Industria y C
SUPERINTEN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-075545- -00000-0000

Fecha: 2012-05-08 16:43:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1395

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** INHIBIDORES DEL VIRUS DE 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.,** Mayo 08, 2012

(FORMA P-10)

115198-Imprenta Nacional de Colombia-2011

PETITO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-075545- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1395

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Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

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

(2) SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

Dirección: Route 206 and Province Line Road
Princeton, New Jersey 08543-4000, U.S.A.

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual _____

Número _____

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakermckenzie.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual _____

Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

Nombre: PACK, Shawn, K.; TYMONKO, Steven; PATEL, Bharat, P.; NATALIE, JR., Kenneth, J.; BELEMA, Makonen

Dirección: c/o Bristol-Myers Squibb Company 1 Squibb Drive New Brunswick, NJ 08903 (US); c/o Bristol-Myers Squibb Company 1 Squibb Drive New Brunswick, NJ 08903 (US); 174 Shrewsbury CT, Pennington NJ 08534, US; c/o Bristol-Myers Squibb Company 1 Squibb Drive New Brunswick, NJ 08903 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US).

Nacionalidad o Domicilio: Estados unidos de América

(5) PCT (85)

Solicitud Internacional No.	PCT/US2010/055045	Fecha 02-11-2010
Publicación Internacional No.	WO 2011/059850	Fecha 19-05-2011

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

(7) Clasificación Internacional (51) C07D 209/54

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	11-11-2009	61/260,115
US	31-08-2010	61/378,806
US	29-10-2010	12/915,605

(9) Comprobante de pago No. 12-0044419 – 12-0044355 **Fecha** Mayo 07, 2012

(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
- [X] Documento de cesión del inventor al solicitante o a su causante
- [X] 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**

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

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

RECIBO DE PAGO

2012/009

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0044419

Bogotá D.C., Mayo 07 de 2012 - 07:38:19

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	181166171	03/05/2012	137.504.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-075545- -00000-0000
Fecha: 2012-05-08 16:43:08 Dep. 2020 DIR.NUEVASCR
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2012/009

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0044355

Bogotá D.C., Mayo 07 de 2012 - 07:38:19

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	181166171	03/05/2012	137.504.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACION DE MARCAS Y LEMAS COMERCIALES	120.000.00	120.000.00
				$120.000.00

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-075545- -00000-0000
Fecha: 2012-05-08 16:43:08 Dep. 2020 DIR.NUEVASCR
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EXTRACTOS

Industria y Comercio
SUPERINTENDENCIA

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

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

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional: C07D 209/54

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

(72) Inventor(es) PACK, Shawn, K.; TYMONKO, Steven; PATEL, Bharat, P.; NATALIE, JR., Kenneth, J.; BELEMA, Makonen

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/260,115	11-11-2009	US
	61/378,806	31-08-2010	US
	12/915,605	29-10-2010	US

(85) Fecha inicio fase nacional: 11-06-2012
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 02-11-2010
No. de solicitud PCT/US2010/055045

(87) Publicación internacional
Fecha: 19-05-2011
N° publicación: WO 2011/059850

(54) Titulo: INHIBIDORES DEL VIRUS DE HEPATITIS C

Industria y Comercio
SUPERINTENDENCIA

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

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

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12/915,605	29-10-2010	US

(85) Fecha límite inicio fase nacional: 11-06-2012
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 02-11-2010
No. de solicitud: PCT/US2010/055045

(87) Publicación internacional:
Fecha: 19-05-2011
No. Publicación: WO 2011/059850

(54)Titulo: INHIBIDORES DEL VIRUS DE HEPATITIS C

(57) Resumen: La presente invención se refiere a procesos para elaborar compuestos útiles en el tratamiento de infección por virus de hepatitis C (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:

(51) Int Cl: C07D 209/54

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

(72) Inventor(es) PACK, Shawn, K.; TYMONKO, Steven; PATEL, Bharat, P.; NATALIE, JR., Kenneth, J.; BELEMA, Makonen

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

(30) Prioridad	(31) *No.*	32) *Fecha*	(33) *País*
	61/260,115	11-11-2009	US
	61/378,806	31-08-2010	US
	12/915,605	29-10-2010	US

(85) Fecha límite inicio fase nacional: 11-06-2012

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 02-11-2010
No. de solicitud PCT/US2010/055045

(87) Publicación internacional
Fecha: 19-05-2011
N° publicación: WO 2011/059850

(54) Titulo: INHIBIDORES DEL VIRUS DE HEPATITIS C

RESUMEN:

La presente invención se refiere a procesos para elaborar compuestos útiles en el tratamiento de infección por virus de hepatitis C (VHC).

COPIA SOLICITUD
INTERNACIONAL

PATENT COOPERATION TREATY PCT/US2010/055045

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

MINGO, Pamela, A.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
24 April 2012 (24.04.2012)

Applicant's or agent's file reference
11370AWOPCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2010/055045

International filing date *(day/month/year)*
02 November 2010 (02.11.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
PATEL, Bharat, P.
c/o Bristol-Myers Squibb Company
1 Squibb Drive
New Brunswick, NJ 08903
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
PATEL, Bharat, P.
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Pennington, NJ 08534
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 95

Authorized officer
Vigne Frederic
e-mail pt04.pct@wipo.int
Telephone No. +41 22 338 74 04

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

(19) World Intellectual Property Organization
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PCT

(10) International Publication Number
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(51) International Patent Classification:
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(22) International Filing Date:
2 November 2010 (02.11.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/260,115	11 November 2009 (11.11.2009)	US
61/378,806	31 August 2010 (31.08.2010)	US
12/915,605	29 October 2010 (29.10.2010)	US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PACK, Shawn, K.** [US/US]; c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, NJ 08903 (US). **TYMONKO, Steven** [US/US]; c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, NJ 08903 (US). **PATEL, Bharat, P.** [US/US]; c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, NJ 08903 (US). **NATALIE, JR., Kenneth, J.** [US/US]; c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, NJ 08903 (US). **BELEMA, Makonen** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US).

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

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

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2011/059850 A1

(54) Title: HEPATITIS C VIRUS INHIBITORS

(57) Abstract: The present disclosure relates to methods for making compounds useful in the treatment of Hepatitis C virus (HCV) infection.

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/260,115 filed November 11, 2009 and U.S. Provisional Application No. 61/378,806 filed August 31, 2010, incorporated herein by reference in their entirety.

[0002] The present disclosure relates to methods for making compounds useful in the treatment of Hepatitis C virus (HCV) infection.

[0003] 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.

[0004] The current standard of care for HCV, which employs a combination of pegylated-interferon and ribavirin, has a non-optimal success rate in achieving sustained viral response and causes numerous side effects. Thus, there is a clear and long-felt need to develop effective therapies to address this undermet medical need.

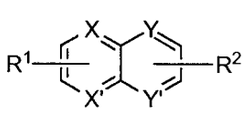
[0005] HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5′ untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

[0006] Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome due to the high error rate of the encoded RNA dependent RNA polymerase which lacks a proof-reading capability. At least six major genotypes have been characterized, and more than 50 subtypes have been described with distribution worldwide. The clinical significance of the genetic heterogeneity of HCV has demonstrated a propensity for mutations to arise during monotherapy treatment, thus additional treatment options for use are desired. The possible modulator effect of genotypes on pathogenesis and therapy remains elusive.

[0007] The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions by both acting as a cofactor for the NS3 protease and assisting in the membrane localization of NS3 and other viral replicase components. The formation of a NS3-NS4A complex is necessary for proper protease activity resulting in increased proteolytic efficiency of the cleavage events. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV with other HCV proteins, including NS5A, in a replicase complex.

[0008] Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in the following references: Tan, S.L. et al., *Virology*, 284:1-12 (2001); Park, K.-J. et al., *J. Biol. Chem.*, 30711-30718 (2003); Tellinghuisen, T.L. et al., *Nature*, 435:374 (2005); Love, R.A. et al., *J. Virol.*, 83:4395 (2009); Appel, N. et al., *J. Biol. Chem.*, 281:9833 (2006); Huang, L., *J. Biol. Chem.*, 280:36417 (2005); Rice, C. et al., World Patent Application WO 2006/093867.

[0009] In its first aspect the present disclosure provides a compound of Formula (I)



(I),

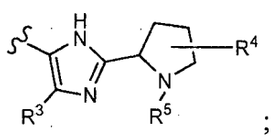
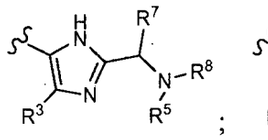
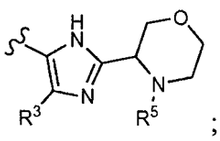
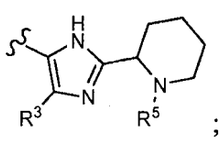
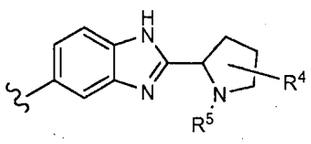
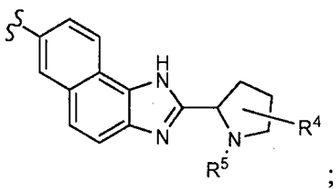
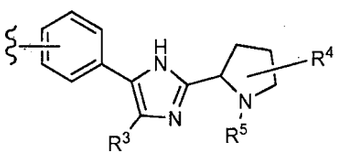
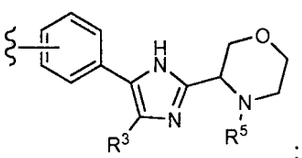
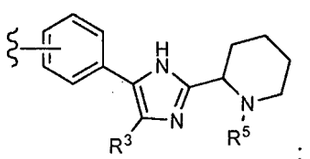
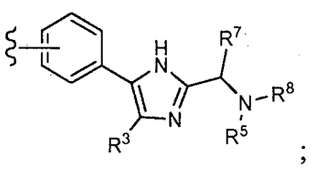
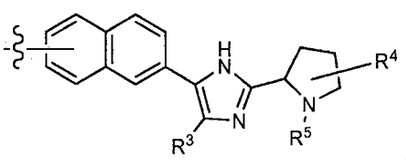
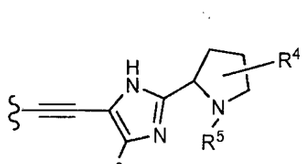
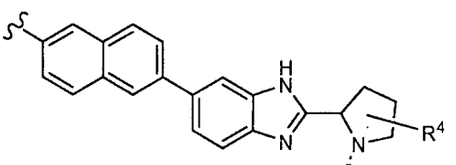
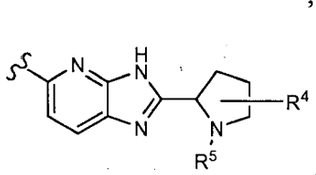
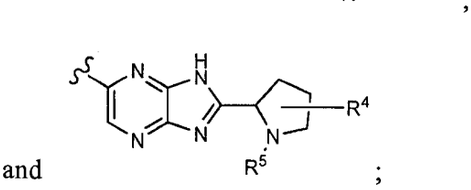
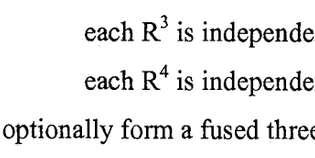
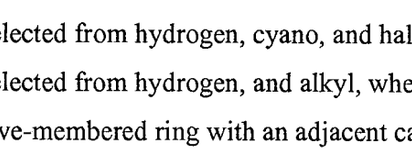
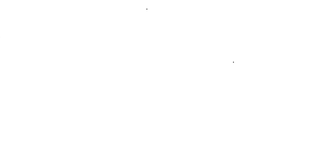
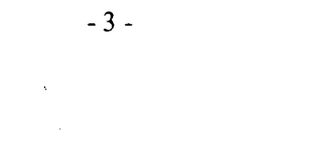
or a pharmaceutically acceptable salt thereof, wherein:

X and X′ are each independently selected from CH, CR^1, and N;

Y and Y′ are each independently selected from CH, CR^2, and N;

provided that no more than two of X, X′, Y, and Y′ are N;

R^1 and R^2 are independently selected from


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each R^3 is independently selected from hydrogen, cyano, and halo;

each R^4 is independently selected from hydrogen, and alkyl, wherein the alkyl can optionally form a fused three- to five-membered ring with an adjacent carbon atom

wherein said ring is optionally substituted with one or two methyl groups; or, R^4 and the carbon to which it is attached form an ethylene group;

each R^5 is independently selected from hydrogen and $-C(O)R^6$;

each R^6 is independently selected from alkoxy, alkyl, arylalkoxy, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl; and

each R^7 and R^8 is independently selected from hydrogen and alkyl.

[0010] In a first embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

X and X′ are independently selected from CH and CR^1; and

Y, and Y′ are independently selected from CH and CR^2.

[0011] In a second embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

X and X′ are independently selected from CH and CR^1; and

Y and Y′ are each N.

[0012] In a third embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

Y and X′ are each N;

X is selected from CH and CR^1; and

Y′ is selected from CH and CR^2.

[0013] In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

X′ is N; and

X is selected from CH and CR^1; and

Y and Y′ are independently selected from CH and CR^2.

[0014] In a second 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 second aspect the

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

[0015] In a fourth embodiment of the second aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

[0016] In a fifth embodiment of the second aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

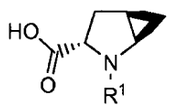
[0017] In a third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the third aspect the method further comprises administering at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment of the third aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the third aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

[0018] In a fourth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient

a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

[0019] In a fifth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

[0020] In a fourth aspect the present disclosure provides a process for preparing a compound of formula (X)

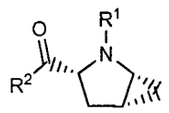


(I);

wherein R^1 is selected from hydrogen and a nitrogen protecting group;

the process comprising:

(a) reacting a compound of formula (II)



(II);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen and a nitrogen protecting group; and

R^2 is selected from amino, alkoxy, and arylalkoxy; and

with a base, and

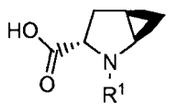
(b) treating the product of step (a) with water.

[0021] In a first embodiment of the fourth aspect R^1 is hydrogen.

[0022] In a second embodiment of the fourth aspect R^1 is a nitrogen protecting group. In a third embodiment of the fourth aspect the nitrogen protecting group is a *tert*-butoxycarbonyl group.

