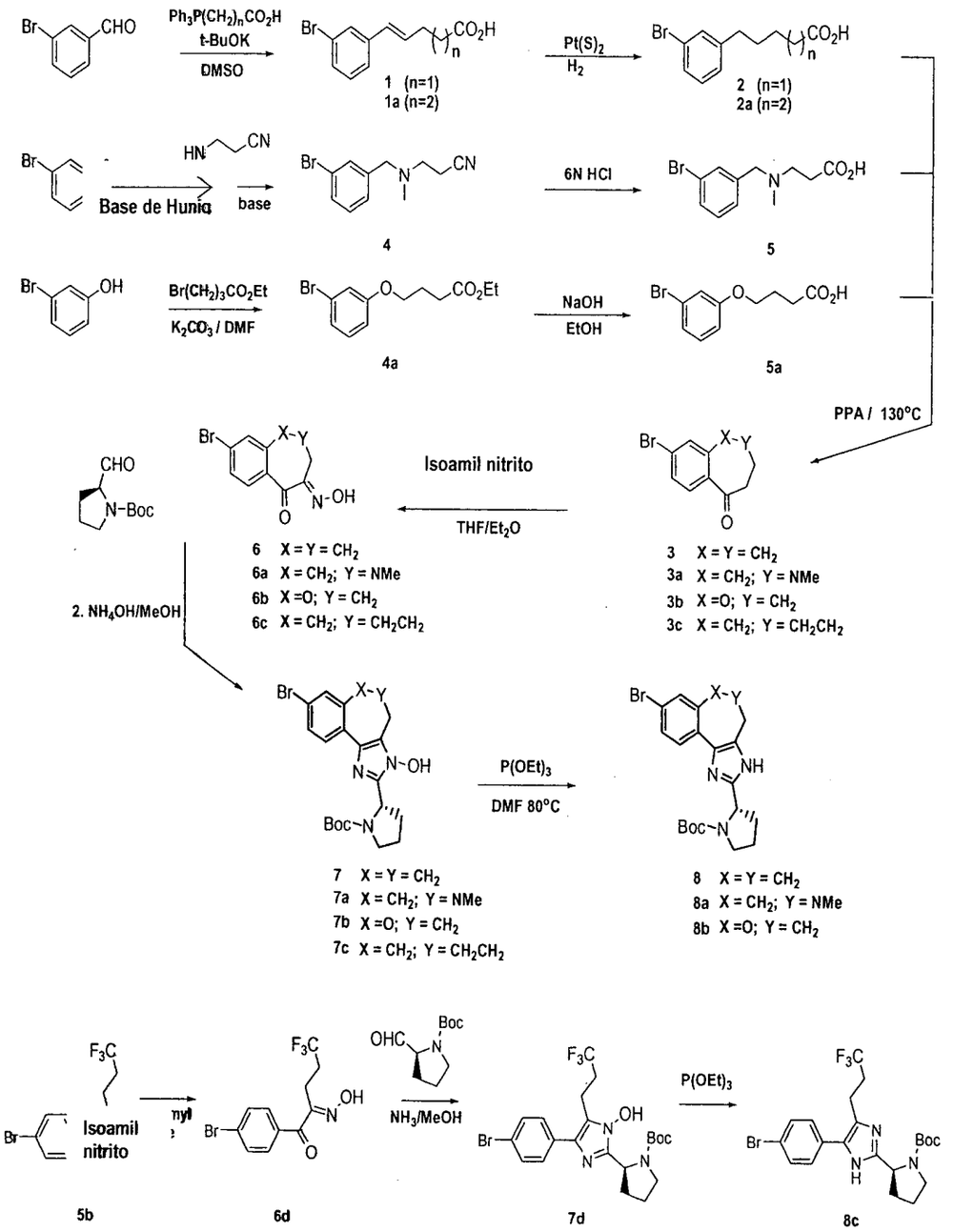
Longitud de onda = 220 nm

Disolvente A = NH_4OAc al 0,1% en acetonitrilo al 10% /H_2O al 90%

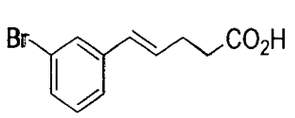
Disolvente B = NH_4OAc al 0,1% en acetonitrilo al 90% /H_2O al 10%

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Ruta de síntesis 1.



Referencia: (Wittig/reducción /ciclización) *J.Med.Chem.* (2005) *48*, 7351-7362.

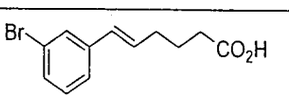


1

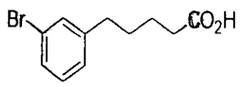
Una solución 1M de terc-butóxido potásico en THF (80 ml) se añadió gota a gota a bromuro de (3-

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carboxipropil)trifenilfosfonio (17 g, 40 mmol) 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 evitar la solvatación y se agitó la reacción 18 horas. La solución se vertió sobre 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 65 (M) Biotage® de gel de sílice; Elución con gradiente desde 15-65% de B (A = Hexanos; B = EtOAc) sobre 2L dando el Ejemplo 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). TR = 2,0 minutos (condición 1); LRMS: Análisis calculado para $C_{11}H_{11}BrO_2$: 252,97; encontrado: 252,98 (M-H).

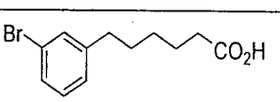
Ejemplo 1a		TR = 2,1 minutos (condición 1); LRMS: Análisis calculado para $C_{12}H_{13}BrO_2$: 267,00; encontrado: 267,00 (M-H).

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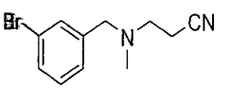
2

El Ejemplo 1, ácido (E)-5-(3-bromofenil)pent-4-enoico (4 g, 15,8 mmol), se disolvió en etanol absoluto (200 ml) y se cubrió con nitrógeno antes de la adición de sulfuro de platino al 5% sobre carbón (2,5 g). La solución se cubrió con hidrógeno a presión atmosférica y se agitó 5 horas. El catalizador se retiró por filtración a través de tierra de diatomeas (Celite®) y el disolvente se eliminó inmediatamente por evaporación rotatoria (con el fin de minimizar la esterificación) dando el Ejemplo 2, ácido 5-(3-bromofenil)pentanoico 4 g (99%) que se llevó hacia adelante sin purificación adicional. RMN de ^1H (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). TR = 2,1 minutos (condición 1); LRMS: Análisis calculado para $C_{11}H_{13}BrO_2$: 255,00; encontrado: 254,99 (M-H).

Ejemplo 2a (Obtenido del Ejemplo 1a).		TR = 2,2 minutos (condición 1); LRMS: Análisis calculado para $C_{12}H_{15}BrO_2$: 269,02; encontrado: 269,04 (M-H).

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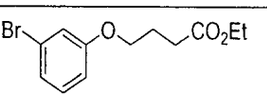
Referencia: (Alquilación/hidrólisis) *J.Am.Chem.Soc.* (1946) *68*, 1468-1470.

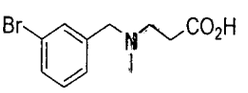


4

Se añadió base de Hunig (26,5 ml, 0,15 mol) a bromuro de 3-bromobencilo (38g, 0,15 mol) y N-metil-β-alanina nitrilo (14,2 ml, 0,15 mol) en DMF seco (400 ml). La solución se agitó 16 h, se concentró a vacío hasta casi sequedad, se trituró con éter/EtOAc y se filtró. [Se repitió una segunda reacción en 12 g]. Los filtrados reunidos se concentraron por evaporación rotatoria y se cargó el residuo (CH_2Cl_2) en una columna 65 (M) Biotage® de gel de sílice; Segmento 1: Elución con gradiente desde 5-15% de B durante 1,3 L; Segmento 2: 15%-100% de B (A = Hexanos; B = EtOAc) sobre 6,75 L dando el Ejemplo 4, 3-((3-bromobencil)(metil)amino)-propanonitrilo 44,4 g (88%). RMN de ^1H (500 MHz, DMSO-d_6) δ 7,54 (s, 1H), 7,46 (d, *J* = 7,6 Hz, 1H), 7,34 (d, *J* = 7,6 Hz, 1H), 7,30 (t, *J* = 7,6 Hz, 1H), 3,54 (s, 2H), 2,71 (t, *J* = 6,4 Hz, 2H), 2,63 (t, *J* = 6,4 Hz, 2H), 2,17 (s, 3H). TR = 1,1 minutos (condición 2); LRMS: Análisis calculado para $C_{11}H_{13}BrN_2$: 253,03; encontrado: 253,05

(M+H).

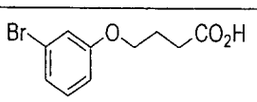
Ejemplo 4a Preparado como en J.Med.Chem.2000 43, 2049		TR = 2,0 minutos (condición 2); LCMS: Análisis calculado para $C_{12}H_{15}BrO_3$: 287,14; encontrado: 289,2 (M+2H).

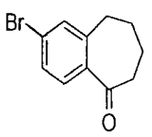


5

Se añadió HCl 6N al Ejemplo 4, 3-((3-bromobencil)(metil)amino)-propanonitrilo (44,4 g, 0,175 mol) en un recipiente con tapón tipo rosca de 1 litro y se calentó la solución sellada a 90°C durante 40 horas. Después de enfriarse, la solución se concentró a vacío hasta ¼ vol. La filtración, concentración de las aguas madres y filtración (2x) dio un rendimiento cuantitativo del Ejemplo 5, ácido 3-((N-(3-bromobencil)-N-metil)amino)propanoico como un sólido blanco (sal HCl). RMN de ^1H (500 MHz, DMSO-d_6) δ 7,90 (t, J = 1,5 Hz, 1H), 7,67 (dd, J = 7,3, 1,5 Hz, 1H), 7,64 (d, J = 7,9 Hz, 1H), 7,43 (t, J = 7,9 Hz, 1H), 4,33 (s ancho, 2H), 3,34 (s ancho, 2H), 2,88 (t, J = 7,6 Hz, 2H), 2,63 (s, 3H). TR = 1,3 minutos (condición 2); LRMS: Análisis calculado para $C_{11}H_{11}BrNO_2$: 272,03; encontrado: 272,10 (M+H).

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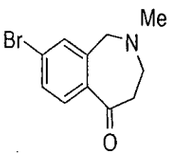
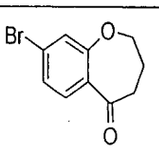
Ejemplo 5a Obtenido de 4a como en J.Med.Chem.2000 43, 2049		TR = 1,05 minutos (condición 2); LCMS: Análisis calculado para $C_{10}H_{11}BrO_3$: 259,09; encontrado: 259,2. (M+2).



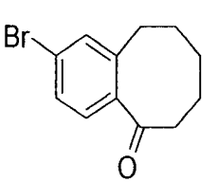
3

El Ejemplo 2, ácido 5-(3-bromofenil)pentanoico (4 g, 15,6 mmol) se suspendió en poli(ácido fosfórico) (15 g) y se calentó hasta 140 °C durante 8 horas en un recipiente a presión de 150 ml, tapado para prevenir pérdidas de producto debido a sublimación. La mezcla de reacción se repartió entre 150 ml de agua y CH_2Cl_2 (600 ml). [Es necesaria precaución para evitar la ebullición de CH_2Cl_2]. 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 eluyó con gradiente desde 5 - 60% (EtOAc/Hex) y dio el Ejemplo 3, 2-bromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona 1,7 g (40%). RMN de ^1H (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). TR = 2,1 minutos (condición 1); LRMS: Análisis calculado para $C_{11}H_{11}BrO$: 239,00; encontrado: 239,14 (M+H).

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Ejemplo 3a (Obtenido del Ejemplo 5)		TR = 1,17 minutos (condición 1); LRMS: Análisis calculado para $C_{11}H_{13}BrNO$: 254,02; encontrado: 254,16 (M+H).
Ejemplo 3b (Obtenido del Ejemplo 5a)		TR = 1,7 minutos (condición 2); LCMS: Análisis calculado para $C_{10}H_9BrO_2$: 241,08; encontrado: 241,2 (M+2).

Referencia: (Ciclización) *JACS* **1962** *27*, 70-76.



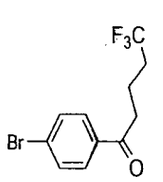
3b

Se añadió cloruro de tionilo (puro)(13,2 ml, 181 mmol) al Ejemplo 2a, ácido 6-(3-bromofenil)hexanoico (16 g, 59,2 mmol) en un matraz de fondo redondo de 1 litro en una atmósfera de nitrógeno. La mezcla se calentó hasta 60°C durante 2 h, se eliminó a vacío el exceso de reaccionante y el residuo se sometió a condiciones azeotrópicas (benceno

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3x). El cloruro de ácido se disolvió en disulfuro de carbono (550 ml) y se canuló en una solución de tricloruro de aluminio (26,3 g, 198 mmol) en disulfuro de carbono (1315 ml) calentado a reflujo. La reacción se agitó 20 h, se enfrió, se decantó, se concentró y los sólidos resultantes se agitaron en éter dietílico/THF (1:1, 1 l) y HCl 1N (500 ml) durante 1,5 horas. La fase orgánica se filtró, se lavó con agua y salmuera dando el Ejemplo 3c, 2-bromo-7,8,9,10-tetrahidrobenzo[8]annulen-5(6H)-ona 10,1 g (66%) como un aceite incoloro. RMN de ^{1}H (300 MHz, $CDCl_3$) δ 7,55 (d, J = 8,4 Hz, 1H), 7,38 (dd, J = 8,4 Hz, 1,8 Hz, 1H), 7,33 (d, J = 1,8 Hz, 1H), 2,99 (t, J = 6,6 Hz, 2H), 2,89 (t, J = 6,6 Hz, 2H), 1,85-1,73 (m, 4H), 1,52-1,44 (m, 2H). TR = 2,8 minutos (condición 2); LRMS: Análisis calculado para $C_{12}H_{13}BrO$: 253,02; encontrado: 253,15 (M+H).

Referencia: J.Org.Chem. USSR (Engl.Transl.) (1985) páginas 2201-2205.



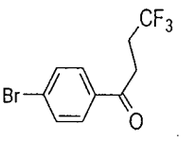
5b

Se añadió magnesio (0,636 g, 26,2 mmol) a una solución de 4-bromo-1,1,1-trifluorobutano (5 g, 26,2 mmol) en THF (100 ml) y en nitrógeno. La solución se agitó durante 18 h a 24 °C, y el reactivo de Grignard se transfirió mediante

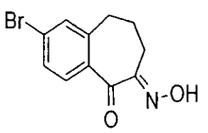
una cánula a una solución de 4-bromobenzaldehído (4,85 g, 26,2 mmol) en THF (50 ml) a -78 °C en nitrógeno. Se retiró el baño frío y se dejó calentar la reacción y se agitó 18 horas, se diluyó con Et_2O (1 vol), se inactivó con solución saturada de NH_4Cl y se lavó con salmuera. Se concentró, se suspendió en CH_2Cl_2 y se cargó en un cartucho de gel de sílice 40M Biotage®. Se llevó a cabo la elución con gradiente desde B al 15% a 100% de B durante 1 l (A/B Hexanos/EtOAc) dando 1-(4-bromofenil)-5,5,5-trifluoropentan-1-ol 6,4 g (82%).

Se mezcló PCC (9,29 g, 43,1 mmol) con 9 g de SiO_2 y se molió con un mortero y una mano antes de añadirse en una porción a una solución de 1-(4-bromofenil)-5,5,5-trifluoropentan-1-ol (6,4 g, 21,54 mmol) disuelto en diclorometano (350 ml). La reacción se agitó 4h, se filtró a través de tierra de diatomeas (Celite®), se concentró y se aplicó en una columna de gel de sílice de 160 g Thomson®. Elución: 10 - 60% de B durante 1,5 l (A/B Hexanos/EtOAc) dieron Ejemplo 5b, 1-(4-bromofenil)-5,5,5-trifluoropentan-1-ona 6,1 g (86%). RMN de ^1H (500 MHz, $CDCl_3$) δ 7,81 (d, J = 8,5 Hz, 2H), 7,61 (d, J = 8,3 Hz, 2H), 3,04 (t, J = 7,0 Hz, 2H), 2,25-2,16 (m, 2H), 2,05-1,99 (m, 2H). TR = 2,1 minutos (condición 1). LCMS: Análisis calculado para $C_{11}H_{11}BrF_3O$: 295,00; encontrado: 295,00 (M+H).

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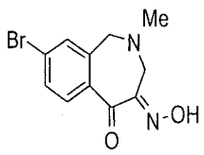
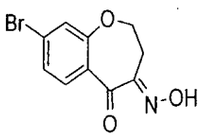
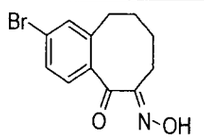
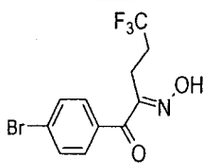
Ejemplo 5b.1 (Preparado a partir de 3-bromo-1,1,1-trifluoropropano)		TR = 1,7 minutos (condición 1); LCMS: Análisis calculado para $C_{10}H_9BrF_3O$: 278,97; encontrado: 278,98 (M-H).

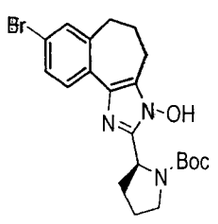
Referencia: (Síntesis de imidazol) *Bioorg. Med. Chem. Lett.* (2002)1009-1011.



6

El Ejemplo 3, 2-bromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona (1,5 g, 5,9 mmol) se disolvió en Et_2O/THF 2:1 (120 ml) y se añadió HCl 1N en Et_2O (9 ml). La solución se enfrió hasta 0°C antes de la adición de *iso*-amilnitrito (1,2 ml, 9 mmol) y la reacción se agitó 18 horas a 24 °C, se concentró y se aplicó en una columna de gel de sílice 25 (M) Biotage®. La elución con gradiente desde 15-100% de B (A = Hexanos; B = EtOAc) sobre 1L y dio el Ejemplo 6, (E)-2-bromo-6-(hidroxiimino)-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona 1 g (64%). TR = 1,9 minutos (condición 1). LCMS: Análisis calculado para $C_{11}H_{10}NBrO_2$: 268; encontrado: 268 (M+H).

Ejemplo 6a (Derivado del Ejemplo 3a)		TR = 1,35 minutos (condición 2); LCMS: Análisis calculado para $C_{11}H_{11}BrN_2O_2$: 283,00; encontrado: 283,03 (M+H).
Ejemplo 6b (Derivado del Ejemplo 3b)		TR = 1,55 minutos (condición 2); LCMS: Análisis calculado para $C_{10}H_8BrNO_3$: 270,08; encontrado: 270 (M+H).
Ejemplo 6c (Derivado del Ejemplo 3c)		TR = 2,51 minutos (condición 2); LCMS: Análisis calculado para $C_{12}H_{12}BrNO_2$: 282,02; encontrado: 282,13 (M+H).
Ejemplo 6d (Derivado del Ejemplo 5b)		TR = 2,1 minutos (condición 1); LCMS: Análisis calculado para $C_{11}H_{10}BrF_3NO_2$: 323,98; encontrado: 323,99 (M+H).

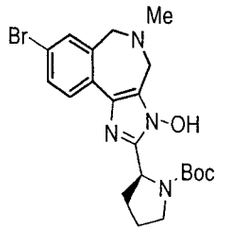


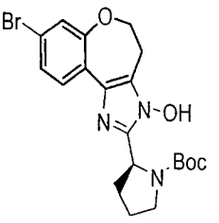
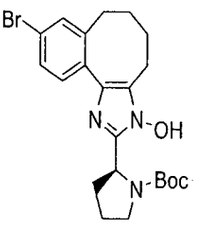
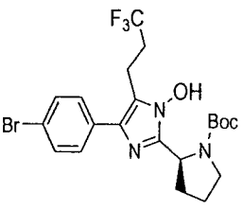
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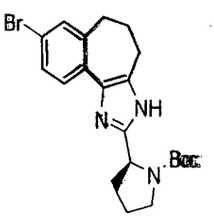
Se añadió solución concentrada al 28% de hidróxido

480

de amonio (12 ml,) a una solución del Ejemplo 6, (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 mezcla de reacción se agitó 18 horas a 24 °C, se concentró parcialmente para eliminar el metanol y el residuo acuoso se extrajo con CH_2Cl_2. La fase orgánica se lavó con agua y se concentró y el producto bruto se cargó (CH_2Cl_2) en una columna de gel de sílice 40 (S) Biotage®; 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/CH_2Cl_2; B = EtOAc) dio el Ejemplo 7, 700 mg (44%). RMN de ^1H (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). TR = 1,9 minutos (condición 1). LRMS: Análisis calculado para $C_{21}H_{26}BrN_3O_3$: 488,12; encontrado: 488,14 (M+H). HRMS: Análisis calculado para $C_{21}H_{26}BrN_3O_3$: 488,1236; encontrado: 488,1242 (M+H).

Ejemplo 7a (Derivado del Ejemplo 6a)		TR = 2,29 minutos (condición 2); LCMS: Análisis calculado para $C_{21}H_{28}N_4BrO_3$: 463,13; encontrado: 463,16 (M+H).

Ejemplo 7b (Derivado del Ejemplo 6b)		TR = 1,67 minutos (condición 1); LCMS: Análisis calculado para $C_{20}H_{24}N_3BrO_4$: 450,34; encontrado: 450 (M+H).
Ejemplo 7c (Derivado del Ejemplo 6c)		TR = 2,53 minutos (condición 2); LCMS: Análisis calculado para $C_{22}H_{29}N_3BrO_3$: 462,13; encontrado: 462,31 (M+H).
Ejemplo 7d (Derivado del Ejemplo 6d)		TR = 1,9 minutos (condición 1); LCMS: Análisis calculado para $C_{21}H_{26}N_3BrF_3O_3$: 504,11; encontrado: 504,17 (M+H).

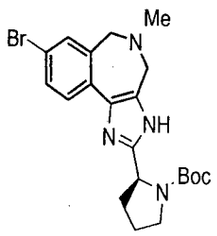
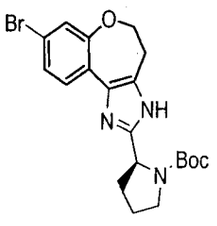
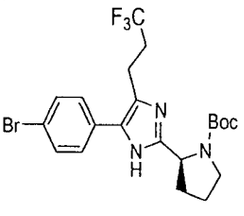


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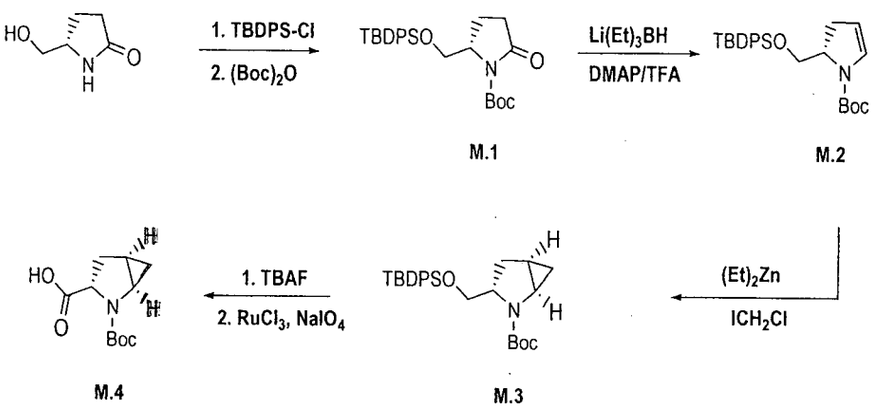
Se añadió trietil fosfito (0,78 ml, 4,7 mmol) a una solución del Ejemplo 7, (700 mg, 1,57 mmol) en DMF (2 ml) y la solución se calentó a 80°C durante 18 horas en una atmósfera de nitrógeno. La mezcla de reacción se suspendió en acetato de etilo (100 ml) y se lavó con agua y salmuera.

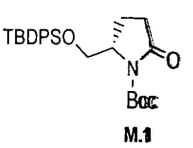
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Después de concentrar el producto bruto se aplicó a una columna de gel de sílice 40 (S) Biotage® y se sometió a elución con gradiente; Segmento 1. 5%-15% de B durante 300 ml; Segmento 2. 15%-100% de B durante 600 ml (A = CH_2Cl_2; B = EtOAc) dando el Ejemplo 8, 675 mg (100%). RMN de ^1H (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). TR = 1,9 minutos (condición 1). LRMS: Análisis calculado para $C_{21}H_{26}BrN_3O_2$: 432,13; encontrado: 432,14 (M+H).

Ejemplo 8a (Derivado del Ejemplo 7a)		TR = 1,83 minutos (condición 2); LCMS: Análisis calculado para $C_{21}H_{28}BrN_4O_2$: 447,14; encontrado: 447,06 (M+H).
Ejemplo 8b (Derivado del Ejemplo 7b)		TR = 1,95 minutos (condición 2); LCMS: Análisis calculado para $C_{20}H_{24}N_3BrO_3$: 433,24; encontrado: 434 (M+H).
Ejemplo 8c (Derivado del Ejemplo 7d)		TR = 1,80 minutos (condición 1); LCMS: Análisis calculado para $C_{21}H_{26}BrF_3N_3O_2$: 488,11; encontrado: 488,17 (M+H).

Ruta sintética 2.

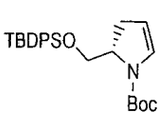




A una solución de (S)-5-(hidroximetil)pirrolidin-2-ona (10 g, 87 mmol) en diclorometano (50 ml) se añadió terc-butilclorodifenilsilano (25,6 g, 93 mmol), Et_3N (12,1 ml, 87 mmol) y DMAP (1,06 g, 8,7 mmol). La mezcla se agitó a temperatura ambiente hasta que se consumió totalmente la pirrolidinona de partida 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 silil éter como un aceite incoloro (22,7 g, 74% de rendimiento). RMN de ^1H (400 MHz, DMSO-d6, 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). LC/MS (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 silil éter (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. Se eliminó la mayor parte de los volátiles a vacío y el material bruto se suspendió en acetato de etilo al 20% /hexanos y se aplicó en un embudo de 2 litros que contenía 1,3 litros de gel de sílice y luego eluyó con 3 litros 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, se filtró una suspensión blanca de sólido formado, se lavó con hexanos y se secó a vacío proporcionando carbamato M.1 como un solido blanco (32,65 g, 82% de rendimiento). RMN de ^1H (400 MHz, DMSO-d6, 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-Boc+H) = 354,58. Calculado 454,24.

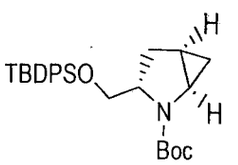


M.2

Se cargó un matraz de tres bocas equipado con un

termómetro y una entrada de nitrógeno con carbamato M.1 (10,05 g, 22,16 mmol) y tolueno (36 ml) y se introdujo en un baño de enfriamiento a -55 °C. Cuando la temperatura interna de la mezcla alcanzó -50 °C, se añadió gota a gota durante 30 minutos trietilborohidruro de litio (23 ml de 1,0 M/tetrahidrofurano, 23,00 mmol) y la mezcla se agitó durante 35 minutos mientras se mantenía la temperatura interna entre -50 °C y -45 °C. Se añadió base de Hunig (16,5 ml, 94 mmol) gota a gota durante 10 minutos. Seguidamente se añadió en un lote DMAP (34 mg, 0,278 mmol), seguido por la adición de anhídrido trifluoracético (3,6 ml, 25,5 mmol) durante 15 min, manteniendo la temperatura interna entre -50 °C y -45 °C. Se retiró el baño 10 minutos después y la mezcla de reacción se agitó durante 14 horas dejando que alcanzara 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 minutos. 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). TR = 2,41 min en las siguientes condiciones 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 metanol/agua

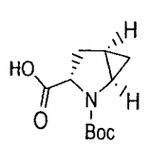
9:1) durante 2 minutos y mantenido durante 1 min; detección a 220 nm; columna Phenomenex-Luna 3,0X50 mm S10 . RMN de ^{1}H (400 MHz, DMSO-d6, δ = 2,5 ppm) 7,62-7,58 (m, 4H), 7,49-7,40 (m, 6H), 6,47 (s ancho, 1H), 5,07/5,01 (d ancho solapando, 1H), 4,18 (s ancho, 1H), 3,89 (s ancho, 0,49H), 3,69 (s ancho, 1,51H), 2,90-2,58 (m ancho, 2H), 1,40/1,26 (s ancho solapando, 9H), 0,98 (s, 9H). LC/MS: (M+Na) = 460,19.



M.3

Se añadió gota a gota dietil cinc (19 ml de ~1,1 M en tolueno, 20,9 mmol) durante 15 min a una solución enfriada (-30 °C) en tolueno (27 ml) de dihidropirrol M.2 (3,94 g, 9,0 mmol). Se añadió cloroyodometano (estabilizado sobre cobre; 3,0 ml, 41,2 mmol) gota a gota durante 10 minutos y se agitó manteniendo la temperatura del baño a -25 °C durante 1 h y entre -25 °C y -21 °C durante 18,5 h. La mezcla de reacción se abrió al aire y se inactivó mediante la adición lenta de solución saturada al 50% de $NaHCO_3$ (40 ml) y luego se retiró el baño de enfriamiento y se agitó a temperatura ambiente durante 20 minutos. Se filtró a través de un papel de filtro y se lavó la torta blanca 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 colocó con acetato de etilo al 7%/hexanos; eluyó con acetato de etilo al 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 isómero cis/trans no se determinó en esta etapa]. TR = 2,39 min en las siguientes condiciones 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 metanol/agua 9:1) 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 ap, 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). LC/MS: (M+Na) = 474,14.



M.4

Se añadió TBAF (7,27 ml de 1,0 M en tetrahidrofurano, 7,27 mmol) gota a gota durante 5 minutos a un solución en tetrahidrofurano (30 ml) de silil éteres M.3 (3,13 g, 6,93 mmol) y la mezcla se agitó a temperatura ambiente durante

4,75 horas. Después de la adición de cloruro amónico saturado (5 ml) se eliminó a vacío la mayoría del material volátil 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 y se concentró a vacío y luego se expuso a alto vacío durante la noche. El material bruto se purificó usando Biotage® (gel de sílice; acetato de etilo al 40-50%/hexanos) proporcionando una mezcla de alcoholes, contaminada con trazas de una mancha de menor Rf, 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 ^1H (400 MHz, dimetilsulfoxido-d6, 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). LC/MS (M+Na) = 236,20.

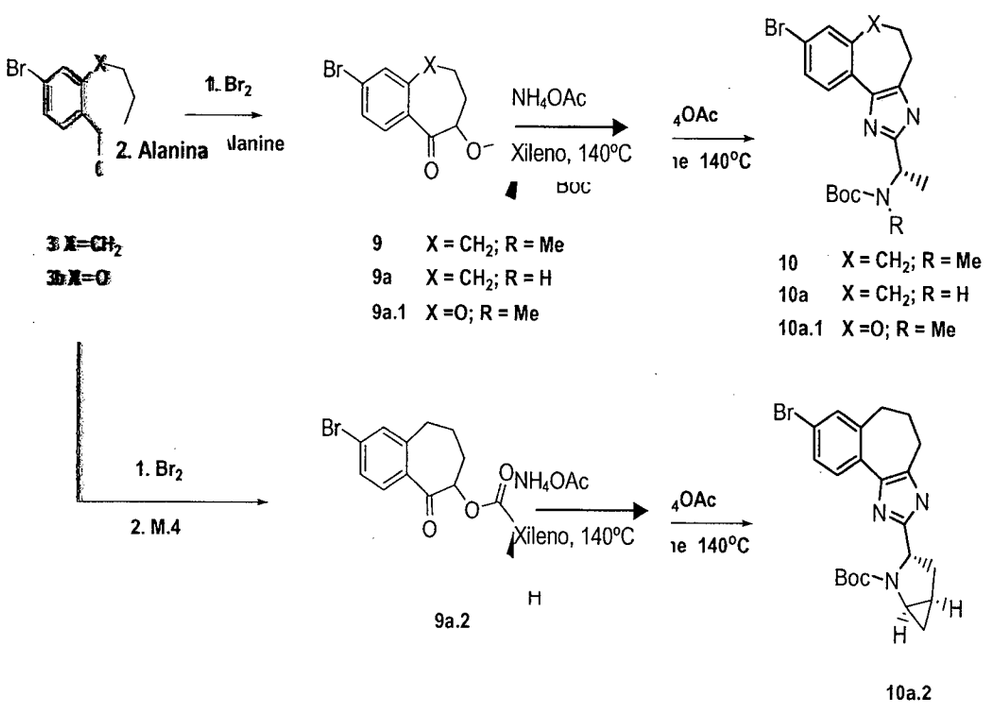
Se añadió una semisolución de periodato sódico (6,46 g, 30,2 mmol) en agua (31 ml) a una solución de alcoholes (2,15 g, 10,08 mmol) en acetonitrilo (20 ml) y tetracloruro de carbono (20 ml). Se añadió inmediatamente tricloruro de rutenio (0,044 g, 0,212 mmol) y la mezcla de reacción heterogénea se agitó vigorosamente 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 de metanol, se dejó reposar durante aproximadamente 5 minutos y luego se filtró a través de tierra de diatomeas (Celite®). Se lavó el lecho con diclorometano (50 ml) y el filtrado se concentró a vacío proporcionando un sólido color carbón claro. El material bruto se disolvió en acetato de etilo (~10 ml) con calentamiento y se dejó reposar a temperatura ambiente con iniciación de cristales. 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 precipitaba más material adicional). La mezcla se filtró y se lavó con hielo/agua-hexanos enfriados/acetato de etilo (relación 2:1; 20 ml) y se secó a alto vacío proporcionando la primera tanda de ácido M.4 (cristales blanquecinos, 1,222 g). Se concentraron las aguas madres a vacío y se disolvió el residuo 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 refrigerador durante ~15 h. Se obtuvo una segunda tanda de ácido M.4 de igual forma (cristales grises, 0,133 g), para un rendimiento combinado de 59%. TR = 1,48 min en las siguientes condiciones 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 metanol/agua 9:1) durante 3 min; detección a

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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, □ = 2,5 ppm) 12,46 (s, 1H), 3,88 (s ancho ap, 1H), 3,27 (s ancho ap, 1H; solapado con la señal de agua), 2,28 (m ancho, 1H), 2,07 (s ancho ap, 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. LC/MS (M+Na) = 250,22. Análisis calculado para $C_{11}H_{17}NO_4$: 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 $CHCl_3$): [□] D = -216 y -212 para la primera y segunda tanda, respectivamente.

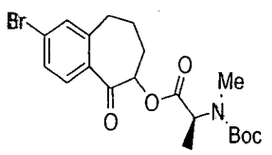
Ruta sintética 3.



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Referencia: (Bromación) *JACS* (1952) 74, 6263.

Referencia: (Desplazamiento/Ciclización) *J.Med.Chem.* (2001) 44, 2990.



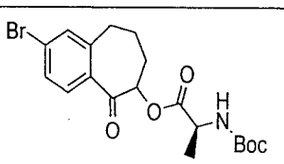
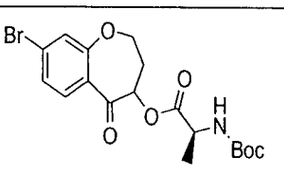
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El Ejemplo 3, 2-bromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona (1,5 g, 5,9 mmol) se disolvió en Et_2O (25 ml), se enfrió hasta 0°C y se añadió bromo (0,35 ml, 6,6 mmol) gota a gota. La solución se agitó a 24°C hasta que la TLC indicó reacción completa (2-18 h; dependiente de la escala). El disolvente se eliminó por evaporación rotatoria y el producto se aplicó a una columna de gel de sílice 25 (M) Biotage®. La elución con gradiente desde 50-100% de B (A = Hexanos; B = 10% EtOAc/hex) sobre 500 ml y dió 2,6-dibromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona 700 mg, y 1,5 g de una segunda fracción que contenía dibromuro (1:1). TR = 2,2 minutos (condición 1).

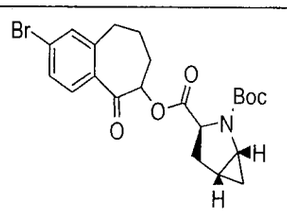
La 2,6-dibromo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-5-ona (700 mg, 2,22 mmol) y N-metil-L-alanina (493 mg, 2,4 mmol) se disolvieron en acetonitrilo (8 ml) y se añadieron 1,1 ml de base de Hunig gota a gota, y la reacción se agitó 18 horas a 55°C. El disolvente se eliminó por evaporación rotatoria y el residuo se suspendió en EtOAc y se

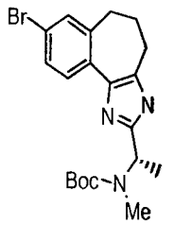
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lavó con solución de HCl 0,1N, solución saturada de $NaHCO_3$ y salmuera y se concentró dando el Ejemplo 9, 2-(terc-butoxicarbonil(metil)amino)propanoato de (2S)-2-bromo-5-oxo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-6-ilo 960 mg (98%) que se llevaron hacia adelante sin purificación adicional. RMN de ^1H (300 MHz, $CDCl_3$) δ 7,55 (dd, J = 8,4, 1,8 Hz, 1H), 7,40 (dd, J = 8,4, 1,8 Hz, 1H), 7,38 (s, 1H), 5,51-5,45/5,36-5,31 (m, 1H), 4,96-4,79/4,72-4,53 (m, 1H), 3,8 (s ancho, 3H), 2,94 (t, J = 4,8 Hz, 2H), 2,82 (t, J = 5,1 Hz, 2H), 2,10-1,95 (m, 2H), 1,43 (s, 9H). TR = 2,3 minutos (condición 1). LRMS: Análisis calculado para $C_{20}H_{26}BrNO_5$: 440,11; encontrado: 440,10 (M+H).

Ejemplo 9a (Derivado del Ejemplo 3)		TR = 2,2 minutos (condición 1); LCMS: Análisis calculado para $C_{19}H_{24}BrNO_5$: 425; encontrado: 425 (M+H).
Ejemplo 9a.1 (Derivado del Ejemplo 3b)		TR = 2,05 minutos (condición 2); LCMS: Análisis calculado para $C_{19}H_{24}BrNO_6$: 442,30; encontrado: 344,2 (M-100), (M+2H).

493

Ejemplo 9a.2 (Derivado del Ejemplo 3)		TR = 2,18 minutos (condición 1); LCMS: Análisis calculado para $C_{22}H_{27}BrNO_5$: 464,10; encontrado: 463,99 (M+H).

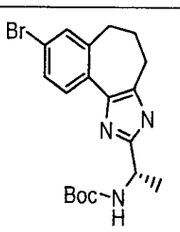
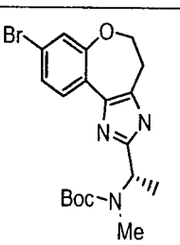
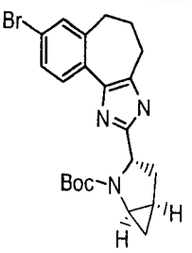


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El Ejemplo 9, 2-(terc-butoxicarbonil(metil)amino)propanoato de (2S)-2-bromo-5-oxo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-6-ilo (960 mg, 2,2 mmol) se suspendió en xileno (20 ml) y se colocó en un recipiente a presión de 100 ml con tapón tipo rosca. Se añadió acetato amónico (1,7 g, 10 equiv) y la mezcla se calentó a 120°C (temperatura de baño de aceite) durante 4 horas. La mezcla enfriada se diluyó con acetato de etilo (150 ml) y se lavó con solución saturada de $NaHCO_3$ y se concentró. El producto bruto se aplicó (CH_2Cl_2) a un cartucho de gel de sílice 25 (M) Biotage. Segmento 1. Mantenido 15% de B durante 300 ml; Segmento 2. Elución con gradiente desde 10 - 100% de B durante 600 ml (A = hexanos; B = EtOAc) dando el Ejemplo 10, 150 mg (16%) NOTA: Se produjo pérdida de compuesto

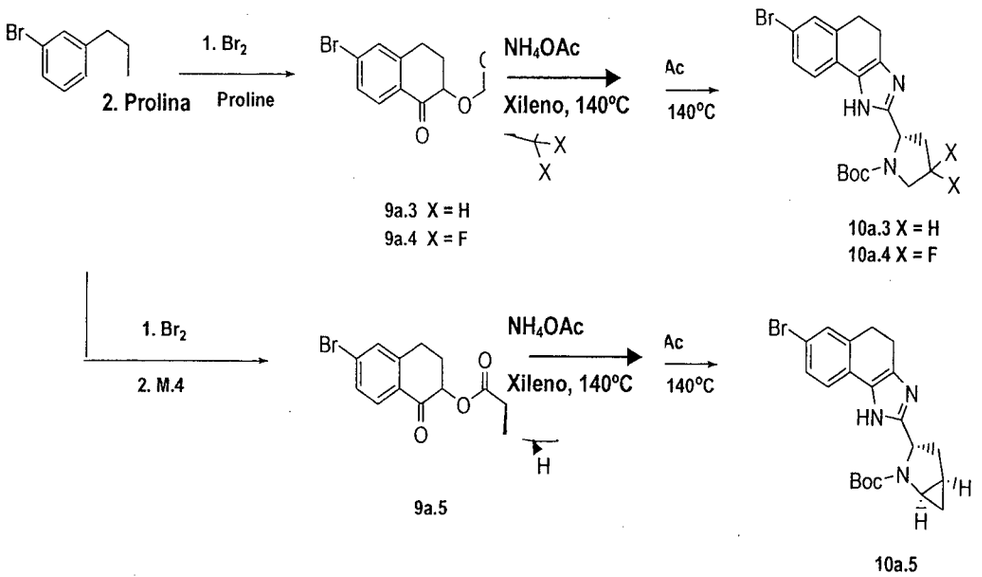
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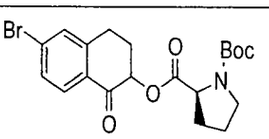
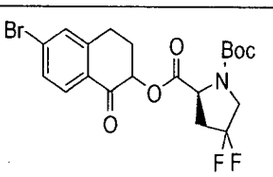
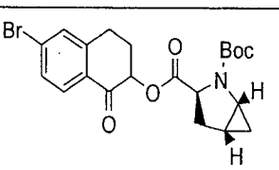
durante la cromatografía (el rendimiento debería haber sido mayor). RMN de ^1H (500 MHz, $CDCl_3$) δ 7,43-,42 (m, 2H), 7,35 (s, 1H), 5,25 (c, J = 7,0 Hz, 1H), 3,02 (t, J = 6,4 Hz, 2H), 2,96 (s, 3H), 2,83-2,81 (m, 2H), 2,0-1,98 (m, 2H), 1,74 (d, J = 7,0 Hz, 3H), 1,47 (s, 9H). TR = 1,8 minutos (condición 1). LRMS: Análisis calculado para $C_{20}H_{26}BrN_3O_2$: 420,13; encontrado: 420,10 (M+H).

Ejemplo 10a (Derivado del Ejemplo 9a)		TR = 1,9 minutos (condición 1); LRMS: Análisis calculado para $C_{19}H_{24}BrN_3O_2$: 406,11; encontrado: 406,23 (M+H).
Ejemplo 10a.1 (Derivado del Ejemplo 9a.1)		RT=1,59 minutos (condición 1); LCMS: Análisis calculado para $C_{19}H_{24}BrN_3O_3$: 422,33; encontrado: 424,2 (M+2H).
Ejemplo 10a.2 (Derivado del Ejemplo 9a.2)		TR = 1,74 minutos (condición 1); LRMS: Análisis calculado para $C_{22}H_{27}BrN_3O_2$: 443,11; encontrado: 443,07 (M+H).

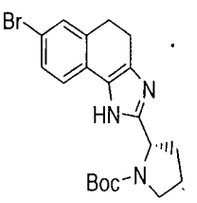
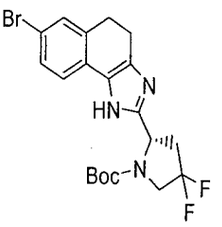
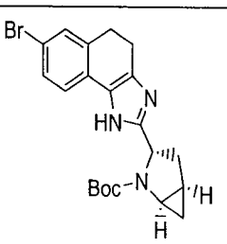
495

Ruta sintética 4.



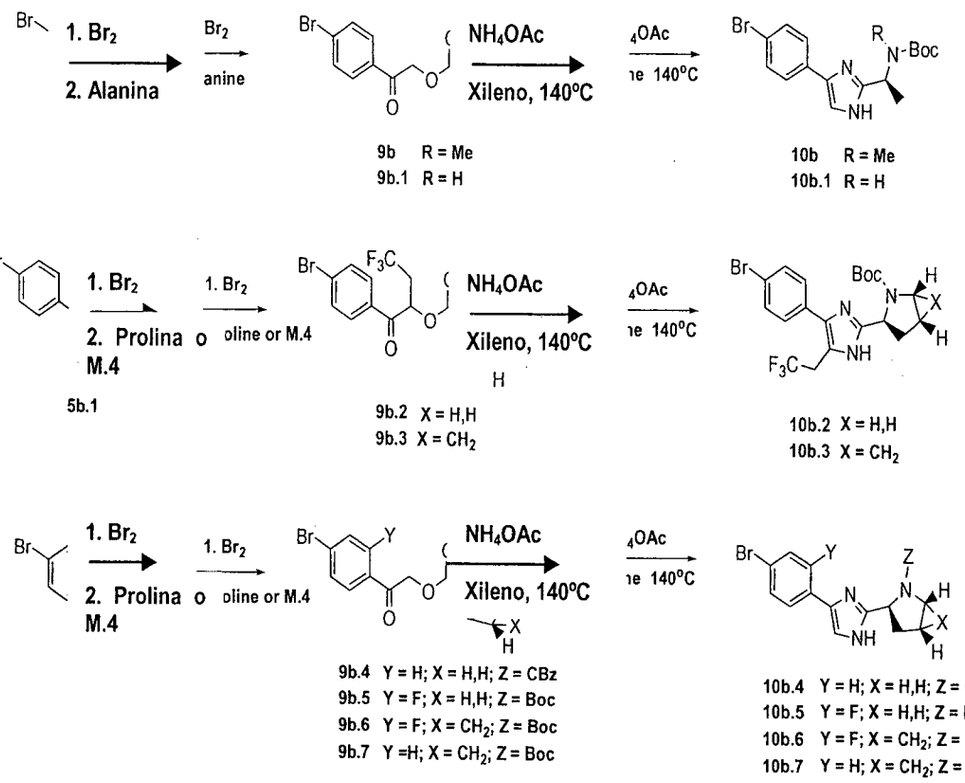
Ejemplo 9a.3 (6-bromo tetral-1-ona derivada obtenida de J & W PharmLab, LLC. El Ejemplo 9a.3 se preparó como se describe para el Ejemplo 9.)		TR = 3,1 minutos (condición 2); LCMS: Análisis calculado para $C_{20}H_{24}BrNO_5$: 438; encontrado: 438 (M+H).
Ejemplo 9a.4 (6-bromo tetral-1-ona derivada obtenida de J & W PharmLab, LLC)		TR = 3,0 minutos (condición 2); LCMS: Análisis calculado para $C_{20}H_{22}BrF_2NO_5$: 474; encontrado: 474 (M+H).
Ejemplo 9a.5 (6-bromo tetral-1-ona derivada obtenida de J & W PharmLab, LLC)		TR = 2,95 minutos (condición 2); LCMS: Análisis calculado para $C_{21}H_{25}BrNO_5$: 472,07, 474,07; encontrado:

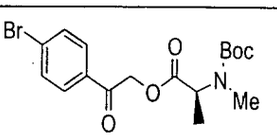
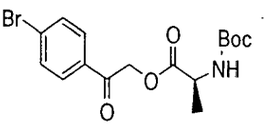
496

		472,02, 474,02 (M+Na).
Ejemplo 10a.3 (Derivado del Ejemplo 9a.3 y preparado como se describe para el Ejemplo 10.)		TR = 2,37 minutos (condición 2); LRMS: Análisis calculado para $C_{20}H_{25}BrN_3O_2$: 418,11 y 420,10; encontrado: 418,21 y 420,17 (M+H).
Ejemplo 10a.4 (Derivado del Ejemplo 9a.4)		TR = 2,3 minutos (condición 2); HRMS: Análisis calculado para $C_{20}H_{22}BrF_2N_3O_2$ 454,09573; encontrado: 454,09362 (M+H).
Ejemplo 10a.5 (Derivado del Ejemplo 9a.5)		TR = 2,25 minutos (condición 2); LCMS: Análisis calculado para $C_{21}H_{25}BrN_3O_2$: 430,12, 432,12; encontrado: 430,02, 432,02 (M+H).

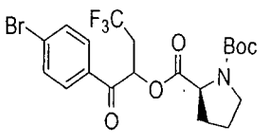
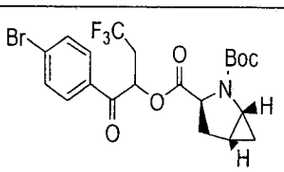
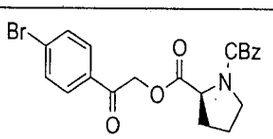
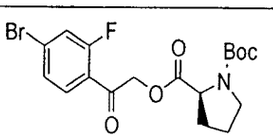
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Ruta sintética 5.

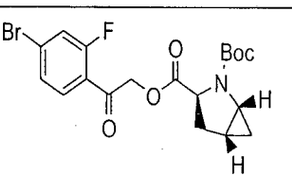
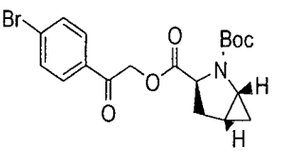
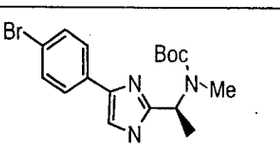
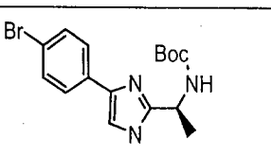


Ejemplo 9b (Preparado como se describe en el Ejemplo 9.)		TR = 2,2 minutos (condición 1); LCMS: Análisis calculado para $C_{15}H_{18}BrNO_5$: 371; encontrado: 371 (M+H).
Ejemplo 9b.1		TR = 2,7 minutos (condición 1); LCMS: Análisis calculado para $C_{16}H_{20}BrNO_5$: 385; encontrado: 385 (M+H).

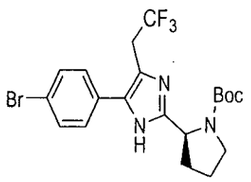
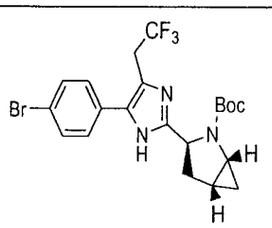
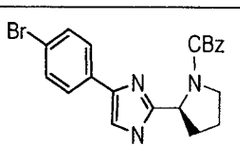
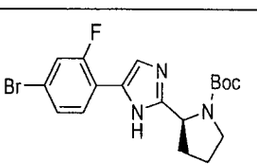
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Ejemplo 9b.2 (Derivado del Ejemplo 5b.1)		TR = 1,9 minutos (condición 1); LCMS: Análisis calculado para $C_{20}H_{24}BrF_3NO_5$ 494,08; encontrado: 494,03 (M+H).
Ejemplo 9b.3 (Derivado del Ejemplo 5b.1 y M.4)		TR = 2,1 minutos (condición 1); LCMS: Análisis calculado para $C_{21}H_{24}BrF_3NO_5$: 526,07; encontrado: 525,91 (M+H).
Ejemplo 9b.4		TR = 2,2 minutos (condición 1); LCMS: Análisis calculado para $C_{21}H_{20}BrNO_5$: 445; encontrado: 445 (M+H).
Ejemplo 9b.5		TR = 2,94 minutos (condición 2); LCMS: Análisis calculado para $C_{18}H_{22}BrFNO_5$: 452,05, 454,05, 466,05; encontrado: 452,06, 454,06 (M+Na) .

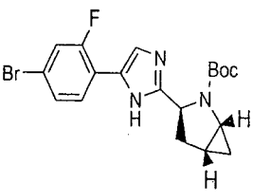
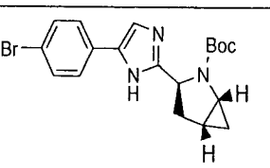
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Ejemplo 9b.6 (Derivado del Ejemplo M.4)		TR = 2,78 minutos (condición 2); LCMS: Análisis calculado para $C_{19}H_{21}BrFNO_5$: 464,05, 466,05; encontrado: 463,92, 465,92 (M+Na) .
Ejemplo 9b.7 (Derivado del Ejemplo M.4)		TR = 2,05 minutos (condición 1); LRMS: Análisis calculado para $C_{19}H_{23}BrNO_5Na$: 446,07; encontrado: 446,08 (M+Na), (M+2).
Ejemplo 10b (Derivado del Ejemplo 9b como se describe para el Ejemplo 10)		TR = 1,6 minutos (condición 1); LRMS: Análisis calculado para $C_{17}H_{22}BrN_3O2$: 380,10; encontrado: 379,98 (M+H).
Ejemplo 10b.1 (Derivado del Ejemplo 9b.1)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{16}H_{20}BrN_3O_2$: 365; encontrado: 365

500

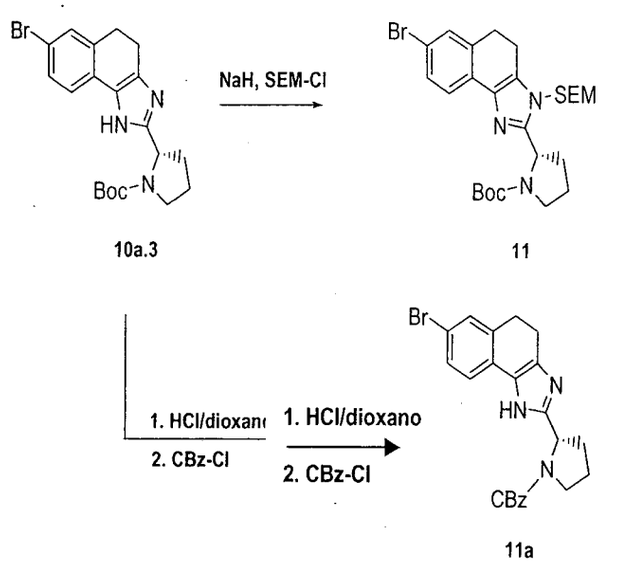
		(M+H).
Ejemplo 10b.2 (Derivado del Ejemplo 9b.2)		TR = 1,66 minutos (condición 1); LCMS: Análisis calculado para $C_{20}H_{24}BrF_3N_3O_2$ 474,10; encontrado: 473,99 (M+H).
Ejemplo 10b.3 (Derivado del Ejemplo 9b.3)		TR = 1,7 minutos (condición 1); LCMS: Análisis calculado para $C_{21}H_{24}BrF_3N_3O_2$: 486,10; encontrado: 486,10 (M+H).
Ejemplo 10b.4 (Derivado del Ejemplo 9b.4)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{21}H_{20}BrN_3O_2$: 426,08; encontrado: 426,09 (M+H).
Ejemplo 10b.5 (Derivado del Ejemplo 9b.5)		TR = 2,27 minutos (condición 2); LCMS: Análisis calculado para $C_{18}H_{22}BrFN_3O_2$ 410,09; encontrado: 410,08 (M+H).

501

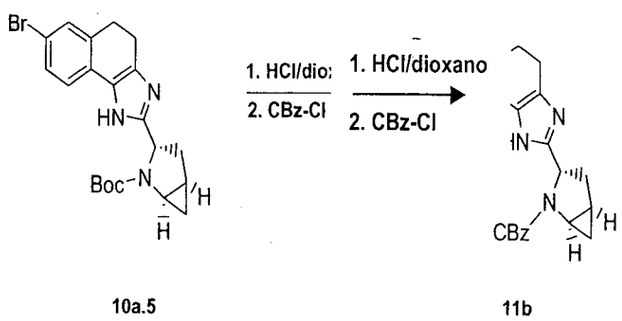
Ejemplo 10b.6 (Derivado del Ejemplo 9b.6)		TR = 2,15 minutos (condición 2); LCMS: Análisis calculado para $C_{19}H_{22}BrFN_3O_2$: 422,09; encontrado: 421,96 (M+H) .
Ejemplo 10b.7 (Derivado del Ejemplo 9b.7)		TR = 1,58 minutos (condición 1); LCMS: Análisis calculado para $C_{19}H_{23}BrN_3O_2$: 404,10; encontrado: 404,09 (M+H) .

502

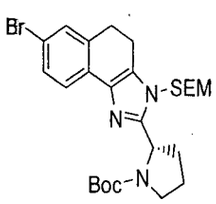
Ruta sintética 6.



10a.3 11 11a



10a.5 11b

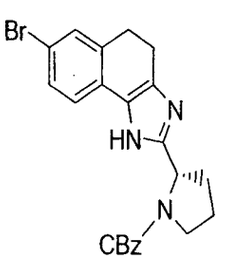


11

Se añadió hidruro sódico al 60% sin lavar (54 mg, 1,35 mmol) en una porción a una solución agitada de 10a.3 (565 mg, 1,35 mmol) en DMF seco (10 ml) en nitrógeno. La mezcla se agitó 5 min antes de la adición de SEM-Cl (0,24 ml, 1,35 mmol), se agitó durante 3 h, se inactivó con cloruro amónico saturado (1 ml), se diluyó con EtOAc (50 ml) y se lavó la fase orgánica con solución saturada de $NaHCO_3$ y

503

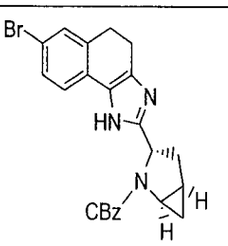
salmuera. La fase acuosa se extrajo dos veces más con EtOAc y se reunió con el extracto orgánico inicial antes de secar. La concentración dio un residuo que se aplicó (CH_2Cl_2) a un cartucho de gel de sílice 40 (S) Biotage®. Segmento 1. Mantenido 15% de B durante 75 ml; Segmento 2. Elución con gradiente desde 15% hasta 50% de B durante 750 ml; Segmento 3: 50-100%B durante 750 ml (A = hex; B = EtOAc) B dando productos regioisoméricos del Ejemplo 11, 497 mg (67 %). TR = 3,0 minutos (condición 2). RMN de ^1H (500 MHz, DMSO-d_6) δ 7,42-7,35 (m, 3H), 5,65/5,39 (d, *J* = 11,6 Hz, 1H), 5,29-5,27 (m, 1H), 5,00/4,93 (s, 1H), 3,54-3,51 (m, 3H), 3,43-3,41 (m, 1H), 3,02-2,99 (m, 2H), 2,89-2,81 (m, 1H), 2,29-2,08 (m, 2H), 1,95 -1,84 (m, 2H), 1,37/1,13 (s, 9H), 0,89-0,86 (m, 2H), -0,02 (s, 9H). LRMS: Análisis calculado para $C_{26}H_{39}BrN_3O_3Si$: 548,19; encontrado: 548,23 (M+H).



11a

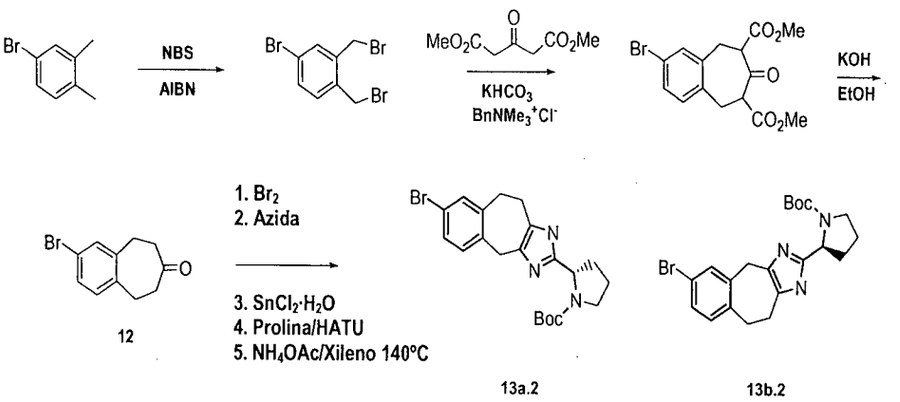
Se añadió HCl 4N frío en dioxano (0,871 ml, 3,49 mmol) a una solución de 10a.3 3-(7-bromo-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo (1,5 g, 3,49 mmol) en MeOH (20 ml) y la reacción se agitó durante 2h a temperatura

ambiente. La concentración proporcionó un sólido castaño que se suspendió en dioxano (20 ml) / agua (20 ml) y se enfrió hasta 0°C. Se añadieron Na_2CO_3 (0,369 g, 3,49 mmol) y CBz-Cl (0,498 ml, 3,49 mmol) y la mezcla de reacción se agitó cuando se calentaba hasta temperatura ambiente durante 5 horas antes de repartirse entre EtOAc y solución saturada de $NaHCO_3$. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El producto bruto se cargó (CH_2Cl_2) en un cartucho de gel de sílice de 110 g Thompson® y eluyó con 20% - 100% de B durante 1,5 l (A/B = hexanos/EtOAc). El rendimiento combinado de 11a 3-(7-bromo-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-bencilo de tres fracciones de varias purezas fue 1,4 g (75%). LCMS Calculado para $C_{24}H_{23}BrN_3O_2$ $(M+H)^+$ 464,10 y 466,10; encontrado: 463,95 y 465,98.

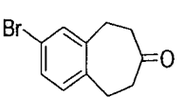
Ejemplo 11b (Derivado del Ejemplo 10a.5)		TR = 2,01 minutos (condición 2); LCMS: Análisis calculado para $C_{24}H_{23}BrN_3O_2$: 464,10, 466,10; encontrado: 464,11, 466,11 $(M+H)^+$.

505

Ruta sintética 7.



Referencia: *J.Chem.Soc. Perkin Trans 2* (1993) p 1305.



12

Se añadió AIBN (98 mg, 0,59 mmol) a 4-bromo-1,2-dimetilbenceno (11 g, 59,4 mmol) y N-bromosuccinimida recién recristalizada (21,1 g, 119 mmol) en CCl_4 (50 ml). La mezcla de reacción se calentó a reflujo durante 2 horas en nitrógeno. Después de enfriar hasta temperatura ambiente, la solución se filtró y se concentró por evaporación rotatoria dando 21 g de una mezcla que contenía aproximadamente (75%) de 4-bromo-1,2-bis(bromometil)benceno junto con 3-bromo-1,2-bis(bromometil)benceno. [NOTA: El material de partida estaba contaminado con 25% de 3-bromo-1,2-dimetilbenceno]. TR = 2,2/2,3 min (condición 1).

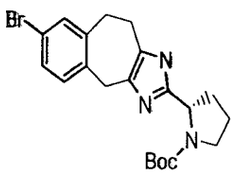
La mezcla bruta de 4- y 3-bromo-1,2-bis(bromometil)benceno (21 g) se suspendió en CH_2Cl_2 (313 ml) y se añadió 3-oxopentanodioato de dimetilo (12,8 g, 73,5

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mmol) y la solución se diluyó con una solución al 20% de $KHCO_3$ (64 g, 0,64 mol) en agua (250 ml). Se añadió catalizador de transferencia de fase, cloruro de benciltrimetilamonio (1,7 g, 9,19 mmol) y la mezcla de reacción se agitó 18h en nitrógeno a 50 °C. Después de la separación de la fase orgánica, la fase acuosa se extrajo con CH_2Cl_2 y las fases orgánicas reunidas se lavaron con salmuera. La concentración dio 23 g de una mezcla compleja (ambos bromo regioisómeros; y diastereoisómeros éster) que contenía 2-bromo-7-oxo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-6,8-dicarboxilato de dimetilo que se llevó adelante sin purificación adicional. TR = 1,87 min (condición 1); LCMS: Anal. Calculado para $C_{15}H_{15}BrO_5$: 377,01; encontrado 377,05 $[M+Na]^+$.

La mezcla de 23 g de material bruto 2-bromo-7-oxo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-6,8-dicarboxilato de dimetilo (que contenía aproximadamente 8 g, 22,5 mmol) se colocó en un matraz de fondo redondo de 1 litro dotado de un condensador de reflujo y se disolvió en etanol (250 ml). Se añadió una solución de KOH (8,8 g, 0,23 mol) disuelta en agua (250 ml) y la suspensión inicialmente color castaño viró a negro tras calentar a reflujo durante 16 horas. La mezcla de reacción se vertió en EtOAc (1 vol) y se separó la fase orgánica. Se añadió salmuera (1/4 vol) a la fase acuosa que se extrajo con EtOAc y las fases orgánicas reunidas se

lavaron con salmuera. Después de concentrar por evaporación rotatoria, el residuo se cargó (CH_2Cl_2) en una columna de gel de sílice 40 (M) Biotage® (vacío aplicado desde debajo de la columna para ayudar a la adsorción) y eluyó con gradiente 10-100% de B (A = Hexanos; B = EtOAc) dando una mezcla 4:1 de bromuros que favorecía el Ejemplo 12, 2-bromo-8,9-dihidro-5H-benzo[7]annulen-7(6H)-ona y contenía 1-bromo-8,9-dihidro-5H-benzo[7]annulen-7(6H)-ona, 8,3 g (61%). La mezcla se llevó adelante sin purificación adicional pero se obtuvo una muestra pura del Ejemplo 12 tras cristalizar dejando la mezcla reposar durante 3 semanas a -5°C. RMN de ^1H (500 MHz, $CDCl_3$) δ 7,37 (d, J = 2,1 Hz, 1H), 7,33 (dd, J = 7,9, 2,1 Hz, 1H), 7,09 (d, J = 7,9 HZ, 1H), 2,87-2,84 (m, 4H), 2,61-2,57 (m, 4H). TR = 1,96 minutos (condición 1). LCMS: Análisis calculado para C11H11BrO: 239,0; encontrado: 239,04 (M+H).



13a.2

Se añadió bromo (1,4 ml, 26,8 mmol) a una solución de la mezcla 4:1, respectivamente de 2- y 1-bromo-8,9-dihidro-5H-benzo[7]annulen-7(6H)-ona (6,4 g, 26,8 mmol) (4:1) en éter dietílico (250 ml). La reacción se agitó durante 4 h, se concentró por evaporación rotatoria y las α-bromo cetonas brutas se suspendieron en acetonitrilo (200 ml). Se

añadió azida de sodio (1,7 g, 26,8 mmol) y la reacción se agitó 16 horas antes de concentrarse por evaporación rotatoria. El residuo se repartió entre EtOAc y solución saturada de $NaHCO_3$, y la fase orgánica se lavó con agua, salmuera y se concentró. TR = 2,0 minutos (pico ancho, condición 1).

Las α-ceto azidas brutas se disolvieron en CH_3OH (350 ml) y se añadió cloruro de estaño (II) dihidratado (13,2 g, 69,6 mmol) y la mezcla de reacción se agitó durante 3,5 horas a 65 °C, se concentró por evaporación rotatoria y se secó a alto vacío durante 18 horas.

Las α-amino cetonas brutas se suspendieron en DMF (300 ml), base de Hunig (24,41 g, 189 mmol), ácido (S)-1-(terc-butoxicarbonil)pirrolidin-2-carboxílico (4,07 g, 18,89 mmol) y se añadió HATU (7,18 g, 18,89 mmol) en una porción con agitación vigorosa. Después de 8 horas la reacción se concentró hasta 1/3 del volumen a vacío y se repartió entre EtOAc (1 l) y HCl 0,1N (150 ml). Las sales de estaño se separaron por filtración a través de tierra de diatomeas (Celite®), y la fase orgánica se lavó con salmuera y se concentró. El producto bruto se cargó (CH_2Cl_2) a un cartucho de gel de sílice 40M Biotage® (dividido en dos ejecuciones). La elución con gradiente desde 15% a 100% de B durante 1,5 l (A = Hexanos; B = Acetato de etilo) dando los Ejemplos 12a.1

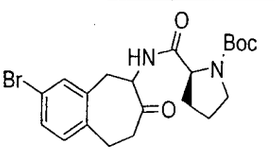
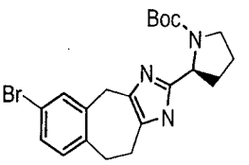
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y 13b.1 (3,8 g, rendimiento combinado 35,7%) como una mezcla de diastereómeros. TR = 1,58/1,51 min (condición 5). LCMS: Análisis calculado para $C_{21}H_{27}BrN_2O_4$: 451,12; encontrado: 450,87 (M+H).

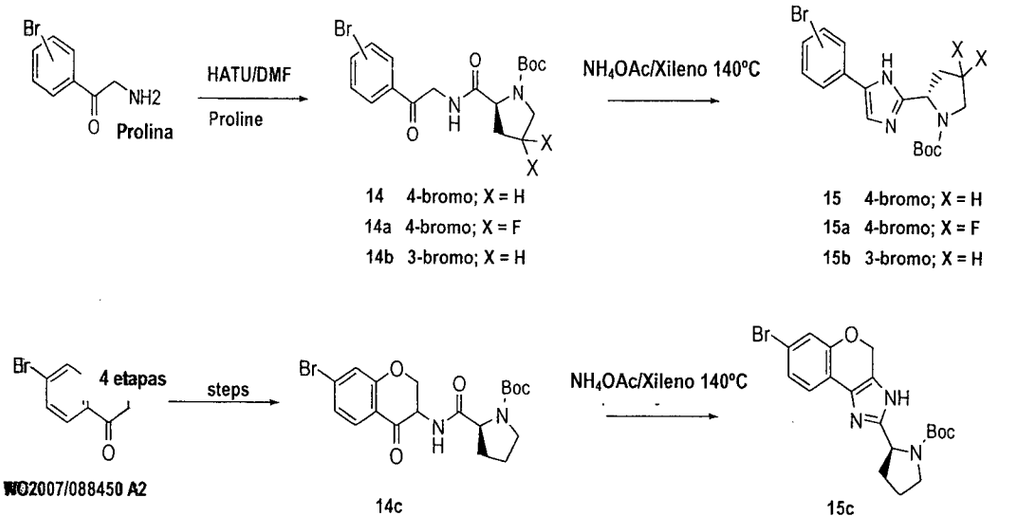
Se añadió acetato amónico (4,4 g, 73,1 mmol) a una solución de las amidas 13a.1 y 13b.1 (3,3 g, 7,31 mmol) que contenían 2-(3-bromo-7-oxo-6,7,8,9-tetrahidro-5H-benzo[7]annulen-6-ilcarbamoil)pirrolidin-1-carboxilato de (2S)-terc-butilo en xileno (75 ml) y se agitó en un recipiente a presión calentado a 140°C durante 4 horas. Después de enfriar, la mezcla de reacción se diluyó con EtOAc (500 ml), se lavó con solución saturada de $NaHCO_3$, salmuera y se concentró la fase orgánica. El producto bruto se cargó (CH_2Cl_2) a un cartucho de gel de sílice 40S Biotage®. La elución con gradiente desde 15% a 100% de B durante 750 ml (A = CH_2Cl_2; B = EtOAc) dio 2,49 g de una mezcla que se sometió a una segunda cromatografía; cartucho de gel de sílice 40S Biotage, elución 5% - 80% de B durante 1 l (A = 1:1 Hex/CH_2Cl_2; B = 10% CH_3OH/EtOAc) y proporcionó una mezcla de los Ejemplos 13a.2 y 13b.2, 1,1 g (34,8%). Se aplicó una muestra del producto a HPLC de fase normal semipreparativa (columna Chiralcel OD, 20x250mm, 10um; Heptano/EtOH 98:2 a 10 ml/min; UV 220/254 nm) y se recogieron los picos eluyendo a 35-36 min. RMN de ^1H (500 MHz, CD_3OD) δ 7,44 (s, 1H), 7,28

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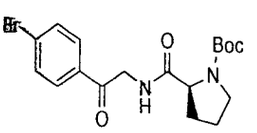
(dd, J = 7,9, 2,1 Hz, 1H), 7,09 (d, J = 8,2 HZ, 1H), 4,73-4,69 (m, 1H), 3,91 (s, 2H), 3,64-3,61 (m, 1H), 3,48-3,44 (m, 1H), 3,09 (t, J = 4,6 Hz, 2H), 2,80 (t, J = 5,8 Hz, 2H), 2,31-2,11 (m, 1H), 2,01-1,88 (m, 3H), 1,46/1,48 (s, 9H). TR = 1,7 minutos (condición 1). HRMS: Análisis calculado para $C_{21}H_{26}BrN_3O_2$: 432,1281; encontrado: 432,1268 (M+H).

Ejemplo 13b.1		TR = 1,59 minutos (condición 5); LCMS: Análisis calculado para $C_{21}H_{27}BrN_2O_4$: 451,12; encontrado: 450,98 (M+H).
Ejemplo 13b.2		TR = 1,7 minutos (condición 1). LCMS: Análisis calculado para $C_{21}H_{26}BrN_3O_2$: 432; encontrado: 432 (M+H).

Ruta sintética 8.



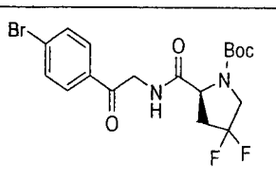
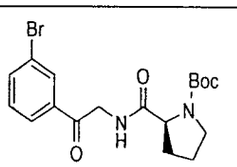
Ejemplo 14



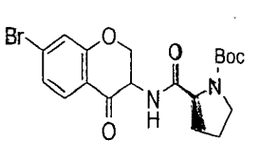
Se añadió N,N-diisopropiletilamina (18 ml, 103,3 mmol) gota a gota, durante 15 minutos, a una mezcla heterogénea de N-Boc-L-prolina (7,139 g, 33,17 mmol), HATU (13,324 g, 35,04 mmol), la sal HCl de 2-amino-1-(4-bromo-fenil)etanona (8,127 g, 32,44 mmol), en DMF (105 ml) y se agitó en condiciones ambientales durante 55 minutos. Se eliminó el DMF 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; 50-60 % de acetato

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de etilo/hexanos) proporcionando el Ejemplo 14, 2-(2-(4-bromofenil)-2-oxoetilcarbamoil)pirrolidin-1-carboxilato de (S)-terc-butilo como un sólido blanco (12,8 g). RMN de ^{1}H (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 ancho ap., 9H). TR = 1,70 min (condición 1); LCMS: Anal. Calculado para $C_{18}H_{23}BrN_2NaO_4$: 433,07; encontrado 433,09 $[M+Na]^+$.

Ejemplo 14a		TR = 1,59 minutos (condición 4); LCMS: Análisis calculado para $C_{18}H_{21}BrF_2N_2O_4$: 446,06; encontrado: 445,43 (M-H)-.
Ejemplo 14b		LCMS: Análisis calculado para $C_{18}H_{23}BrN_2O_4$: (M+Na)+ = 433,08; encontrado: 433,12

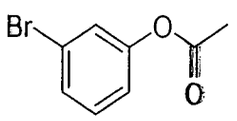
Ejemplo 14c



14c

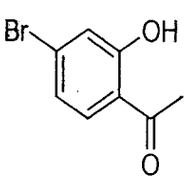
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Ejemplo 14c; etapa 1:



Se añadió cloruro de acetilo (10,2 ml, 144 mmol) gota a gota durante 1 hora a una solución fría (baño de hielo) de 3-bromofenol (25 g,144 mmol) y piridina (10,8 ml, 144 mmol) en diclorometano (100 ml), y la reacción se agitó 18 horas a temperatura ambiente. Se añadió agua (150 ml) y la fase orgánica se extrajo con diclorometano. Las fases orgánicas reunidas se lavaron con $NaHSO_4$ 2,5N, NaOH 3N, agua, salmuera y se secaron sobre Na_2SO_4 y se filtraron. La concentración dio el acetato de 3-bromofenilo como un líquido rosa (28 g, 96%). Datos GC-MS: 214 (M^+); RMN de ^1H (DMSO-d_6): 7,37-7,39 (d, 1H), 7,26-7,30 (m, 2H), 7,04-7,07(t, 1H), 2,30 (s, 3H).