[0023] In a fifth embodiment of the fourth aspect the base is selected from a metal alkoxide and a metal hydroxide. In a sixth embodiment of the fourth aspect the base is selected from sodium ethoxide, sodium isopropoxide, sodium *tert*-butoxide, sodium hydroxide, lithium hydroxide, potassium hydroxide, potassium isopropoxide, potassium *tert*-butoxide, lithium *tert*-butoxide, and lithium isopropoxide.

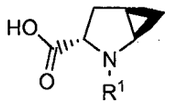
[0024] In a seventh embodiment of the fourth aspect the process further comprises treating a product of formula (I)



(I),

wherein R^1 is hydrogen;

with a nitrogen protecting reagent to provide a compound of formula (I)

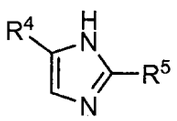


(I),

wherein R^1 is a nitrogen protecting group.

[0025] In an eight embodiment of the fourth aspect the nitrogen protecting group is *tert*-butoxycarbonyl.

[0026] In a fifth aspect the present disclosure provides a process for preparing a compound of formula (Z)



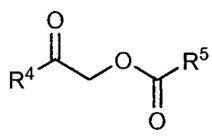
(III),

or a pharmaceutically acceptable salt thereof, wherein:

$R^4$and R^5 are independently selected from hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, and heterocyclylalkyl;

the process comprising:

treating a compound of formula (Q)

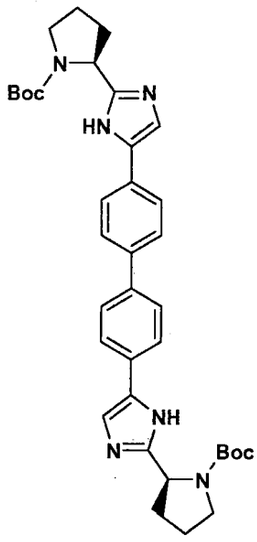


(IV),

with a base in the presence of ammonium acetate.

[0027] In a first embodiment of the fifth aspect the base is selected from a tertiary amine, an aromatic amine, an aniline, and a substituted imidazole. In a second embodiment of the fifth aspect the base is selected from 1,4-dimethylpiperazine, 3-quinuclidinol, 3-methylpyridine, 1-methylimidazole, dimethylbutylamine, N,N-dimethylaniline, dimerpranol, quinoxazoline, creatinine, 2-methylimidazole, 4-methylimidazole, imidazole, morpholine, N-methylmorpholine, 1,8-diazabicycloundec-7-ene, 1,4-diazabicyclo[2.2.2]octane, collidine, 4-chloroimidazole, 2-chloroimidazole, 4-cyanoimidazole, benzimidazole, diisopropylethylamine and 2,6-lutidine. In a third embodiment the base is imidazole.

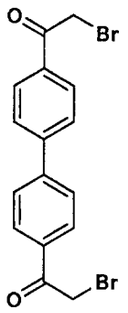
[0028] In a sixth aspect the present disclosure provides a process for the preparation of Example 145



Example 145,

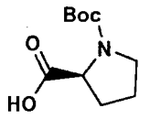
the process comprising:

(a) treating Example 143



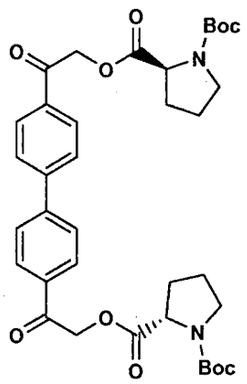
Example 143,

with Example 144



Example 144,

in the presence of a base to produce a compound of formula (V)



(V);

(b) treating the compound of formula (V) with ammonium acetate in the presence of a base; and

(c) treating the product of step (b) with methanol.

[0029] In a first embodiment of the seventh aspect the process is a continuous process.

[0030] Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

[0031] Yet other aspects and embodiments may be found in the description provided herein.

[0032] The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substituent at any given location.

[0033] It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

[0034] It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when R^1 and R^2 both contain an R4 group, the two R^4 groups may be the same or different.

[0035] 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.

[0036] As used in the present specification, the following terms have the meanings indicated:

[0037] As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

[0038] 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".

[0039] 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.

[0040] The term "alkenyloxy," as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

[0041] The term "alkenyloxycarbonyl," as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

[0042] The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

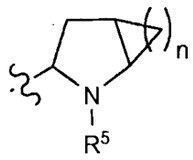
[0043] The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

[0044] The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0045] The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

[0046] The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

[0047] 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 R^4 is alkyl, the alkyl can optionally form a fused three-membered ring with an adjacent carbon atom to provide the structure shown below.



wherein n is selected from 1 and 2.

[0048] The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

[0049] The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

[0050] The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

[0051] The term "amino," as used herein, refers to $-NR^qR^s$, wherein R^q and R^s are independently selected from hydrogen, alkyl, and arylalkyl.

[0052] 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 alkenyl, 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.

[0053] The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0054] The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0055] 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 substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, $-NR^xR^y$, and oxo.

[0056] The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

[0057] The term "base," as used herein, refers to a compound that accepts protons.

[0058] The term "continuous process," as used herein, refers to a multi-step process wherein the intermediates formed are not isolated.

[0059] The term "cyano," as used herein, refers to -CN.

[0060] The term "cycloalkyl," as used herein, refers to a saturated monocyclic or bicyclic hydrocarbon ring system having three to fourteen carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[3.1.1]heptyl, and adamantyl. 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 further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, nitro, and oxo.

[0061] The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0062] The term "cycloalkyloxycarbonyl," as used herein, refers to a cycloalkyloxy group attached to the parent molecular moiety through a carbonyl group.

[0063] The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

[0064] The term "ethylene," as used herein, refers to $=CH_2$.

[0065] The term "formyl," as used herein, refers to -CHO.

[0066] The terms "halo" and "halogen," as used herein, refers to Cl, Br, F, or I.

[0067] The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0068] The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0069] The term "haloalkyl," as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

[0070] 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 three- to seven-membered aromatic or non-aromatic carbocyclic ring; bicyclic groups in which the heterocyclyl ring is substituted with a three- to seven-membered spirocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl, and 2-azabicyclo[2.2.2]oct-3-yl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, quinolinyl, tetrahydropyranyl, thiazolyl, thienyl, and thiomorpholinyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxycarbonyl, 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.

[0071] The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

[0072] The term "heterocyclylalkoxycarbonyl," as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0073] 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 substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

[0074] The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

[0075] The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

[0076] The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

[0077] The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.

[0078] The term "hydroxy," as used herein, refers to -OH.

[0079] The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

[0080] The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0081] The term "metal alkoxide," as used herein, refers to M-OR, wherein M is a metal selected from sodium, lithium, and potassium and R is an alkyl group.

[0082] The term "metal hydroxide," as used herein, refers to M-OH, wherein M is a metal selected from sodium, lithium, and potassium.

[0083] The term "nitro," as used herein, refers to $-NO_2$.

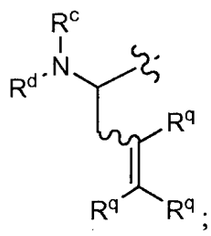
[0084] The term "nitrogen protecting group," as used herein, refers to groups intended to protect an amino group against undesirable reactions during synthetic procedures. Common N-protecting groups include, but are not limited to, acyl groups such as acetyl, benzoyl, 2-bromoacetyl, 4-bromobenzoyl, *tert*-butylacetyl, carboxaldehyde, 2-chloroacetyl, 4-chlorobenzoyl, α-chlorobutyryl, 4-nitrobenzoyl, o-nitrophenoxyacetyl, phthalyl, pivaloyl, propionyl, trichloroacetyl, and trifluoroacetyl; sulfonyl groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, benzyloxycarbonyl (Cbz), *tert*-butyloxycarbonyl (Boc), p-chlorobenzyloxycarbonyl, and p-methoxybenzyloxycarbonyl.

[0085] The term "nitrogen protecting reagent," as used herein, refers to a compound that under the reaction conditions adds a nitrogen protecting group to a protectable nitrogen atom.

[0086] 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, cycloalkyloxy, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkyloxycarbonyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR′, and $-C(NCN)NR^xR^y$, wherein R′ is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the

heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0087] The term "(NR^cR^d)alkenyl," as used herein, refers to



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

[0088] 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, C_2 alkynyl, arylalkoxycarbonyl, carboxy, cyano, cycloalkyl, halo, 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.

[0089] 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.

[0090] The term "(NR^eR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^eR^f$ groups.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^xR^y groups.

[0096] 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.

[0097] 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 and alkyl.

[0098] The term "($NR^{x'}R^{y'}$)carbonyl," as used herein, refers to an -$NR^{x'}R^{y'}$ group attached to the parent molecular moiety through a carbonyl group.

[0099] The term "oxo," as used herein, refers to =O.

[00100] The term "sulfonyl," as used herein, refers to -SO_2-.

[00101] 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 stereoisomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of stereoisomers 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.

[00102] 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.

[00103] The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

[00104] The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable stereoisomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

[00105] The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

[00106] The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-

hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

[00107] 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 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.

[00108] 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 sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether

administered in combination, serially, or simultaneously. The compounds of Formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more 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.

[00109] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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*, 3(6):318 (1986).

[00121] Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

[00122] For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

[00123] Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

[00124] Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

[00125] Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

[00126] 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.

[00127] 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.

[00128] Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

[00129] 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.

[00130] 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.

[00131] The term "patient" includes both human and other mammals.

[00132] 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.

[00133] The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology*, 38:1282 (2003); *Biochem. Biophys. Res. Commun.*, 313:42 (2004); *J. Gastroenterol.*, 38:567 (2003)).

[00134] Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
NIM811 Debio-025		Cyclophilin inhibitors	Novartis Debiopharm
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-Tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	Antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Summetrel	Antiviral	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO 2005/047288 26 May 2005	Antiviral	HCV inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	Monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA / Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B replicase inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B replicase inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B replicase inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B replicase inhibitor	Gene Labs / Novartis

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
2'C MeA	Antiviral	NS5B replicase inhibitor	Gilead
PSI 6130	Antiviral	NS5B replicase inhibitor	Roche
R1626	Antiviral	NS5B replicase inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B replicase inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	Ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	Ribavirin	Schering-Plough Corporation, Kenilworth, NJ
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

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Ceplene	Immunomodulator	Immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CELLCEPT®	Immunosuppressant	HCV IgG immuno-suppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immuno-suppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	Albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
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

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

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b / ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	Antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	Caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B replicase inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
Boceprevir	Antiviral	Serine protease inhibitor	Schering-Plough
TMS-435	Antiviral	Serine protease inhibitor	Tibotec BVBA, Mechelen, Belgium
BI-201335	Antiviral	Serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
MK-7009	Antiviral	Serine protease inhibitor	Merck
PF-00868554	Antiviral	Replicase inhibitor	Pfizer
ANA598	Antiviral	Non-Nucleoside NS5B polymerase inhibitor	Anadys Pharmaceuticals, Inc., San Diego, CA, USA

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
IDX375	Antiviral	Non-Nucleoside replicase inhibitor	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	NS5B polymerase inhibitor	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada
PSI-7851	Antiviral	Nucleoside polymerase inhibitor	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	NS5B polymerase inhibitor	Vir °Chem Pharma
VCH-916	Antiviral	NS5B polymerase inhibitor	Vir °Chem Pharma
GS-9190	Antiviral	NS5B polymerase inhibitor	Gilead
Peg-interferon lamda	Antiviral	Interferon	ZymoGenetics / Bristol-Myers Squibb

[00135] 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.

[00136] 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.

[00137] 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*.

[00138] The abbreviations used in the present application, including particularly in the illustrative examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: Ph for phenyl; DME for 1,2-dimethoxyethane; TFA for trifluoroacetic acid; DCM for dichloromethane; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate; DMF for N,N-dimethylformamide; iPr_2EtN, DIEA, or DIPEA for diisopropylethylamine; h, hr, or hrs for hrs; MeOD for CD_3OD; MeOH for methanol; min or mins for minutes; EtOH for ethanol; Et for ethyl; DMSO for dimethylsulfoxide; rt or RT or Rt for room temperature or retention time (context will dictate); EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Boc, boc, or BOC for *tert*-butoxycarbonyl; EtOAc or EtOAc for ethyl acetate; THF for tetrahydrofuran; TBDPS for *t*-butyldimethylsilyl; DMAP for 4-dimethylaminopyridine; TBAF for tetrabutylammonium fluoride; OAc for acetate; AcOH for acetic acid; SEMCl for 2-(trimethylsilyl)ethoxymethyl chloride; d for days; TEA or Et_3N for triethylamine; ACN or MeCN for acetonitrile; NCS for N-chlorosuccinimide; NBS for N-bromosuccinimide; Et_2O for diethyl ether; DCE for 1,2-dichloroethane; d for days; and DEA for diethylamine.

[00139] 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.

[00140] Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art.

SYNTHESIS OF COMMON CAPS

Compound Analysis Conditions

[00141] Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters MICROMASS® ZQ MS system. It should be noted that retention times may vary slightly between machines. Additional LC conditions applicable to the current section, unless noted otherwise.

Cond.-MS-W1

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

Cond.-MS-W2

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

Cond.-MS-W5

Column = XTERRA® 3.0 X 50 mm S7

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

Cond.-D1
Column = XTERRA® C18 3.0 X 50 mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-D2
Column = PHENOMENEX® Luna 4.6 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-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

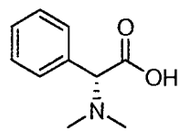
Flow Rate = 4 mL/min

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

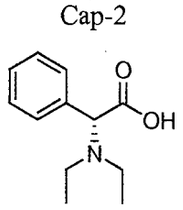
Cap-1



(R)-2-(Dimethylamino)-2-phenylacetic acid

[00142] 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 (Condition 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.

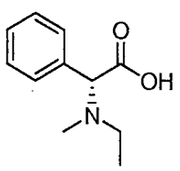
Cap-2



(R)-2-(Diethylamino)-2-phenylacetic acid

[00143] $NaBH_3CN$ (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). ^1H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}$ -102.21° (c=0.357, H_2O); crop-2: $[\alpha]^{25}$ -99.7° (c=0.357, H_2O). LC (Condition 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

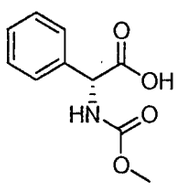


[00144] Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred 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 (Condition 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.

[00145] 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 (Condition 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



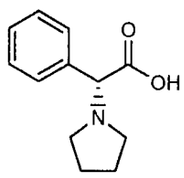
(R)-2-(Methoxycarbonylamino)-2-phenylacetic acid

[00146] $ClCO_2Me$ (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). ^{1}H 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 (Condition 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.