Ejemplo 14c; etapa 2:

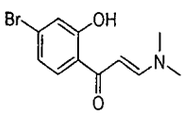


Se calentaron durante 2 horas a 140-150°C acetato de 3-bromofenilo (36 g, 167 mmol) y $AlCl_3$ anhidro (33,5 g, 251 mmol). Después de enfriar, se añadió solución de HCl al 5% (100ml) y la mezcla se calentó (baño de vapor) hasta que se disolvieron los materiales sólidos. Se separó un aceite marrón y se extrajo en diclorometano. Al extracto se añadió

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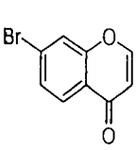
NaOH 5N (300 ml) y agua suficiente para disolver el precipitado resultante. La fase acuosa se separó, se acidificó (pH 2,0) y se extrajo con acetato de etilo. El extracto se secó sobre Na_2SO_4, se filtró y se concentró dando 1-(4-bromo-2-hidroxifenil)etanona, cristales (35,8 g, 99%). GC-MS (214 M^+); RMN de ^1H (DMSO-d_6) 11,99 (s, 1H, OH), 7,77-7,80 (d, 1H), 7,20 (s, 1H), 7,13-7,15 (dd, 1H), 2,6 (s, 3H).

Ejemplo 14c; etapa 3:



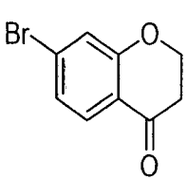
A 1-(4-bromo-2-hidroxifenil)etanona (35,8g, 167 mmol) en benceno seco (800 ml) se añadió dimetilacetal de N,N-dimetilformamida (44 ml, 333 mmol) y la solución se calentó a reflujo durante 4 horas y se concentró hasta sequedad. El residuo resultante se disolvió en diclorometano (300 ml) y se filtró sobre SiO_2. La fase orgánica se concentró proporcionando (E)-1-(4-bromo-2-hidroxifenil)-3-(dimetilamino)prop-2-en-1-ona como un sólido amarillo brillante (31,9 g, 71%). LCMS 270 (M+H); RMN de ^1H (DMSO-d6) 14,96 (s, 1H), 7,86-7,94 (m, 2H), 6,96-7,02 (dd, 2H), 5,92-5,96 (d, 1H), 3,32 (s, 3H), 3,20 (s, 3H).

Ejemplo 14c; etapa 4:



Se añadió HCl conc. (100 ml) a una solución de (E)-1-(4-bromo-2-hidroxifenil)-3-(dimetilamino)prop-2-en-1-ona (31,9 g, 118 mmol) en diclorometano (900 ml) y la mezcla de reacción se calentó a reflujo 40 minutos con agitación vigorosa. Después de enfriar hasta temperatura ambiente, la fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Las fases orgánicas reunidas se lavaron con solución de carbonato potásico 3M, agua, y se secaron sobre Na_2SO_4. La filtración y concentración dieron 7-bromo-4H-cromen-4-ona como un sólido amarillo pálido. LCMS 224,9 (M+H); RMN de ^1H (DMSO-d6) 8,29-8,31 (d, 1H), 7,92-7,99 (m, 2H), 7,64-7,66 (dd, 1H), 6,37-6,39 (d, 1H).

Ejemplo 14c; etapa 5:



Se enfrió hasta -80°C una solución de 7-bromo-4H-cromen-4-ona (26 g, 116 mmol) en THF seco (500 ml) en nitrógeno durante 1 hr y se añadieron durante 30 minutos 173 ml de hidruro de diisobutilaluminio (2M en tolueno). La reacción se agitó a la misma temperatura durante 30 minutos, se inactivó con una suspensión de SiO_2 (52 g) / agua (52 ml), y se dejó calentar hasta 0°C. La solución se filtró, la SiO_2 se lavó con EtOAc y el filtrado reunido se concentró hasta sequedad. El residuo se disolvió en $CHCl_3$ (400 ml), se lavó

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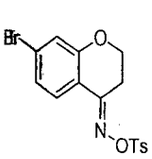
con NaOH 1N (300 ml), se secó sobre Na_2SO_4 y se concentró. La purificación por cromatografía sobre SiO_2 (malla 60-120) EtOAc/éter de petróleo (elución con gradiente de 0-15%) proporcionó 7-bromocroman-4-ona 18,1 g (69%) como un sólido amarillo pálido. LCMS 229,0 (M+2H); RMN de ^1H (DMSO-d6) 7,64-7,67 (d, 1H), 7,32 (s, 1H), 7,22-7,25(d, 1H), 4,53-4,57 (t, 2H), 2,76-2,80 (t, 2H).

Ejemplo 14c; etapa 6:



Se añadió NaOAc (3,78 g, 46,2 mmol) en H_2O (30 ml) a una solución de 7-bromo 4-cromanona (3,5 g, 15,4 mmol) y clorhidrato de hidroxil-amina (1,75 g, 23,1 mmol) en EtOH (70 ml). La reacción se calentó a reflujo durante 2 horas, se enfrió hasta temperatura ambiente y se concentró. El residuo se diluyó con H_2O y se filtró un precipitado dando oxima de 7-bromocroman-4-ona obtenida como cristales aciculares, 3,5 g (98%). LCMS 244 (M+2H) TR = 1,7 min (condición 2); RMN de ^1H (DMSO-d_6) 11,37 (s, OH, 1H), 7,76-7,70 (d, 1H), 7,09-7,13 (d, 2H), 4,16- 4,20 (t, 2H), 2,79-2,83 (t, 2H).

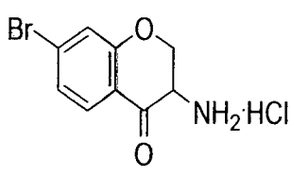
Ejemplo 14c; etapa 7:



Se añadió anhídrido p-toluenosulfónico (5 g, 16

mmol) a una solución de oxima de 7-bromocroman-4-ona (3,5g, 14,46 mmol) y trietilamina (2,4 ml, 17,35 mmol) en diclorometano (125 ml). La mezcla se agitó durante 3 h a temperatura ambiente se lavó con agua, salmuera y se secó (Na_2SO_4). La filtración y concentración a presión reducida proporcionaron 7-bromocroman-4-ona-O-p-toluenosulfoxima 5,5 g (96 %) como un sólido blanquecino que se usó sin más purificación. LCMS 398 (M+2H) TR = 1,92 min (condición 1). RMN de ^1H (DMSO-d6) 7,89-7,91 (d, 2H), 7,56-7,58 (d, 1H), 7,48-7,50 (d, 2H), 7,22 (s, 1H), 7,16-7,18 (d, 1H), 4,20,4,23 (t, 2H), 2,97-3,00 (t, 2H), 2,40 (s, 1H).

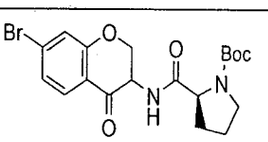
Ejemplo 14c; etapa 8:

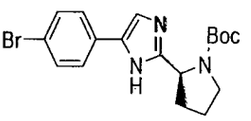


Se añadió una solución de etóxido potásico (1,27 g, 15,11 mmol) en etanol (35 ml) a una solución de 7-bromocroman-4-ona-O-p-toluenosulfoxima (5,7 g, 14,3 mmol) en tolueno (60 ml) y la mezcla se agitó durante 15 h a temperatura ambiente. Se separó un precipitado (tosilato potásico) por filtración y se lavó con éter dietílico. A los filtrados reunidos se añadió HCl 3N (20 ml) en metanol y la solución se agitó 2 h a temperatura ambiente formando la sal HCl. Después de eliminar el disolvente, el residuo se trituró con éter dietílico. El sólido resultante se filtró, se lavó

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con éter y se secó proporcionando clorhidrato de 7-bromo-3-amino-croman-4-ona 2,8 g, (80 %) como polvo blanquecino. LCMS 244 (M+2H) TR = 3,77 (condición 2); RMN de ^{1}H (DMSO-d_6) 8,79 (s ancho, 2H), 7,71-7,74 (d, 1H), 7,45 (s, 1H), 7,34-7,37 (d, 1H), 4,67-4,80 (m, 2H), 4,43-4,51 (t, 1H).

Ejemplo 14c (Preparado como se describe en el Ejemplo 14, y derivado del producto de la etapa 8)		TR = 1,76 minutos (condición 2); LCMS: Análisis calculado para $C_{19}H_{24}BrN_2O_5$: 439,09; encontrado: 439 (M+H)

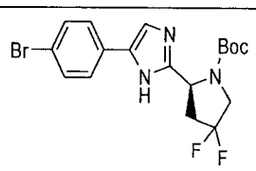
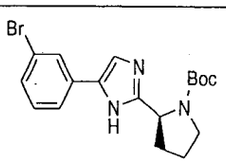


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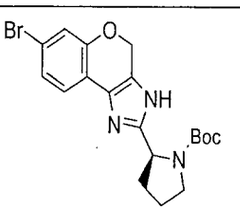
Se calentó en un tubo sellado a 140°C durante 2 horas una mezcla del Ejemplo 14, 2-(2-(4-bromofenil)-2-oxoetilcarbamoil)-pirrolidin-1-carboxilato de (S)-terc-butilo (12,8 g, 31,12 mmol) y NH_4OAc (12,0 g, 155,7 mmol) en xilenos (155 ml). El componente volátil se eliminó a vacío, y el residuo se repartió cuidadosamente entre acetato de etilo y agua, después de lo cual se añadió suficiente solución saturada de $NaHCO_3$ para hacer el pH de la fase acuosa ligeramente básico después de agitar el sistema bifásico. Se separaron las fases y la fase acuosa se extrajo con más

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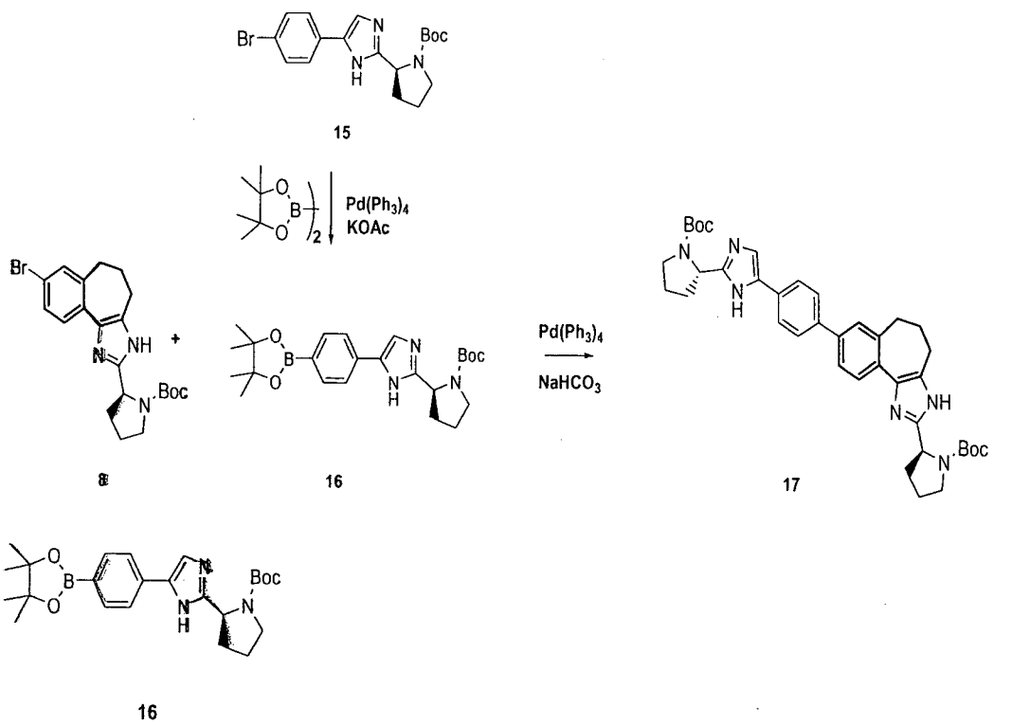
acetato de etilo. La fase orgánica reunida se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El material resultante se recristalizó en acetato de etilo/hexanos proporcionando dos tandas del Ejemplo 15, 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo 5,85 g. Las aguas madres se concentraron a vacío y se sometieron a cromatografía ultrarrápida (gel de sílice; 30% de acetato de etilo/hexanos) proporcionando otros 2,23 g. RMN de ^1H (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 ap, 1H), 3,36 (m, 1H), 2,30-1,75 (m, 4H), 1,40/1,15 (s ancho ap, 9H). TR = 1,71 min (condición 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,10; encontrado 391,96; HRMS: Análisis calculado para $C_{18}H_{23}BrN_3O_2$: 392,0974; encontrado 392,0959 [M+H].

Ejemplo 15a (Derivado del Ejemplo 14a)		TR = 1,59 minutos (condición 4); LRMS: Análisis calculado para $C_{18}H_{20}BrF_2N_3O_2$: 428,27; encontrado: 428,02 (M+H).
Ejemplo 15b (Derivado del Ejemplo 14b)		LRMS Análisis calculado para $C_{18}H_{22}BrN_3O_2$: 392,10; encontrado: 391,96 (M+H).

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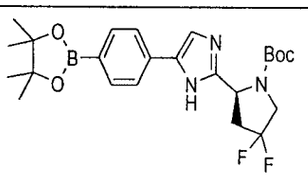
Ejemplo 15c (Derivado del Ejemplo 14c)		RT = 1,6 min (condición 1); LCMS: Análisis calculado para $C_{19}H_{22}BrN_3O_3$: 420,33; encontrado 422,2 (M+2H).

Ruta sintética 9.

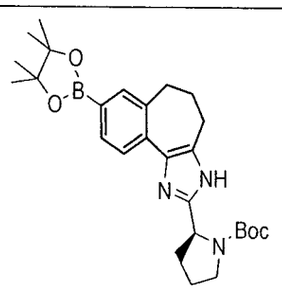
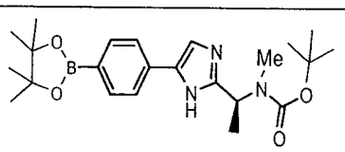
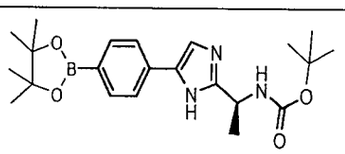
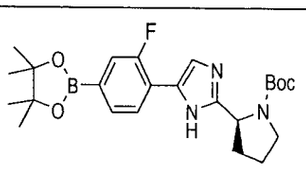


Se añadió $Pd(Ph_3P)_4$ (469 mg, 0,406 mmol) a un tubo de presión con tapón de tipo rosca que contenía una mezcla de Ejemplo 15, 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (4 g, 10,22 mmol), bis(pinacolato)diboro (5,4 g, 21,35 mmol), acetato potásico (2,6 g, 26,21 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

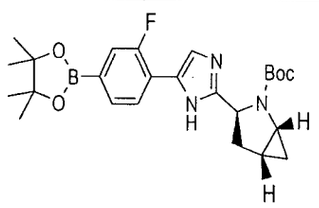
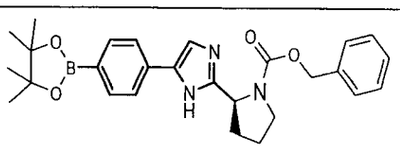
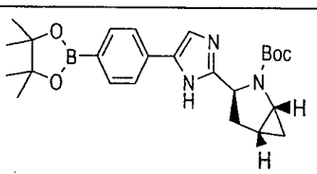
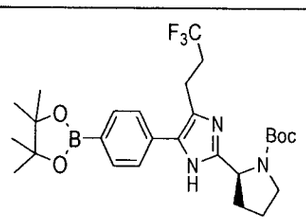
filtró y el filtrado se concentró a vacío. El material bruto se repartió cuidadosamente entre CH_2Cl_2 (150 ml) y un medio acuoso (50 ml agua + 10 ml de solución saturada de $NaHCO_3$). La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío. El material resultante se purificó por cromatografía ultrarrápida (muestra se cargo con disolvente de elución; 20-35% de acetato de etilo/CH_2Cl_2) proporcionando el Ejemplo 16, 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 blanquecino denso; la relación relativa de Ejemplo 16 a pinacol fue de aproximadamente 10:1 (RMN de ^1H). La muestra pesaba 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 ap, 1H), 3,36 (m, 1H), 2,27-1,77 (m, 4H), 1,45-1,10 (m, 21H). TR = 1,64 min (condición 1); LC/MS: Análisis calculado para [M+H] $C_{24}H_{35}BN_3O_4$: 440,27; encontrado 440,23.

Ejemplo 16a (Derivado del Ejemplo 15a)		TR = 1,62 minutos (condición 3); LCMS: Análisis calculado para $C_{34}H_{32}BF_2N_3O_4$: 475,34; encontrado:

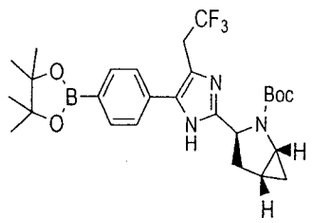
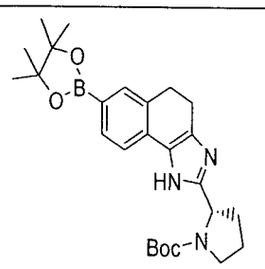
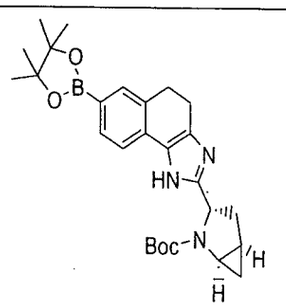
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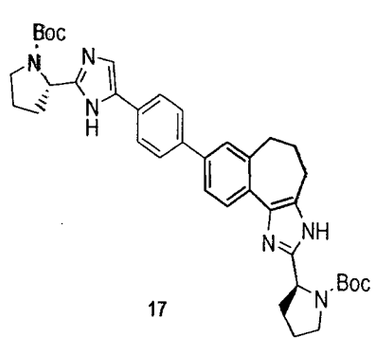
		474,78 (M-H).
Ejemplo 16b (Derivado del Ejemplo 8)		TR = 1,9 minutos (condición 1); LCMS: Análisis calculado para $C_{27}H_{38}BN_3O_4$: 497,3; encontrado: 479 (M+H).
Ejemplo 16c (Derivado del Ejemplo 10b).		TR = 1,83 minutos (condición 1); LCMS: Análisis calculado para $C_{23}H_{34}BN_3O_4$ 427; encontrado: 427 (M+H).
Ejemplo 16d (Derivado del Ejemplo 10b.1)		TR = 1,84 minutos (condición 1); LCMS: Análisis calculado para $C_{22}H_{32}BN_3O_4$ 413; encontrado: 414 (M+H).
Ejemplo 16e (Derivado del Ejemplo 10b.5)		TR = 2,62 minutos (condición 2); LRMS: Análisis calculado para $C_{24}H_{34}BFN_3O_4$ 458,26; encontrado: 458,23 (M+H).

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Ejemplo 16e.1 (Derivado del Ejemplo 10b.6)		TR = 2,46 minutos (condición 2); LRMS: Análisis calculado para $C_{25}H_{34}BFN_3O_4$ 470,26; encontrado: 470,19 (M+H).
Ejemplo 16f (Derivado del Ejemplo 10b.4)		TR = 1,84 minutos (condición 2); LCMS: Análisis calculado para $C_{27}H_{32}BN_3O_4$ 473; encontrado: 474 (M+H).
Ejemplo 16g (Derivado del Ejemplo 10b.7)		TR = 1,59 minutos (condición 1); LCMS: Análisis calculado para $C_{25}H_{35}BN_3O_4$ 452,27; encontrado: 452,23 (M+H).
Ejemplo 16h (Derivado del Ejemplo 8c)		TR = 1,9 minutos (condición 1); LCMS: Análisis calculado para $C_{27}H_{38}BF_3N_3O_4$ 536,29; encontrado: 536,37 (M+H).

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Ejemplo 16i (Derivado del Ejemplo 10b.3)		TR = 1,9 minutos (condición 1); LCMS: Análisis calculado para $C_{27}H_{36}BF_3N_3O_4$ 534,27; encontrado: 534,21 $(M+H)^+$.
Ejemplo 16j (Derivado del Ejemplo 10a.3)		TR = 2,46 minutos (condición 2); LRMS: Análisis calculado para $C_{26}H_{37}BN_3O_4$ 466,29; encontrado: 466,27 $M+H)^+$.
Ejemplo 16k (Derivado del Ejemplo 10a.5)		TR = 2,48 minutos (condición 2); LRMS: Análisis calculado para $C_{27}H_{37}BN_3O_4$ 478,29; encontrado: 478,27 $(M+H)^+$.



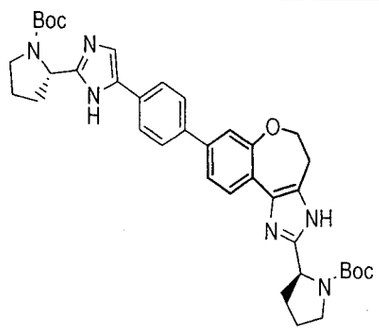
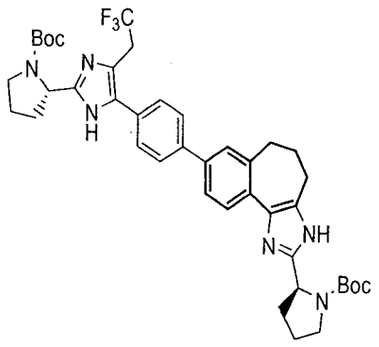
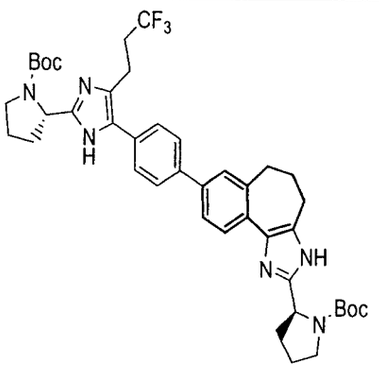
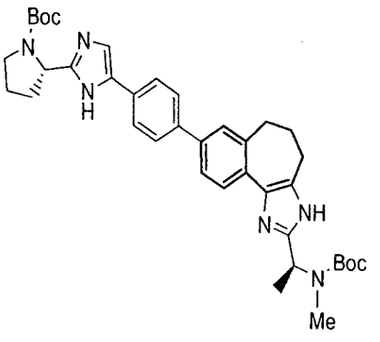
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El Ejemplo 8, (950 mg, 2,19 mmol); Ejemplo 16, 2-

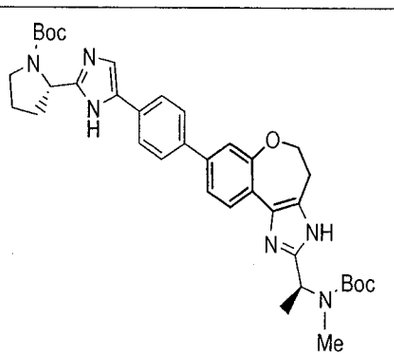
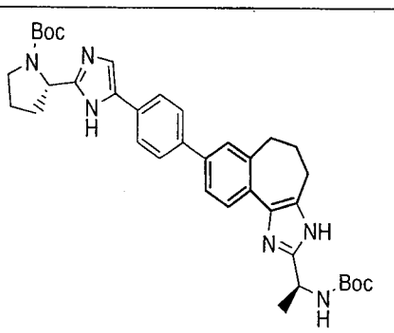
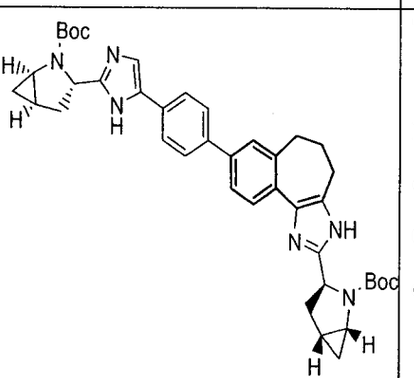
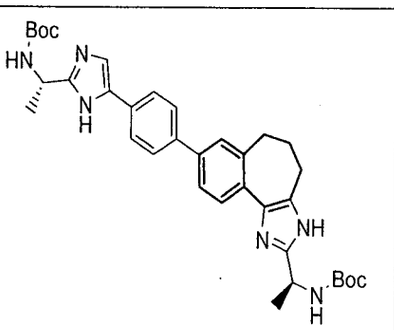
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(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (965 mg, 2,2 mmol) y $NaHCO_3$ (462 mg, 5,5 mmol) se disolvieron en 1,2-dimetoxietano (25 ml) y se añadió agua (4 ml). La mezcla de reacción se evacuó y se llenó con nitrógeno (3x), se añadió $Pd(Ph_3P)_4$ (127 mg, 0,11 mmol) y la mezcla se calentó (baño de aceite a 80°C) en un recipiente a presión de 100 ml durante 8 horas. Se añadió más catalizador (35 mg) y se continuó agitando durante 16 horas. Después de enfriar, la solución se repartió entre EtOAc/agua y la fase orgánica se lavó con salmuera. El producto bruto se aplicó (CH_2Cl_2) a una columna de gel de sílice 40 (S) Biotage®, y eluyó con gradiente desde 20-100% de B (A = CH_2Cl_2; B = EtOAc) durante 1 litro dando Ejemplo 17, 680 mg (49%). RMN de ^1H (300 MHz, DMSO-d_6) δ 8,05 (s ancho, 1H), 7,78 (d, *J* = 8,0 Hz, 2H), 7,66 (d, *J* = 8,0 Hz, 2H), 7,53-7,45 (m, 3H), 4,86-4,70 (m, 2H), 3,57-3,51 (m, 2H), 3,17 - 3,16 (m, 2H), 2,89-2,85 (m, 4H), 2,27-2,18 (m, 2H), 1,99-1,83 (m, 8H), 1,40/1,16 (s, 9H). TR = 1,7 minutos (condición 1). LRMS: Análisis calculado para $C_{39}H_{48}N_6O_4$: 665,38; encontrado: 665,39 (M+H). HRMS: Análisis calculado para $C_{39}H_{48}N_6O_4$: 665,3815; encontrado: 665,33845 (M+H).

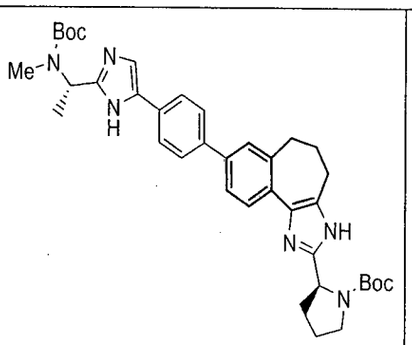
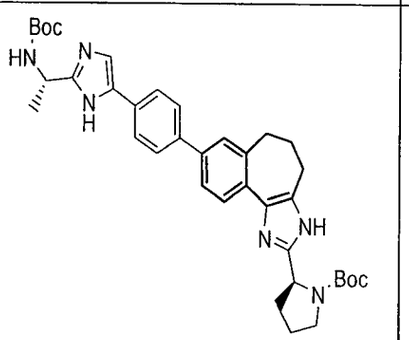
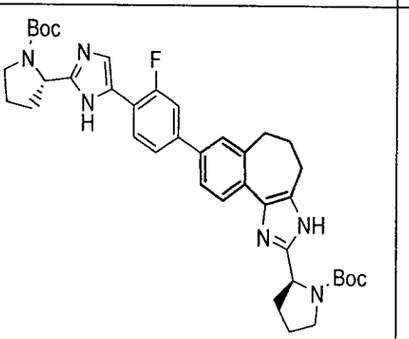
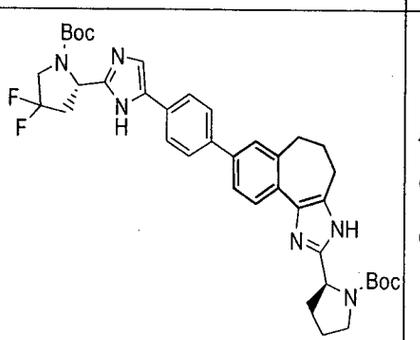
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Ejemplo 17a (Derivado del Ejemplo 16 y Ejemplo 8b)		TR = 2,38 minutos (condición 2) LCMS: Análisis calculado para $C_{38}H_{46}N_6O_5$: 666,80; encontrado: 665,2 (M-H).
Ejemplo 17a.1 (Derivado del Ejemplo 16b y Ejemplo 10b.2)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{41}H_{50}F_3N_6O_4$: 747,38; encontrado: 747,33 (M+H).
Ejemplo 17a.2 (Derivado del Ejemplo 16b y Ejemplo 8c)		TR = 1,7 minutos (condición 1); HRMS: Análisis calculado para $C_{42}H_{52}F_3N_6O_4$: 761,3997; encontrado: 761,4005 (M+H).
Ejemplo 17b (Derivado del Ejemplo 16 y Ejemplo 10)		TR = 1,8 minutos (condición 1); LRMS: Análisis calculado para $C_{38}H_{48}N_6O_4$: 675,37; encontrado: 675,35 (M+Na).

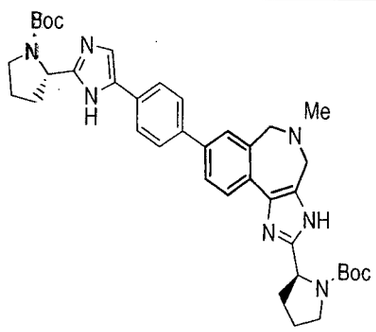
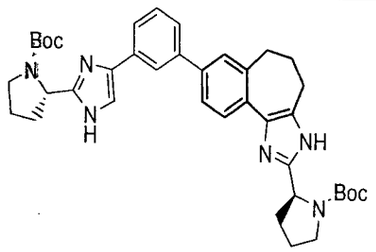
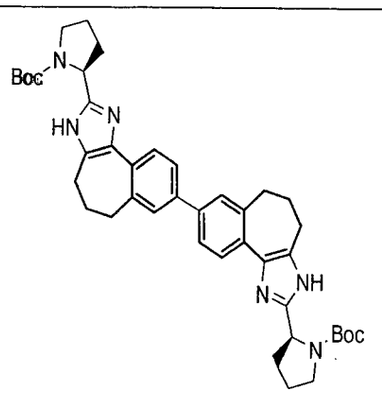
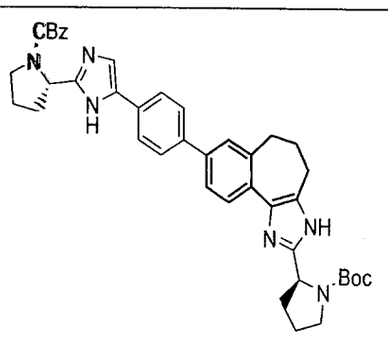
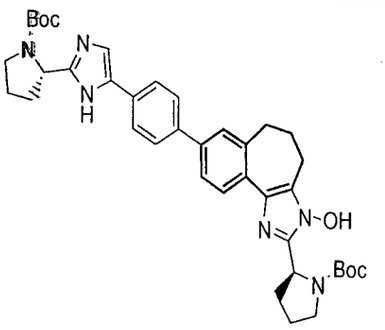
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Ejemplo 17b.1 (Derivado del Ejemplo 16 y Ejemplo 10a.1)		TR = 1,65 minutos (condición 1) LCMS: Análisis calculado para $C_{37}H_{46}N_6O_5$: 654,82; encontrado: 655,4 (M+H).
Ejemplo 17c (Derivado del Ejemplo 16 y Ejemplo 10a)		TR = 1,8 minutos (condición 1); LRMS: Análisis calculado para $C_{37}H_{46}N_6O_4$: 639,37; encontrado: 639,32 (M+H).
Ejemplo 17c.1 (Derivado del Ejemplo 16g y Ejemplo 10a.2)		TR = 1,6 minutos (condición 1); LRMS: Análisis calculado para $C_{41}H_{49}N_6O_4$: 689,38; encontrado: 689,43 (M+H).
Ejemplo 17d (Derivado del Ejemplo 16d y Ejemplo 10a)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{35}H_{44}N_6O_4$: 613,34; encontrado: 613,28 (M+H).

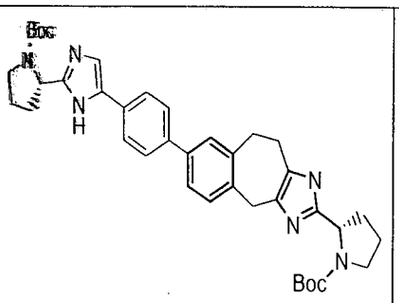
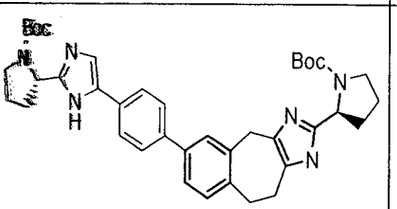
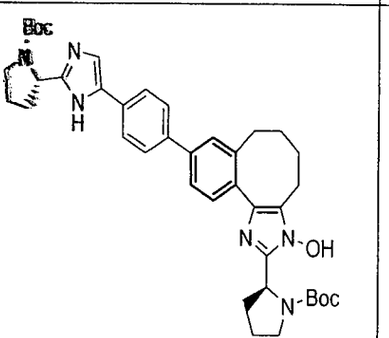
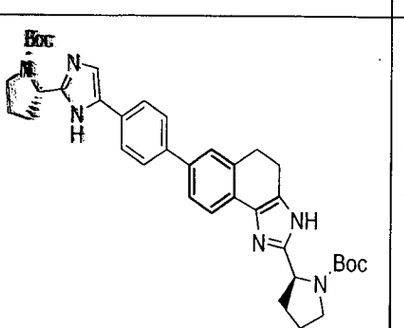
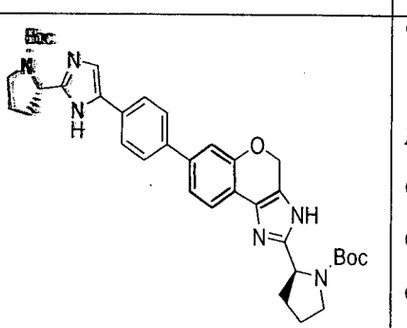
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Ejemplo 17e (Derivado del Ejemplo 16c y Ejemplo 8		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{38}H_{48}N_6O_4$: 653,38; encontrado: 653,50 (M+H).
Ejemplo 17f (Derivado del Ejemplo 16d y Ejemplo 8)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{37}H_{46}N_6O_4$: 639,37; encontrado: 639,50 (M+H).
Ejemplo 17g (Derivado del Ejemplo 16e y Ejemplo 8)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{39}H_{47}FN_6O_4$: 683,37; encontrado: 683,18 (M+H).
Ejemplo 17h (Derivado del Ejemplo 16a y Ejemplo 8)		TR = 2,31 minutos (condición 2); LRMS: Análisis calculado para $C_{39}H_{47}F_2N_6O_4$: 701,35; encontrado: 701,69 (M+H).

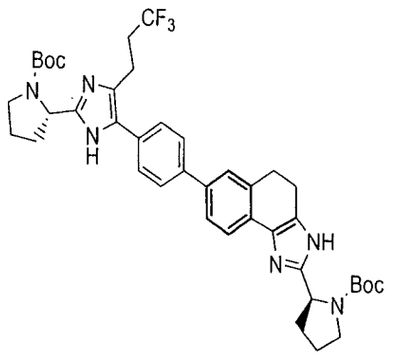
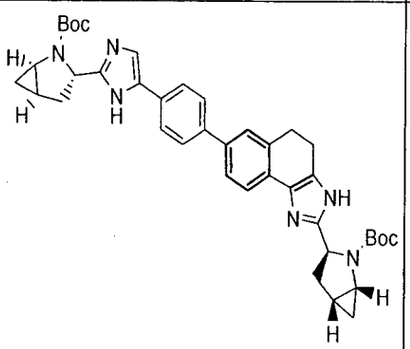
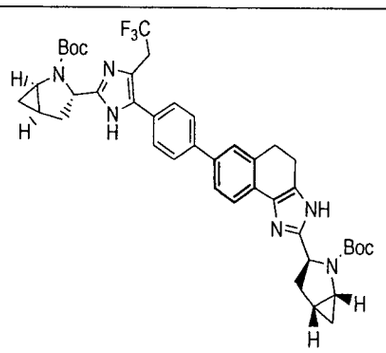
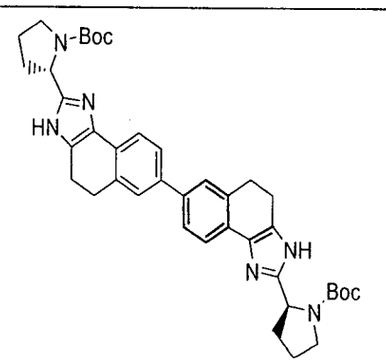
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Ejemplo 17i (Derivado del Ejemplo 16 y Ejemplo 8a)		TR = 2,02 minutos (condición 2); HRMS: Análisis calculado para $C_{39}H_{50}N_7O_4$: 680,3924; encontrado: 680,3957 (M+H).
Ejemplo 17j (Derivado del Ejemplo 16b y Ejemplo 15b)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{39}H_{48}N_6O_4$: 665,38; encontrado: 665,37 (M+H).
Ejemplo 17k (Derivado del Ejemplo 16b y Ejemplo 8)		TR = 1,8 minutos (condición 1); LRMS: Análisis calculado para $C_{42}H_{52}N_6O_4$: 705,41; encontrado: 705,40 (M+H).
Ejemplo 17m (Derivado del Ejemplo 16f y Ejemplo 8)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{42}H_{46}N_6O_4$ 699,37; encontrado: 699,47 (M+H).
Ejemplo 17n (Derivado del Ejemplo 16 y Ejemplo 7)		TR = 2,41 minutos (condición 2); LRMS: Análisis calculado para $C_{39}H_{49}N_6O_5$ 681,38; encontrado: 681,49 (M+H).