[00147] 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 (Condition 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.

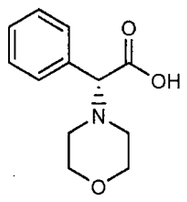
Cap-5



[00148] 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). ^1H 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

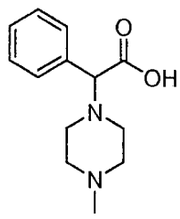
(Condition I); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

Cap-6



[00149] 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 (Condition 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

[00150] A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a freezer (-25 °C) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide benzyl 2-phenyl-2-(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 7.78 (d, *J*= 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m,

2H), 6.12 (s, 1H), 5.16 (d, *J*=12.5, 1H), 5.10 (d, *J*=12.5, 1H), 2.39 (s, 3H). RT=3.00 (Condition III); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

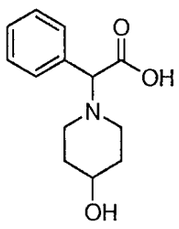
[00151] A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was 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 stereoisomers in a 38.2 to 58.7 ratio. The separation of the stereoisomers 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. Stereoisomer-1 (1.474 g) and stereoisomer-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 (Condition III); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

[00152] A methanol (10 mL) solution of either stereoisomer 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 (Condition 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.

[00153] 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 intermediates, as described below.

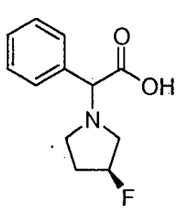
Cap-8



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

[00154] The stereoisomeric 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 stereoisomer-1 and 209.1 mg of stereoisomer-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 (Condition 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.

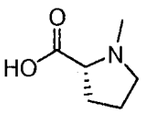
Cap-9



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

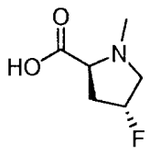
[00155] The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective stereoisomers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water + 1 mL saturated $NaHCO_3$ solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to prepare Cap-9a and Cap-9b. Cap-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H_2O/methanol/TFA solvent): ^{1}H NMR (DMSO-d_6, δ=2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, *J*=53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT=0.42 (Condition I); >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; Cap-9b (diastereomer-2): ^{1}H NMR (DMSO-d_6, δ=2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, *J*=55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT=0.44 (Condition I); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

Cap-10



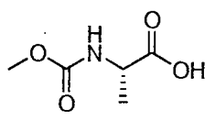
[00156] To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (CELITE®) and concentrated *in vacuo* to provide Cap-10 as an off-white solid (2.15 g). ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J*=9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT=0.28 (Condition II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

Cap-11



[00157] 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 (Condition II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

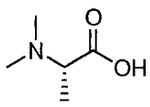
Cap-12 (same as Cap-52)



(S)-2-(Methoxycarbonylamino)propanoic acid

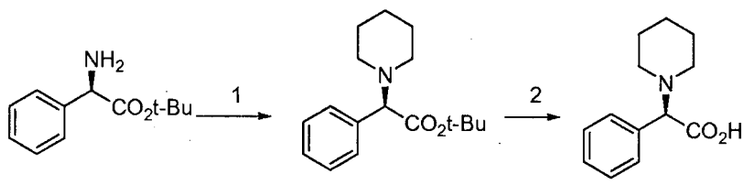
[00158] L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid 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



[00159] 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



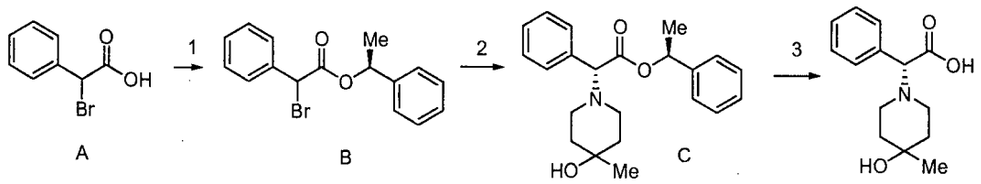
Cap-14

(R)-2-Phenyl-2-(piperidin-1-yl)acetic acid

[00160] 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 $(M+H)^+$.

[00161] 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



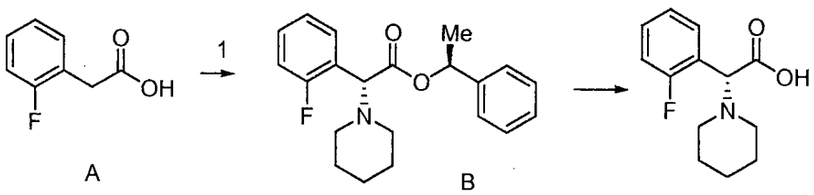
[00162] Step 1: (S)-1-Phenylethyl 2-bromo-2-phenylacetate. To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution 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).

[00163] 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 $(M+H)^+$.

[00164] Step 3: (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid. To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish solid (0,128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

Cap-16



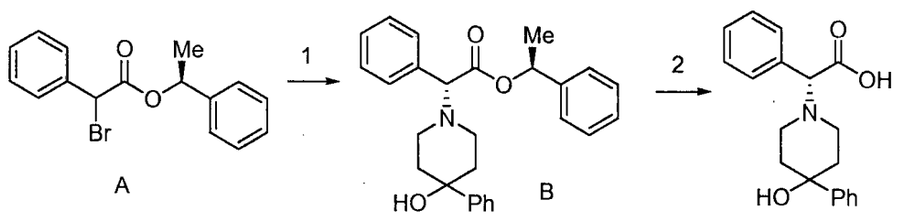
A B *(R)*-Cap-16

[00165] 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).

[00166] 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 $(M+H)^+$.

[00167] 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

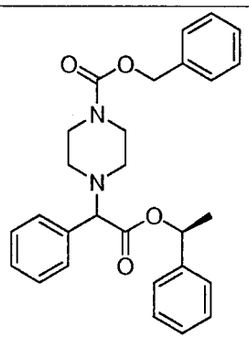
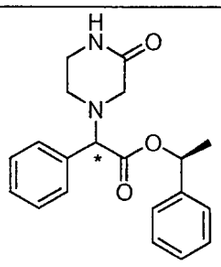


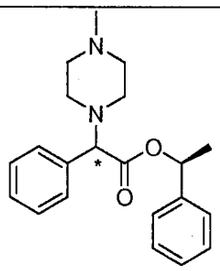
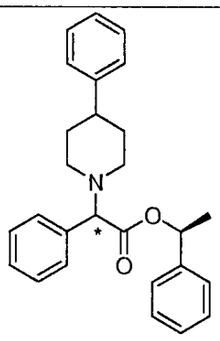
A B *(R)*-Cap-17

[00168] 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^1NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, *J*=11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, *J*=11.1, 2.5 Hz, 1H), 2.25 (dt, *J*=12.1, 4.6 Hz, 1H), 2.12 (dt, *J*=12.1, 4.6 Hz, 1H), 1.73 (dd, *J*=13.6, 3.0 Hz, 1H), 1.64 (dd, *J*=13.6, 3.0 Hz, 1H), 1.40 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

[00169] 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		Diastereomer 1: RT=11.76 minutes (Condition 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 (Condition 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 (Condition 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 (Condition 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 (Condition I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22. Found: 400.48 $(M+H)^+$. Diastereomer 2: RT=9.76 minutes (Condition 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% CO_2-10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored at 220 nm

Injection: 1.0 mg/3mL methanol

Condition II

Column: CHIRALCEL® OD-H Column, 4.62x50 mm, 5μm

Solvents: 90% CO_2-10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

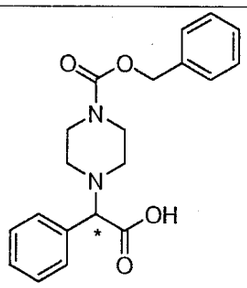
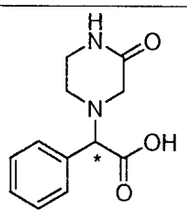
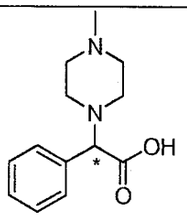
Flow rate: 2.0 mL/min.

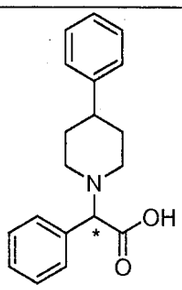
UV monitored at 220 nm

Injection: 1.0 mg/mL methanol

[00170] 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 $(M+H)^+$.

[00171] The following carboxylic acids were prepared in optically pure form in a similar fashion:

Cap-17a		RT=2.21 (Condition II); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.20-2.35 (m, 2H) 2.34-2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06-7.53 (m, 10H). LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_4$ 354.16; Found: 355.38 $(M+H)^+$.
Cap-17b		RT=0.27 (Condition III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.10; Found: 235.22 $(M+H)^+$.
Cap-17c		RT=0.48 (Condition II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.14; Found: 235.31 $(M+H)^+$.

Cap-17d		RT=2.21 (Condition 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

Final % B=100

Gradient Time=4 min

Flow Rate=4 mL/min

Wavelength=220

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

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

Condition II

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B=0

Final % B=100

Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

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

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

Condition III

Column: PHENOMENEX® 10µ 3.0 X 50 mm

Start % B=0

Final % B=100

Gradient Time=2 min

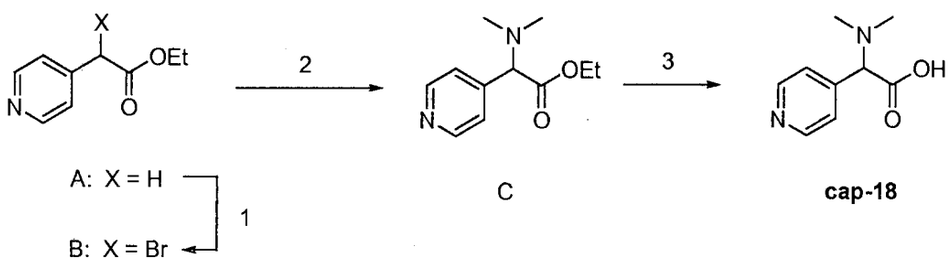
Flow Rate=4 mL/min

Wavelength=220

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

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

Cap-18



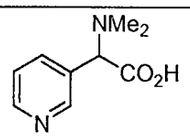
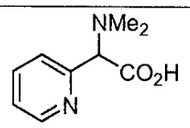
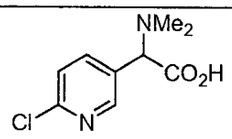
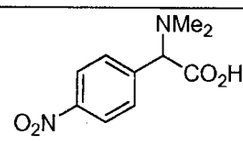
[00172] Step 1: (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate. To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °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 $(M+H)^+$.

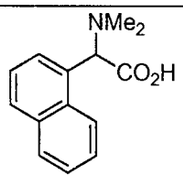
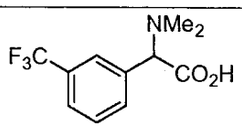
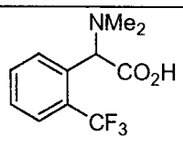
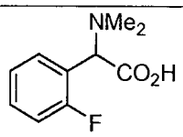
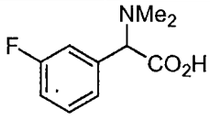
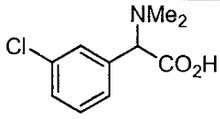
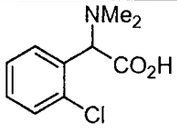
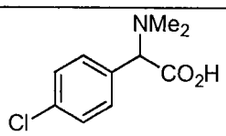
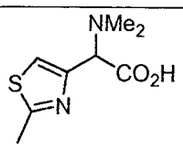
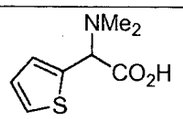
[00173] Step 2: (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate. To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (BIOTAGE®, 40+M SiO_2 column; 50%-100% ethyl acetate-hexane) to provide the title

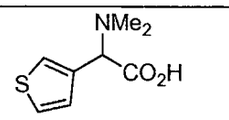
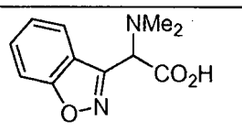
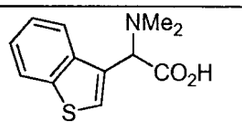
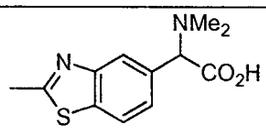
compound (0.539 g, 31%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J=6.0 Hz, 2H), 7.36 (d, J=6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, J=7.0 Hz). LCMS: Anal. Calcd. for $C_{11}H_{16}N_2O_2$: 208; found: 209 $(M+H)^+$.

[00174] 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).

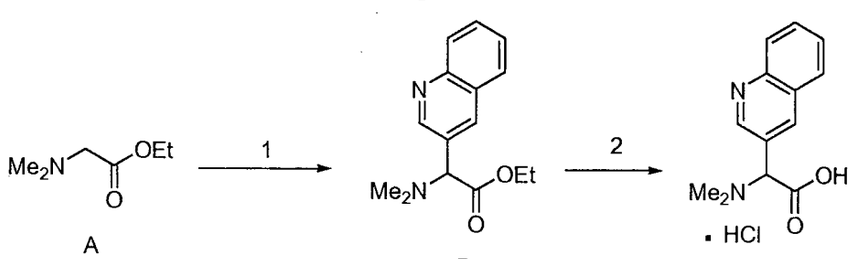
[00175] The following examples were prepared in similar fashion using the method described above:

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

Cap-23		LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 229; found: 230 $(M+H)^+$.
Cap-24		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{12}N_2O_2S$: 200; found: 201 $(M+H)^+$.
Cap-32		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.

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

Cap-37



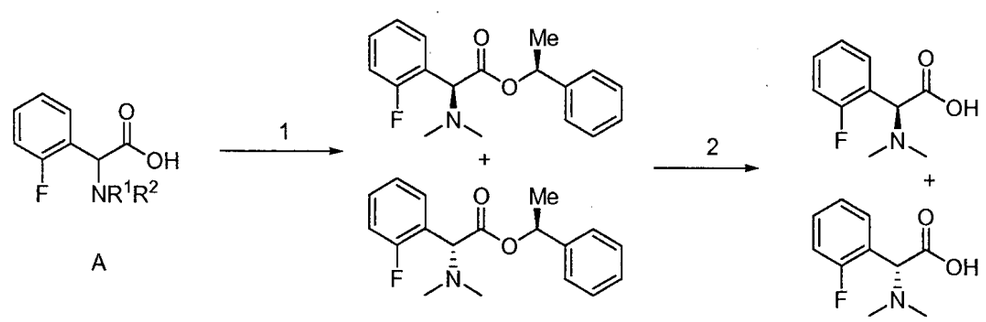
A B cap-37

[00176] 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 $(M+H)^+$.

[00177] 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



[00178] 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 $(M+H)^+$.

[00179] Step 2: (R)-2-(Dimethylamino)-2-(2-fluorophenyl)acetic acid. A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (CELITE®), and concentrated *in vacuo*. This gave the title compound as a colorless solid (0.503 g, 98%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.

[00180] The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

Cap-39

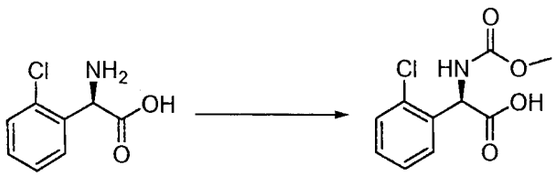


cap-39

[00181] 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 the TFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H),

5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.

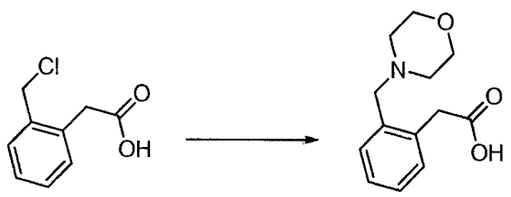
Cap-40



cap-40

[00182] 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

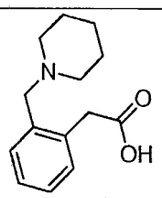
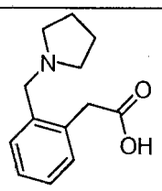
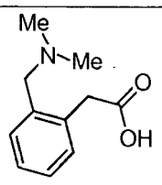
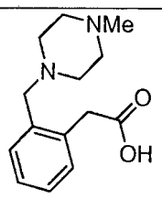


cap-41

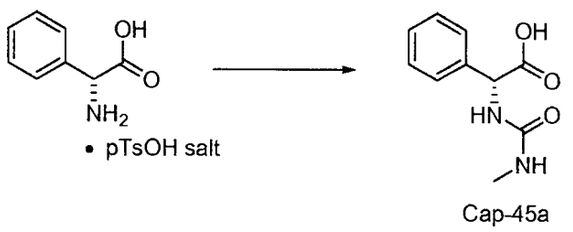
[00183] To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous 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 $(M+H)^+$.

[00184] 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

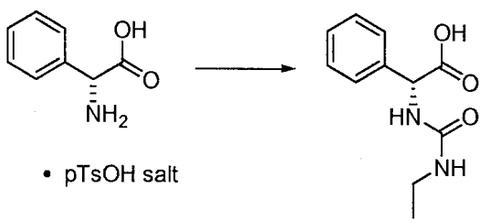


Cap-45a

[00185] 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.

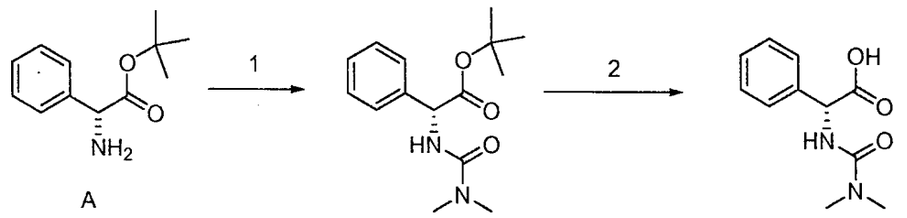
Cap-46



cap-46

[00186] 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.

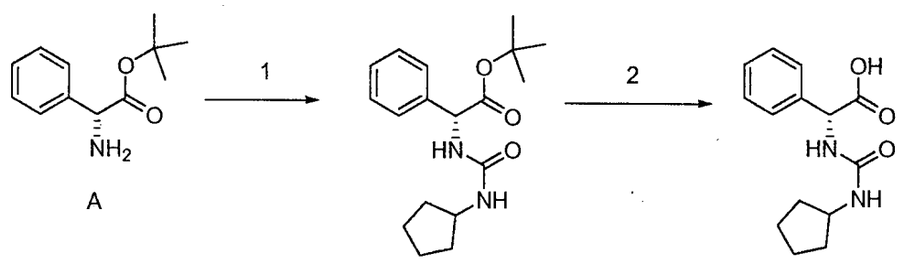
Cap-47



[00187] 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.

[00188] 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



A B Cap-48

[00189] 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 taken 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.

[00190] 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.

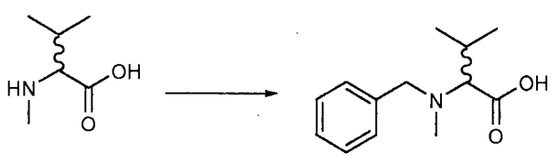
Cap-49



cap-49

[00191] To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (XTERRA® 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29-7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.09; Found: 180.20 $(M+H)^+$.

Cap-50

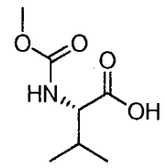


Cap-50

[00192] 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 $(M+H)^+$.

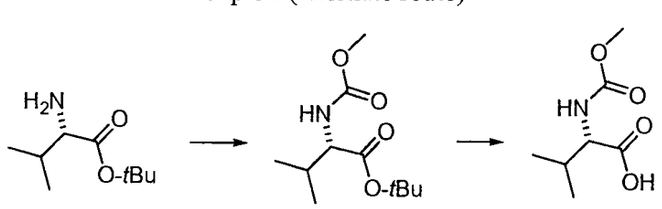
Cap-51



(S)-2-(Methoxycarbonylamino)-3-methylbutanoic acid

[00193] Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added dropwise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford Cap-51 as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, δ=2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, *J*=8.6, 1H), 3.84 (dd, *J*=8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922.

Cap-51 (alternate route)



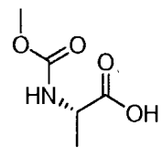
(S)-2-(Methoxycarbonylamino)-3-methylbutanoic acid

[00194] DIEA (137.5 mL, 0.766 mol) was added to a suspension of (*S*)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride (75.0 g, 0.357 mol) in THF (900 mL), and the mixture was cooled to 0 °C (ice/water bath). Methyl chloroformate (29.0 mL, 0.375 mol) was added dropwise over 45 min, the cooling bath was removed and the heterogeneous mixture was stirred at ambient temperature for 3 h. The solvent was removed under diminished pressure and the residue partitioned between EtOAc and water (1 L each). The organic layer was washed with H_2O (1 L) and brine (1 L), dried ($MgSO_4$), filtered and concentrated under diminished pressure. The crude material was passed through a plug of silica gel (1 kg), eluting with hexanes (4 L) and 15:85 EtOAc/hexanes (4 L) to afford (S)-*tert*-butyl 2-(methoxycarbonylamino)-3-methylbutanoate as a clear oil (82.0 g, 99% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ = 2.5 ppm) 7.34 (d, J = 8.6, 1 H), 3.77 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.05 (m, 1 H), 1.39 (s, 9 H), 0.83 - 0.92 (m, 6 H). ^{13}C-NMR (126 MHz, DMSO-d_6, δ = 39.2 ppm) 170.92, 156.84, 80.38, 60.00, 51.34, 29.76, 27.62, 18.92, 17.95. LC/MS: $[M+Na]^+$ 254.17.

[00195] Trifluoroacetic acid (343 mL, 4.62 mol) and Et_3SiH (142 mL, 0.887 mol) were added sequentially to a solution of (S)-*tert*-butyl 2-(methoxycarbonylamino)-3-methylbutanoate (82.0 g, 0.355 mol) in CH_2Cl_2 (675 mL), and the mixture was stirred at ambient temperature for 4 h. The volatile component was removed under diminished pressure and the resultant oil triturated with petroleum ether (600 mL) to afford a white solid, which was filtered and washed with hexanes (500 mL) and petroleum ether (500 mL). Recrystallization from EtOAc/petroleum ether afforded Cap-51 as white flaky crystals (54.8 g, 88 % yield). MP = 108.5-109.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6, δ = 2.5 ppm) 12.52 (s, 1 H), 7.31 (d, J = 8.6, 1 H), 3.83 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.07 (m, 1 H), 0.86 (dd, J = 8.9, 7.0, 6 H). ^{13}C NMR (126 MHz, DMSO-d_6, δ = 39.2 ppm) 173.30, 156.94, 59.48, 51.37, 29.52, 19.15, 17.98. LC/MS: $[M+H]^+$ = 176.11. Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 48.17; H, 7.55; N, 7.99. Optical Rotation: $[\alpha]_D$ = -4.16 (12.02 mg/mL; MeOH). Optical purity: >99.5 % ee. Note: the optical purity assessment was made on the methyl ester derivative of Cap-51, which was prepared under a standard $TMSCHN_2$ (benzene/MeOH) esterification protocol. HPLC analytical conditions: column, CHIRALPAK® AD-H (4.6 x 250mm, 5μm); solvent, 95% heptane / 5% IPA (isocratic); flow rate, 1 mL/min; temperature, 35 °C; UV monitored at 205 nm.

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

Cap-52 (same as Cap-12)

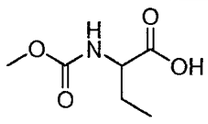


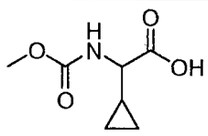
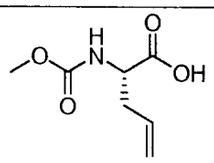
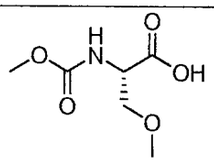
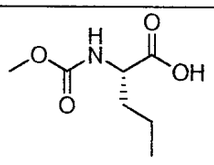
(S)-2-(Methoxycarbonylamino)propanoic acid

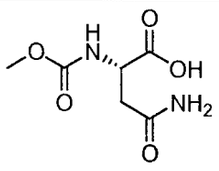
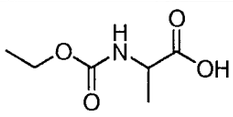
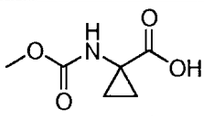
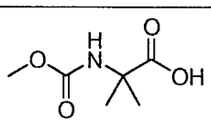
[00196] Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to afford Cap-52 as a colorless viscous oil. ^1H NMR (DMSO-d_6, δ=2.5 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).

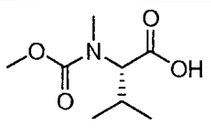
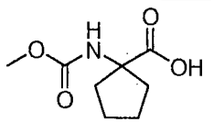
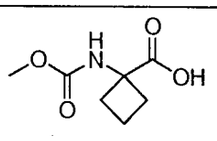
Cap-53 to Cap-64

[00197] Cap-53 to Cap-64 were prepared from appropriate starting materials according to the procedure described for the synthesis of Cap-51, with noted modifications if any.

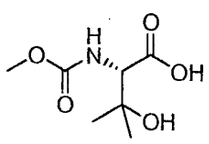
Cap	Structure	Data
Cap-53a: (R) Cap-53b: (S) ((S)-2-(methoxy-carbonyl-amino)butanoic acid)		^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, J = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, J = 7.3, 3H). RT = 0.77 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	Structure	Data
Cap-54a: (R) Cap-54b: (S) ((S)-2-cyclopropyl-2-(methoxy-carbonyl-amino)acetic acid)		^{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 (S)-3-methoxy-2-(methoxy-carbonyl-amino)propanoic acid		^{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	Structure	Data
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	Structure	Data
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

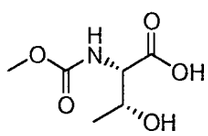


[00198] Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-2-amino-3-hydroxy-3-methylbutanoic acid (1.04 g, 7.81

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).

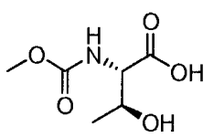
[00199] Cap-66 and Cap-67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of Cap-65.

Cap-66



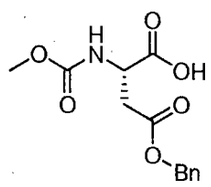
[00200] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



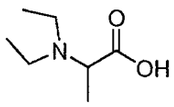
[00201] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (br d, *J* = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Note: only the dominant signals of NH were noted].

Cap-68



[00202] 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 Cap-69b



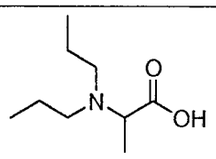
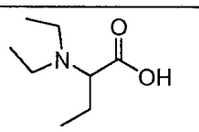
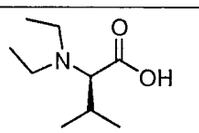
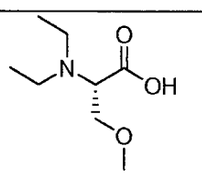
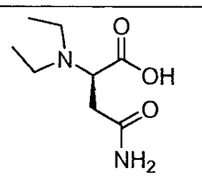
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

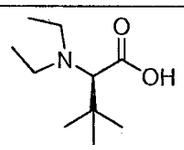
[00203] $NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a DOWEX® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford Cap-69 (2.0 g) as an off-white soft hygroscopic solid. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ

3.44 (q, J = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, J = 7.1, 3H), 1.13 (t, J = 7.3, 6H).

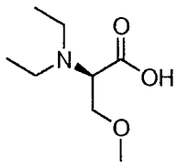
Cap-70 to Cap-74x

[00204] Cap-70 to Cap-74x were prepared according to the procedure described for the synthesis of Cap-69 by employing appropriate starting materials.

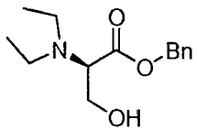
Cap-70a: (R) Cap-70b: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, J = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, J = 7.3, 3H), 0.85 (t, J = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) Cap-71b: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, J = 7.2, 6H), 0.91 (t, J = 7.3, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06.
Cap-72		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, J = 7.1, 6H), 0.91 (d, J = 6.5, 3H), 0.85 (d, J = 6.5, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15.
Cap-73		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, J = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, J = 7.2, 6H).
Cap-74		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, J = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, J = 15.6, 7.0, 1H), 2.36 (dd, J = 15.4, 6.3, 1H), 1.09 (t, J = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13.