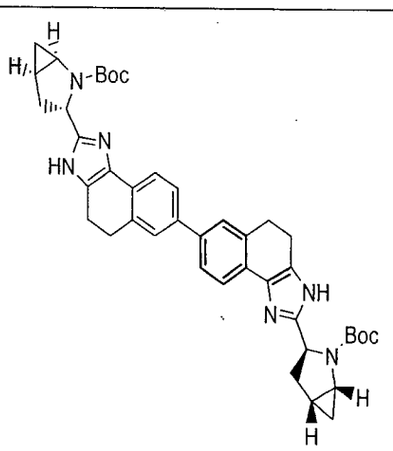
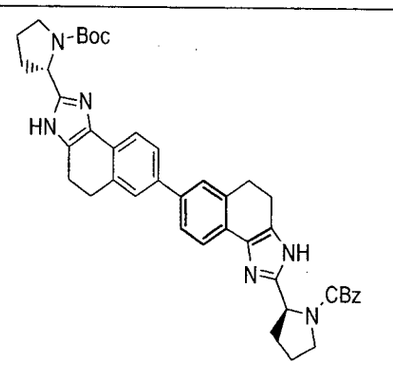
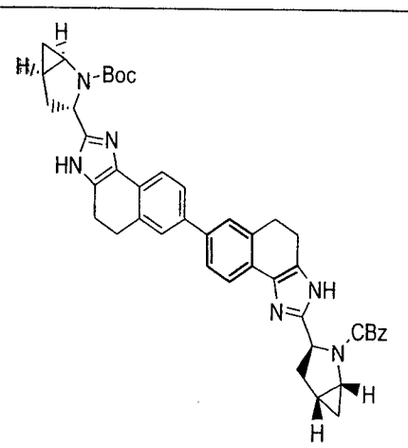
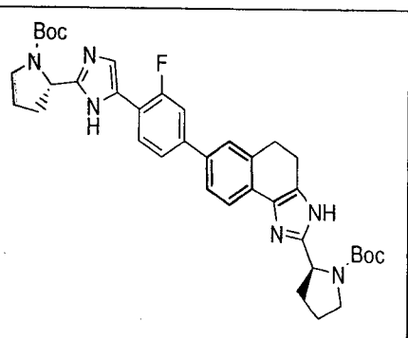
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Ejemplo 17o (Derivado del Ejemplo 16 y Ejemplo 13a.2)		TR = 1,7 minutos (condición 1) ; HRMS: Análisis calculado para $C_{39}H_{38}N_6O_4$ 665,3810; encontrado: 655,3789 (M+H).
Ejemplo 17p (Derivado del Ejemplo 16 y Ejemplo 13b.2)		TR = 1,7 minutos (condición 1) ; LCMS: Análisis calculado para $C_{39}H_{38}N_6O_4$ 665; encontrado: 655 (M+H).
Ejemplo 17q (Derivado del Ejemplo 16 y Ejemplo 7c)		TR = 2,43 minutos (condición 2) ; LRMS: Análisis calculado para $C_{40}H_{51}N_6O_5$ 695,39; encontrado: 695,55 (M+H).
Ejemplo 17r (Derivado del Ejemplo 16 y Ejemplo 10a.3)		TR = 2,25 minutos (condición 2); LRMS: Análisis calculado para $C_{38}H_{47}N_6O_4$ 651,37; encontrado: 651,33 (M+H).
Ejemplo 17r.a (Derivado del Ejemplo 16 y Ejemplo 15c)		TR = 2,05 minutos (condición 2) LCMS: Anal. Calculado para $C_{37}H_{44}N_6O_5$: 652,78; encontrado: 653,4 (M+H).

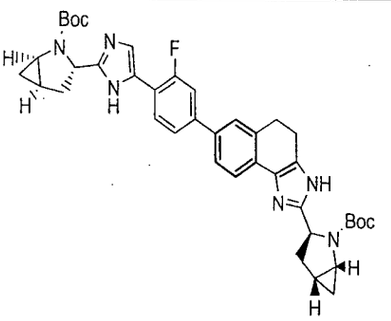
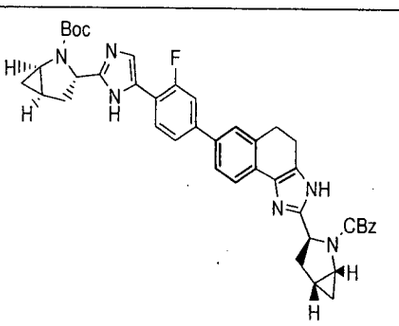
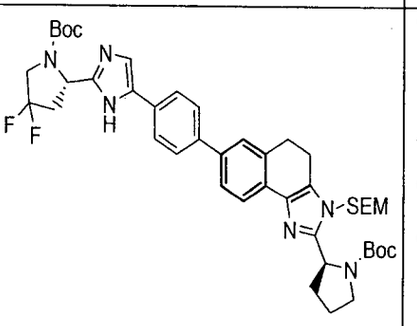
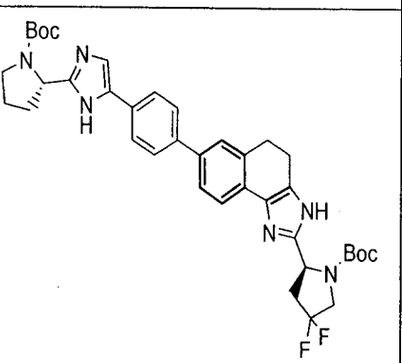
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Ejemplo 17r.1 (Derivado del Ejemplo 16h y Ejemplo 10a.3)		TR = 1,73 minutos (condición 1); LRMS: Análisis calculado para $C_{41}H_{50}F_3N_6O_4$ 747,38; encontrado: 747,46 (M+H).
Ejemplo 17r.2 (Derivado del Ejemplo 16g y Ejemplo 10a.5)		TR = 2,17 minutos (condición 2); LRMS: Análisis calculado para $C_{40}H_{47}N_6O_4$ 675,37; encontrado: 675,39 (M+H). HRMS: Análisis calculado para $C_{40}H_{47}N_6O_4$ 675,3653; encontrado: 675,3680 (M+H).
Ejemplo 17r.3 (Derivado del Ejemplo 16i y Ejemplo 10a.5)		TR = 1,72 minutos (condición 1). HRMS: Análisis calculado para $C_{42}H_{48}F_3N_6O_4$ 757,3684; encontrado: 757,3684 (M+H).
Ejemplo 17r.4 (Derivado del Ejemplo 16j y Ejemplo 10a.3)		TR = 2,21 minutos (condición 2); LRMS: Análisis calculado para $C_{40}H_{49}N_6O_4$ 677,38; encontrado: 677,36 (M+H). HRMS: Análisis calculado para $C_{40}H_{49}N_6O_4$ 677,3810; encontrado:

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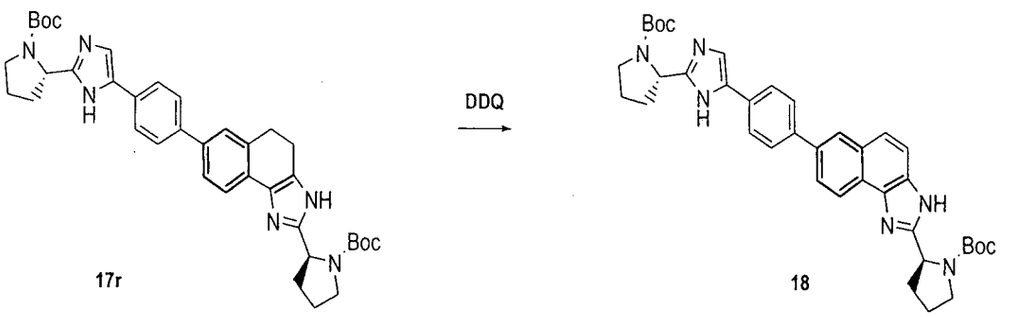
		677,3803 (M+H).
Ejemplo 17r.5 (Derivado del Ejemplo 16k y Ejemplo 10a.5)		TR = 2,25 minutos (condición 2); LRMS: Análisis calculado para $C_{42}H_{49}N_6O_4$ 701,38; encontrado: 701,36 (M+H). HRMS: Análisis calculado para $C_{42}H_{49}N_6O_4$ 701,3810; encontrado: 701,3798 (M+H).
Ejemplo 17r.6 (Derivado del Ejemplo 16j y Ejemplo 11a)		TR = 2,21 minutos (condición 2); LRMS: Análisis calculado para $C_{43}H_{47}N_6O_4$ 711,37; encontrado: 711,52 (M+H).
Ejemplo 17r.7 (Derivado del Ejemplo 16k y Ejemplo 11b)		TR = 2,06 minutos (condición 2); LRMS: Análisis calculado para $C_{45}H_{47}N_6O_4$ 735,37; encontrado: 735,38 (M+H).
Ejemplo 17s (Derivado del Ejemplo 16e y Ejemplo 10a.3)		TR = 2,31 minutos (condición 2); LRMS: Análisis calculado para $C_{38}H_{46}FN_6O_4$ 669,36; encontrado: 669,60 (M+H).

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Ejemplo 17s.1 (Derivado del Ejemplo 16e,1 y Ejemplo 10a.5)		TR = 2,22 minutos (condición 2); LRMS: Análisis calculado para $C_{40}H_{46}FN_6O_4$ 693,36; encontrado: 693,36 (M+H). HRMS: Análisis calculado para $C_{40}H_{46}FN_6O_4$ 693,3559; encontrado: 693,3584 (M+H).
Ejemplo 17s.2 (Derivado del Ejemplo 16e.1 y Ejemplo 11b)		TR = 2,2 minutos (condición 2); LRMS: Análisis calculado para $C_{43}H_{44}FN_6O_4$ 727,34; encontrado: 727,35 (M+H).
Ejemplo 17t (Derivado del Ejemplo 16a y Ejemplo 11)		TR = 2,71 minutos (condición 2); LRMS: Análisis calculado para $C_{44}H_{59}F_2N_6O_5Si$ 817,42; encontrado: 817,71 (M+H).
Ejemplo 17t.1 (Derivado del Ejemplo 16 y Ejemplo 10a.4)		TR = 2,25 minutos (condición 2); HRMS: Análisis calculado para $C_{38}H_{45}F_2N_6O_4$ 687,3465; encontrado: 687,3497 (M+H).

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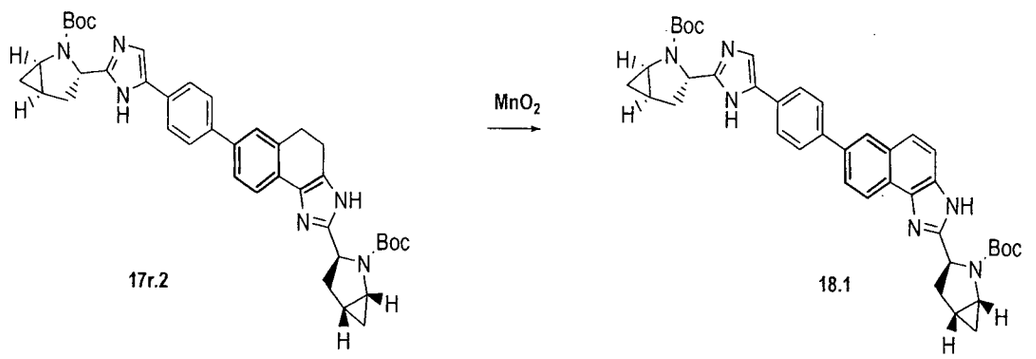
Ruta sintética 10.



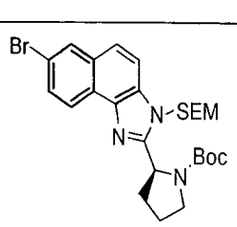
Se añadió DDQ (116 mg, 0,51 mmol) a una solución de Ejemplo 17r 2-(7-(4-(5-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-2-il)fenil)-4,5-dihidro-1H-nafto[1,2d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (332 mg, 0,51 mmol) en benceno (5 ml) en atmósfera de nitrógeno y la mezcla marrón oscuro se calentó a reflujo durante 2 horas. El disolvente se eliminó a vacío y el residuo se cargó (CH_2Cl_2) a una columna de gel de sílice 25 (M) Biotage. Segmento 1; Gradiente eluido desde 50-100% de B durante 720 ml (A = CH_2Cl_2; B = 20% CH_3OH en CH_2Cl_2) Segmento 2; Gradiente eluido desde 0-50% de B durante 720 ml (A = CH_2Cl_2; B = CH_3OH) dio el Ejemplo 18, 261 mg (79%). RMN de ^1H (500 MHz, DMSO-d_6) δ 8,46 (s ancho, 1H), 8,31 (s, 1H), 7,95-7,55 (m, 8H), 5,1-4,8 (rotámeros, 2H), 3,67 (s ancho, 1H), 3,57 (s ancho, 1H), 3,48-3,47 (m, 1H), 3,39 - 3,38 (m, 1H), 2,42-1,89 (m, 8H), 1,42/1,18 (s, 9H). TR = 2,24 minutos (condición 2). LRMS: Análisis calculado para $C_{38}H_{44}N_6O_4$: 649,35; encontrado: 649,65 (M+H).

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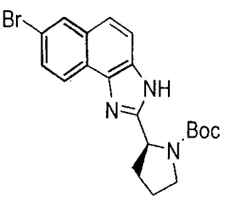
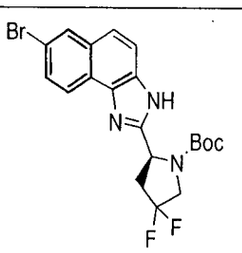
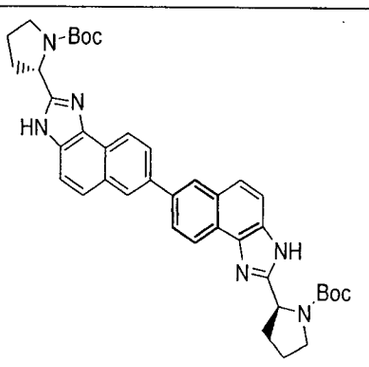
Ruta sintética 10a.



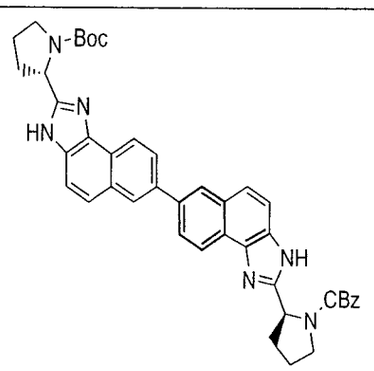
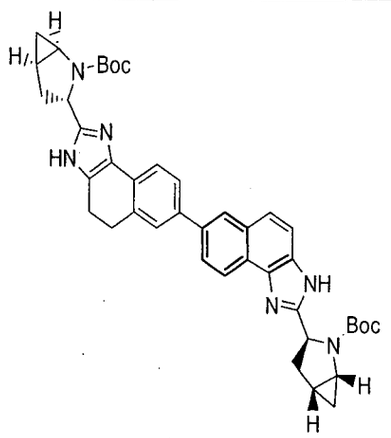
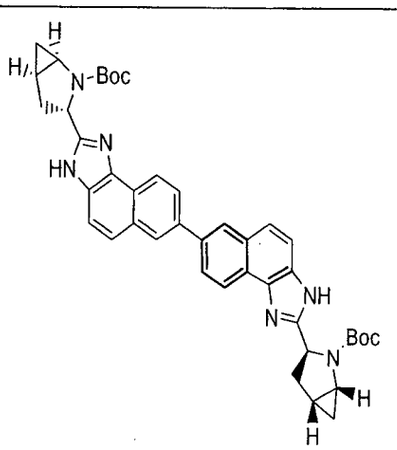
Se añadió MnO_2 activado (77 mg, 0,889 mmol) en una porción a una solución agitada del Ejemplo 17r.2 (200 mg, 0,296 mmol) en CH_2Cl_2 seco (2 ml) y la suspensión se agitó durante. Se añadió más MnO_2 (300 mg) y la mezcla se agitó 16h. Esta secuencia se repitió hasta que la LCMS reveló que no quedaba material de partida. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®), se concentró y se secó a alto vacío durante 1 hora dando Ejemplo 18,1 (185,8 mg, 92 %) como un sólido amarillento-naranja. LCMS: TR = 2,24 minutos, Calculado para $C_{40}H_{45}N_6O_4$ 673,35; encontrado: 673,36 (M+H). HRMS: Calculado para $C_{40}H_{45}N_6O_4$ 673,3497; encontrado: 673,3525 (M+H).

Ejemplo 18a (Derivado del Ejemplo 11)		TR = 3,5 minutos (condición 2); LCMS: Análisis calculado para $C_{26}H_{37}BrN_3O_3Si$ 546,18; encontrado:

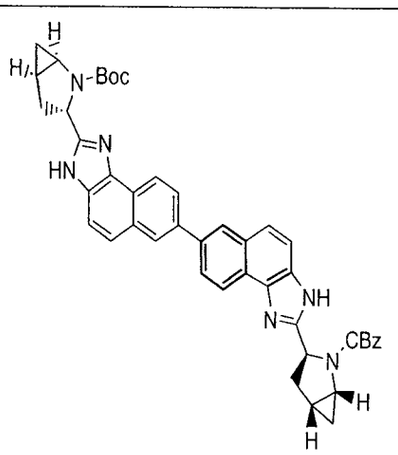
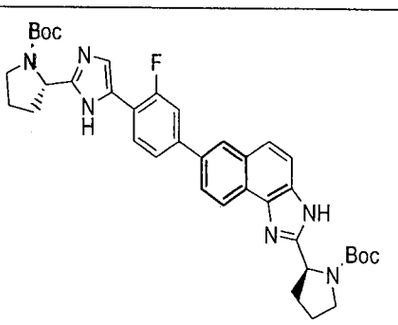
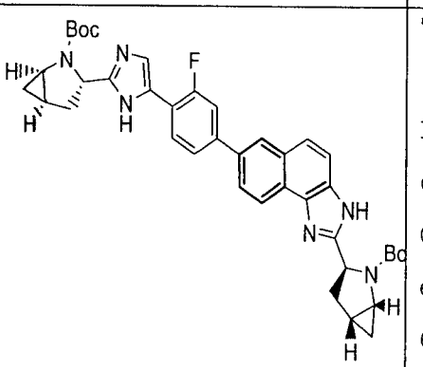
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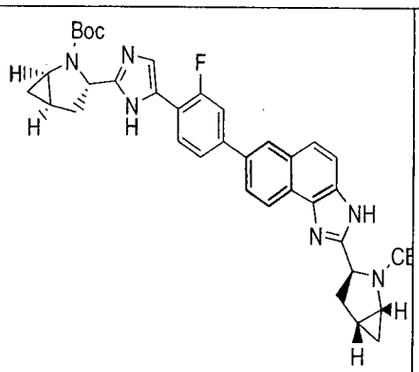
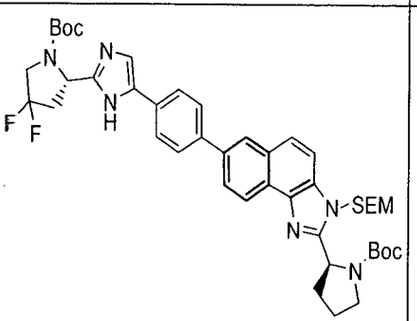
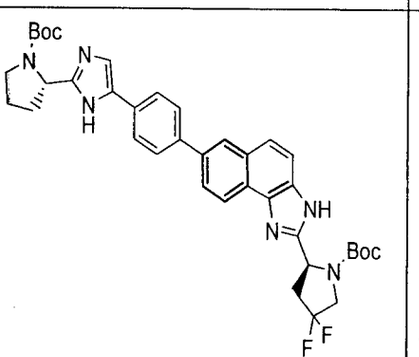
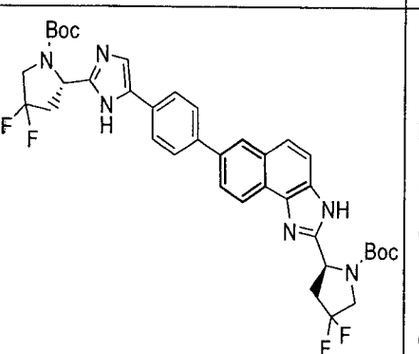
		546,21 (M+H).
Ejemplo 18b (Derivado del Ejemplo 10a.3)		TR = 2,74 minutos (condición 2); LCMS: Análisis calculado para $C_{20}H_{23}BrN_3O_2$ 416,08; encontrado: 416,08 (M+H).
Ejemplo 18b.1 (Derivado del Ejemplo 10a.4)		TR = 2,62 minutos (condición 2); LCMS: Análisis calculado para $C_{20}H_{21}BrF_2N_3O_2$ 454,08 y 452,08; encontrado: 454,01 y 454,01 (M+H).
Ejemplo 18b.2 (Derivado del Ejemplo 17r.4)		TR = 2,28 minutos (condición 2); LRMS: Análisis calculado para $C_{40}H_{45}N_6O_4$ 673,35; encontrado: 673,36 (M+H). HRMS: Análisis calculado para $C_{40}H_{45}N_6O_4$ 673,3497; encontrado: 673,3498 (M+H).

537

Ejemplo 18b.3 (Derivado del Ejemplo 17r.6)		TR = 2,30 minutos (condición 2); LRMS: Análisis calculado para $C_{43}H_{43}N_6O_4$ 707,34; encontrado: 707,52 (M+H).
Ejemplo 18b.4 (Derivado del Ejemplo 17r.5)		Ejemplo no caracterizado.
Ejemplo 18b.5 (Derivado del Ejemplo 17r.5)		TR = 2,32 minutos (condición 2); LRMS: Análisis calculado para $C_{42}H_{45}N_6O_4$ 697,35; encontrado: 697,36 (M+H). HRMS: Análisis calculado para $C_{42}H_{45}N_6O_4$ 697,3497; encontrado: 697,3488 (M+H).

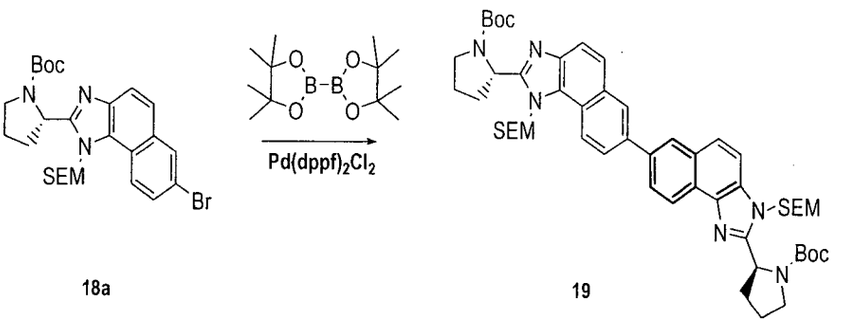
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Ejemplo 18b.6 (Derivado del Ejemplo 17r.7)		TR = 2,13 minutos (condición 2); LRMS: Análisis calculado para $C_{45}H_{43}N_6O_4$ 731,34; encontrado: 731,32 (M+H).
Ejemplo 18c (Derivado del Ejemplo 17s)		TR = 2,3 minutos (condición 2). HRMS: Análisis calculado para $C_{38}H_{44}FN_6O_4$ 667,3403; encontrado: 667,3419 (M+H).
Ejemplo 18c.1 (Derivado del Ejemplo 17s.1)		TR = 2,29 minutos (condición 2); LRMS: Análisis calculado para $C_{40}H_{44}FN_6O_4$ 691,34; encontrado: 691,33 (M+H). HRMS: Análisis calculado para $C_{40}H_{44}FN_6O_4$ 691,3403; encontrado: 691,3420 (M+H).

Ejemplo 18c.2 (Derivado del Ejemplo 17s.2)		TR = 2,05 minutos (condición 2); LRMS: Análisis calculado para $C_{43}H_{42}FN_6O_4$ 725,32; encontrado: 725,25 (M+H).
Ejemplo 18d (Derivado del Ejemplo 17t)		TR = 2,87 minutos (condición 2); HRMS: Análisis calculado para $C_{44}H_{57}F_2N_6O_4Si$ 815,4122; encontrado: 815,4149 (M+H).
Ejemplo 18e (Derivado del Ejemplo 17t.1)		TR = 2,34 minutos (condición 2); HRMS: Análisis calculado para $C_{38}H_{43}F_2N_6O_4$ 685,3308; encontrado: 685,3342 (M+H).
Ejemplo 18f (Derivado de los Ejemplos 16a y 18b.1 de acuerdo con el procedimiento descrito para Ejemplo 17)		TR = 2,34 minutos (condición 2); HRMS: Análisis calculado para $C_{38}H_{41}F_4N_6O_4$ 721,3120; encontrado: 721,3128 (M+H).

540

Ruta sintética 11

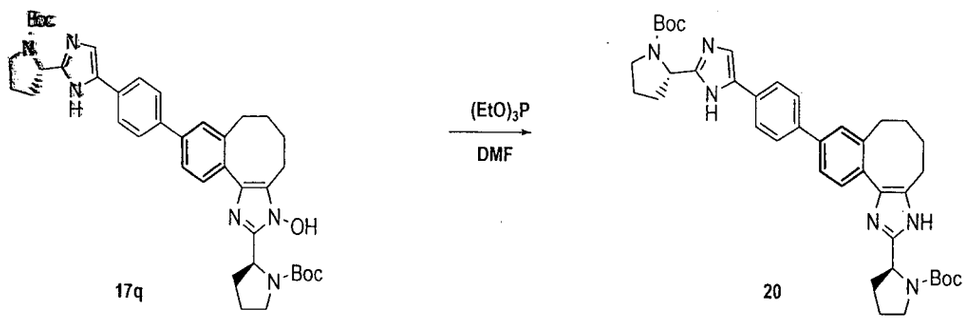


18a 19

Se añadió complejo de [1,1'-Bis(difenilfosfino)ferroceno)-dicloropaladio (ii) con diclorometano (11,2 mg, 0,014 mmol) a una solución agitada de Ejemplo 18a (150 mg, 0,274 mmol), diborano (34,8 mg, 0,137 mmol), dppf (7,61 mg, 0,014 mmol) y K_2CO_3 (114 mg, 0,823 mmol) en DMSO (2,5 ml) en atmósfera de argon en un recipiente a presión con tapón tipo rosca. La solución se cubrió totalmente con argon y se sumergió en un baño de aceite previamente calentado a 80 °C y se agitó 18 horas. La mezcla se enfrió, se diluyó con EtOAc y se lavó con solución saturada de $NaHCO_3$, salmuera y se secó (Na_2SO_4) y filtró. El disolvente se eliminó a vacío y el residuo se cargó (CH_2Cl_2) a una columna de gel de sílice 25 (M) Biotage: Segmento 1. 10% de B durante 75 ml; Segmento 2. Gradiente eluido desde 10-100% de B durante 1,8 L; (A = Hexanos; B = EtOAc) dio el Ejemplo 19, 88,7 mg (33%). RMN de ^1H (500 MHz, DMSO-d_6) δ 8,56-8,54 (m, 2H), 8,48 (s, 2H), 8,12-8,10 (m, 2H), 7,95-7,91 (m, 4H), 5,83-5,76 (m, 4H), 5,30-5,22 (m, 2H), 3,72-3,61 (m, 4H), 3,53 (t, *J* = 7,3 Hz, 4H), 2,44-2,18 (m, 4H) 2,11-2,08

(m, 2H), 2,0-1,94 (m, 2H), 1,38/1,08 (s, 18H), 0,91-0,81 (m, 4H), -0,06 (s, 18H). TR = 3,2 minutos (condición 2); HRMS: Análisis calculado para $C_{52}H_{73}N_6O_6Si_2$ 933,5125; encontrado: 933,5132 $(M+H)^+$.

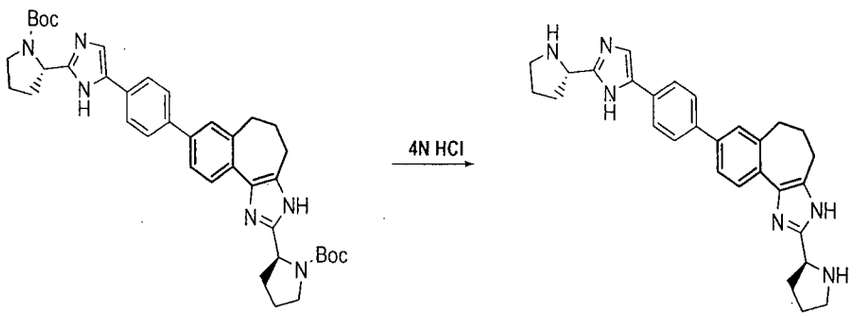
Ruta sintética 12



Se añadió trietilfosfito (0,257 ml, 1,48 mmol) al Ejemplo 17q, (340 mg, 0,489 mmol) en DMF (5 ml) y se agitó a 80°C durante 16 horas. Se añadió más trietilfosfito (0,3 ml y 0,6 ml) a intervalos de 8 horas hasta que se completó la reacción indicado por LCMS. El disolvente se eliminó a vacío y el residuo se cargó (CH_2Cl_2) en una columna de gel de sílice 25 (M) Biotage. Segmento 1. 0% de B durante 300 ml; Segmento 2. Gradiente eluido desde 0-50% de B durante 1440 ml; Segmento 3. Gradiente eluido 50-100% de B durante 600 ml (A = CH_2Cl_2; B = 20% CH_3OH en CH_2Cl_2) dio el Ejemplo 20, 286 mg (82%). RMN de ^1H (500 MHz, DMSO-d_6) δ 7,84-7,80 (m, 8H), 4,87-4,68 (m, 2H), 3,55-3,54 (m, 2H), 3,40-3,30 (m, 6H), 2,82-2,76 (m, 2H), 2,25-1,82 (m, 8H), 1,63-1,57 (m, 2H), 1,42/1,18 (s, 9H). TR = 2,32 minutos (condición 2); LRMS: Análisis calculado para $C_{40}H_{51}N_6O_4$ 679,40; encontrado: 679,57 $(M+H)^+$.

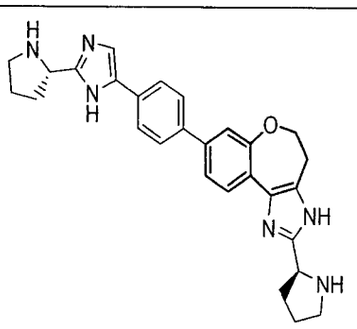
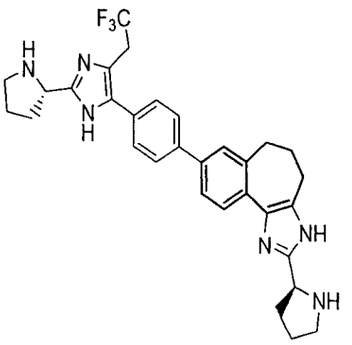
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Ruta sintética 13

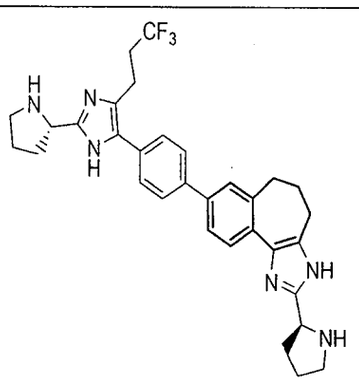
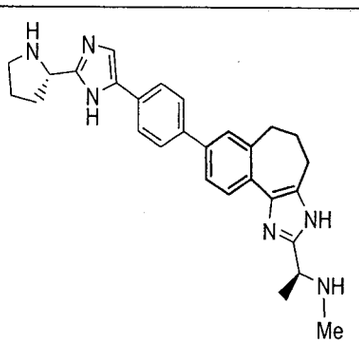
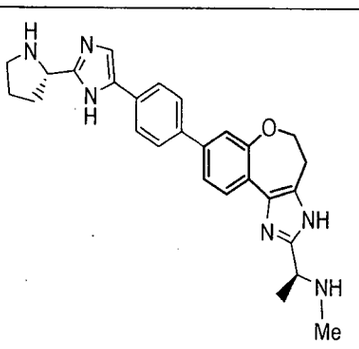
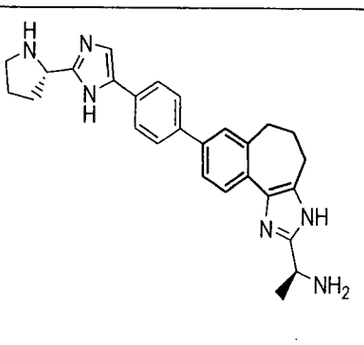
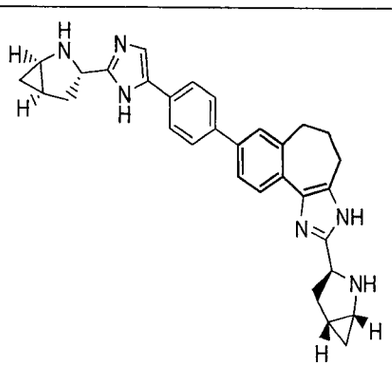


17 21

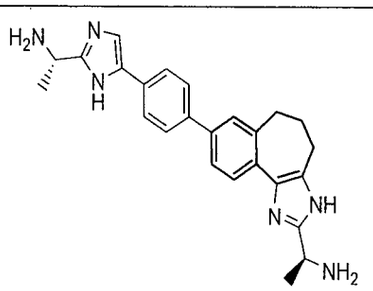
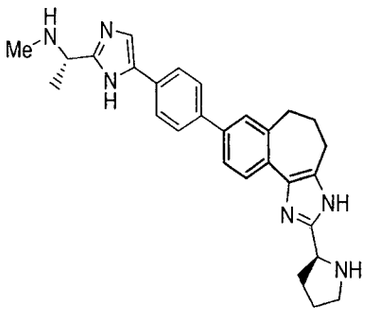
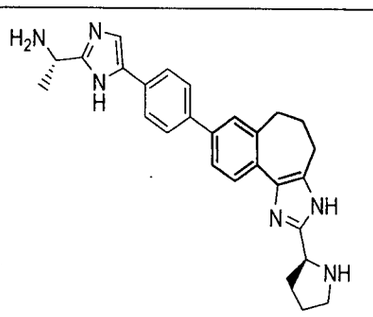
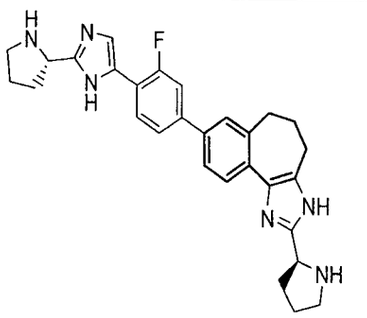
El Ejemplo 17, (411 mg, 0,62 mmol) se disolvió en CH_3OH (20 ml) y se añadió HCl/Dioxano (100 ml de 4N) y la reacción se agitó 4 hr. Los disolventes se eliminaron a vacío y se expuso la sal tetra HCl a alto vacío durante 18 horas dando el Ejemplo 21, 350 mg (94%) como una sal HCl que se usó sin purificación adicional. TR = 1,3 minutos (condición 1). LCMS: Análisis calculado para $C_{29}H_{33}N_6$: 465; encontrado: 465 (M+H).

Ejemplo 21a (Derivado del Ejemplo 17a)		TR = 2,99 minutos (condición 2); LCMS: Análisis calculado para $C_{37}H_{46}N_6O_5$: 466,57; encontrado: 467,2,2 (M+H).
Ejemplo 21a.1 (Derivado del Ejemplo 17a.1)		TR = 1,4 minutos (condición 1); LCMS: Análisis calculado para $C_{31}H_{34}F_3N_6$ 547,28; encontrado: 547,19 (M+H).

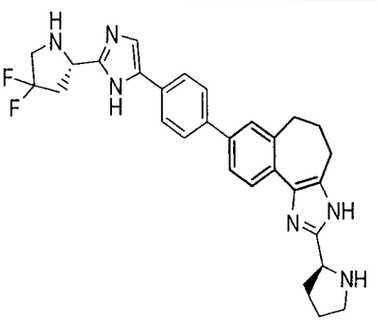
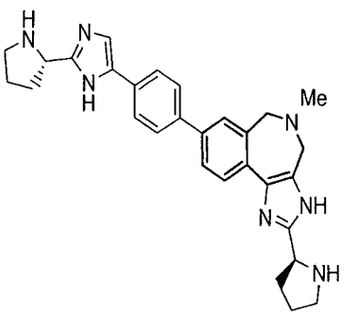
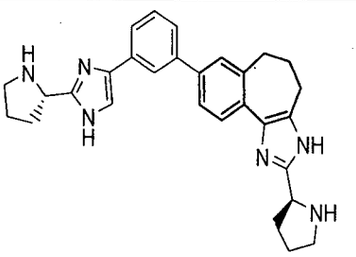
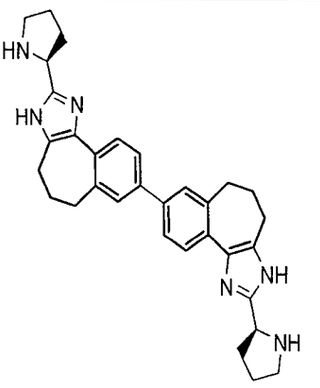
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Ejemplo 21a.2 (Derivado del Ejemplo 17a.2)		TR = 1,4 minutos (condición 1); LCMS: Análisis calculado para $C_{32}H_{36}F_3N_6$: 561,29; encontrado: 561,36 (M+H).
Ejemplo 21b (Derivado del Ejemplo 17b)		TR = 1,3 minutos (condición 1); LCMS: Análisis calculado para $C_{28}H_{32}N_6$ 452; encontrado: 452 (M+H).
Ejemplo 21b.1 (Derivado del Ejemplo 17b.1)		TR = 1,2 minutos (condición 2); LCMS: Análisis calculado para $C_{37}H_{46}N_6O_5$: 454,25; encontrado: 455,2 (M+H).
Ejemplo 21c (Derivado del Ejemplo 17c)		TR = 1,3 minutos (condición 1); LCMS: Análisis calculado para $C_{27}H_{30}N_6$ 438; encontrado: 438 (M+H).
Ejemplo 21c.1 (Derivado del Ejemplo 17c.1)		TR = 1,2 minutos (condición 1); LCMS: Análisis calculado para $C_{31}H_{33}N_6$ 489,28; encontrado: 489,28 (M+H).