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

Cap-75



Cap-75, step a



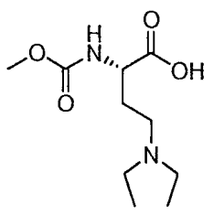
[00205] $NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC ($MeOH/H_2O$/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

[00206] 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

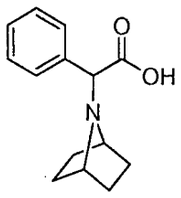


[00207] $NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(*tert*-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was 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).

[00208] 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.

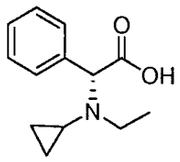
Cap-77a and Cap-77b



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

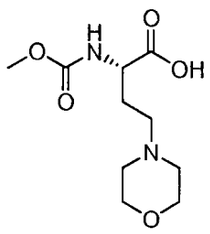
[00209] The synthesis of Cap-77 was conducted according to the procedure described for Cap-7 by using 7-azabicyclo[2.2.1]heptane for the SN_2 displacement step, and by effecting the stereoisomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following 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 stereoisomer-1 and 133.8 mg of stereoisomer-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



[00210] $NaCNBH_3$ (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



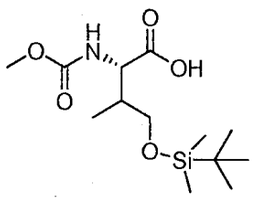
[00211] Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution Cap-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °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.

[00212] $NaBH_3CN$ (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.

[00213] 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 Cap-80b



Cap-80a: S/S-diastereomer
Cap-80b: S/R-diastereomer

[00214] $SOCl_2$ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed *in vacuo* and the residue was carefully partitioned between EtOAc (150 mL) and saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, J = 6.6, 1H), 3.55

(s, 3H), 2.68 (dd, J = 15.9, 6.3, 1H), 2.58 (dd, J = 15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT = 0.90 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; found 238.22.

[00215] $Pb(NO_3)_2$ (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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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

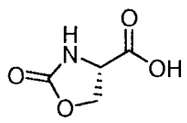
NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 3.0, 1H), 7.80 (d, *J* = 3.1, 1H), 7.39-7.10 (m, 16H), 4.66 (d, *J* = 12.4, 1H), 4.39 (d, *J* = 12.4, 1H), 3.61 (dd, *J* = 9.9, 5.6, 1H), 3.45 (d, *J* = 9.5, 1H), 3.41 (dd, *J* = 10, 6.2, 1H), 2.55 (dd, *J* = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, *J* = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

[00220] 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.

[00221] 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.

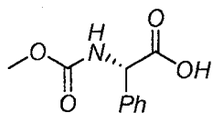
Cap-81



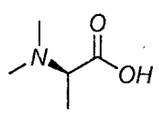
[00222] Prepared according to the protocol described by Falb et al., *Synthetic Communications*, 23:2839 (1993).

Cap-82 to Cap-85

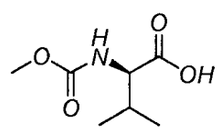
[00223] Cap-82 to Cap-85 were synthesized from appropriate starting materials according to the procedure described for Cap-51 or Cap-13. The samples exhibited similar spectral profiles as that of their stereoisomers (*i.e.*, Cap-4, Cap-13, Cap-51 and Cap-52, respectively).



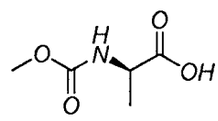
Cap-82



Cap-83

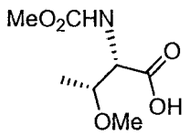


Cap-84



Cap-85

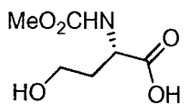
Cap-86



(2S,3R)-3-Methoxy-2-(methoxycarbonylamino)butanoic acid

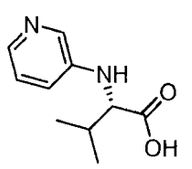
[00224] To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0 °C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 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. ^1H NMR (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



[00225] 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. ^1H NMR (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 $(M+H)^+$.

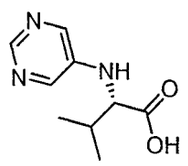
Cap-88



[00226] 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)

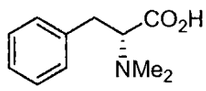
was heated at 100 °C for 12h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 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}H NMR (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



[00227] 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}H NMR (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 $(M+H)^+$.

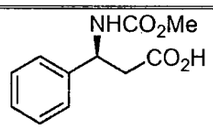
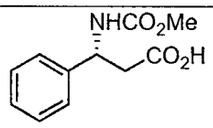
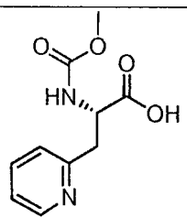
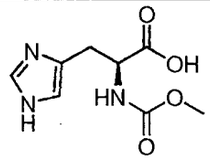
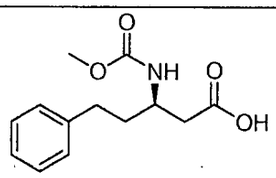
Cap-90

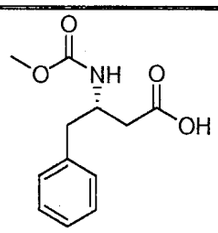
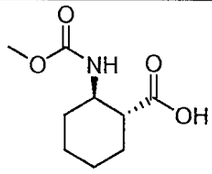
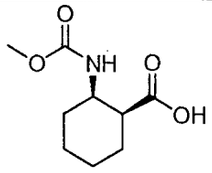
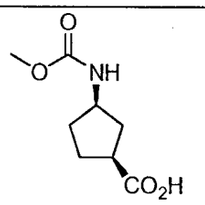
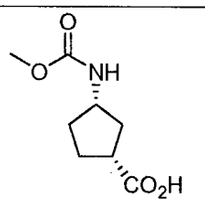
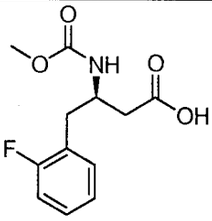


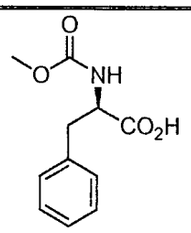
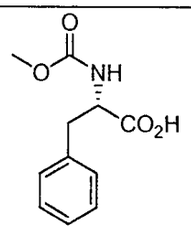
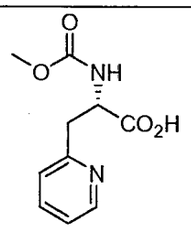
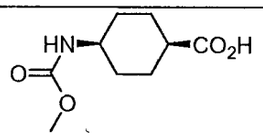
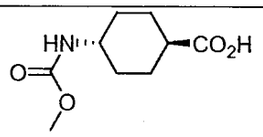
[00228] Cap-90 was prepared according to the method described for the preparation of Cap-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

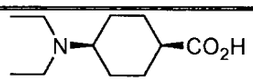
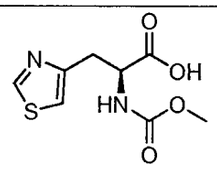
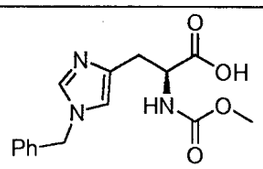
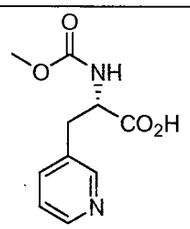
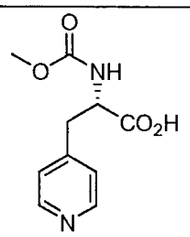
Cap-91 to Cap-116

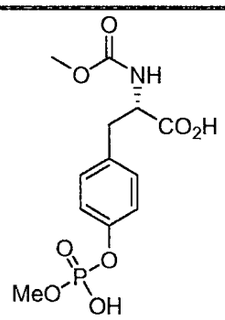
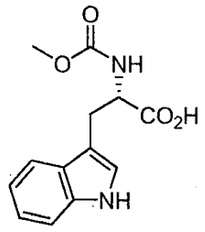
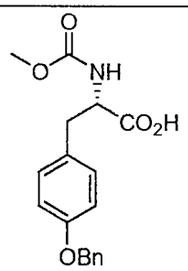
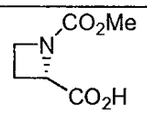
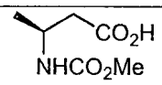
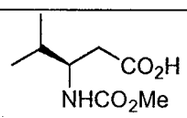
[00229] The following Caps were prepared according to the method used for preparation of Cap-51 unless noted otherwise:

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	Structure	LCMS
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}H NMR (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}H NMR (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 $(M+H)^+$.

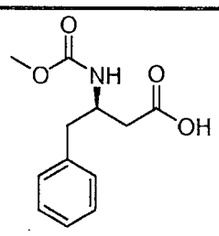
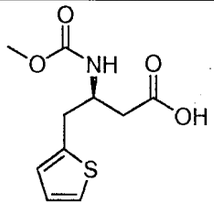
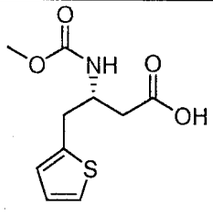
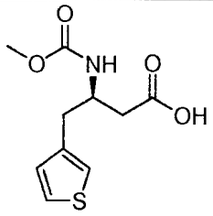
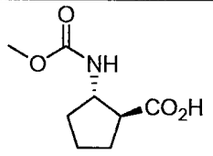
Cap	Structure	LCMS
Cap-101		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}H NMR (400 MHz, CD_3OD) δ 3.60 (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}H NMR (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).

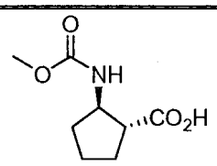
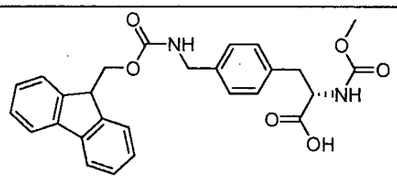
Cap	Structure	LCMS
Cap-106	 Prepared from cis-4-aminocyclohexane carboxylic acid and acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX ($MeOH/H_2O/CH_2Cl_2$ wash; 2 N NH_3/MeOH elution) to afford an oil, which was dissolved in CH_3CN/H_2O and lyophilized to afford a tan solid.	^{1}H NMR (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 - 2.31 (m, 2H), 1.79 - 1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H)
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.

Cap	Structure	LCMS
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}H NMR (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}H NMR (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}H NMR (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).

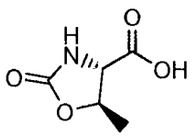
Cap-117 to Cap-123

[00230] 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		^1H NMR (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).

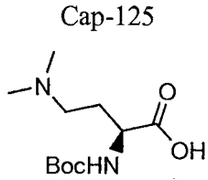
Cap	Structure	LCMS
Cap-122		^{1}H NMR profile is similar to that of its stereoisomer, Cap-121.
Cap-123		LCMS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$.

Cap-124



[00231] 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}H NMR (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 $(M+H)^+$.

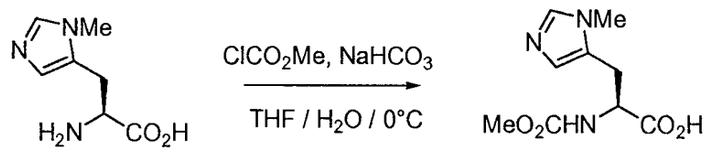
Cap-125



[00232] 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 temperature. 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

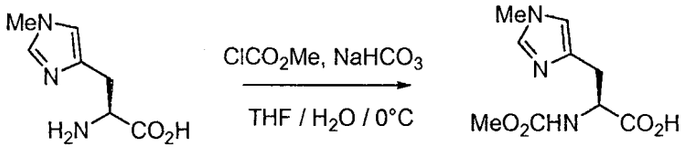


cj-25 *cap-126*

[00233] 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.

[00234] The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2. The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LCMS and ^1H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10mL) and H_2O (10mL), cooled to 0 °C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LCMS and ^1H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification. ^1H NMR (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 $(M+H)^+$.

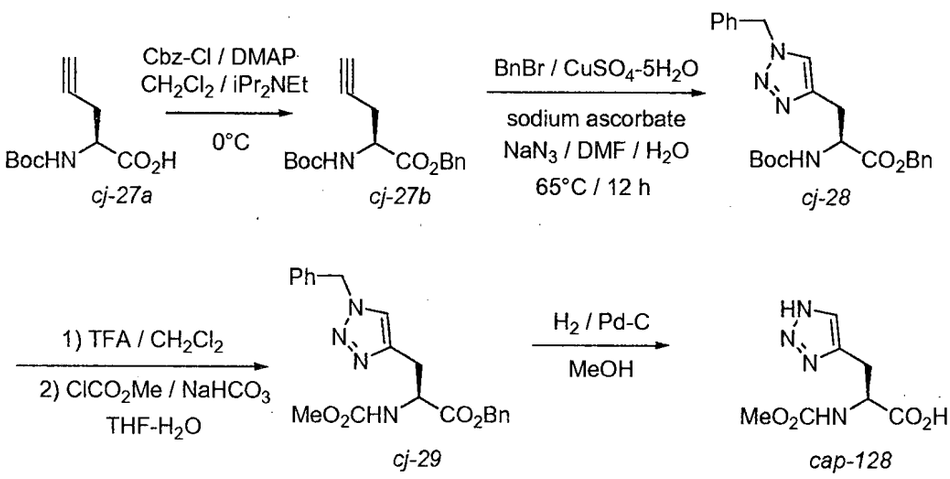
Cap-127



cj-26 *cap-127*

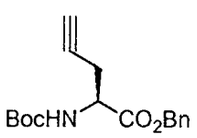
[00235] Cap-127 was prepared according to the method for Cap-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and ^1H NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification. ^1H NMR (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



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

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

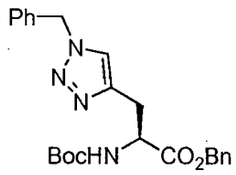


cj-27b

[00236] 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. ^1H NMR (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 $(M+H)^+$.

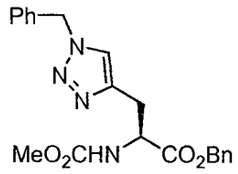
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(*tert*-butoxycarbonylamino)propanoate (cj-28).



cj-28

[00237] 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. ^1H NMR (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 $(M+H)^+$.

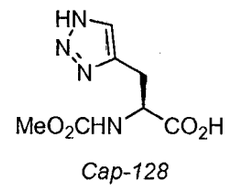
Step 3. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



cj-29

[00238] 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}H NMR (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).