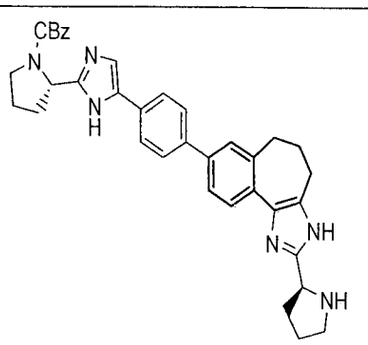
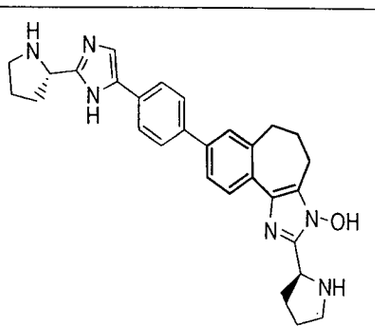
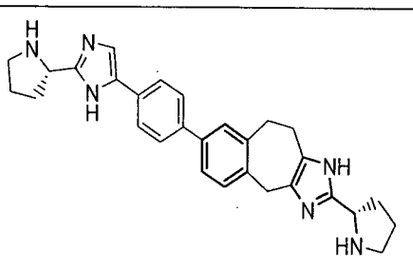
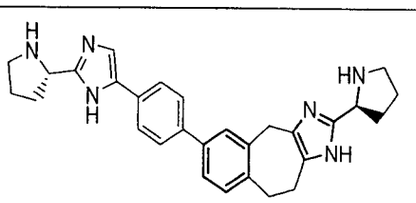
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Ejemplo 21d (Derivado del Ejemplo 17d)		TR = 1,2 minutos (condición 1); LCMS: Análisis calculado para $C_{25}H_{28}N_6$ 412; encontrado: 412 (M+H).
Ejemplo 21e (Derivado del Ejemplo 17e)		TR = 1,4 minutos (condición 1); LCMS: Análisis calculado para $C_{28}H_{32}N_6$ 452; encontrado: 452 (M+H).
Ejemplo 21f (Derivado del Ejemplo 17f)		TR = 1,2 minutos (condición 1); LCMS: Análisis calculado para $C_{27}H_{30}N_6$ 438; encontrado: 438 (M+H).
Ejemplo 21g (Derivado del Ejemplo 17g)		TR = 1,3 minutos (condición 1); LCMS: Análisis calculado para $C_{29}H_{31}FN_6$ 483; encontrado: 483 (M+H).

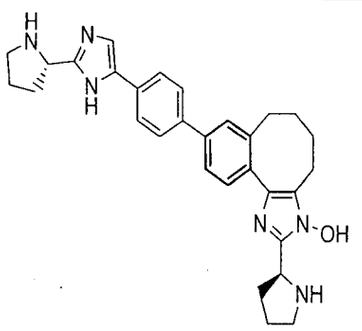
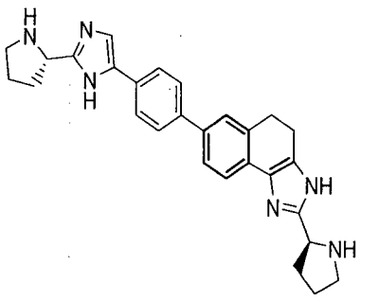
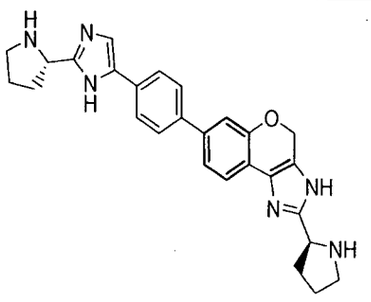
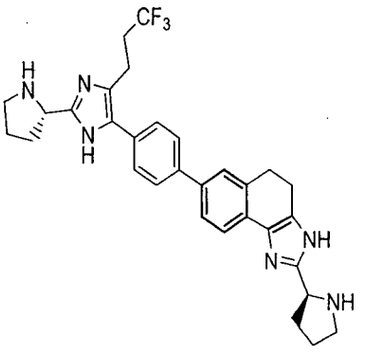
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Ejemplo 21h (Derivado del Ejemplo 17h)		TR = 1,7 minutos (condición 2); LCMS: Análisis calculado para $C_{29}H_{31}F_2N_6$ 501,25; encontrado: 501,51 (M+H).
Ejemplo 21i (Derivado del Ejemplo 17i)		TR = 1,5 minutos (condición 2); LRMS: Análisis calculado para $C_{29}H_{34}N_7$ 480,28; encontrado: 480,26 (M+H).
Ejemplo 21j (Derivado del Ejemplo 17j)		TR = 1,3 minutos (condición 1); LRMS: Análisis calculado para $C_{29}H_{32}N_6$ 464; encontrado: 464 (M+H).
Ejemplo 21k (Derivado del Ejemplo 17k)		TR = 1,3 minutos (condición 1); LCMS: Análisis calculado para $C_{32}H_{36}N_6$ 505; encontrado: 505 (M+H).

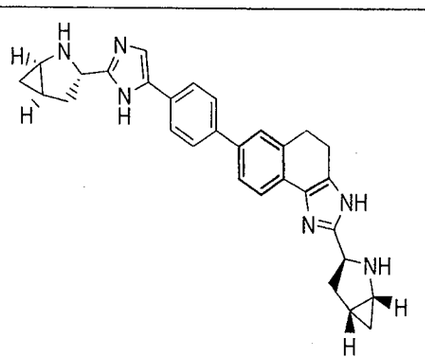
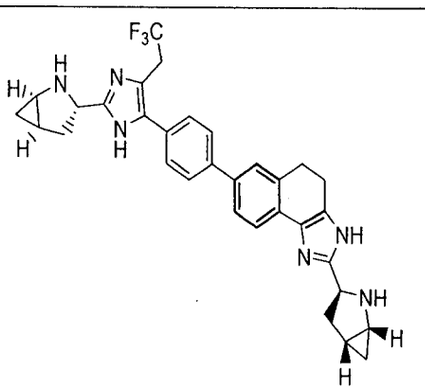
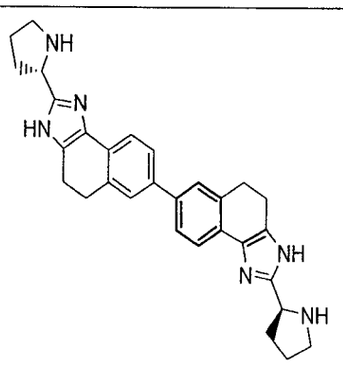
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Ejemplo 21m (Derivado del Ejemplo 17m)		TR = 1,5 minutos (condición 1); LRMS: Análisis calculado para $C_{37}H_{38}N_6O_2$ 598; encontrado: 598 (M+H).
Ejemplo 21n (Derivado del Ejemplo 17n)		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{29}H_{33}N_6O$ 481,26; encontrado: 481,37 (M+H).
Ejemplo 21o (Derivado del Ejemplo 17o)		TR = 2,1 minutos (condición 1) LCMS: Análisis calculado para $C_{29}H_{32}N_6$ 464; encontrado: 464 (M+H).
Ejemplo 21p (Derivado del Ejemplo 17p)		TR = 2,0 minutos (condición 1) LCMS: Análisis calculado para $C_{29}H_{32}N_6$ 464; encontrado: 464 (M+H).

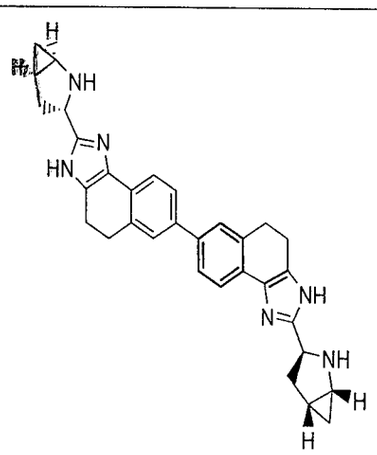
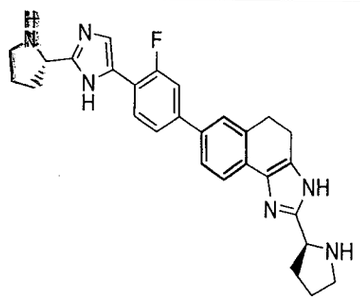
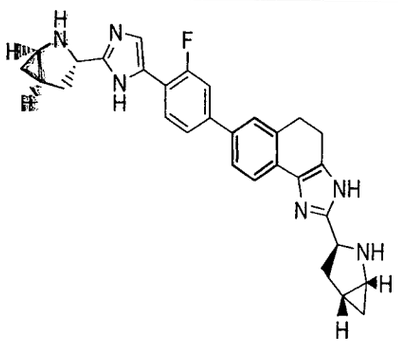
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Ejemplo 21q (Derivado del Ejemplo 17q)		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{30}H_{35}N_6O$ 495,28; encontrado: 495,37 $(M+H)$.
Ejemplo 21r (Derivado del Ejemplo 17r)		TR = 1,5 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{30}N_6$ 451,26; encontrado: 451,33 $(M+H)^+$.
Ejemplo 21r.a (Derivado del Ejemplo 17r.a)		TR = 1,1 minutos (condición 1); LCMS: Análisis calculado para $C_{37}H_{44}N_6O_5$: 452,18; encontrado: 453,2 $(M+H)$.
Ejemplo 21r.1 (Derivado del Ejemplo 17r.1)		TR = 1,4 minutos (condición 1) LCMS: Análisis calculado para $C_{31}H_{34}F_3N_6$ 547,28; encontrado: 547,26 $(M+H)^+$.

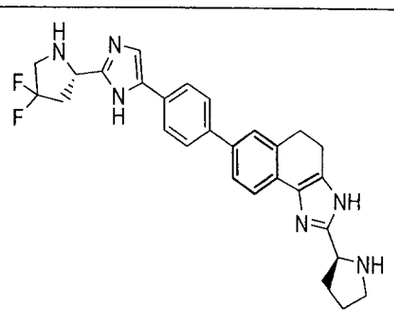
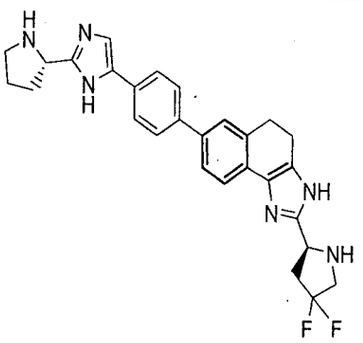
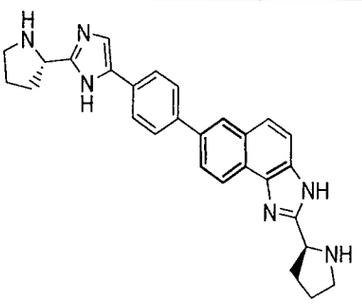
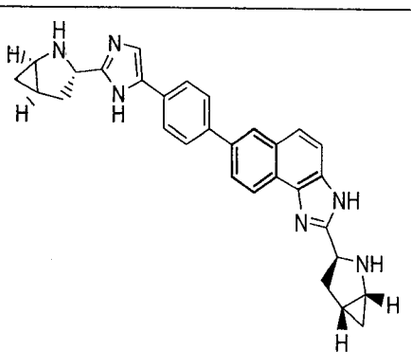
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Ejemplo 21r.2 (Derivado del Ejemplo 17r.2)		TR = 1,46 min, (condición 2), LCMS: Anal. Calculado para $C_{30}H_{31}N_6$ (M+H) 475,26; encontrado: 475,25. HRMS: Anal. Calculado para $C_{30}H_{31}N_6$ 475,2605; encontrado: 475,2616 (M+H).
Ejemplo 21r.3 (Derivado del Ejemplo 17r.3)		TR = 1,4 minutos (condición 1) LCMS: Análisis calculado para $C_{32}H_{32}F_3N_6$ 557,26; encontrado: 557,22 (M+H).
Ejemplo 21r.4 (Derivado del Ejemplo 17r.4)		TR = 1,43 minutos (condición 2) LCMS: Análisis calculado para $C_{30}H_{33}N_6$ 477,28; encontrado: 477,22 (M+H). HRMS: Calculado para $C_{30}H_{33}N_6$ 477,2761; encontrado 477,2765 (M+H).

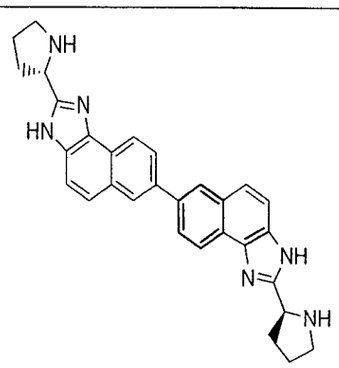
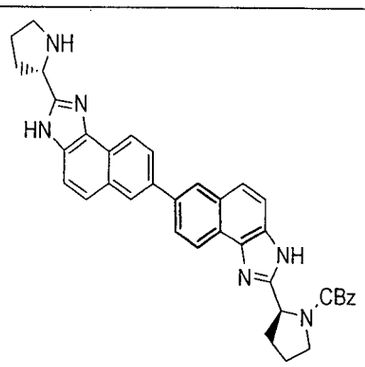
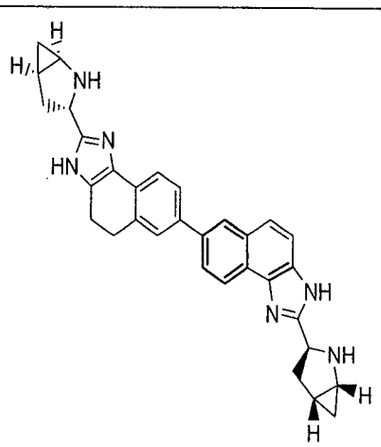
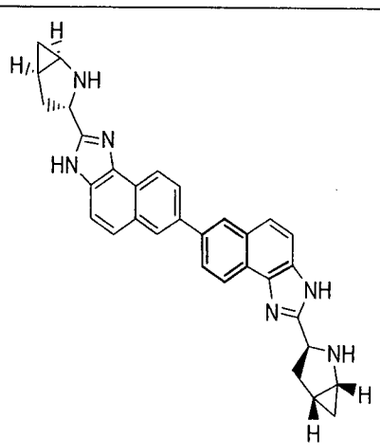
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Ejemplo 21r.5 (Derivado del Ejemplo 17r.5)		TR = 1,56 minutos (condición 2) LCMS: Análisis calculado para $C_{32}H_{33}N_6$ 501,28; encontrado: 501,29 (M+H). HRMS: Calculado para $C_{32}H_{33}N_6$ 501,2761; encontrado 501,2761 (M+H).
Ejemplo 21s (Derivado del Ejemplo 17s)		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{30}FN_6$ 469,25; encontrado: 469,47 $(M+H)^+$.
Ejemplo 21s.1 (Derivado del Ejemplo 17s.1)		TR = 1,62 min, (condición 2), LCMS: Anal. Calculado para $C_{30}H_{30}FN_6$ 493,25; encontrado: 493,28 (M+H). HRMS: Calculado para $C_{30}H_{30}FN_6$ 493,2511; encontrado 493,2520 (M+H).

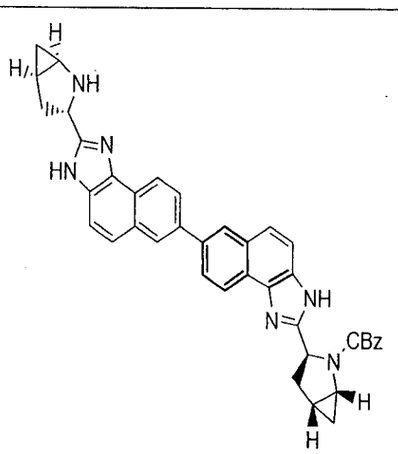
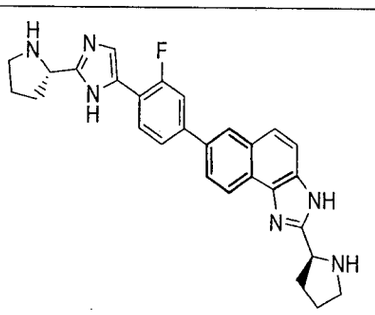
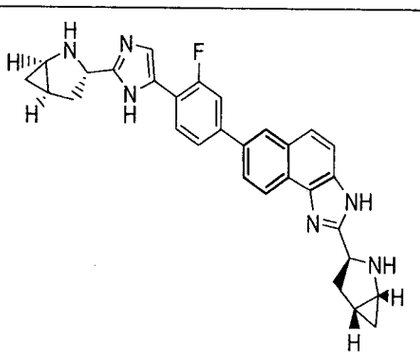
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Ejemplo 21t (Derivado del Ejemplo 17t)		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{29}F_2N_6$ 487,23; encontrado: 487,51 (M+H).
Ejemplo 21t.1 (Derivado del Ejemplo 17t.1)		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{29}F_2N_6$ 487,24; encontrado: 487,51 (M+H).
Ejemplo 21u (Derivado del Ejemplo 18)		TR = 1,6 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{29}N_6$ 449,25; encontrado: 449,46 (M+H).
Ejemplo 21u.1 (Derivado del Ejemplo 18.1)		TR = 1,61 min, (condición 2), LCMS: Anal. Calculado para $C_{30}H_{29}N_6$ 473,36; encontrado: 473,28 (M+H). HRMS: Análisis calculado para $C_{30}H_{29}N_6$ 473,2448; encontrado: 473,2457 (M+H).

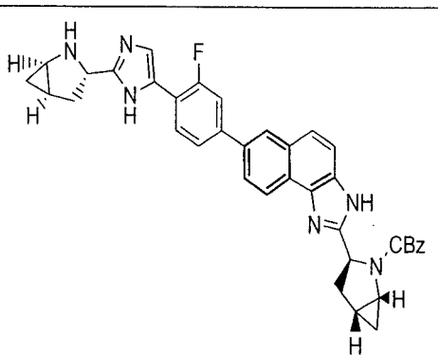
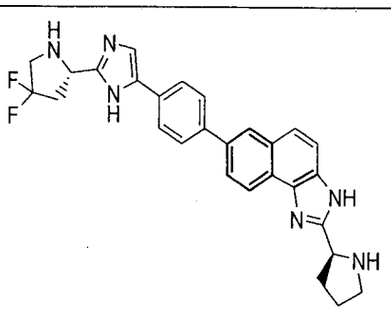
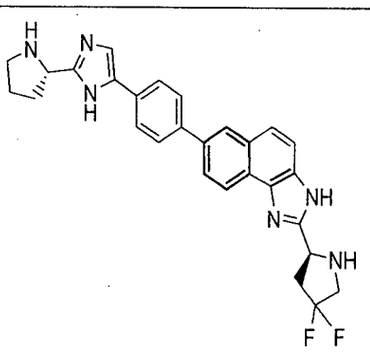
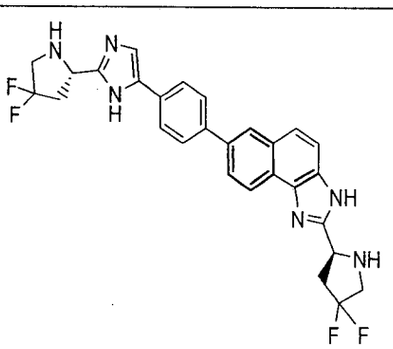
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Ejemplo 21u.2 (Derivado del Ejemplo 18b.2)		Véase el Ejemplo 21x más adelante para la caracterización.
Ejemplo 21u.3 (Derivado del Ejemplo 18b.3)		TR = 2,10 min, (condición 2), LCMS: Anal. Calculado para $C_{38}H_{35}N_6O_2$ 607,46; encontrado: 607,46 (M+H).
Ejemplo 21u.4 (Derivado del Ejemplo 18b.4)		Ejemplo no caracterizado.
Ejemplo 21u.5 (Derivado del Ejemplo 18b.5)		TR = 1,82 minutos (condición 2); LRMS: Análisis calculado para $C_{32}H_{29}N_6$ 497,25; encontrado: 497,29 (M+H). HRMS: Calculado para $C_{32}H_{29}N_6$ 497,2448; encontrado 497,2448 (M+H).

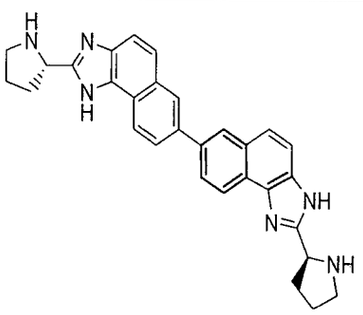
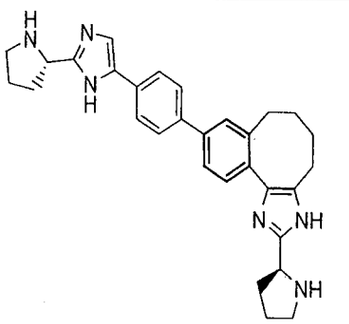
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Ejemplo 21u.6 (Derivado del Ejemplo 18b.6)		TR = 1,91 min (condición 2); LCMS: Análisis calculado para $C_{40}H_{35}N_6O_2$ 631,28; encontrado: 631,27 (M+H).
Ejemplo 21v (Derivado del Ejemplo 18c)		TR = 1,8 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{28}FN_6$ 467,24; encontrado: 467,43 (M+H).
Ejemplo 21v.1 (Derivado del Ejemplo 18c.1)		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{30}H_{28}FN_6$ 491,24; encontrado: 491,25 (M+H). HRMS: Calculado para $C_{30}H_{28}FN_6$ 491,2354; encontrado 491,2364 (M+H).

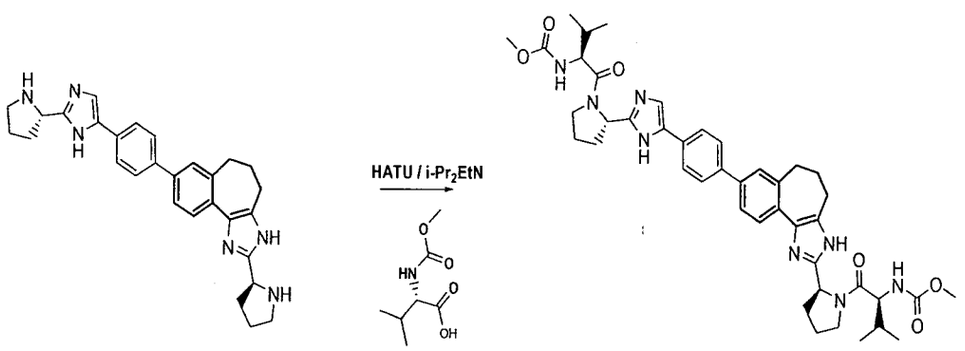
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Ejemplo 21v.2 (Derivado del Ejemplo 18c.2)		TR = 1,76 minutos (condición 2) LCMS: Análisis calculado para $C_{38}H_{34}FN_6O_2$ 625,27; encontrado: 625,19 (M+H).
Ejemplo 21w (Derivado del Ejemplo 18d)		TR = 1,9 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{27}F_2N_6$ 485,23; encontrado: 485,46 (M+H).
Ejemplo 21w.1 (Derivado del Ejemplo 18e)		TR = 1,8 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{27}F_2N_6$ 485,23; encontrado: 485,30 (M+H).
Ejemplo 21w.2 (Derivado del Ejemplo 18f)		TR = 2,3 minutos (condición 2) LCMS: Análisis calculado para $C_{28}H_{25}F_4N_6$ 521,21; encontrado: 521,28 (M+H).

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Ejemplo 21x (Derivado del Ejemplo 19) NOTA: Mismo que el Ejemplo 21u.2		TR = 1,7 minutos (condición 2) LCMS: Análisis calculado para $C_{30}H_{29}N_6$ 473,24; encontrado: 473,27 (M+H).
Ejemplo 21x.1 (Derivado del Ejemplo 20)		TR = 1,6 minutos (condición 2) LCMS: Análisis calculado para $C_{30}H_{35}N_6$ 479,29; encontrado: 479,39 (M+H).

Ruta sintética 14

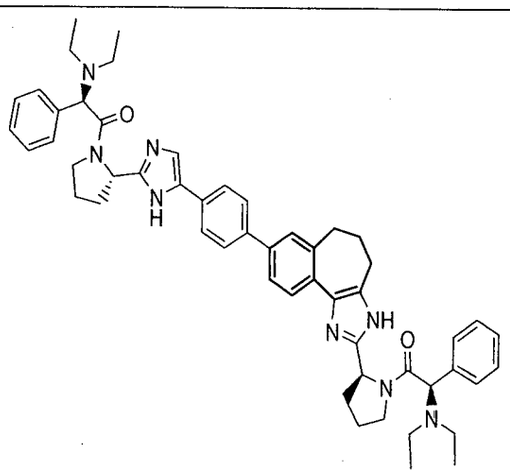


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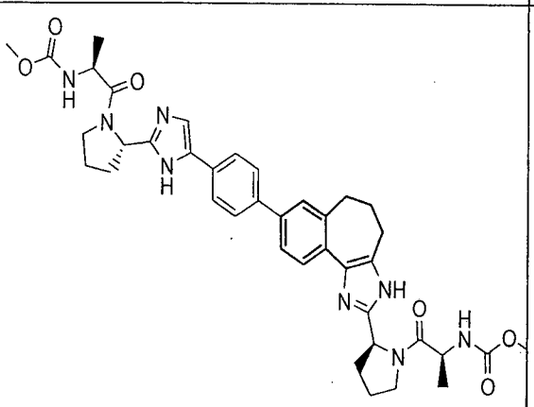
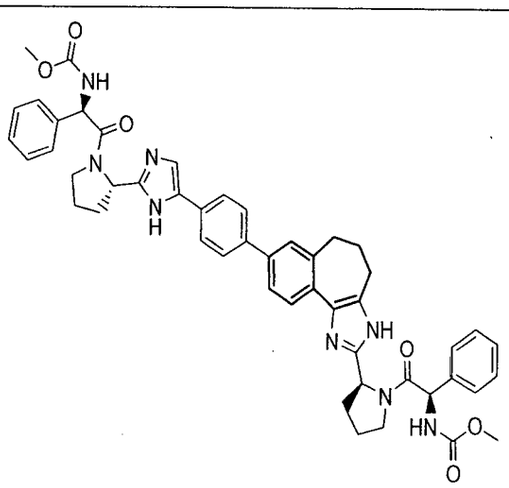
Se añadió HATU (88 mg, 0,33 mmol) y solución del Ejemplo 21 rápidamente agitada (87,5 mg, 0,145 mmol), Extremo-51: N-metoxicarbonil-L-valina (63,3 mg, 0,36 mmol) y base de Hunig (0,23 ml, 1,25 mmol) en DMF (3,5 ml). La mezcla de reacción se agitó 16 horas antes de diluir con CH_3OH (1 vol) y se sometió directamente a HPLC semipreparativa (4 inyecciones a 2 ml cada una; columna Dynamax 60A prep C8; 25% - 100% de B

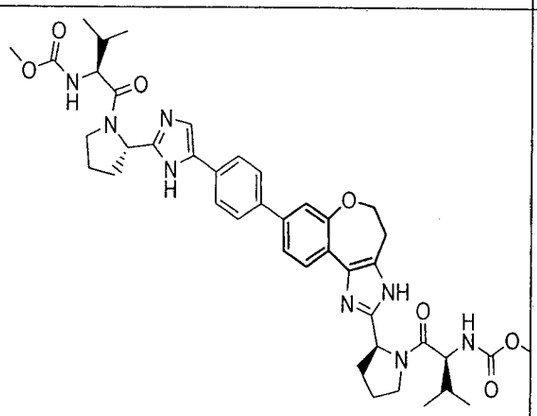
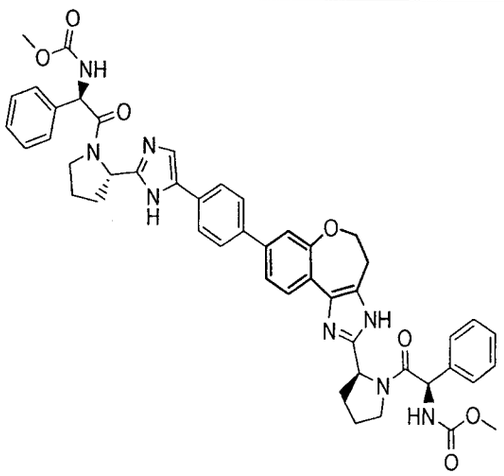
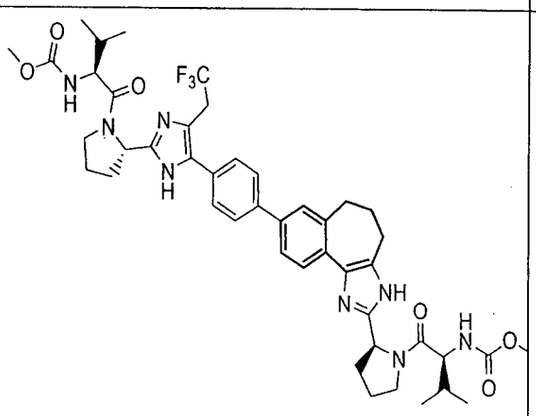
555

durante 30 min; Caudal = 20 ml/min; Longitud de onda = 220 nm; Disolvente A = 0,1% de TFA en metanol al 10%/H_2O al 90%; Disolvente B = 0,1% de TFA en metanol al 90%/H_2O al 10%) dando el Ejemplo 22, (sal TFA). RMN de ^1H (300 MHz, DMSO-d_6) δ 8,04-8,02 (m, 1H), 7,78-7,58 (m, 4H), 7,49-7,41(m, 3H), 7,30-7,24 (m, 2H), 5,09-5,01 (m, 2H), 4,1-4,03 (m, 2H), 3,81-3,79 (m, 4H), 3,54 (s, 6H), 2,92-2,84 (m, 4H), 2,17-2,09 (m, 4H), 2,00-1,87 (m, 8H), 0,79-0,81 (m, 12H). TR = 1,57 minutos (condición 1). LRMS: Análisis calculado para $C_{43}H_{55}N_8O_6$: 779,42; encontrado: 779,48 (M+H). HRMS: Análisis calculado para $C_{43}H_{55}N_8O_6$: 779,4245; encontrado: 779,4249 (M+H).

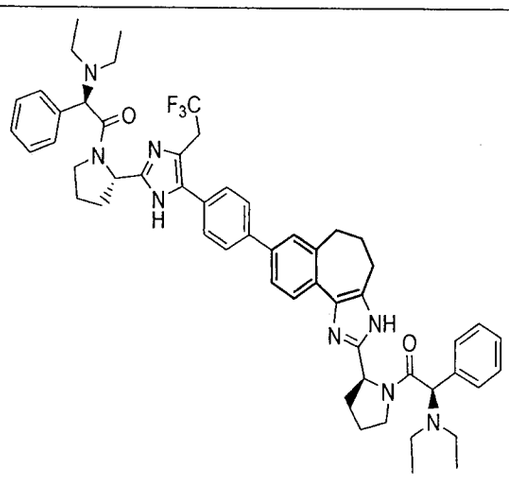
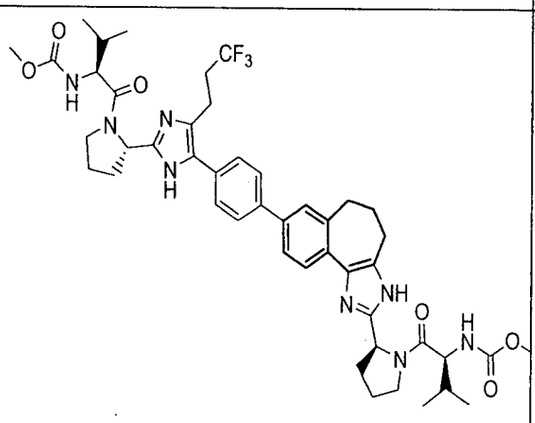
Ejemplo 22.1 (Derivado del Ejemplo 21 y Extremo-2)		TR = 1,4 minutos (condición 1); LRMS: Análisis calculado para $C_{53}H_{62}N_8O_2$ 843,51; encontrado: 843,89 (M+H). HRMS: Análisis calculado para $C_{53}H_{62}N_8O_2$ 843,5047; encontrado: 843,5099

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		(M+H).
Ejemplo 22.2 (Derivado del Ejemplo 21 y Extremo-52)		TR = 1,4 minutos (condición 1); LRMS: Análisis calculado para $C_{39}H_{46}N_8O_6$ 723,36; encontrado: 723,39 (M+H). HRMS: Análisis calculado para $C_{39}H_{46}N_8O_6$ 723,3619; encontrado: 723,3643 (M+H).
Ejemplo 22.3 (Derivado del Ejemplo 21 y Extremo-4)		TR = 1,7 minutos (condición 1); LRMS: Análisis calculado para $C_{49}H_{50}N_8O_6$ 723,39; encontrado: 723,40 (M+H). HRMS: Análisis calculado para $C_{49}H_{50}N_8O_6$ 847,3932;

		encontrado: 847,3953 (M+H).
Ejemplo 22a (Derivado del Ejemplo 21a y Extremo-51)		TR = 2,0 minutos (condición 4); LRMS: Análisis calculado para $C_{42}H_{53}N_8O_7$ 781,41; encontrado: 781,33 (M+H).
Ejemplo 22a.1 (Derivado del Ejemplo 21a y Extremo-4)		TR = 2,2 minutos (condición 4); LRMS: Análisis calculado para $C_{48}H_{49}N_8O_7$ 849,37; encontrado: 849,25 (M+H).
Ejemplo 22a.2 (Derivado del Ejemplo 21a.1 y Extremo-51)		TR = 1,6 minutos (condición 1); HRMS: Análisis calculado para $C_{45}H_{56}F_3N_8O_6$

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		861,4281; encontrado: 861,4269 (M+H).
Ejemplo 22a.3 (Derivado del Ejemplo 21a.1 y Extremo-2)		TR = 1,4 minutos (condición 1); HRMS: Análisis calculado para $C_{55}H_{64}F_3N_8O_2$ 925,5099; encontrado: 925,5096 (M+H).
Ejemplo 22a.4 (Derivado del Ejemplo 21a.2 y Extremo-51)		TR = 1,6 minutos (condición 1); HRMS: Análisis calculado para $C_{46}H_{57}F_3N_8O_6$ 875,4426; encontrado: 875,4406 (M+H).

Los compuestos de la presente invención pueden inhibir VHC por mecanismos diferentes o distintos de la inhibición de NS5A. En una modalidad los compuestos de la presente invención inhiben el replicón del VHC y en otra modalidad los compuestos de la presente invención inhiben NS5A.

Tabla 2

Ejemplo	*Actividad o Intervalo*
22	5 pM
22.1	D
22.2	D
22.3	D
22a.1	D
22a.2	D
22a.3	10 pM
22a.4	D
22b	D
22b.1	D
22b.2	D
22b.3	D
22c	D
22c.1	D
22c.3	D
22d	D
22e	3 pM
22f	D
22g	1 pM

22g.1	D
22g.2	20 pM
22g.3	D
22h	D
22h.1	D
22i	130 pM
22j	14 nM
22j.1	B
22k	D
22k.1	D
22m	D
22n	D
22n.1	D
22o	C
22p	160 pM
22q	D
22q.1	D
22r	D
22r.a	D
22r.b	D
22r.1	D
22r.2	D
22r.2a	D
22r.2b	D
22r.3	3 pM
22r.4	D
22r.5	D
22s	D
22s.a	D

22s.c	20 pM
22s.1	D
22s.1a	D
22s.1b	D
22t	1 pM
22t.a	D
22t.1	D
22t.1a	D
22u	D
22u.a	10 pM
22u.b	D
22u.1	D
22u.2	D
22u.2a	D
22u.2b	20 pM
22u.4	D
22u.5	D
22u.5a	D
22v	D
22v.a	C
22v.1	D
22v.1a	D
22v.1b	D
22w	D
22w.a	120 pM
22w.1	D
22w.1a	D
22w.2	D
22w.2a	D

22x.1	D
22x.1a	D
24	320 pM
24.a	D
24.b	D
24.1	D
24.1a	D
24.1b	D
24.1c	D
24.1d	D
24.2	D
24.2a	D
24.2b	D
24.2c	D
24.2d	D
24.3	

Será evidente para un experto en la técnica que la presente invención 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 que 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

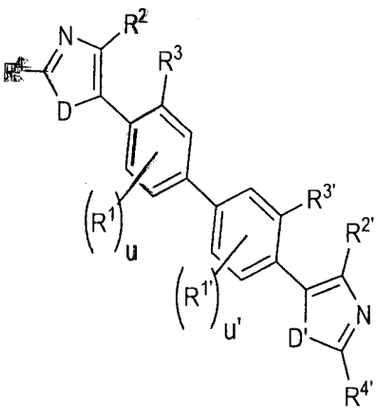
incluidos en la presente.

Los compuestos de la presente invención pueden inhibir VHC por mecanismos diferentes o distintos a la inhibición de NS5A. En una modalidad los compuestos de la presente invención inhiben el replicón del VHC y en otra modalidad los compuestos de la presente invención inhiben NS5A. Los compuestos de la presente invención pueden inhibir múltiples genotipos de VHC.