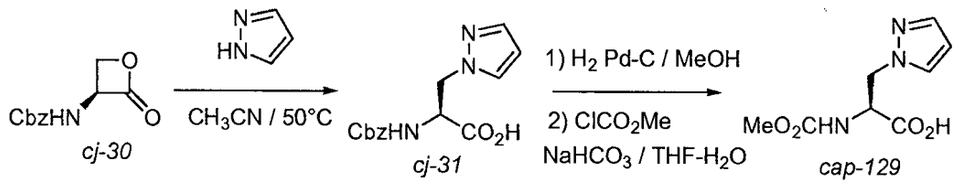


Cap-128

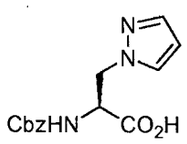
[00239] (S)-Benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture

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}H NMR (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



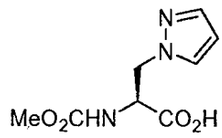
Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



cj-31

[00240] 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.*, 107:7105 (1985)]. ^{1}H NMR (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 $(M+H)^+$.

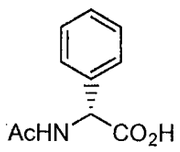
Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (Cap-129).



cap-129

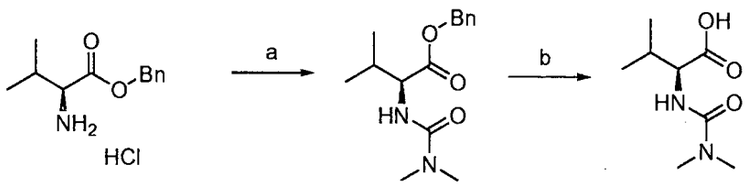
[00241] (S)-2-(Benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the reaction mixture was diluted with 5mL H_2O and a few 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%). ^1H NMR (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



[00242] Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analogous to the procedure given in: Calmes, M. et al., *Tetrahedron*, 43(10):2285 (1987).

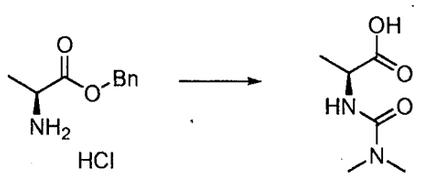
Cap-131



[00243] 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.

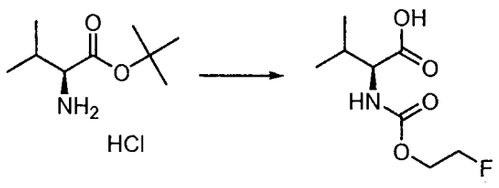
[00244] Step b: To an MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N_2 (3x) and placed under 1 atm of H_2. The mixture was stirred at room temperature overnight and filtered though a microfiber 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



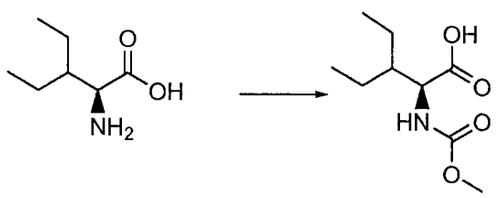
[00245] Cap-132 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for Cap-131. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; found 161.00.

Cap-133



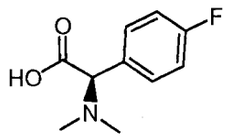
[00246] Cap-133 was prepared from (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for Cap-47. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 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



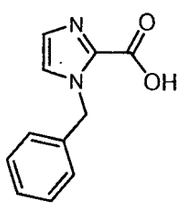
[00247] Cap-134 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for Cap-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, *J* = 8.85, 5.19 Hz, 1H), 7.24 (d, *J* = 8.85 Hz, 1H), 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



[00248] 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.

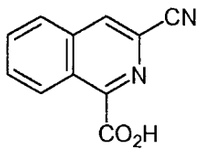
Cap-136



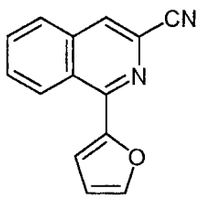
[00249] To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -50 °C, dry carbon dioxide (passed through Drierite) was 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

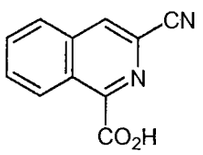


Cap-137, step a



[00250] 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.

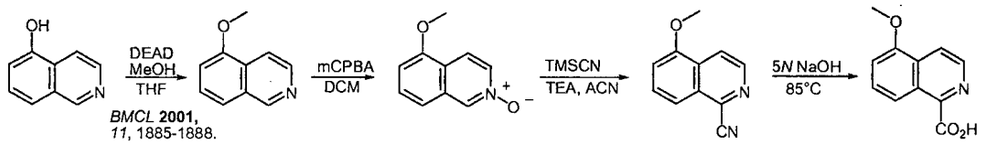
Cap-137



[00251] 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.

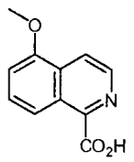
Cap-138 to Cap-158

Synthetic Strategy. Method A.

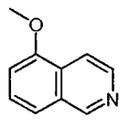


BMCL **2001**, *11*, 1885-1888.

Cap-138



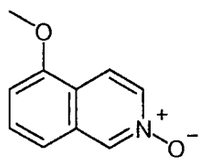
Cap-138, step a



[00252] 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

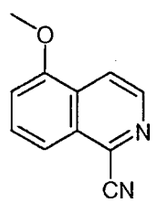
purified (elution with 40% ethyl acetate/hexanes) to afford Cap-138, step a as a light yellow solid (1.00 g, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); R_t = 0.66 min (Cond. D2); 95% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO$: 160.08; found 160.10.

Cap-138, step b



[00253] 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.

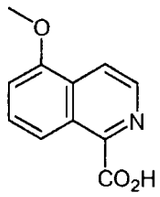
Cap-138, step c



[00254] 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

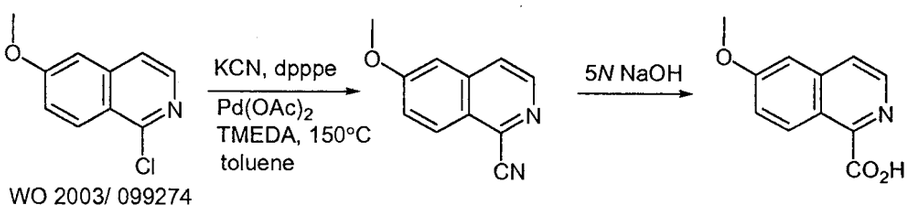
concentration. The residue was flash chromatographed on silica gel (elution with 5% ethyl acetate/hexanes) to 25% ethyl acetate/hexanes to afford Cap-138, step c (498.7 mg) as a white, crystalline solid along with 223 mg of additional Cap-138, step c recovered from the filtrate. ^{1}H NMR ($CDCl_3$, 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



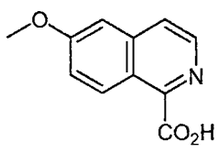
[00255] Cap-138, step c (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried 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*, 42:6707 (2001)).

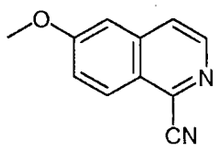


WO 2003/ 099274

Cap-139

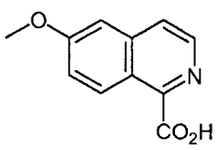


Cap-139, step a



[00256] 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.

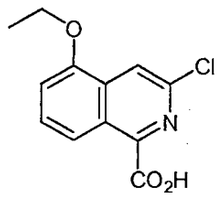
Cap-139



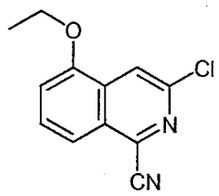
[00257] Cap-139 was prepared from the basic hydrolysis of Cap-139, step a with 5*N* NaOH according to the procedure described for Cap-138. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (v br s, 1H), 8.60 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.44 (dd, 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

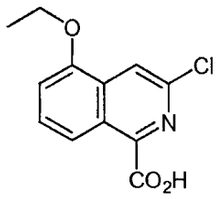


Cap-140, step a



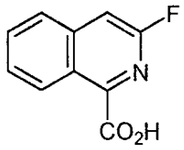
[00258] To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry dimethylacetamide (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

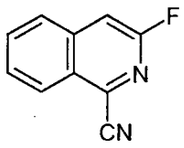


[00259] Cap-140 was prepared by the acid hydrolysis of Cap-140, step a with 12*N* HCl as described in the procedure for the preparation of Cap-141, described below. R_t = 2.24 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; found: 252.02.

Cap-141

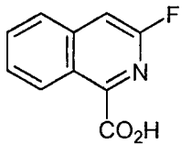


Cap-141, step a



[00260] 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.*, 13:613 (1970)) 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.

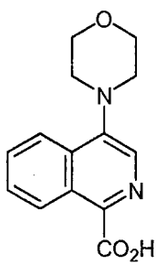
Cap-141



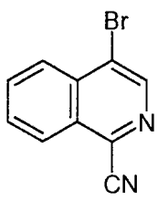
[00261] Cap-141, step a (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature

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%). ^1H 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

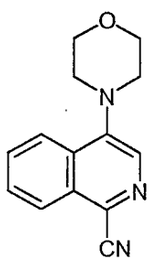


Cap-142, step a



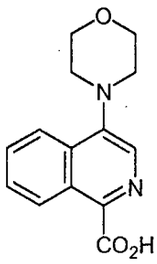
[00262] Cap-142, step a was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of Cap-138, steps b and c. R_t = 1.45 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

Cap-142, step b



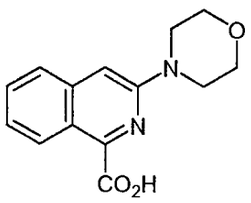
[00263] To an argon-degassed suspension of Cap-142, step a (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 μL, 0.70 mmol). The 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

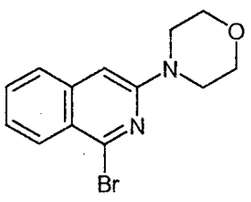


[00264] Cap-142 was prepared from Cap-142, step b with 5*N* sodium hydroxide as described in the procedure for Cap-138. R_t = 0.72 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-143

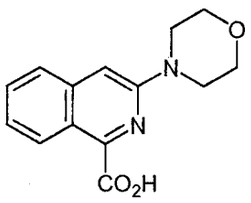


Cap-143, step a



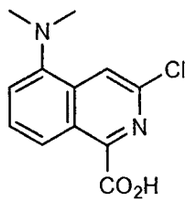
[00265] To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 μL, 2.00 mmol) was added. The 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

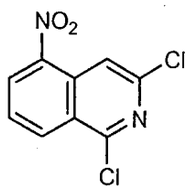


[00266] To a cold (-60 °C) solution of Cap-143, step a (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 0.25 mL, 0.633 mmol). After 10 min, dry carbon dioxide was bubbled into the reaction mixture for 10 min before it was quenched with 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

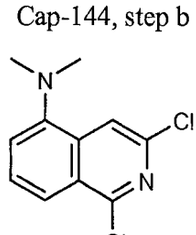


Cap-144, step a



[00267] 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.

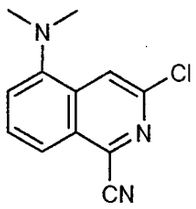
Cap-144, step b



[00268] 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

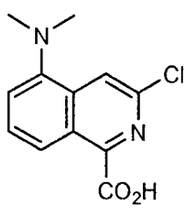
title compound as a yellow solid which was flash chromatographed on silica gel eluting with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes to afford Cap-144, step b (231 mg, 78%) as a pale yellow solid. R_t = 2.36 min (Cond.-D1); 95% homogenity index; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (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



[00269] 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.

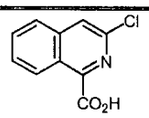
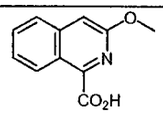
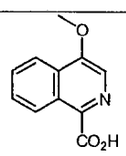
Cap-144

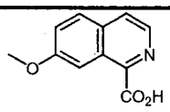
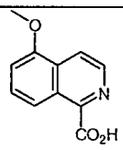
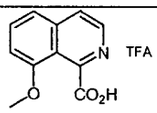


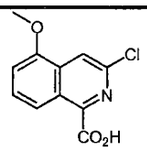
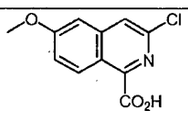
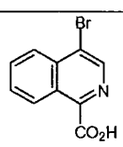
[00270] Cap-144 was prepared according to the procedure described for Cap-141. R_t = 2.36 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; found: 238.09.

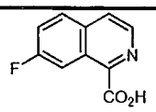
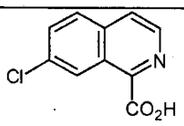
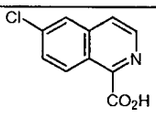
Cap-145 to Cap-162

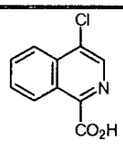
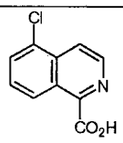
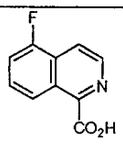
[00271] Cap-145 to Cap-162 were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of Cap-138 (Method A) or Cap-139 (Method B) unless noted otherwise as outlined below.

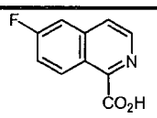
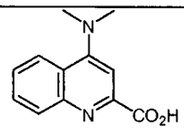
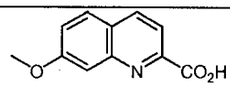
Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-145	 Prepared from commercially available 1,3-dichloroisoquinoline	B	12*N* HCl	1.14 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-146	 Prepared from commercially available 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 #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-148	 Prepared from commercially available 7-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-149	 Prepared from commercially available 5-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-150	 Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	A	12*N* HCl	0.26 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.04.

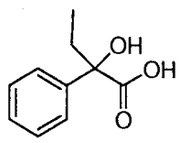
Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-151 3-chloro-5-methoxyisoquinoline-1-carboxylic acid	 Prepared from 5-methoxy-1,3-dichloroisoquinoline, which can be synthesized following the procedure in WO 2005/051410	B	12*N* HCl	1.78 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; found: 238.09.
Cap-152	 Prepared from commercially available 6-methoxy-1,3-dichloroisoquinoline	B	12*N* HCl	1.65 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00; found: 238.09.
Cap-153	 Prepared from 4-bromoisoquinoline, which can be synthesized following the procedure in WO 2003/062241	A	6*N* HCl	1.18 min (Cond.-MS-W1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; found: 251.95.

Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-154	 Prepared from 7-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.28 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-155	 Prepared from 1,7-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.59 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-156	 Prepared from 1,6-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.60 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.03.

Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
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.

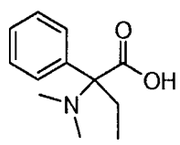
Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-160	 Prepared from 6-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.30 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
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.*, 17 (1993) and *Heterocycles*, 60:953 (2003).	--	--	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



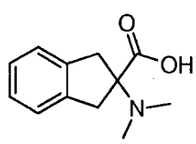
[00272] To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 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



[00273] 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).

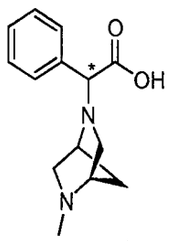
Cap-165



[00274] 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). ^{1}H 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.

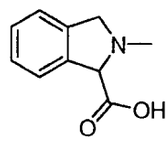
Cap-166a and Cap-166b



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

[00275] Cap-166a and Cap-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: ^{1}H 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.

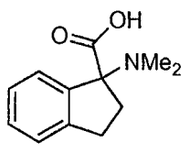
Cap-167



[00276] 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-

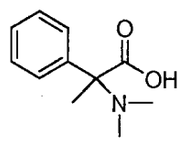
d_6, δ = 2.5 ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, J = 14 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.07 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; found: 178.65.

Cap-168



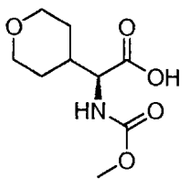
[00277] Racemic Cap-168 was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of Cap-167. The crude material was employed as such.

Cap-169



[00278] 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). ^1H 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.

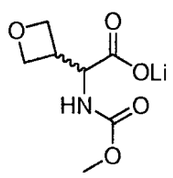
Cap-170



(S)-2-(Methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid

[00279] 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

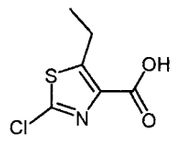


[00280] A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (200 mg, 0.721 mmol; Il Farmaco (2001), 56, 609-613) in ethyl acetate (7 ml) and CH_2Cl_2 (4.00 ml) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 ml, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) 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: visualized 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

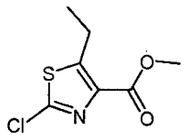
(81%) of methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 3.29 - 3.40 (m, *J*=6.71 Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, *J*=6.41 Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (br s, 1 H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; found 204.0.

[00281] 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 overnight 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 overnight providing 55 mg lithium 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless solid. ^{1}H NMR (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

Cap-172



Cap-172, step a



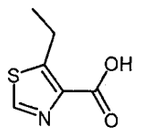
[00282] The following diazotization step was adapted from Barton, A. et al., *J. C. S. Perkin Trans I*, 159-164 (1982): A solution of $NaNO_2$ (166 mg, 2.4 mmol) in water (0.6 mL) was added slowly to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol), $CuSO_4$•$5H_2O$ (330 mg, 1.32 mmol), NaCl (260 mg, 4.45 mmol) and H_2SO_4 (5.5 mL) in water (7.5 mL). The mixture was stirred at 0 °C for 45 min and allowed to warm up to room temperature where it stirred further for 1 h before CuCl (118 mg) was added. This mixture was stirred further at room temperature

for 16 h before it was diluted with brine and extracted with ether twice. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 2-chloro-5-ethylthiazole-4-carboxylate (*i.e.*, Cap-172, step a) (175 mg, 85%) as an orange oil (80% pure) which was used directly in the next reaction. R_t = 1.99 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_9ClNO_2S$: 206.01; found: 206.05.

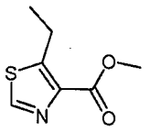
Cap-172

[00283] To a solution of methyl 2-chloro-5-ethylthiazole-4-carboxylate (175 mg) in THF/H_2O/MeOH (20 mL/ 3 mL/ 12 mL) was added LiOH (305 mg, 12.76 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield Cap-172 (60 mg, 74%) as a red solid which was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 13.03-13.42 (1 H, m), 3.16 (2 H, q, J = 7.4 Hz), 1.23 (3 H, t, J = 7.5 Hz). R_t = 1.78 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_7ClNO_2S$: 191.99; found: 191.99.

Cap-173



Cap-173, step a



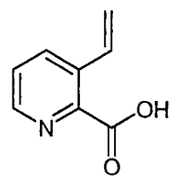
[00284] The following diazotization step was adapted from Barton, A. et al., *J.C.S. Perkin Trans I*, 159-164 (1982): A solution of $NaNO_2$ (150 mg, 2.17 mmol) in water (1.0 mL) was added dropwise to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol) in 50% H_3PO_2 (3.2 mL). The mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature where it stirred further for 2h. After recooling to 0 °C, the mixture was treated slowly with a solution of NaOH

(85 mg) in water (10 mL). The mixture was then diluted with saturated $NaHCO_3$ solution and extracted twice with ether. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 5-ethylthiazole-4-carboxylate (*i.e.*, Cap-173, step a) (134 mg, 78%) as an orange oil (85% pure) which was used directly in the next reaction. R_t = 1.58 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{10}NO_2S$: 172.05; found: 172.05.

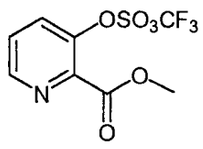
Cap-173

[00285] To a solution of methyl 5-ethylthiazole-4-carboxylate (134 mg) in THF/H_2O/MeOH (18 mL/ 2.7 mL/ 11 mL) was added LiOH (281 mg, 11.74 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield Cap-173 (90 mg, 73%) as an orange solid which was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 12.74-13.04 (1 H, m), 3.20 (2 H, q, J = 7.3 Hz), 1.25 (3 H, t, J = 7.5 Hz). R_t = 1.27 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_8NO_2S$: 158.03; found: 158.04.

Cap-174



Cap-174, step a



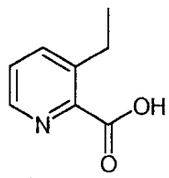
[00286] Triflic anhydride (5.0 g, 18.0 mmol) was added dropwise to a cold (0 °C) solution of methyl 3-hydroxypicolinate (2.5 g, 16.3 mmol) and TEA (2.5 mL, 18.0 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at 0 °C for 1h before it was allowed to warm up to room temperature where it stirred for an additional 1 h. The mixture was then

quenched with saturated $NaHCO_3$ solution (40 mL) and the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to give methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e.*, Cap-174, step a) (3.38 g, 73%) as a dark brown oil (>95% pure) which was used directly without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.72-8.79 (1 H, m), 7.71 (1 H, d, J = 1.5 Hz), 7.58-7.65 (1 H, m), 4.04 (3 H, s). R_t = 1.93 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_7F_3NO_5S$: 286.00; found: 286.08.

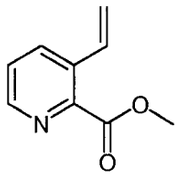
Cap-174

[00287] To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (570 mg, 2.0 mmol) in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C overnight before a saturated solution of KF (20 mL) was added to the reaction mixture at room temperature. This mixture was stirred for 4 h before it was filtered through CELITE® and the pad of CELITE® was washed with ethyl acetate. The aqueous phase of the filtrate was then separated and concentrated down *in vacuo*. The residue was treated with 4*N* HCl in dioxanes (5 mL) and the resulting mixture was extracted with methanol, filtered and evaporated to afford Cap-174 (260 mg) as a green solid which was slightly contaminated with inorganic salts but was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 8.21 (1 H, d, J = 3.7 Hz), 7.81-7.90 (1 H, m), 7.09 (1 H, dd, J = 7.7, 4.8 Hz), 6.98 (1 H, dd, J = 17.9, 11.3 Hz), 5.74 (1 H, dd, J = 17.9, 1.5 Hz), 5.20 (1 H, d, J = 11.0 Hz). R_t = 0.39 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_8NO_2$: 150.06; found: 150.07.

Cap-175

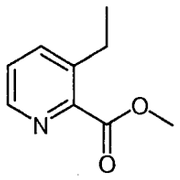


Cap-175, step a



[00288] To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e.*, Cap-174, step a) (570 mg, 2.0 mmol), an intermediate in the preparation of Cap-174, in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C for 4 h before the solvent was removed *in vacuo*. The residue was taken up in acetonitrile (50 mL) and hexanes (50 mL) and the resulting mixture was washed twice with hexanes. The acetonitrile layer was then separated, filtered through CELITE®, and evaporated. Purification of the residue by flash chromatography on a Horizon instrument (gradient elution with 25% ethyl acetate in hexanes to 65% ethyl acetate in hexanes) afforded methyl 3-vinylpicolinate (*i.e.*, Cap-175, step a) (130 mg, 40%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.60 (1 H, dd, J = 4.6, 1.7 Hz), 7.94 (1 H, d, J = 7.7 Hz), 7.33-7.51 (2 H, m), 5.72 (1 H, d, J = 17.2 Hz), 5.47 (1 H, d, J = 11.0 Hz), 3.99 (3 H, s). R_t = 1.29 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{10}NO_2$: 164.07; found: 164.06.

Cap-175, step b

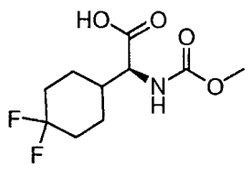


[00289] Palladium on carbon (10%, 25 mg) was added to a solution of methyl 3-vinylpicolinate (120 mg, 0.74 mmol) in ethanol (10 mL). The suspension was stirred at room temperature under an atmosphere of hydrogen for 1 h before it was filtered through CELITE® and the pad of CELITE® was washed with methanol. The filtrate was concentrated down to dryness to yield methyl 3-ethylpicolinate (*i.e.*, Cap-175, step b) which was taken directly into the next reaction. R_t = 1.15 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{12}NO_2$: 166.09; found: 166.09.

Cap-175

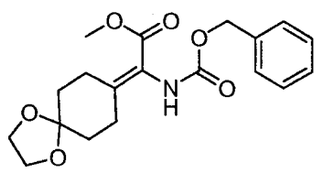
[00290] To a solution of methyl 3-ethylpicolinate in THF/H_2O/MeOH (5 mL/ 0.75 mL/ 3 mL) was added LiOH (35 mg, 1.47 mmol). The mixture was stirred at room temperature for 2 d before additional LiOH (80 mg) was added. After an additional 24 h at room temperature, the mixture was filtered and the solvent was removed *in vacuo*. The residue was then treated with 4*N* HCl in dioxanes (5 mL) and the resulting suspension was concentrated down to dryness to yield Cap-175 as a yellow solid which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.47 (1 H, dd, J = 4.8, 1.5 Hz), 7.82-7.89 (1 H, m), 7.53 (1 H, dd, J = 7.7, 4.8 Hz), 2.82 (2 H, q, J = 7.3 Hz), 1.17 (3 H, t, J = 7.5 Hz). R_t = 0.36 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{10}NO_2$: 152.07; found: 152.10.

Cap-176



(S)-2-(4,4-Difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid

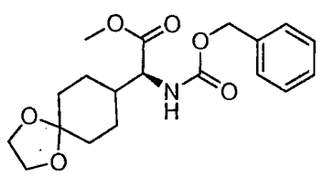
Cap-176, step a



[00291] A solution of 1,4-dioxaspiro[4.5]decan-8-one (15 g, 96 mmol) in EtOAc (150 mL) was added to a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (21.21 g, 64.0 mmol) in 1,1,3,3-tetramethylguanidine (10.45 mL, 83 mmol) and EtOAc (150 mL). The resulting solution was the stirred at ambient temperature for 72 h and then it was diluted with EtOAc (25 mL). The organic layer was washed with 1N HCl (75 mL), H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified via BIOTAGE® (5% to 25 % EtOAc/Hexanes; 300g column). The combined fractions containing the product were then concentrated under vacuum and the residue was re-crystallized from hexanes/EtOAc

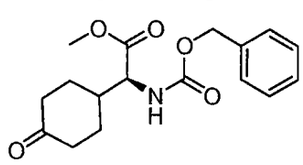
to give white crystals that corresponded to methyl 2-(benzyloxycarbonylamino)-2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (6.2 g) ^{1}H NMR (400 MHz, $CDCl_3$-d) δ ppm 7.30 - 7.44 (5 H, m), 6.02 (1 H, br. s.), 5.15 (2 H, s), 3.97 (4 H, s), 3.76 (3 H, br. s.), 2.84 - 2.92 (2 H, m), 2.47 (2 H, t, *J*=6.40 Hz), 1.74 - 1.83 (4 H, m). LC (Cond. OL1): R_t = 2.89 min. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745.21; found: 745.47.

Cap-176, step b



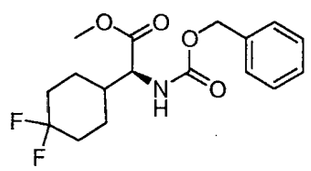
[00292] Ester Cap-176, step b was prepared from alkene Cap-176, step a according to the method of Burk, M.J. et al. (*J. Am. Chem. Soc.*, 117:9375-9376 (1995)) and references therein): A 500 mL high-pressure bottle was charged with alkene Cap-176, step a (3.5 g, 9.68 mmol) in degassed MeOH (200 mL) under a blanket of N_2. The solution was then charged with (-)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane(cyclooctadiene) rhodium (I) tetrafluoroborate (0.108 g, 0.194 mmol) and the resulting mixture was flushed with N_2 (3x) and charged with H_2 (3x). The solution was shaken vigorously under 70 psi of H_2 at ambient temperature for 72 h. The solvent was removed under reduced pressure and the remaining residue was taken up in EtOAc. The brownish solution was then filtered through a plug of Silica Gel and eluted with EtOAc. The solvent was concentrated under vacuum to afford a clear oil corresponding to ester Cap-176, step b (3.4 g).^{1}H NMR (500 MHz, $CDCl_3$-d) δ ppm 7.28 - 7.43 (5 H, m), 5.32 (1 H, d, *J*=9.16 Hz), 5.06 - 5.16 (2 H, m), 4.37 (1 H, dd, *J*=9.00, 5.04 Hz), 3.92 (4 H, t, *J*=3.05 Hz), 3.75 (3 H, s), 1.64 - 1.92 (4 H, m), 1.37 - 1.60 (5 H, m). LC (Cond. OL1): R_t = 1.95 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{26}NO_6$: 364.18; found: 364.27.