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REIVINDICACIONES

1. Un compuesto de fórmula (I)



(I),

o una de sus sales farmacéuticamente aceptables, caracterizado porque

u y u' son independientemente 0, 1, 2 ó 3;

D y D' se seleccionan cada uno independientemente de NR^5, O, y S; en donde cada R^5 se selecciona independientemente de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, hidroxi, (NR^aR^b)carbonilo y trialquilsililalcoxialquilo;

cada R^1 y $R^{1'}$ se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo;

R^2 se selecciona de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo y

(NR^aR^b)carbonilo; y

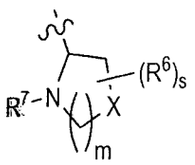
R^3 se selecciona de hidrógeno, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo; o

R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; estando el anillo de cinco a ocho miembros opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo, (NR^aR^b)carbonilo, oxo y espirociclo;

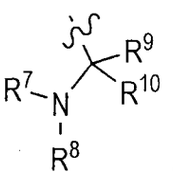
$R^{2'}$ y $R^{3'}$, junto con los átomos de carbono a los que están unidos, forman un anillo aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; en donde el anillo de cinco a ocho miembros está opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo,

hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo, (NR^aR^b)carbonilo, oxo y espirociclo;

cada uno de R^4 y $R^{4'}$ se selecciona independientemente de



y



; en las que

cada m es independientemente 0, 1 ó 2;

cada s es independientemente 0, 1, 2, 3 ó 4;

cada X se selecciona independientemente de O, S, S(O), SO_2, CH_2, CHR^6 y $C(R^6)_2$; con la condición de que cuando n es 0, X se selecciona de CH_2, CHR^6 y $C(R^6)_2$;

cada R^6 se selecciona independientemente de alcoxi, alquilo, arilo, halo, haloalquilo, hidroxi y $-NR^aR^b$, en donde puede formar el alquilo opcionalmente un anillo condensado de tres a seis miembros con un átomo de carbono adyacente, en donde el anillo de tres a seis miembros está opcionalmente sustituido con uno o dos grupos alquilo;

cada R^7 se selecciona independientemente de hidrógeno y R^{11}-C(O)-, y

R^{11}-C(S)-;

R^8 se selecciona de hidrógeno y alquilo;

cada uno de R^9 y R^{10} se selecciona independientemente de hidrógeno, alquenilo, alcoxialquilo, alquilo, haloalquilo y (NR^aR^b)alquilo; o,

R^9 y R^{10}, junto con el átomo de carbono al que están

unidos, forman un anillo saturado de cinco o seis miembros que opcionalmente contiene uno o dos heteroátomos seleccionados de NR^z, O, y S; en donde R^z se selecciona de hidrógeno y alquilo; y

cada R^{11} se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alcoxicarbonilalquilo, alquilo, alquilcarbonilalquilo, arilo, arilalquenilo, arilalcoxi, arilalquilo, ariloxialquilo, cicloalquilo, (cicloalquil)alquenilo, (cicloalquil)alquilo, cicloalquiloxialquilo, haloalquilo, heterociclilo, heterociclilalquenilo, heterociclilalcoxi, heterociclilalquilo, heterocicliloxialquilo, hidroxialquilo, $-NR^cR^d$, (NR^cR^d)alquenilo, (NR^cR^d)alquilo y (NR^cR^d)carbonilo.

2. Un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, caracterizado porque cada uno de D y D' es NR^5.

3. Un compuesto de conformidad con la reivindicación 2, o una de sus sales farmacéuticamente aceptables, caracterizado porque cada R^5 se selecciona independientemente de hidrógeno y hidroxi.

4. Un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, caracterizado porque cada uno de u y u' es 0.

5. Un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, caracterizado porque R^2 se selecciona de hidrógeno y haloalquilo.

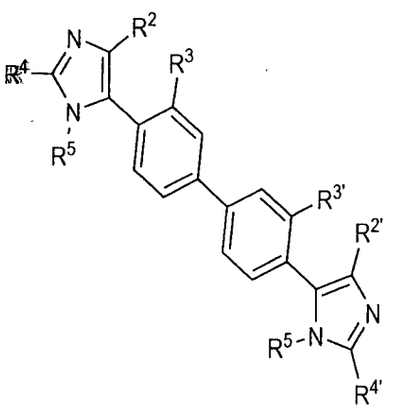
6. Un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, caracterizado

porque R^3 se selecciona de hidrógeno y halo.

7. Un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, caracterizado porque R^2 y R^3, junto con los átomos de carbono a los que están unidos, forman un anillo carbocíclico de seis o siete miembros.

8. Un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, caracterizado porque $R^{2'}$ y $R^{3'}$, junto con los átomos de carbono a los que están unidos, forman un anillo de seis a ocho miembros que opcionalmente contiene un heteroátomo seleccionado de oxígeno, nitrógeno y azufre; en donde el anillo está opcionalmente sustituido con uno o dos grupos alquilo.

9. Un compuesto de Fórmula (II)



(II),

o una de sus sales farmacéuticamente aceptables, caracterizado porque

R^2 se selecciona de hidrógeno y haloalquilo; y

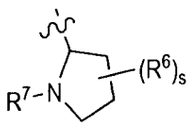
R^3 se selecciona de hidrógeno y halo; o

R^2 y R^3, junto con los átomos de carbono a los que

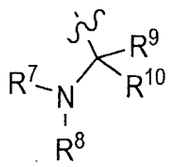
están unidos, forman un anillo carbocíclico aromático o no aromático de cinco o seis miembros;

$R^{2'}$ y $R^{3'}$, junto con los átomos de carbono a los que están unidos, forma un anillo aromático o no aromático de seis a ocho miembros que opcionalmente contiene un heteroátomo seleccionado de oxígeno, nitrógeno y azufre; en donde el anillo está opcionalmente sustituido con uno o dos grupos alquilo;

R^4 y $R^{4'}$ se seleccionan cada uno independientemente de



y



; en las que

cada s es 0 ó 2;

cada R^6 se selecciona independientemente de alquilo y halo, en donde el alquilo forma un anillo condensado de tres miembros con un átomo de carbono adyacente;

cada R^7 se selecciona independientemente de hidrógeno y R^{11}-C(O)-;

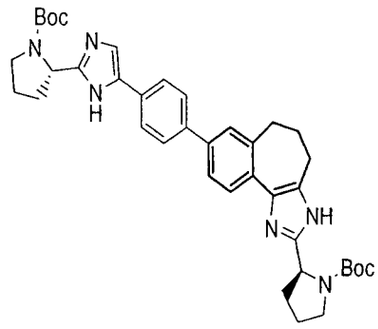
R^8 se selecciona de hidrógeno y alquilo;

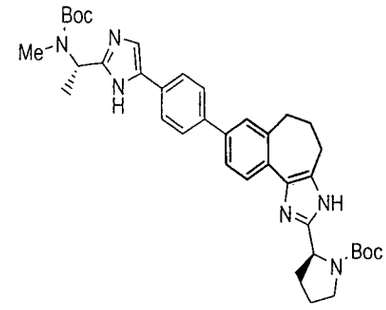
cada uno de R^9 y R^{10} se selecciona independientemente de hidrógeno y alquilo; y

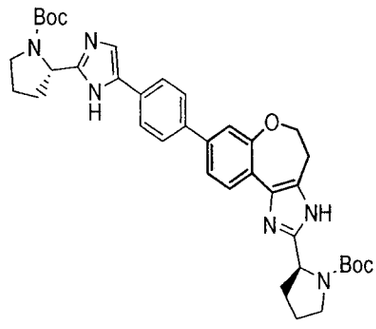
cada R^{11} se selecciona independientemente de alquilo, arilalcoxi, arilalquilo y (NR^cR^d)alquilo.

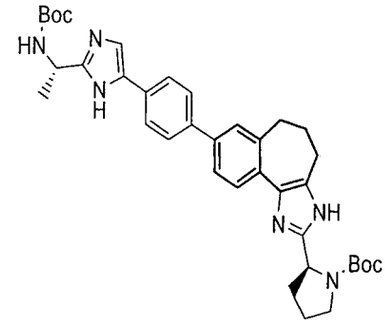
10. Un compuesto caracterizado porque se selecciona de:

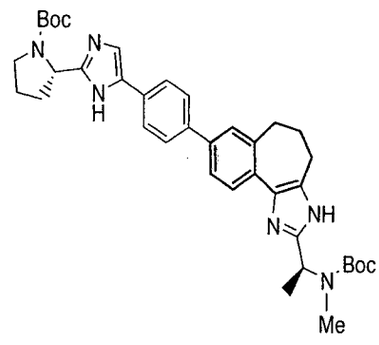
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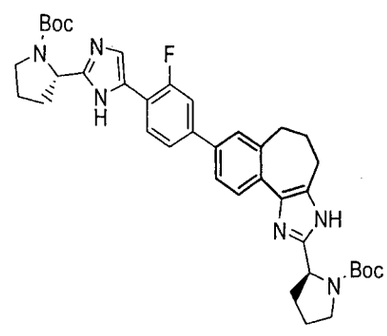


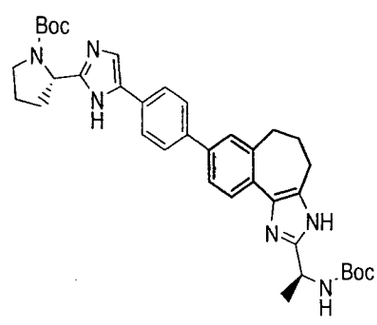


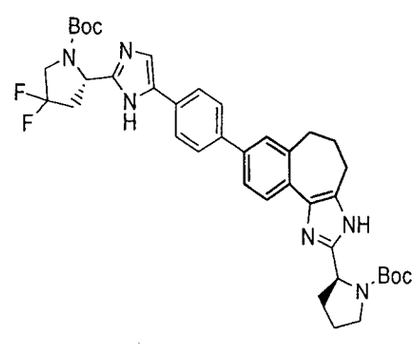


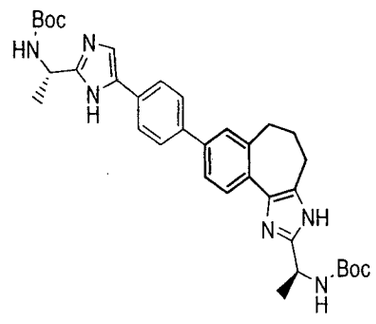


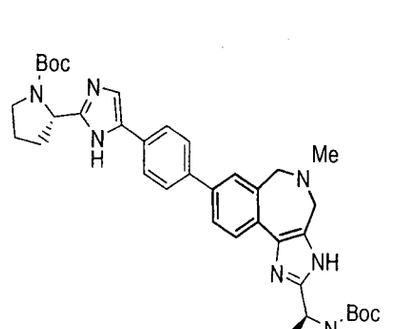


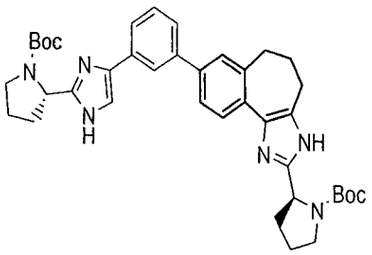


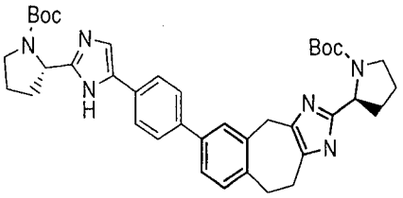


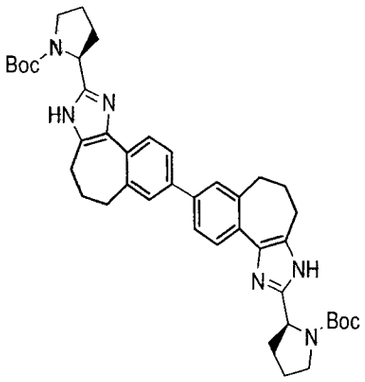


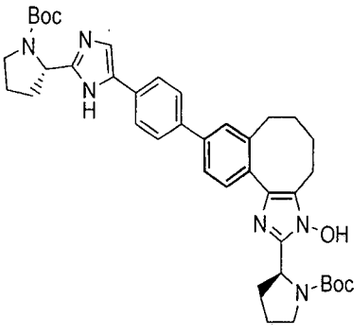


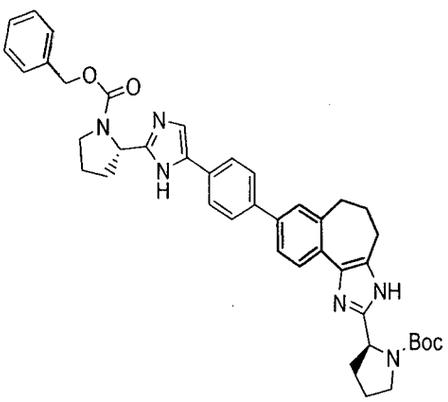


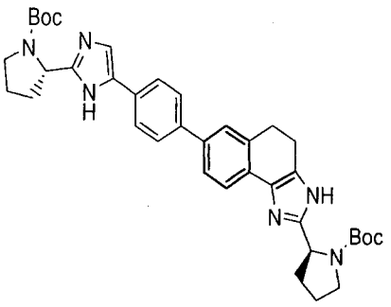


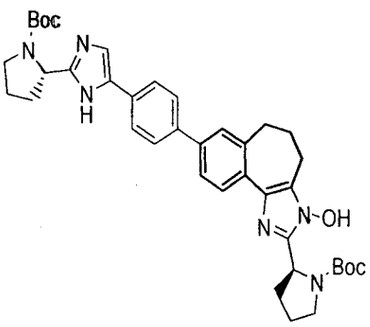


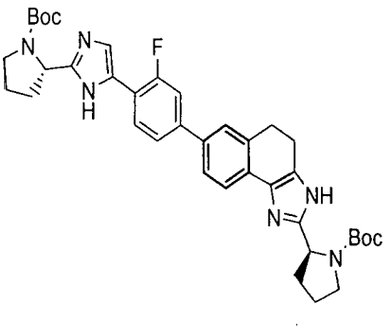


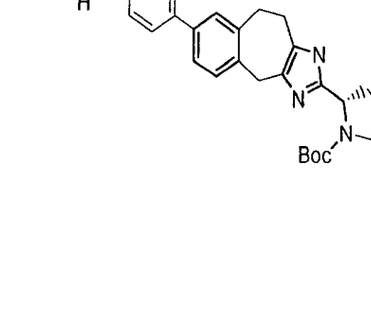


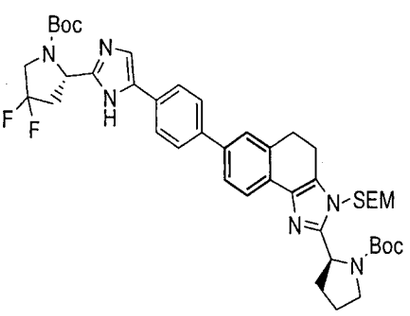


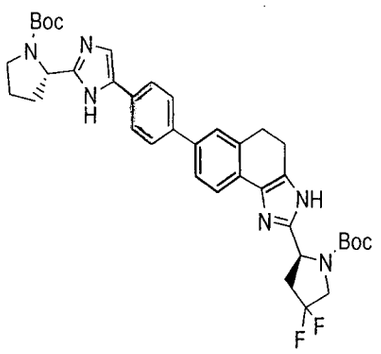


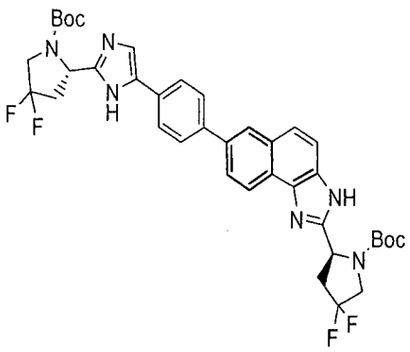


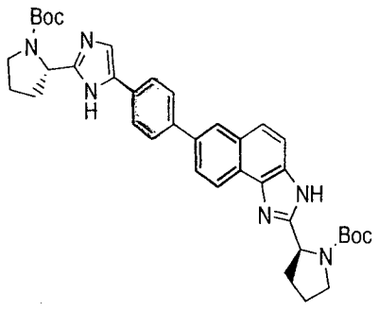


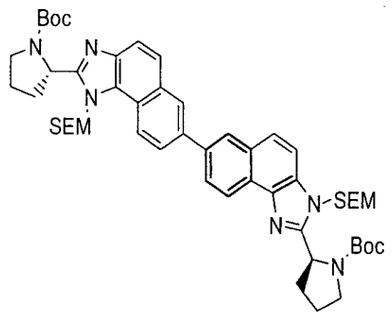


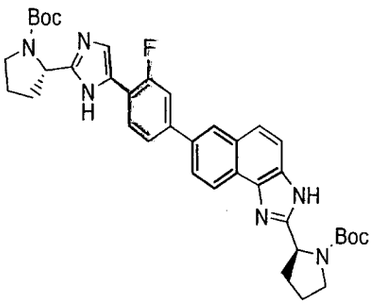


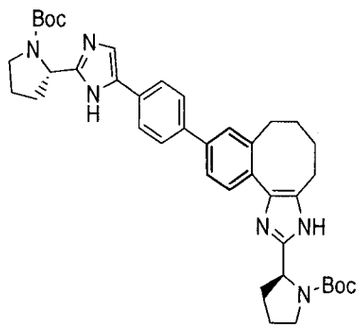


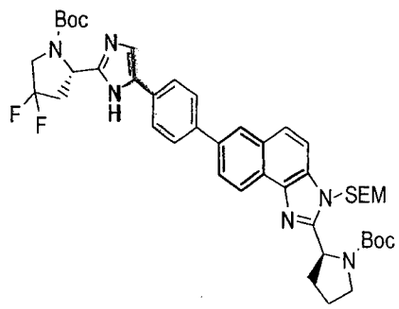


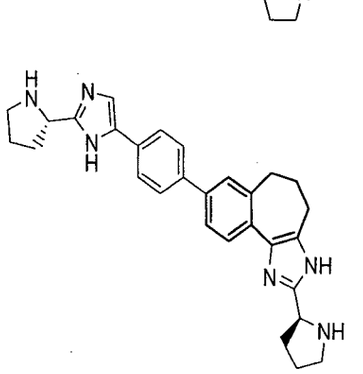


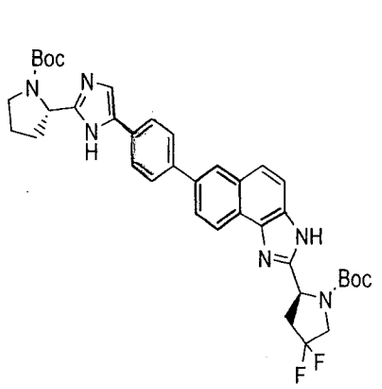


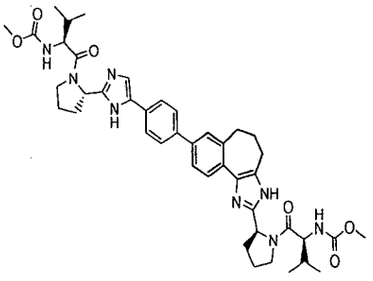






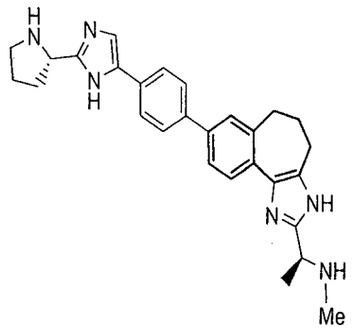


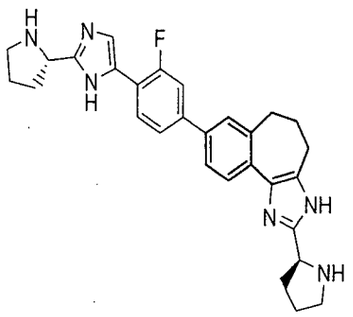


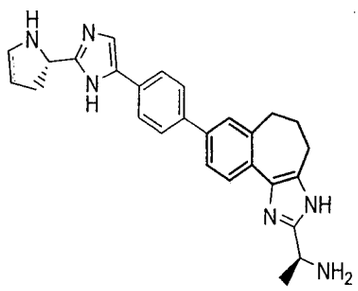


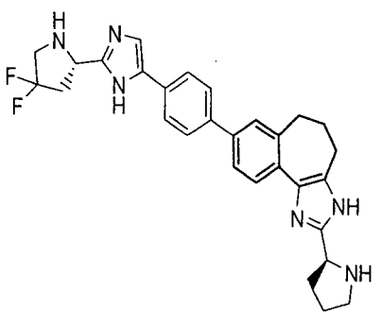


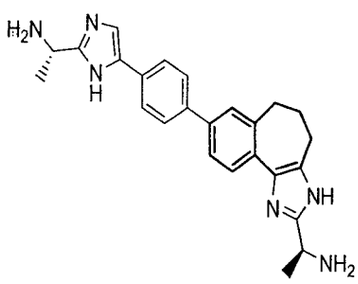
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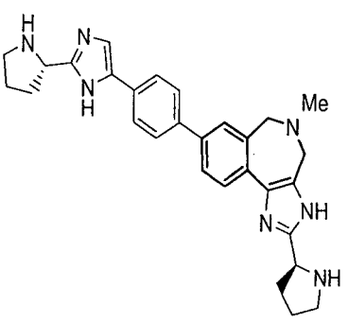


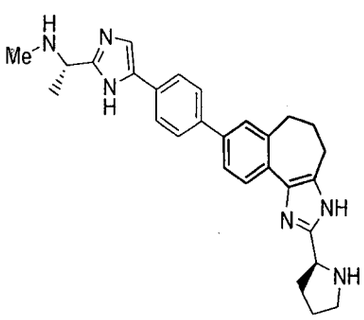


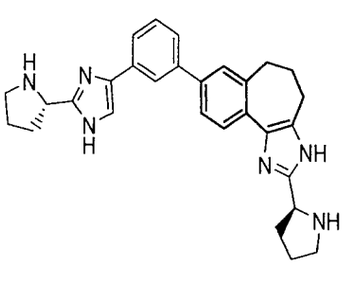


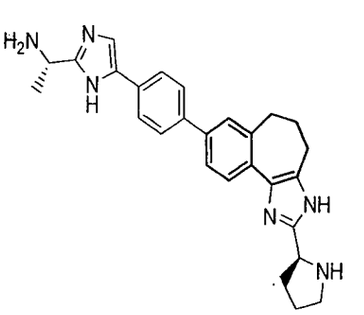


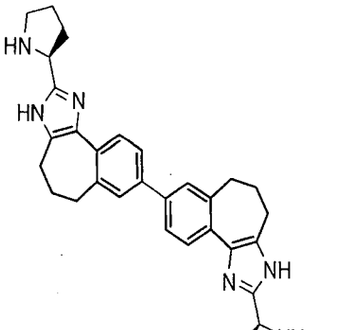


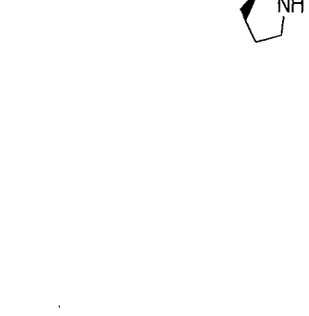


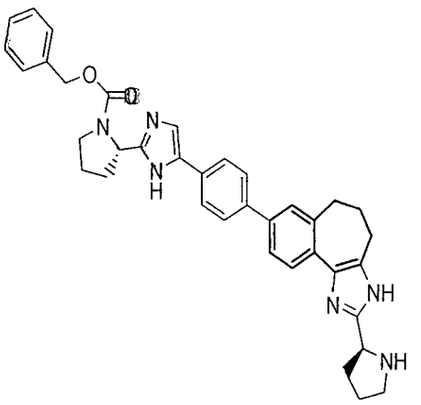


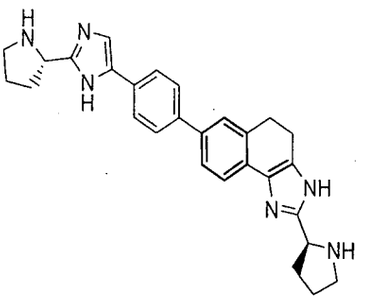


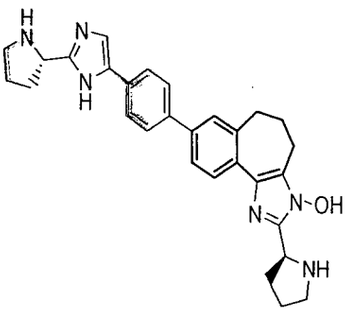


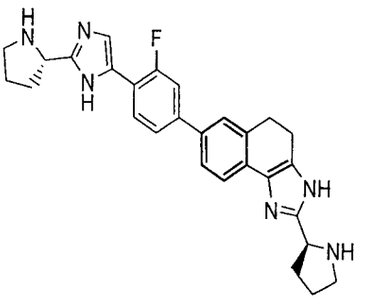


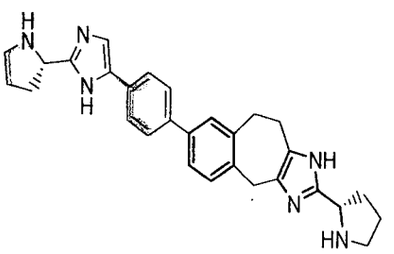


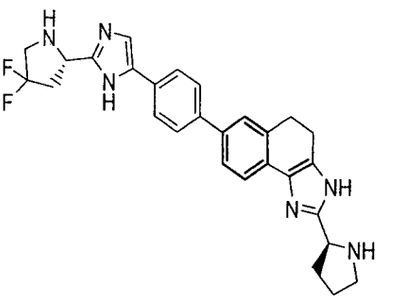


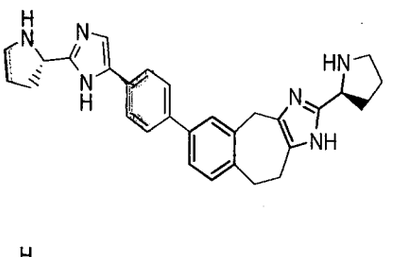


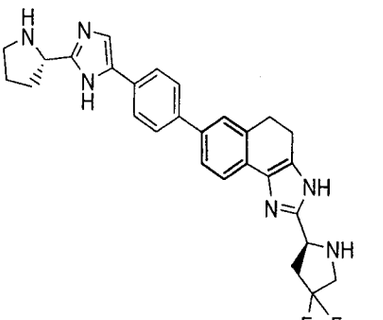


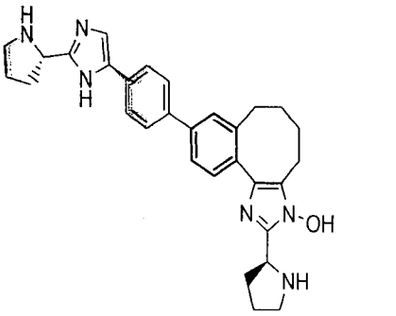


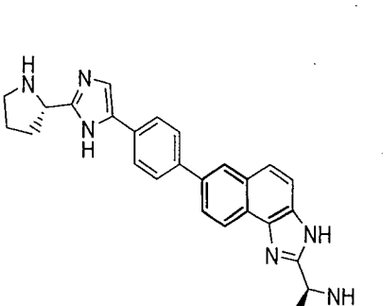


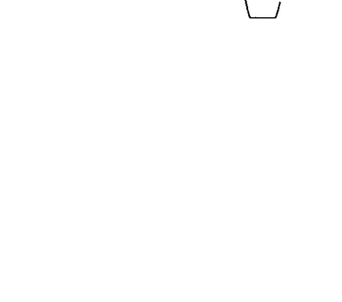






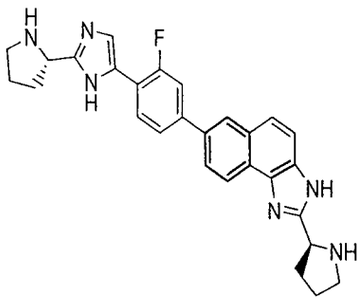


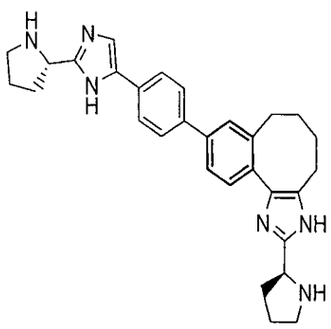


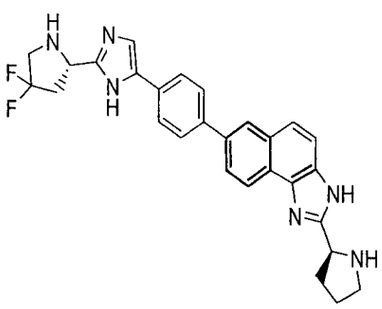


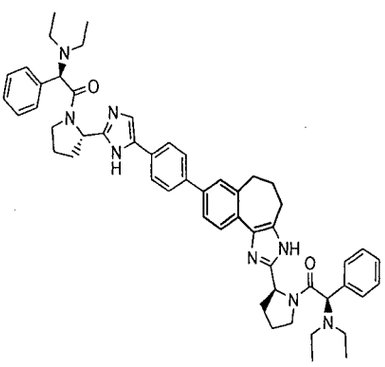


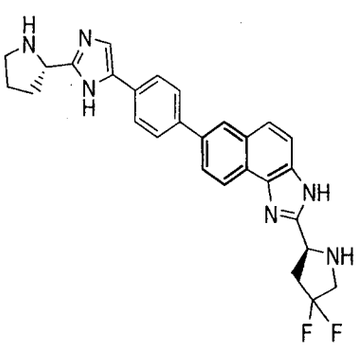
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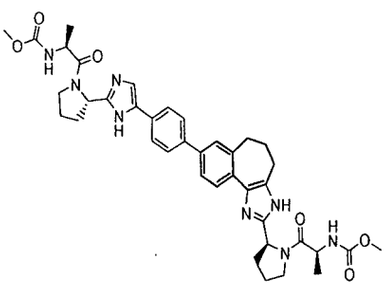


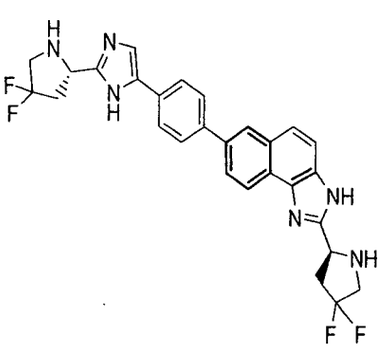


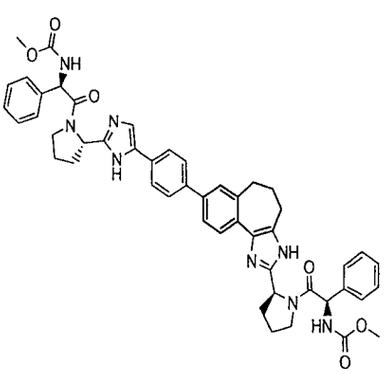


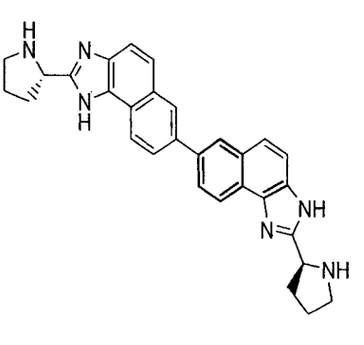


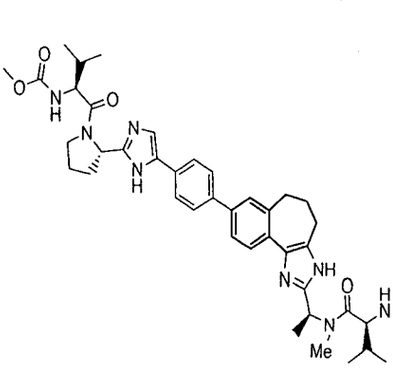


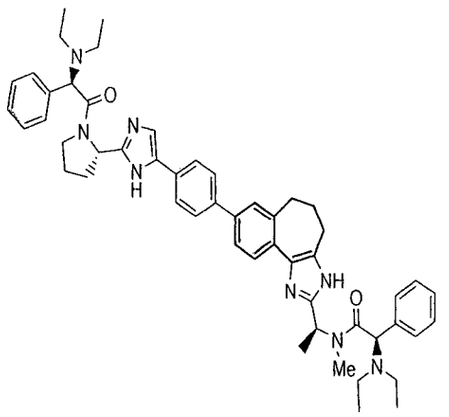


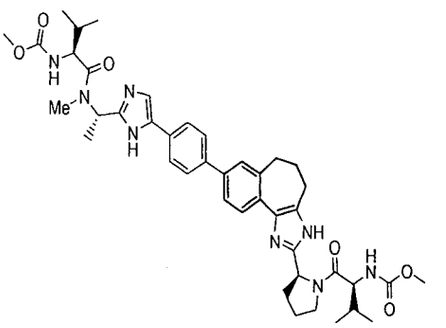


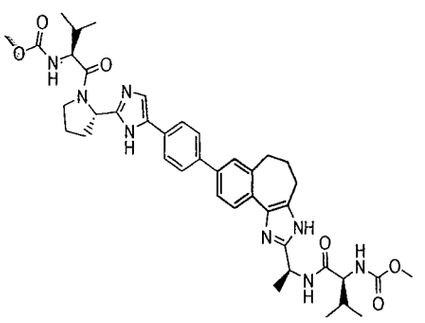


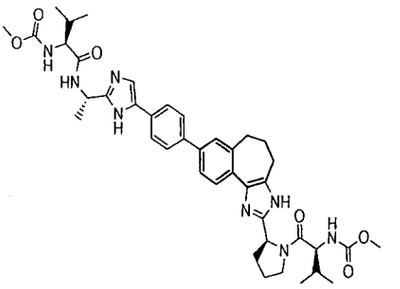


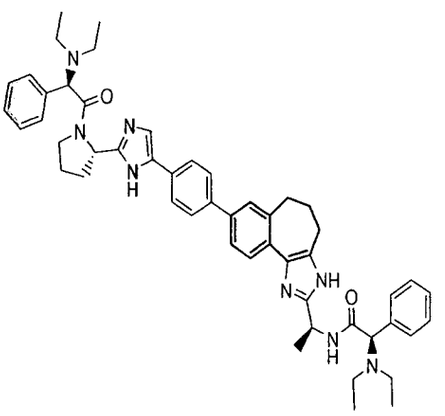


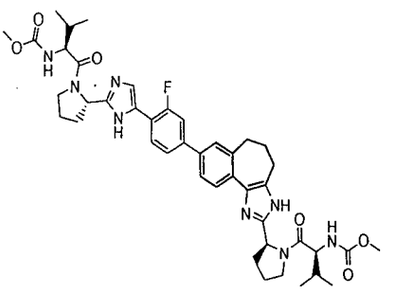


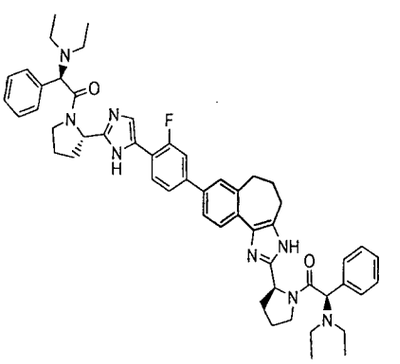


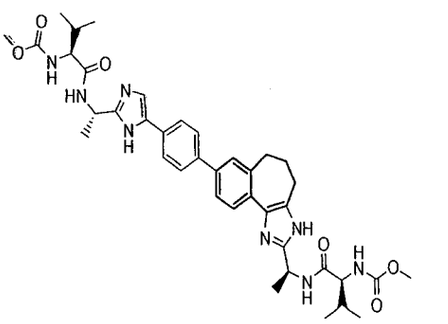


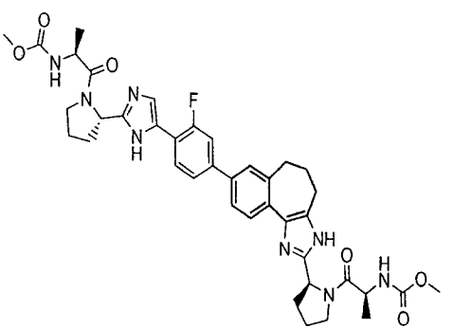




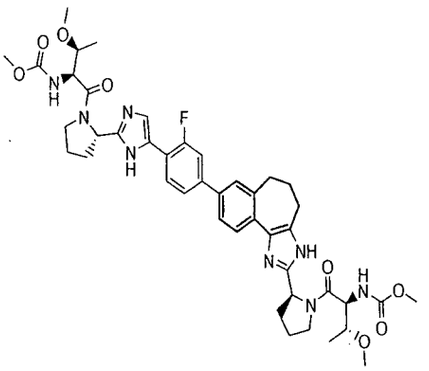


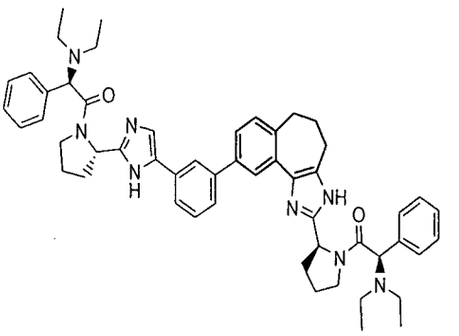


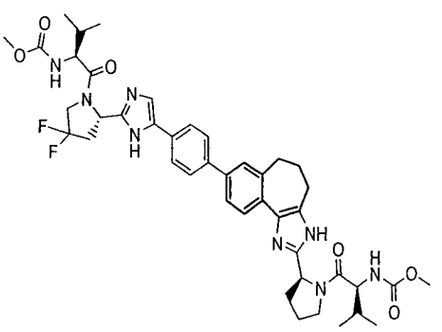


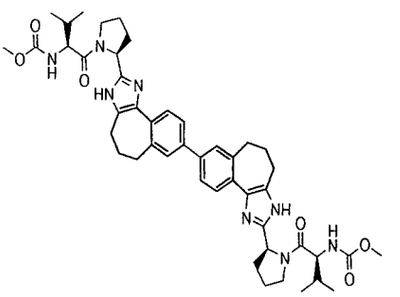


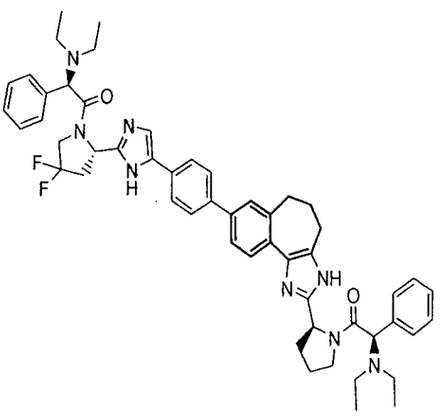
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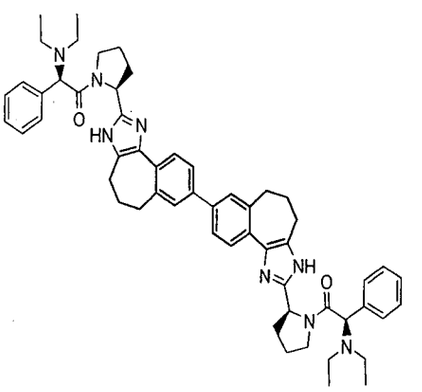


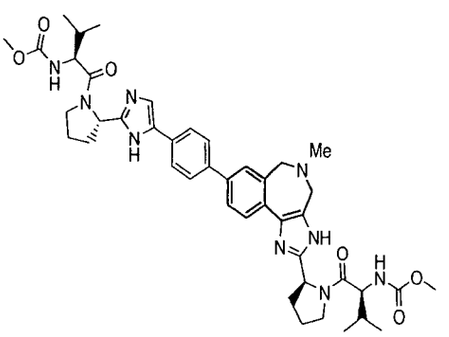


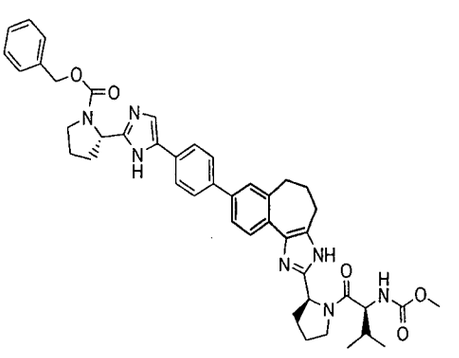


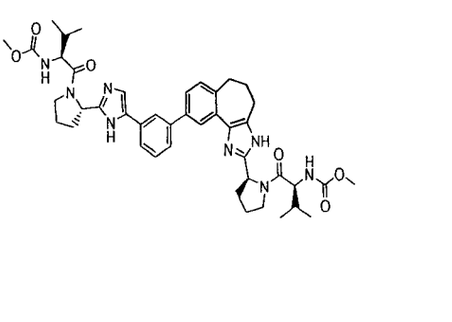




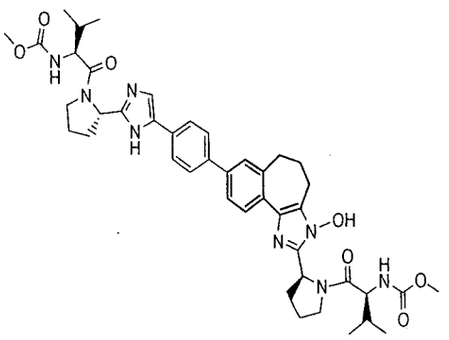


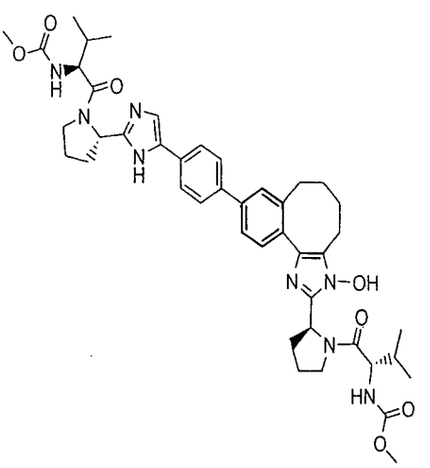


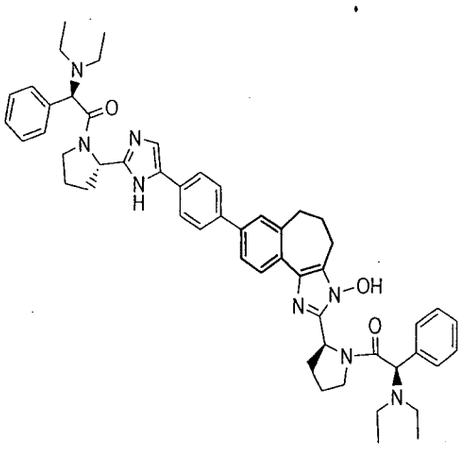


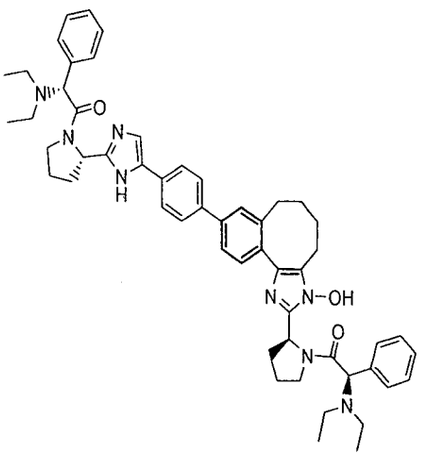


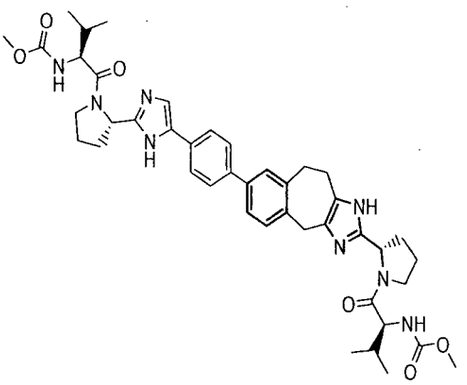
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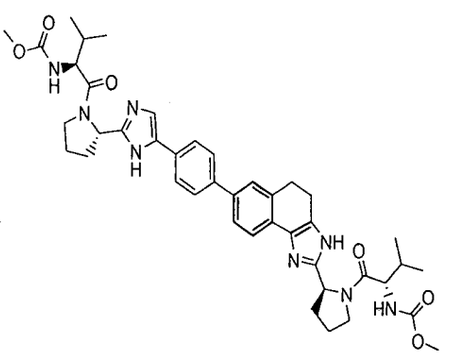


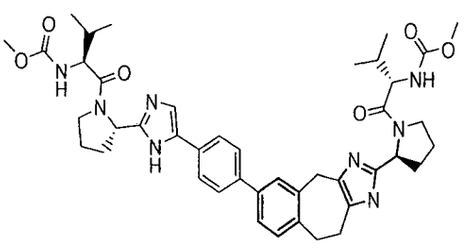




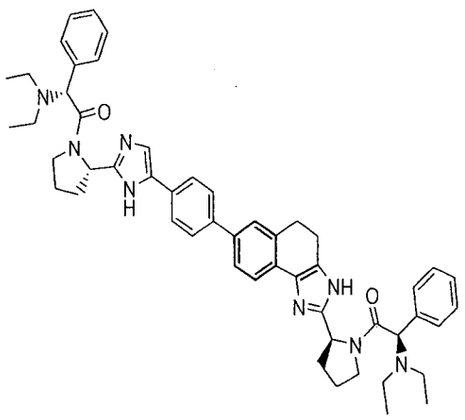


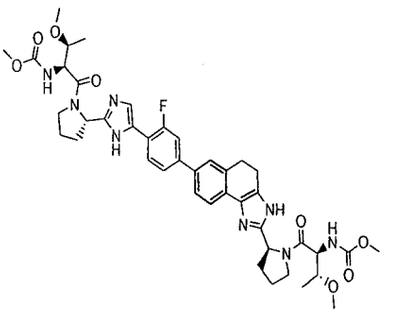


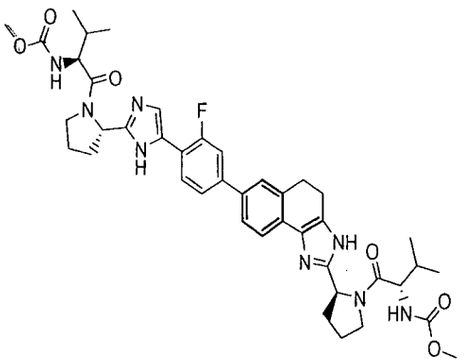


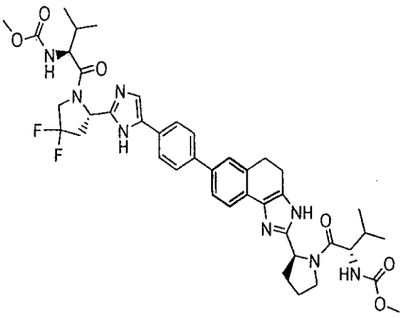


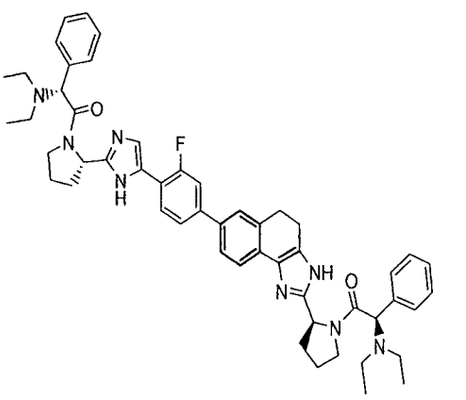
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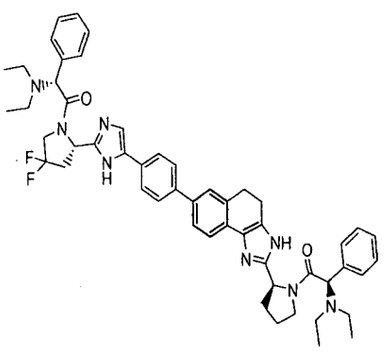


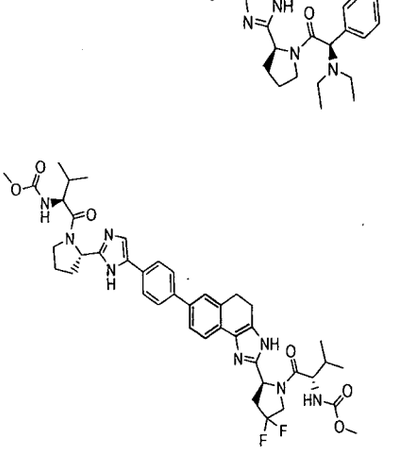


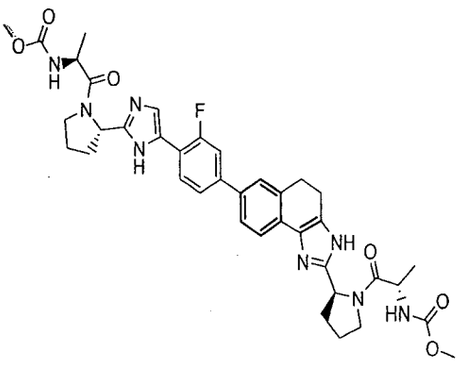


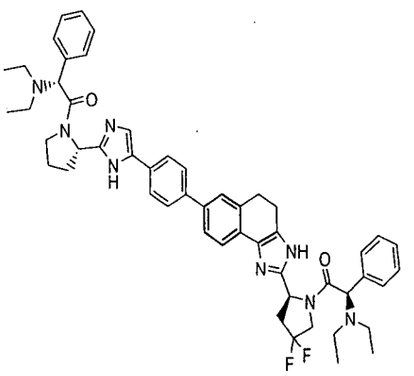




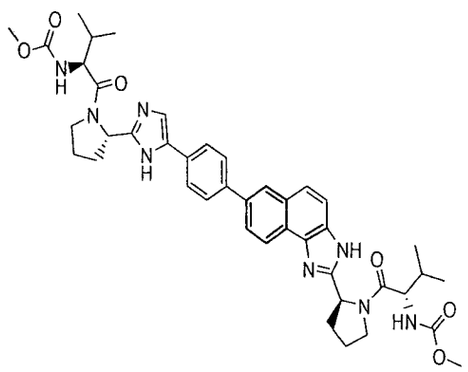


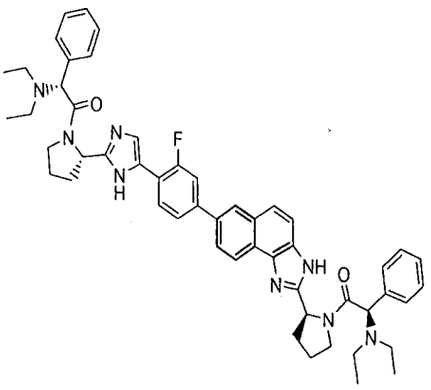


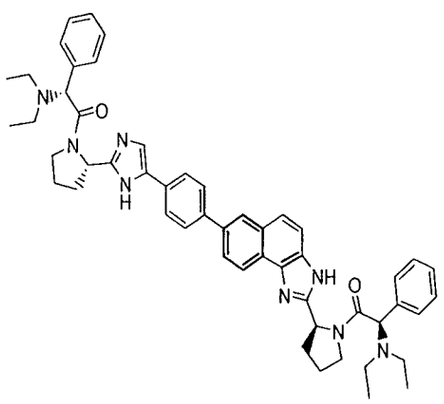


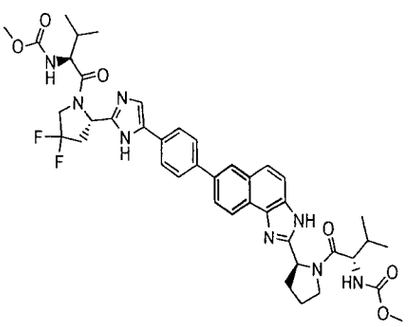


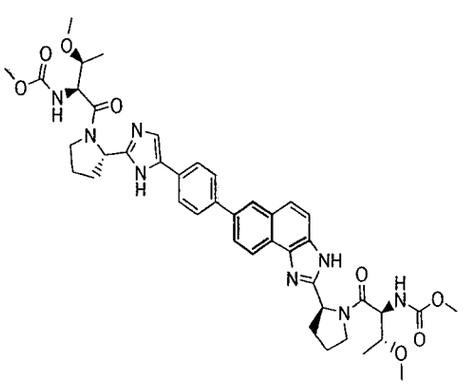
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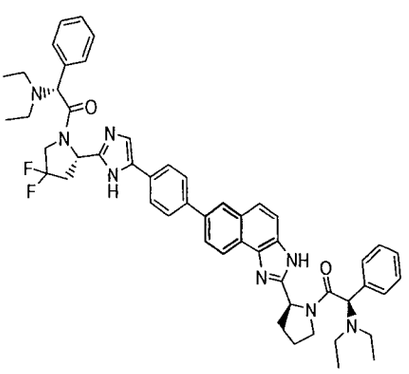


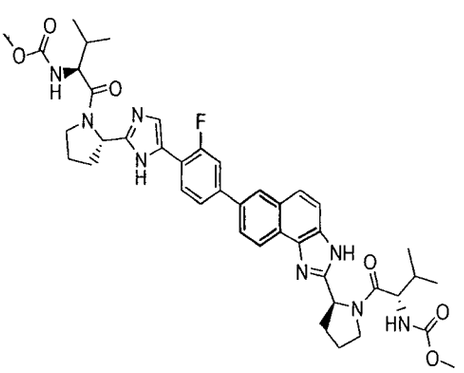


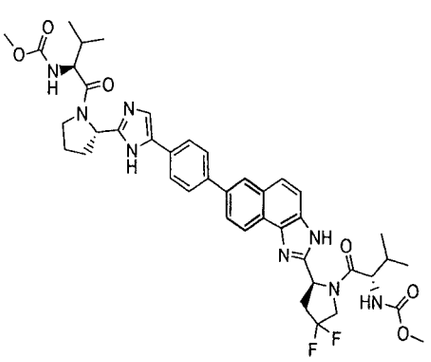




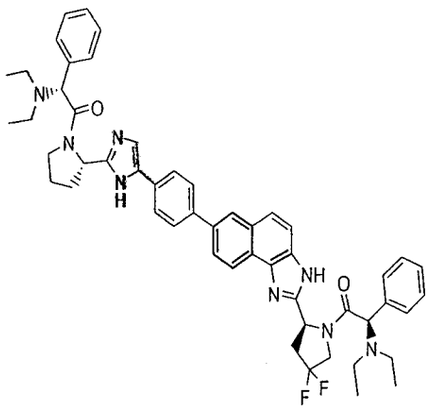


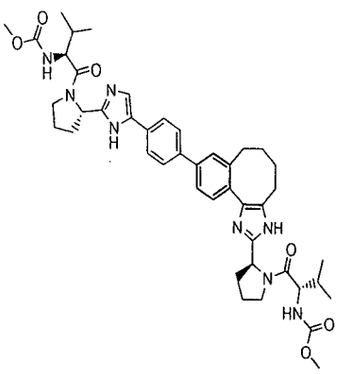


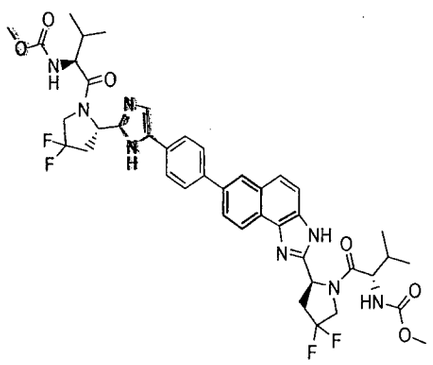


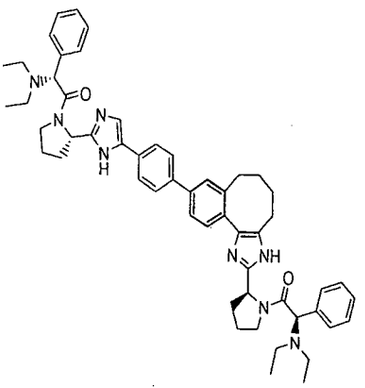


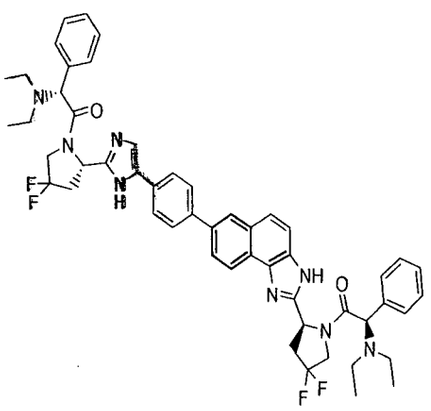
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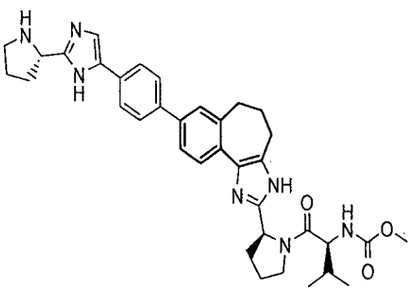


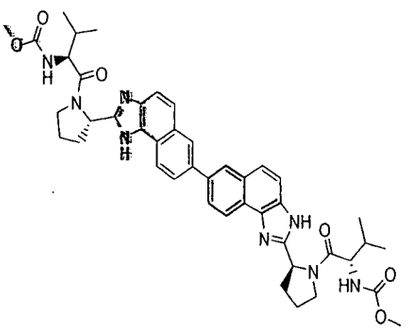


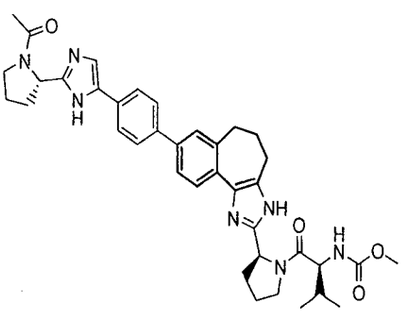


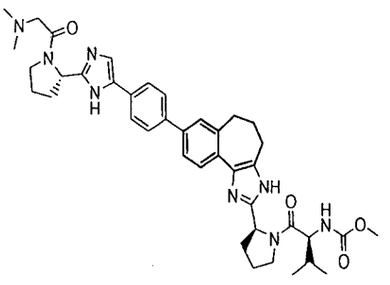


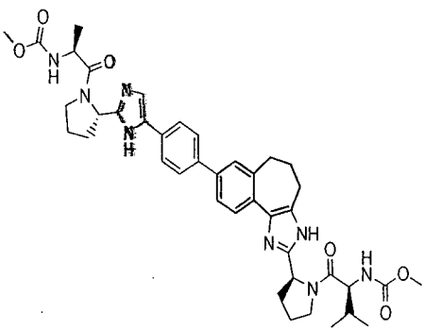


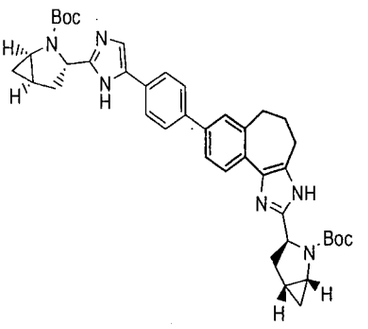


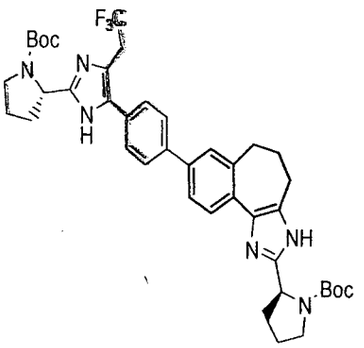


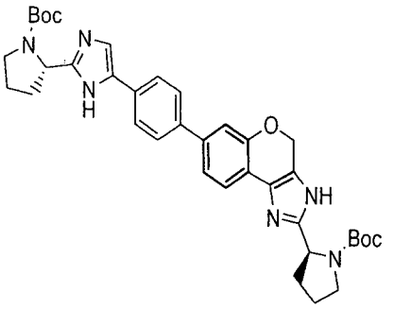


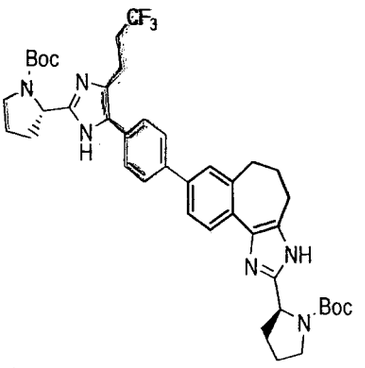


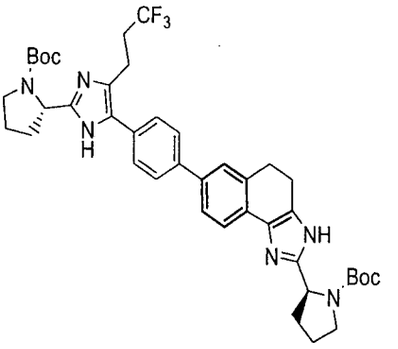


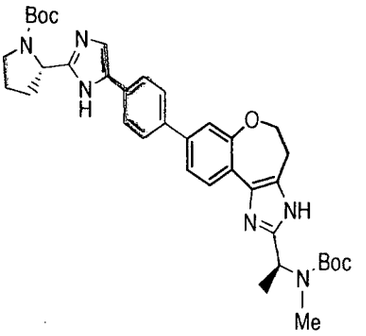


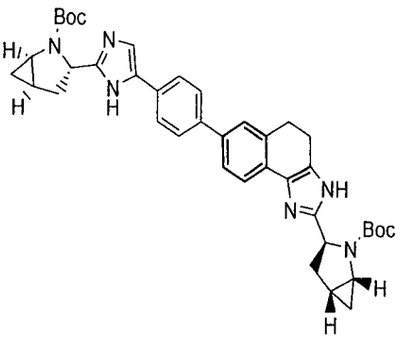


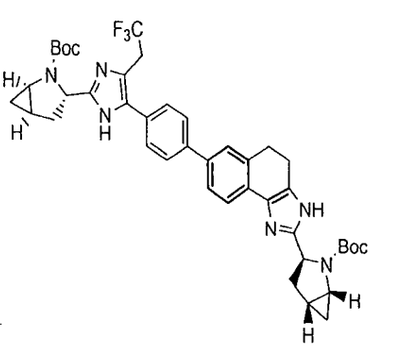




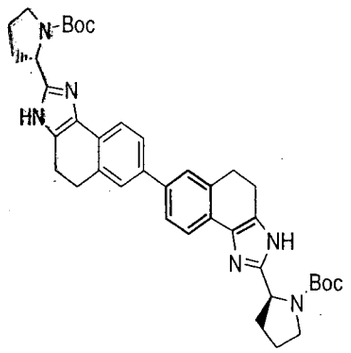


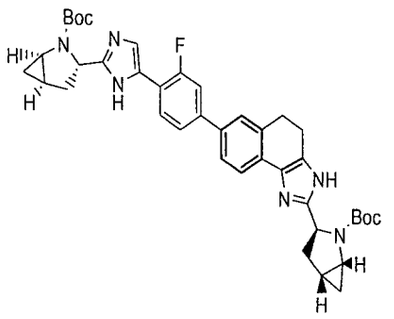


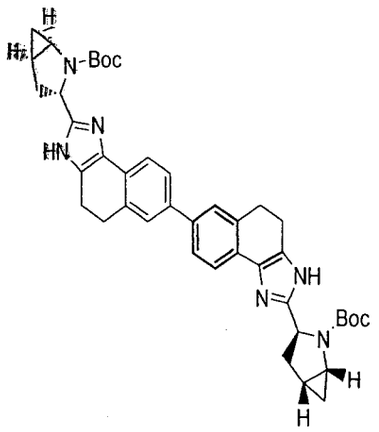


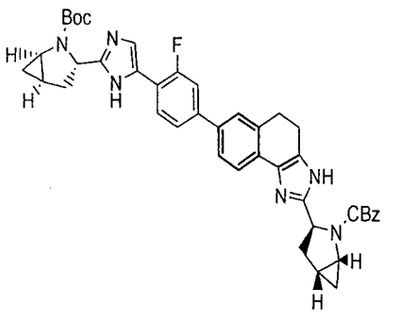


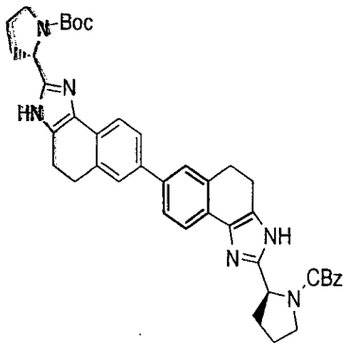
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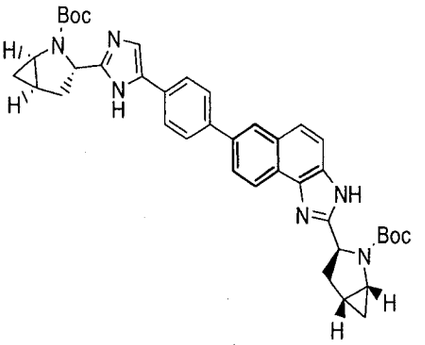


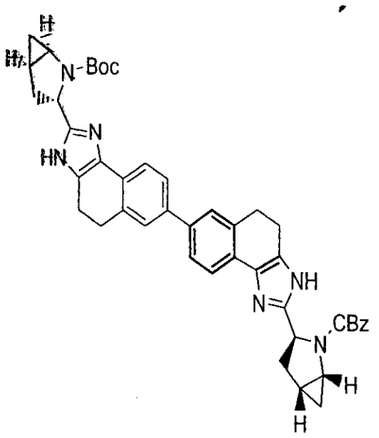


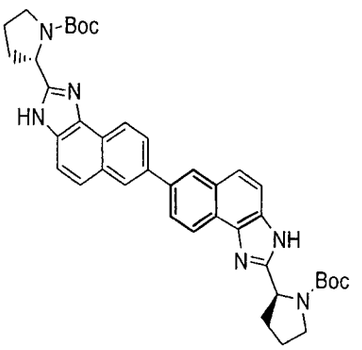


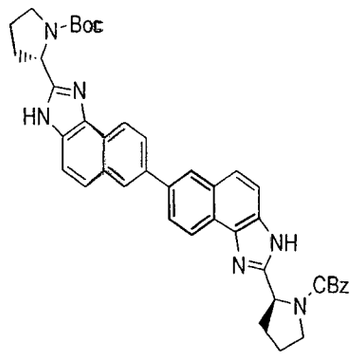


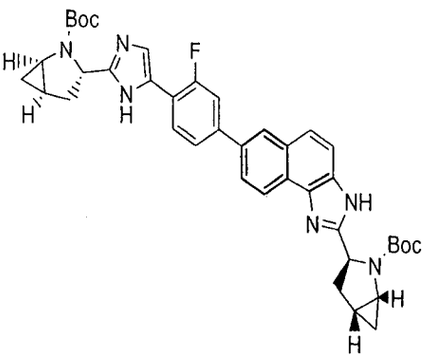


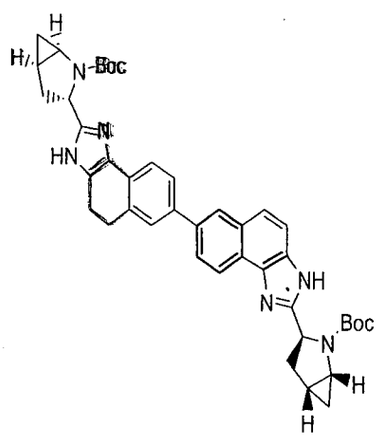


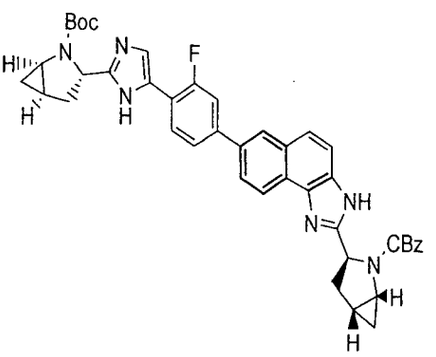


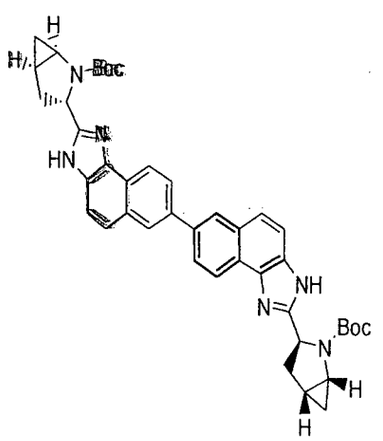


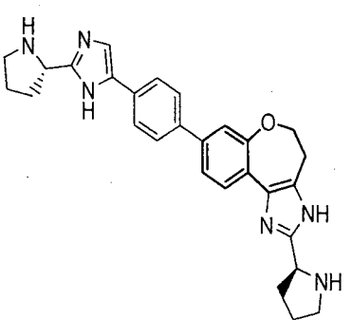


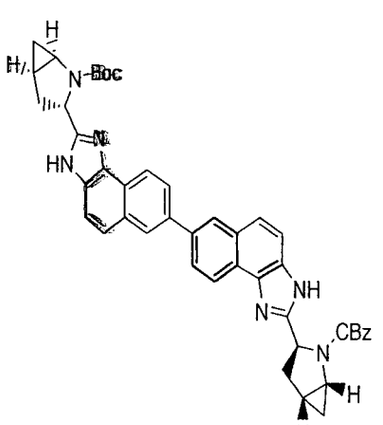


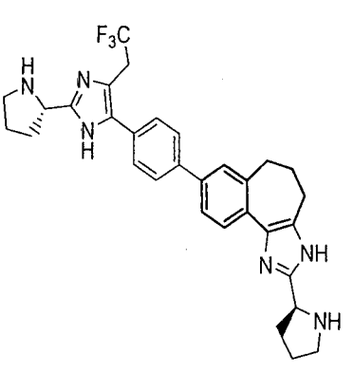


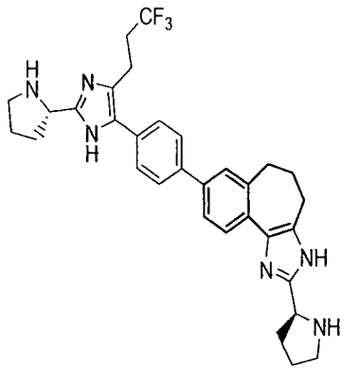


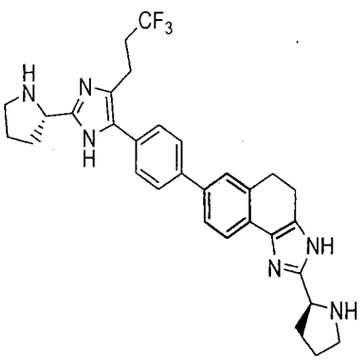


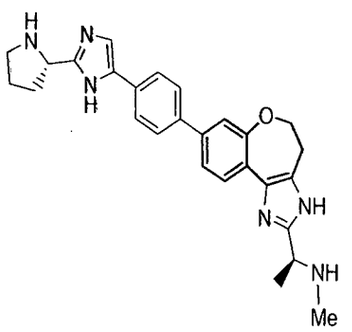


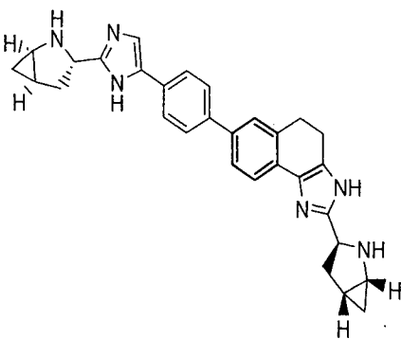


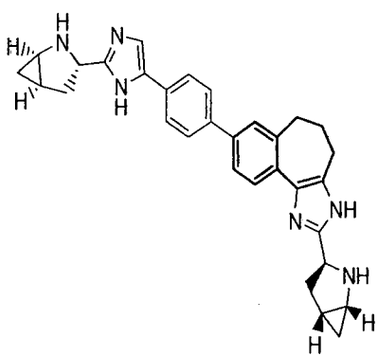


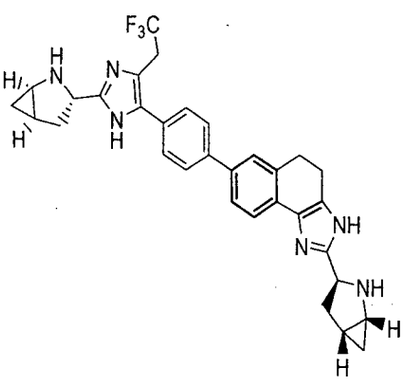


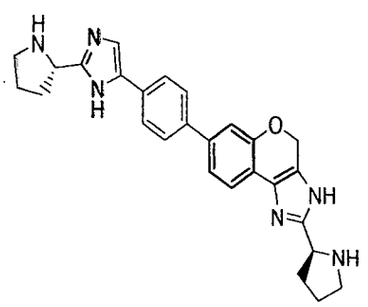


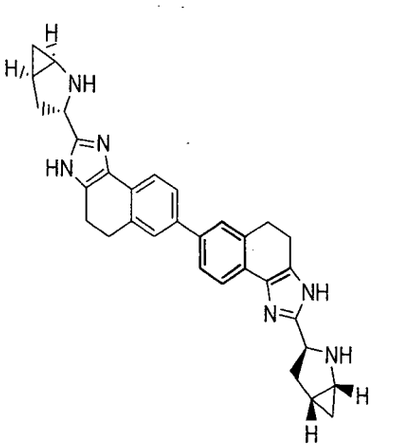


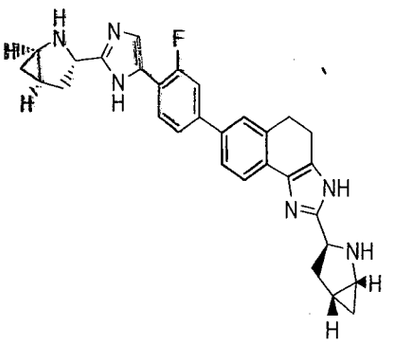


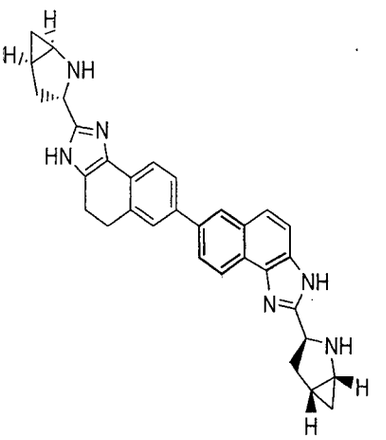


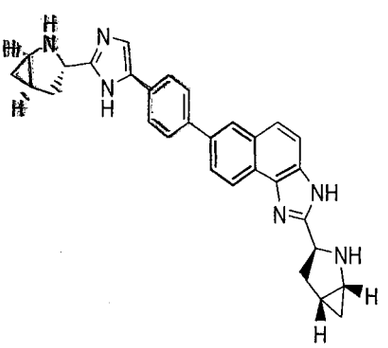


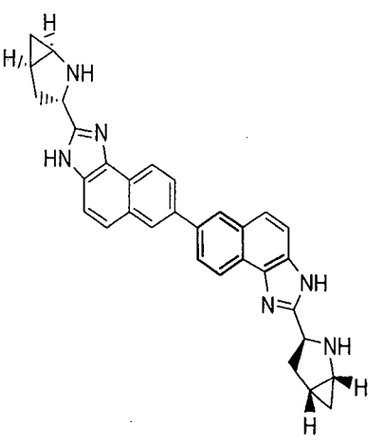


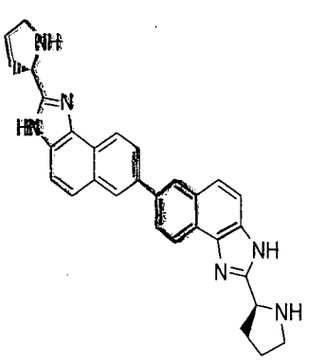


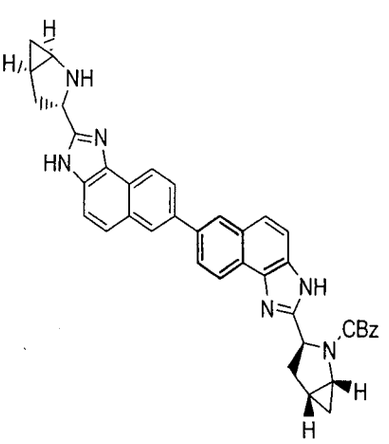


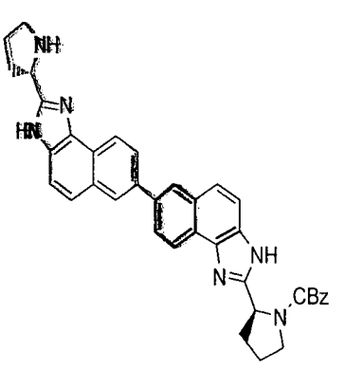


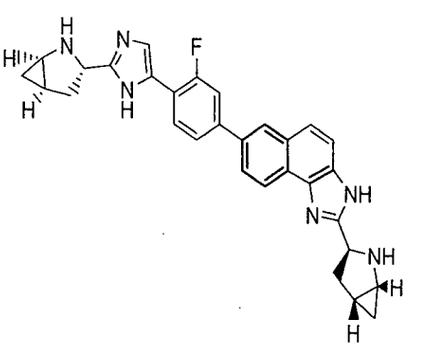




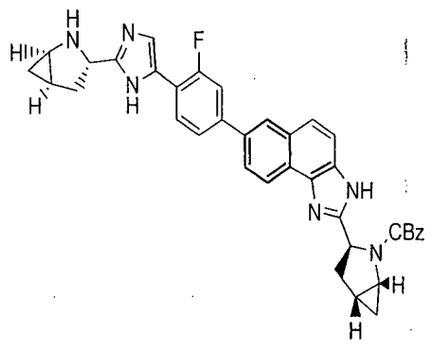


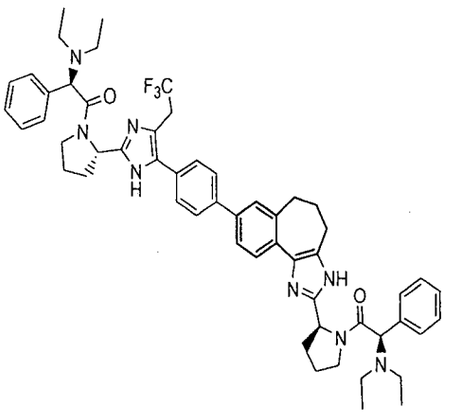


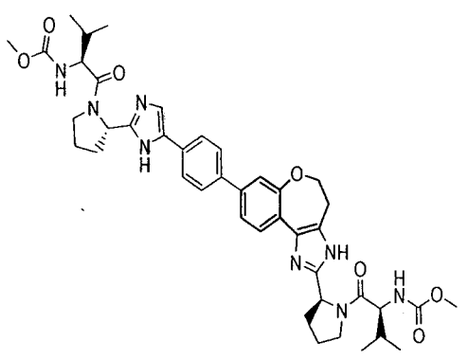


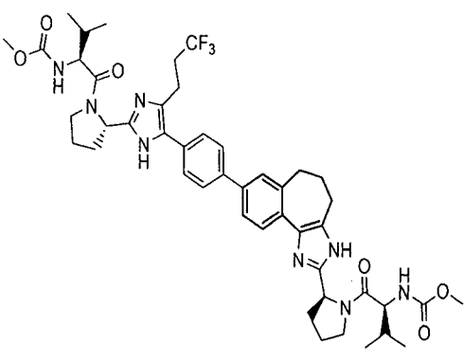


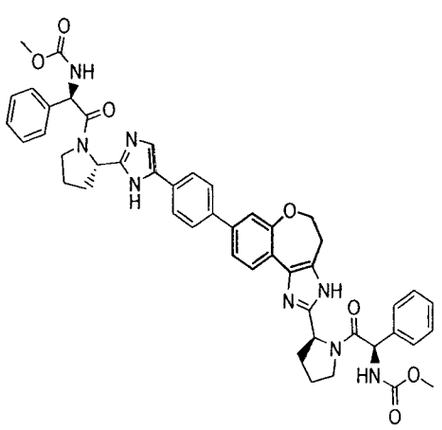
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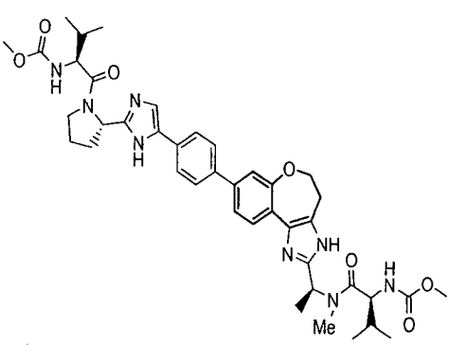


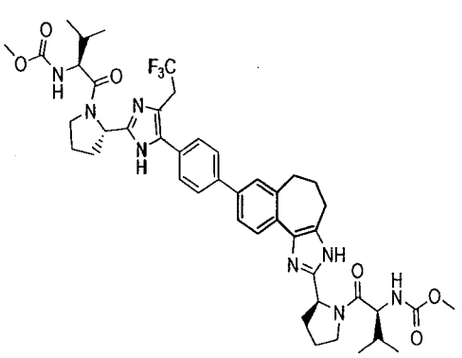


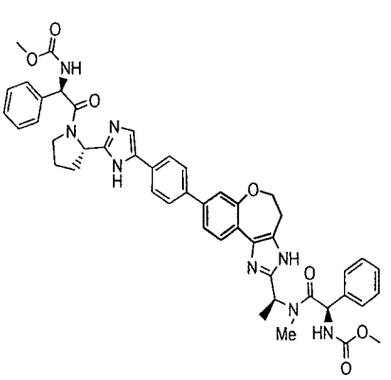




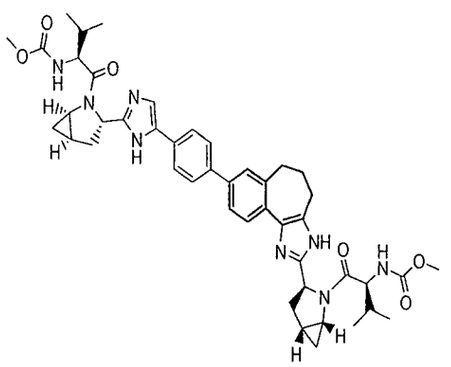


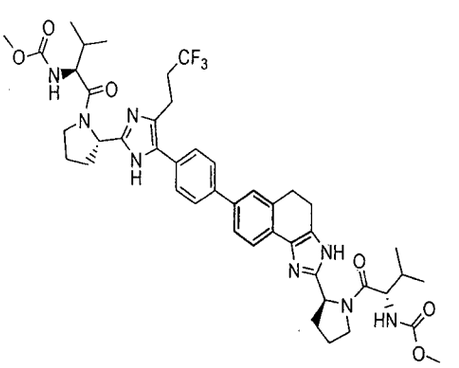


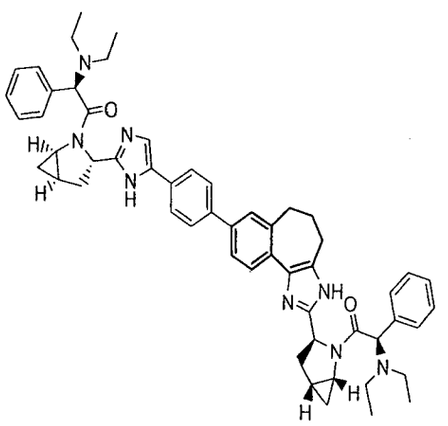


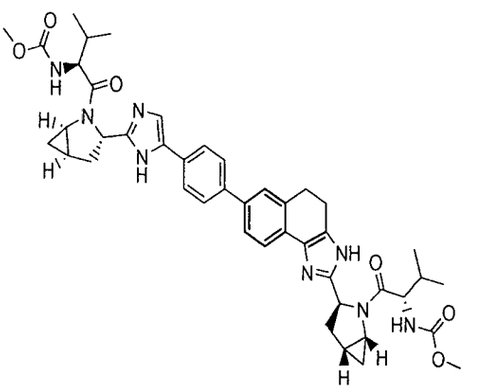


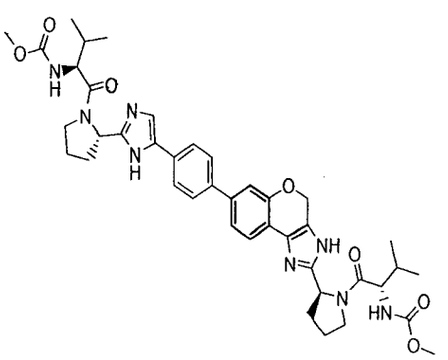
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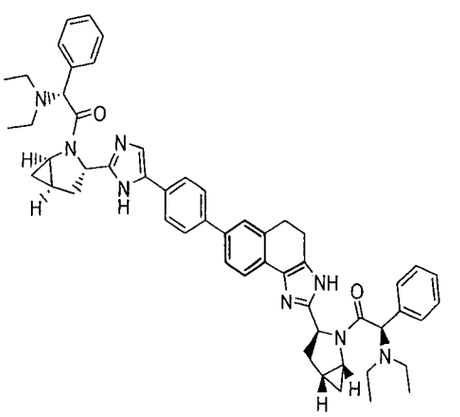


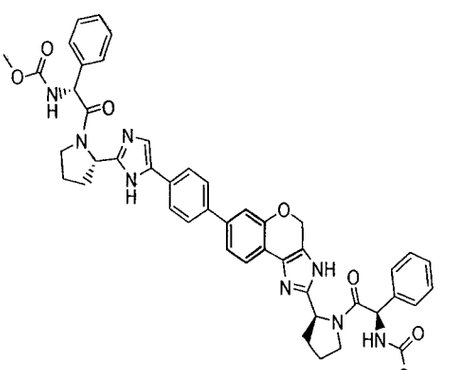


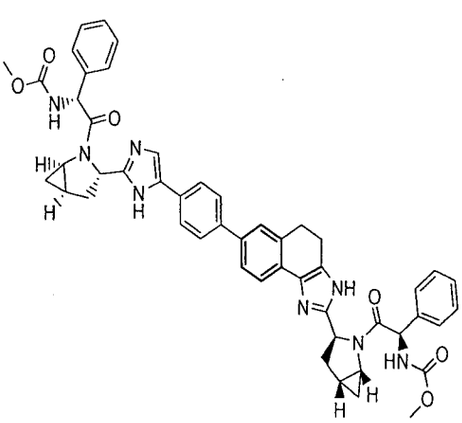


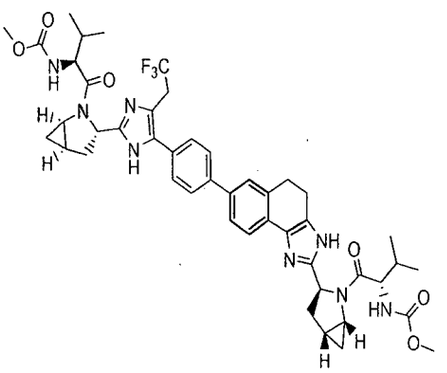


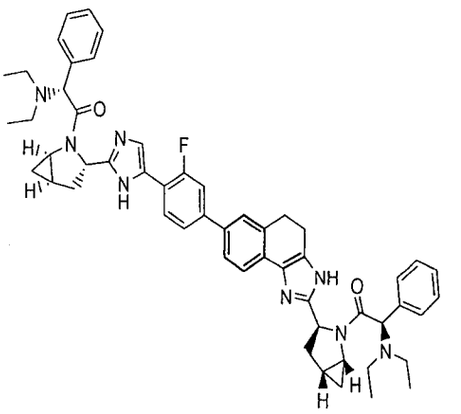


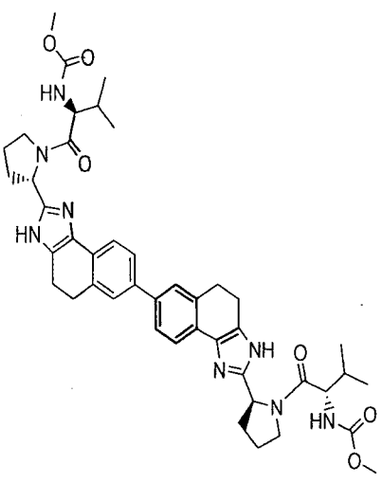


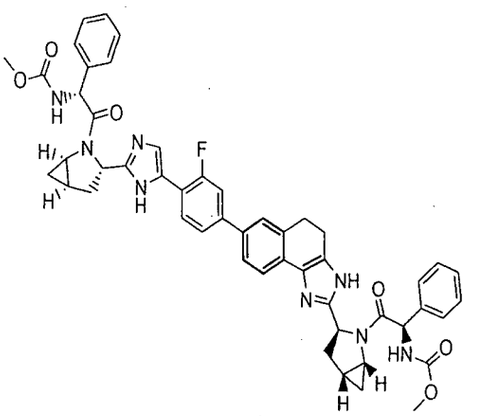


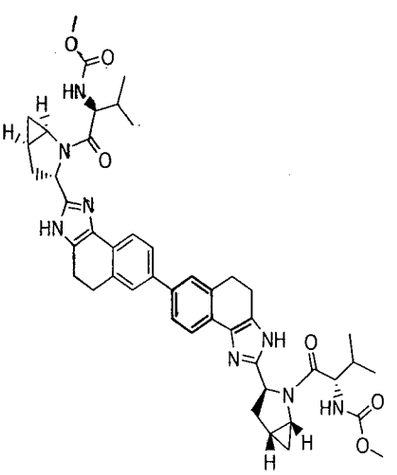


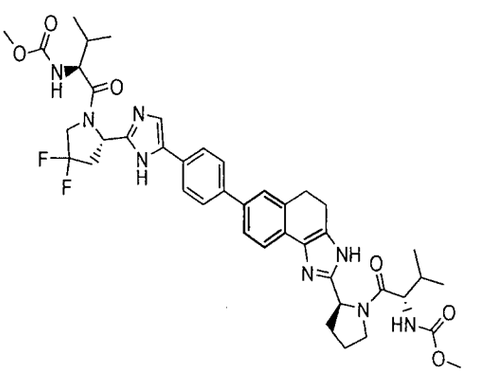


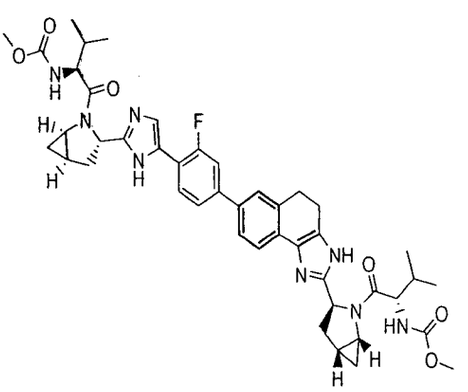


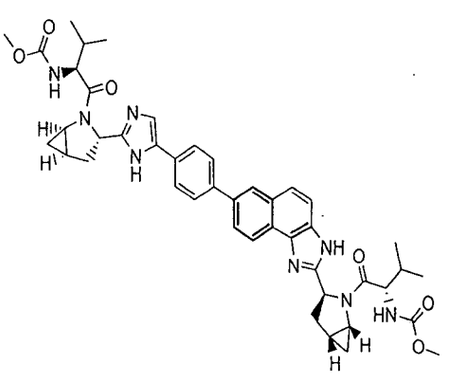


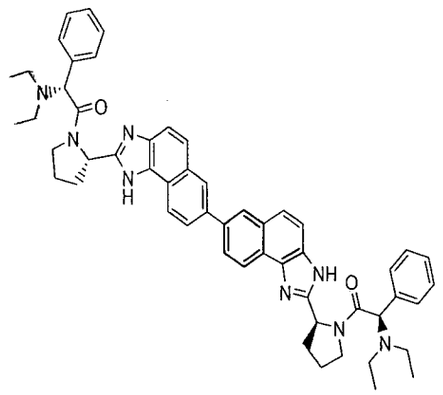


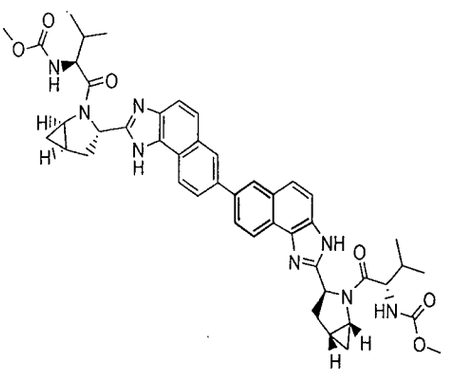


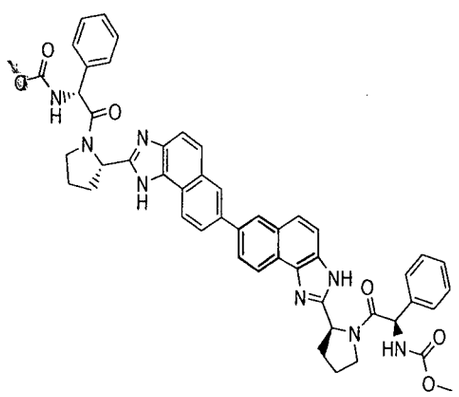


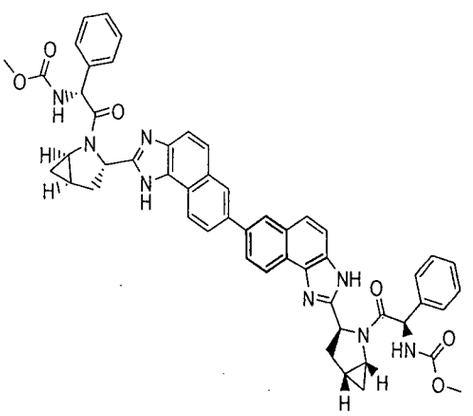


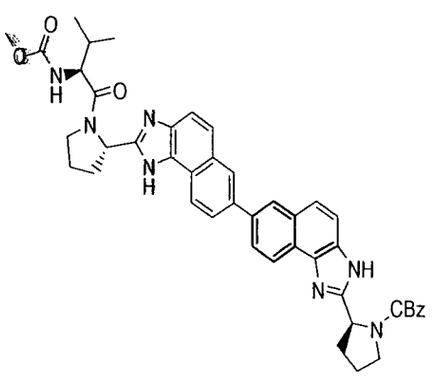


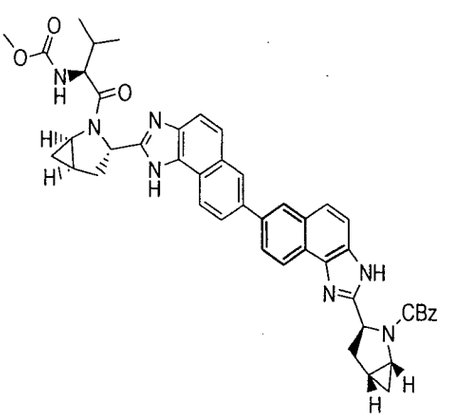


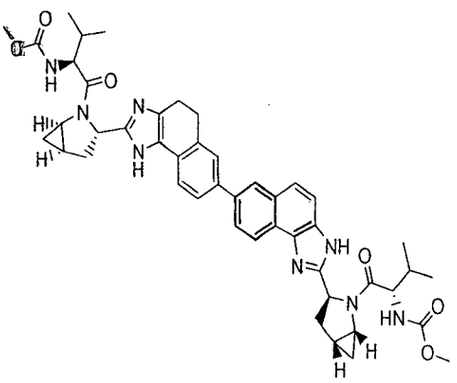


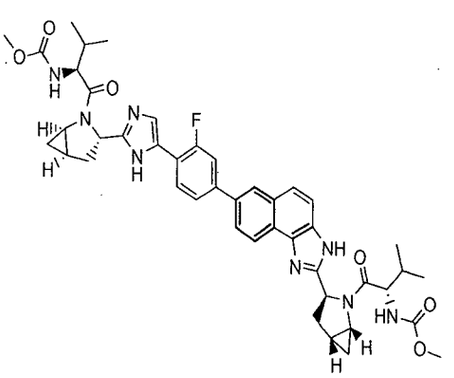




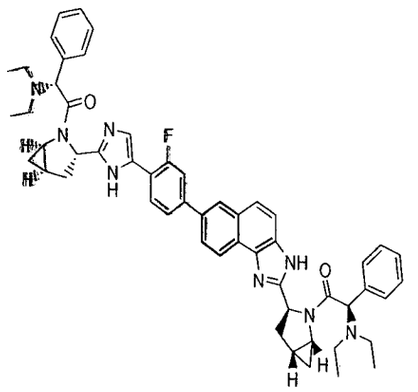


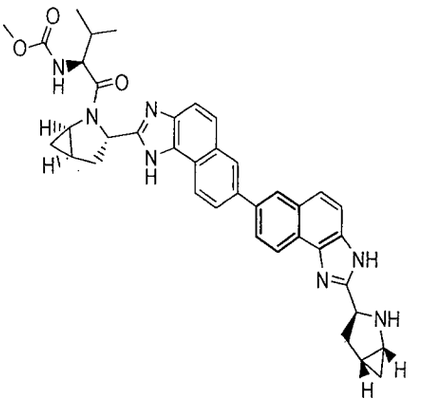


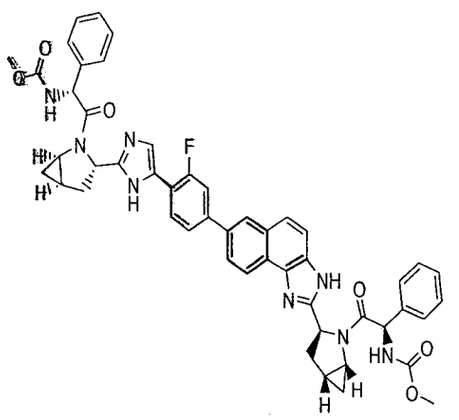


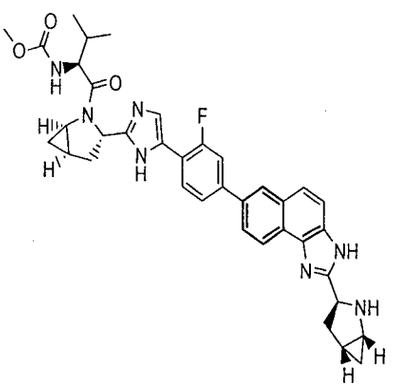


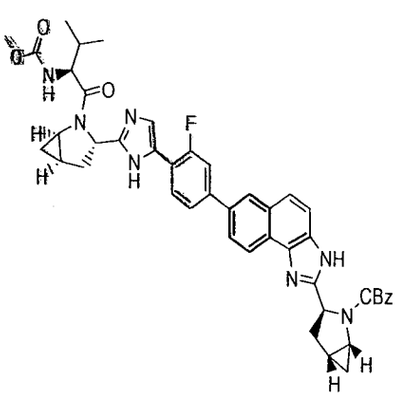
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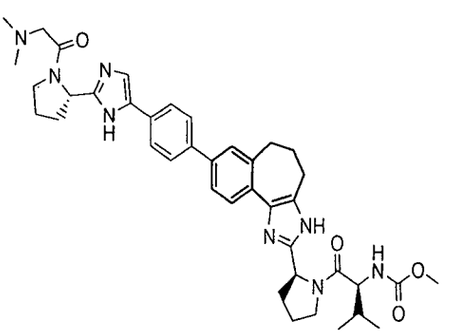


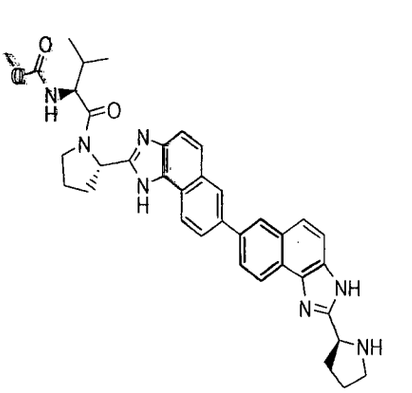


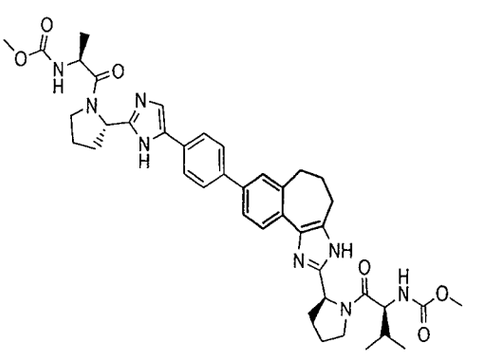




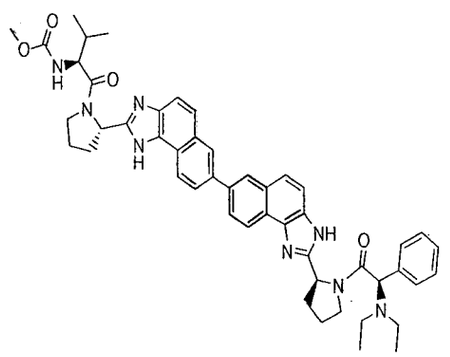


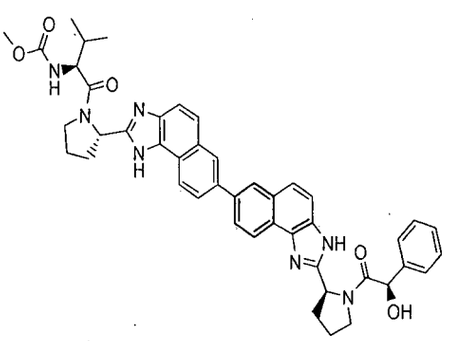


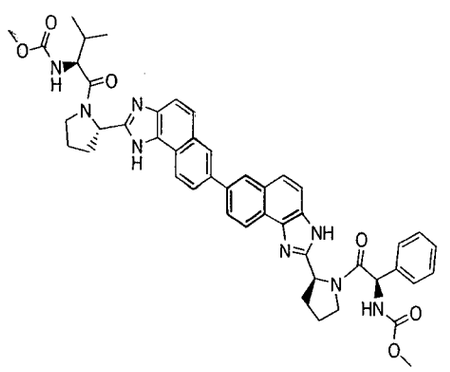


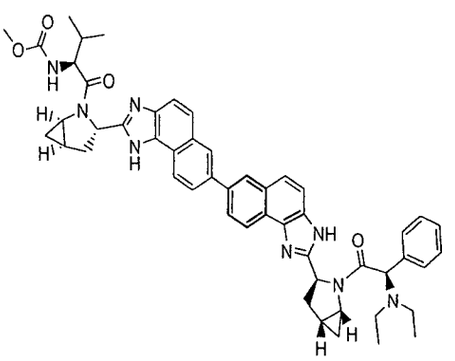


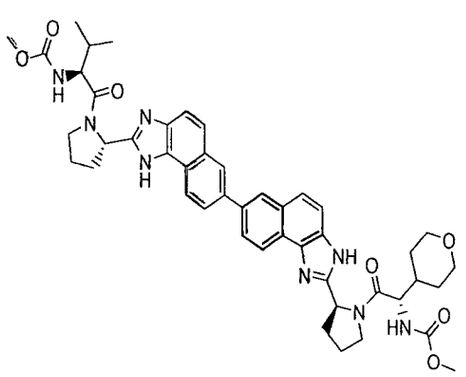
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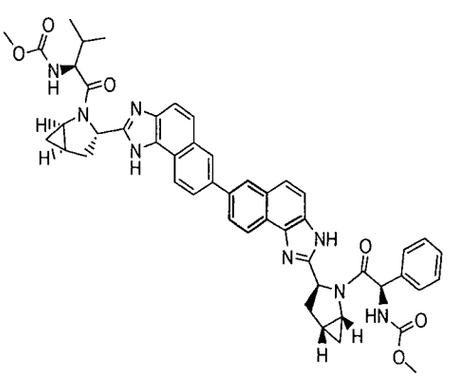


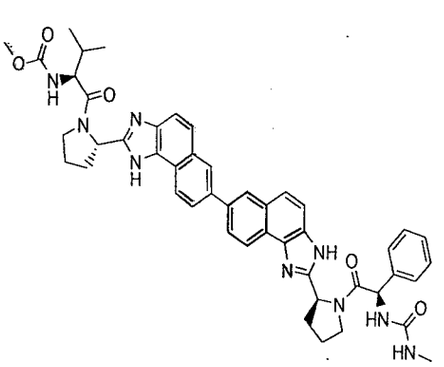


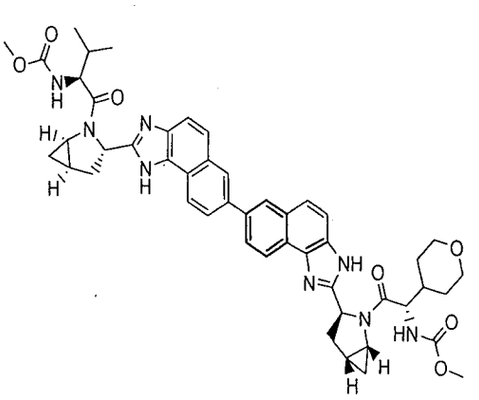


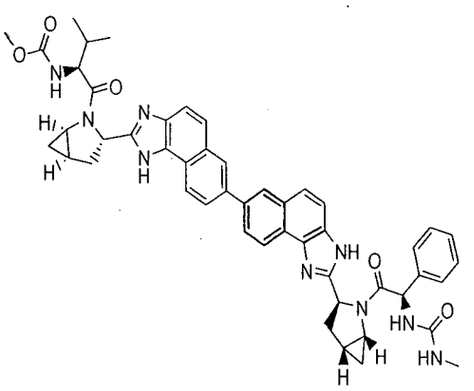


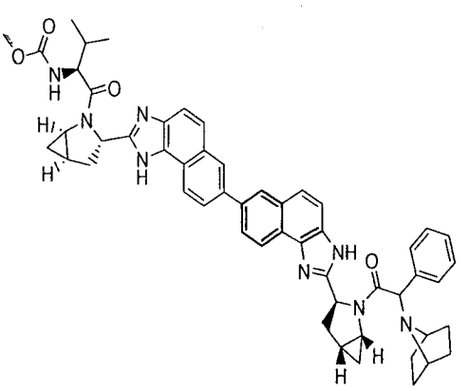




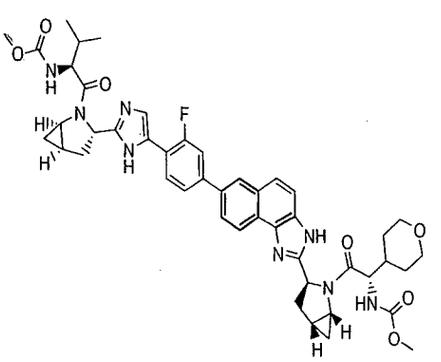








; y



o una de sus sales farmacéuticamente aceptables.

11. Una composición caracterizada porque comprende un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, y un vehículo farmacéuticamente aceptable.

12. La composición de conformidad con la reivindicación 11, caracterizada porque comprende además uno o dos compuestos adicionales que tienen actividad anti-VHC.

13. La composición de conformidad con la reivindicación 12, caracterizada porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

14. La composición de conformidad con la reivindicación 13, caracterizada porque el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

15. La composición de conformidad con la reivindicación 14, caracterizada porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T colaboradores tipo I, ARN interferente, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

16. La composición de conformidad con la reivindicación 15, caracterizada porque al menos uno de los compuestos

adicionales es eficaz para inhibir la función de una diana seleccionada de metaloproteinasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A del VHC e IMPDH para el tratamiento de una infección por VHC.

17. Un método para tratar una infección por VHC en un paciente caracterizado porque comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de conformidad con la reivindicación 1, o una de sus sales farmacéuticamente aceptables.

18. El método de conformidad con la reivindicación 17, caracterizado porque comprende además administrar uno o dos compuestos adicionales que tienen actividad anti-VHC antes de, después de, o de forma simultánea al compuesto de la reivindicación 1, o una de sus sales farmacéuticamente aceptables.

19. El método de conformidad con la reivindicación 18, caracterizado porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

20. El método de conformidad con la reivindicación 19, caracterizado porque el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

21. El método de conformidad con la reivindicación 18,

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

22. El método de conformidad con la reivindicación 18, caracterizado porque al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana seleccionada de metaloproteinasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A del VHC e IMPDH para el tratamiento de una infección por VHC.

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos, composiciones y procedimientos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se revelan composiciones farmacéuticas que contienen tales compuestos y procedimientos de uso de estos compuestos en el tratamiento de infección por VHC.

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from BACHAND, Carol to BRISTOL-MYERS SQUIBB COMPANY, dated 17 March 2008 (17.03.2008)
VIII-2-1(iv)		an assignment from BELEMA, Makonen to BRISTOL-MYERS SQUIBB COMPANY, dated 21 February 2008 (21.02.2008)
VIII-2-1(iv)		an assignment from DEON, Daniel H. to BRISTOL-MYERS SQUIBB COMPANY, dated 07 April 2008 (07.04.2008)
VIII-2-1(iv)		an assignment from GOOD, Andrew C. to BRISTOL-MYERS SQUIBB COMPANY, dated 25 February 2008 (25.02.2008)
VIII-2-1(iv)		an assignment from GOODRICH, Jason to BRISTOL-MYERS SQUIBB COMPANY, dated 22 February 2008 (22.02.2008)
VIII-2-1(iv)		an assignment from JAMES, Clint A. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 April 2008 (03.04.2008)
VIII-2-1(iv)		an assignment from LAVOIE, Rico to BRISTOL-MYERS SQUIBB COMPANY, dated 21 February 2008 (21.02.2008)
VIII-2-1(iv)		an assignment from LOPEZ, Omar D. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 March 2008 (05.03.2008)
VIII-2-1(iv)		an assignment from MARTEL, Alain to BRISTOL-MYERS SQUIBB COMPANY, dated 03 April 2008 (03.04.2008)
VIII-2-1(iv)		an assignment from MEANWELL, Nicholas A. to BRISTOL-MYERS SQUIBB COMPANY, dated 25 February 2008 (25.02.2008)
VIII-2-1(iv)		an assignment from NGUYEN, Van N. to BRISTOL-MYERS SQUIBB COMPANY, dated 21 February 2008 (21.02.2008)

VIII-2-1(iv)		an assignment from ROMINE, Jeffrey Lee to BRISTOL-MYERS SQUIBB COMPANY, dated 22 February 2008 (22.02.2008)
VIII-2-1(iv)		an assignment from RUEDIGER, Edward H. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 April 2008 (03.04.2008)
VIII-2-1(iv)		an assignment from SNYDER, Lawrence B. to BRISTOL-MYERS SQUIBB COMPANY, dated 22 February 2008 (22.02.2008)
VIII-2-1(iv)		an assignment from ST. LAURENT, Denis R. to BRISTOL-MYERS SQUIBB COMPANY, dated 21 February 2008 (21.02.2008)
VIII-2-1(iv)		an assignment from YANG, Fukang to BRISTOL-MYERS SQUIBB COMPANY, dated 21 February 2008 (21.02.2008)
VIII-2-1(iv)		an assignment from LANGLEY, David R. to BRISTOL-MYERS SQUIBB COMPANY, dated 22 February 2008 (22.02.2008)
VIII-2-1(iv)		an assignment from WANG, Gan to BRISTOL-MYERS SQUIBB COMPANY, dated 21 February 2008 (21.02.2008)
VIII-2-1(iv)		an assignment from HAMANN, Lawrence G. to BRISTOL-MYERS SQUIBB COMPANY, dated 29 February 2008 (29.02.2008)

POD-4002

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR: SALLY B. HANSEN
3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY
4. LLEVA EL SELLO DE: SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY
6. EL 28 DE JUNIO DE 2007
7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY
8. N° A295716
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

AUTENTICACIÓN DE COPIA DE ORIGINAL
06 AGO 2007
Eduardo Duarte Gómez
NOTARIO 38 DE BOGOTÁ, D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

AUTENTICACIÓN DE COPIA DE ORIGINAL ARTÍCULO 260 DECRETO LEY 019 DE 2012 EL SUSCRITO NOTARIO HACE CONSTAR QUE EL PRESENTE COPIA COINCIDE CON EL ORIGINAL TENIDO A LA VISTA

BOGDM5 #8242406

06 AGO 2010

Eduardo Durán Gómez
NOTARIO 38 DE BOGOTÁ D.C.

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

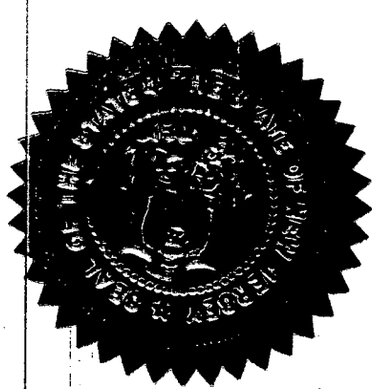
7. BY: Bradley Abelow, NEW JERSEY TREASURER

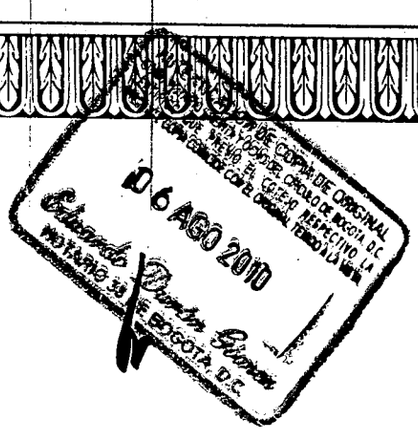
8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow





BAKER & MCKENZIE

Raisbeck, Lara, Rodríguez & 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

AUTENTICACIÓN DE COPIA DE ORIGINAL
COMO NOTARIO TERCERA (3) DEL CÍRCULO DE BOGOTÁ, D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA CONCUERDA CON EL ORIGINAL TENIDO A LA VISTA
06 AGO 2010
Eduardo Durán Gómez
NOTARIO 38 DEL CIRCULO DE BOGOTÁ, D.C.

PODER DE ABOGADO

La abajo firmada,

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en

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

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

BAKER & MCKENZIE

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

06 AGO 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow mayor y domiciliado en Princeton, NJ Estados Unidos de América suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de Abogados de Patentes Senior de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY** con sede en **Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América** está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL-MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	10 098657
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	113103

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 08 OCT. 2010
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