Cap-176, step c



[00293] Ester Cap-176, step b (4.78 g, 13.15 mmol) was dissolved in THF (15 mL) followed by sequential addition of water (10 mL), glacial acetic acid (26.4 mL, 460 mmol) and dichloroacetic acid (5.44 mL, 65.8 mmol). The resulting mixture was stirred for 72 h at ambient temperature, and the reaction was quenched by slow addition of solid Na_2CO_3 with vigorous stirring until the release of gas was no longer visible. Crude product was extracted into 10% ethyl acetate-dichloromethane and the organic layers were combined, dried ($MgSO_4$) filtered and concentrated. The resulting residue was purified via BIOTAGE® (0 to 30% EtOAc/Hex; 25 g column) to afford ketone Cap-176, step c (3.86g) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ ppm 7.28 - 7.41 (5 H, m), 5.55 (1 H, d, *J*=8.28 Hz), 5.09 (2 H, s), 4.46 (1 H, dd, *J*=8.16, 5.14 Hz), 3.74 (3 H, s), 2.18 - 2.46 (5 H, m), 1.96 - 2.06 (1 H, m), 1.90 (1 H, ddd, *J*=12.99, 5.96, 2.89 Hz), 1.44 - 1.68 (2 H, m, *J*=12.36, 12.36, 12.36, 12.36, 4.77 Hz). LC (Cond. OL1): R_t = 1.66 min. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342.13; found: 342.10.

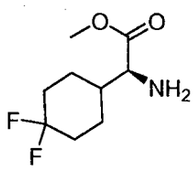
Cap-176, step d



[00294] DEOXO-FLUOR® (3.13 mL, 16.97 mmol) was added to a solution of ketone Cap-176, step c (2.71 g, 8.49 mmol) in CH_2Cl_2 (50 mL) followed by addition of a catalytic amount of EtOH (0.149 mL, 2.55 mmol). The resulting yellowish solution was stirred at rt overnight. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (25 mL) and the mixture was extracted with EtOAc (3X75 mL)). The combined organic layers were dried ($MgSO_4$), filtered and dried to give a yellowish oil. The residue was purified via BIOTAGE® chromatography (2% to 15% EtOAc/Hex; 90g column) and a white solid corresponding to the difluoro amino acid difluoride Cap-176, step d (1.5 g) was recovered. ^{1}H NMR (400 MHz,, $CDCl_3$-d) δ ppm 7.29 - 7.46 (5 H, m), 5.34 (1 H, d, *J*=8.28 Hz), 5.12 (2 H, s), 4.41 (1 H, dd, *J*=8.66, 4.89 Hz), 3.77 (3 H, s), 2.06 - 2.20 (2 H, m), 1.83 - 1.98 (1 H, m), 1.60 - 1.81 (4 H, m), 1.38 - 1.55 (2 H, m). ^{19}F NMR (376 MHz, $CDCl_3$-d) δ ppm -92.15 (1 F, d, *J*=237.55 Hz), -102.44 (1 F, d, *J*=235.82 Hz). LC (Cond.

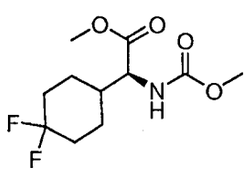
OL1): R_t = 1.66 min. LC/MS: Anal. Calcd. for $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705.28; found: 705.18.

Cap-176, step e



[00295] Difluoride Cap-176, step d (4 g, 11.72 mmol) was dissolved in MeOH (120 mL) and charged with Pd/C (1.247 g, 1.172 mmol). The suspension was flushed with N_2 (3x) and the reaction mixture was placed under 1 atm of H_2 (balloon). The mixture was stirred at ambient temperature for 48 h. The suspension was then filtered though a plug of CELITE® and concentrated under vacuum to give an oil that corresponded to amino acid Cap-176, step e (2.04 g) and that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.62 (3 H, s), 3.20 (1 H, d, *J*=5.77 Hz), 1.91 - 2.09 (2 H, m), 1.50 - 1.88 (7 H, m), 1.20 - 1.45 (2 H, m). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -89.39 (1 F, d, *J*=232.35 Hz), -100.07 (1 F, d, *J*=232.35 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 175.51 (1 C, s), 124.10 (1 C, t, *J*=241.21, 238.90 Hz), 57.74 (1 C, s), 51.39 (1 C, s), 39.23 (1 C, br. s.), 32.02 - 33.83 (2 C, m), 25.36 (1 C, d, *J*=10.02 Hz), 23.74 (1 C, d, *J*=9.25 Hz). LC (Cond. OL2): R_t = 0.95 min. LC/MS: Anal. Calcd. for $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415.22; found: 415.40.

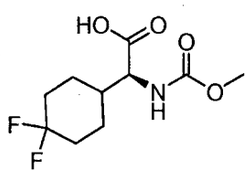
Cap-176, step f



[00296] Methyl chloroformate (1.495 mL, 19.30 mmol) was added to a solution of amino acid Cap-176, step e (2 g, 9.65 mmol) and DIEA (6.74 mL, 38.6 mmol) in CH_2Cl_2 (100 mL). The resulting solution was stirred at rt for 3 h and volatiles were removed under reduced pressure. The residue was purified via BIOTAGE® (0% to 20% EtOAc/Hex; 90g column). A clear oil that solidified upon standing under vacuum and corresponding to carbamate Cap-176, step f (2.22 g) was recovered. ^{1}H NMR (500 MHz,

$CDCl_3$-d) δ ppm 5.27 (1 H, d, *J*=8.55 Hz), 4.39 (1 H, dd, *J*=8.85, 4.88 Hz), 3.77 (3 H, s), 3.70 (3 H, s), 2.07 - 2.20 (2 H, m), 1.84 - 1.96 (1 H, m), 1.64 - 1.82 (4 H, m), 1.39 - 1.51 (2 H, m). ^{19}F NMR (471 MHz, $CDCl_3$-d) δ ppm -92.55 (1 F, d, *J*=237.13 Hz), -102.93 (1 F, d, *J*=237.12 Hz). ^{13}C NMR (126 MHz, $CDCl_3$-d) δ ppm 171.97 (1 C, s), 156.69 (1 C, s), 119.77 - 125.59 (1 C, m), 57.24 (1 C, br. s.), 52.48 (1 C, br. s.), 52.43 (1 C, s), 39.15 (1 C, s), 32.50 - 33.48 (2 C, m), 25.30 (1 C, d, *J*=9.60 Hz), 24.03 (1 C, d, *J*=9.60 Hz). LC (Cond. OL1): R_t = 1.49 min. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288.10; found: 288.03.

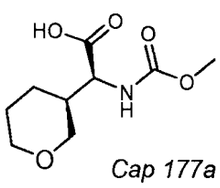
Cap-176



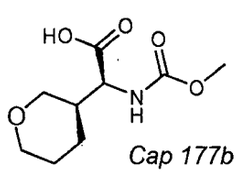
(S)-2-(4,4-Difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid

[00297] A solution of LiOH (0.379 g, 15.83 mmol) in water (25 mL) was added to a solution of carbamate Cap-176, step f (2.1 g, 7.92 mmol) in THF (75 mL) and the resulting mixture was stirred at ambient temperature for 4 h. THF was removed under vacuum and the remaining aqueous phase was acidified with 1N HCl solution (2 mL) and then extracted with EtOAc (2 X 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a white foam corresponding to Cap-176 (1.92 g). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.73 (1 H, s), 7.50 (1 H, d, *J*=8.78 Hz), 3.97 (1 H, dd, *J*=8.53, 6.02 Hz), 3.54 (3 H, s), 1.92 - 2.08 (2 H, m), 1.57 - 1.90 (5 H, m), 1.34 - 1.48 (1 H, m), 1.27 (1 H, qd, *J*=12.72, 3.26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -89.62 (1 F, d, *J*=232.35 Hz), -99.93 (1 F, d, *J*=232.35 Hz). LC (Cond. OL2): R_t = 0.76 min. LC/MS: Anal. Calcd. for $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250.09; found: 250.10.

Cap-177a and Cap-177b

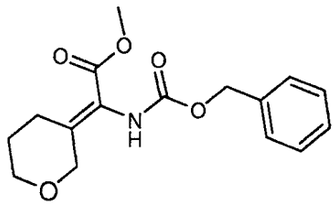


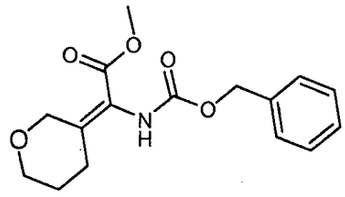
Cap 177a



Cap 177b

Cap-177a and Cap-177b, step a

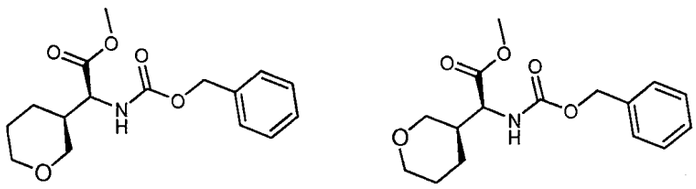




[00298] 1,1,3,3-Tetramethylguanidine (0.985 mL, 7.85 mmol) was added to a stirred solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (2.0 g, 6.0 mmol) in EtOAc (40 mL) and the mixture was stirred at rt under N_2 for 10 min. Then dihydro-2H-pyran-3(4H)-one [23462-75-1] (0.604 g, 6.04 mmol) was added and the mixture was stirred at rt for 16 h. The reaction mixture was then cooled in freezer for 10 min and neutralized with aq. citric acid (1.5 g in 20 mL water). The two phases were partitioned and the organic layer was washed with 0.25 N aq.HCl and brine, and then dried ($MgSO_4$) and concentrated to a colorless oil. The crude material was purified by flash silica chromatography (loading solvent: DCM, eluted with EtOAc/Hexanes, gradient from 20% to 30% EtOAc) to yield two isomeric products: The first eluted product was (Z)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate (490 mg) (white solid), and the second was (E)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate (433 mg) (white solid). LC-MS retention time 1.398 min (for Z-isomer) and 1.378min (for E-isomer); m/z 304.08 (for Z-isomer) and 304.16 (for E-isomer) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) (for Z-isomer) δ ppm 7.30 - 7.44 (m, 5 H), 6.18 (br. s., 1 H), 5.10 - 5.17 (m, 2 H), 4.22 (s, 2 H), 3.78 (br. s., 3 H), 2.93 - 3.02 (m, 2 H), 1.80 (dt, *J*=11.7, 5.8 Hz, 2 H), 1.62 (s, 2 H). ^{1}H NMR (400 MHz,

chloroform-d) (for E-isomer) δ ppm 7.31 - 7.44 (m, 5 H), 6.12 (br. s., 1 H), 5.13 - 5.17 (m, 2 H), 4.64 (br. s., 2 H), 3.70 - 3.82 (m, 5 H), 2.49 (t, *J*=6.5 Hz, 2 H), 1.80 (br. s., 2 H). (Note: the absolute regiochemistry was determined by ^{1}H NMR shifts and coupling constants).

Cap-177a and Cap-177b, step b

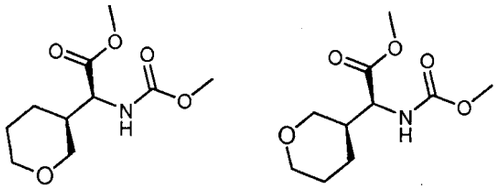


[00299] (-)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane(cyclooctadiene)-rhodium(I)tetrafluoroborate (28.2 mg, 0.051 mmol) was added to a stirred solution of (Z)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate (310 mg, 1.015 mmol) in MeOH (10 mL) and the mixture was vacuum flushed with N_2, followed by H_2, and then the reaction was stirred under H_2 (60 psi) at rt for 2d. The reaction mixture was concentrated and the residue was purified by flash silica chromatography (loading solvent: DCM, eluted with 20% EtOAc in hexanes) to yield (S)-methyl 2-(benzyloxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (204 mg) as clear colorless oil. LC-MS retention time 1.437 min; m/z 307.89 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 7.30 - 7.46 (m, 5 H), 5.32 (d, *J*=8.8 Hz, 1 H), 5.12 (s, 2 H), 4.36 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.98 (m, 2 H), 3.77 (s, 3 H), 3.28 - 3.37 (m, 1 H), 3.23 (dd, *J*=11.3, 10.5 Hz, 1 H), 2.04 - 2.16 (m, 1 H), 1.61 - 1.75 (m, 3 H), 1.31 - 1.43 (m, 1 H).

[00300] The other stereoisomer ((E)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate) (360 mg, 1.18 mmol) was reduced in a similar

manner to yield (S)-methyl 2-(benzyloxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate (214 mg) as clear colorless oil. LC-MS retention time 1.437 min; m/z 308.03 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 7.30 - 7.44 (m, 5 H), 5.31 (d, *J*=9.0 Hz, 1 H), 5.12 (s, 2 H), 4.31 (dd, *J*=8.7, 6.9 Hz, 1 H), 3.80 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.37 (td, *J*=10.8, 3.5 Hz, 1 H), 3.28 (dd, *J*=11.3, 9.8 Hz, 1 H), 1.97 - 2.10 (m, 1 H), 1.81 (d, *J*=11.5 Hz, 1 H), 1.61 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

Cap-177a and Cap-177b, step c

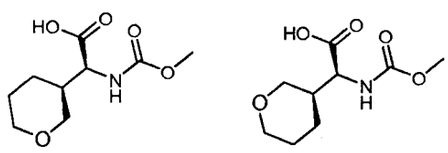


[00301] 10% Pd/C (69.3 mg, 0.065 mmol) was added to a solution of (S)-methyl 2-(benzyloxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (200 mg, 0.651 mmol) and dimethyl dicarbonate [4525-33-1] (0.104 mL, 0.976 mmol) in MeOH (10 mL). The reaction mixture was vacuum flushed with N_2, followed by H_2, and then the reaction was stirred under H_2 (55 psi) at rt for 5 h. The reaction mixture was filtered through CELITE®/silica pad and the filtrate was concentrated to a colorless oil. The crude oil was purified by flash silica chromatography (loading solvent: DCM, eluted with 30% EtOAc in hexanes) to yield product (S)-methyl 2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (132 mg) as colorless oil. LC-MS retention time 0.92 min; m/z 231.97 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution

conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 5.24 (d, *J*=8.5 Hz, 1 H), 4.34 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.97 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.29 - 3.38 (m, 1 H), 3.23 (dd, *J*=11.2, 10.4 Hz, 1 H), 2.03 - 2.14 (m, 1 H), 1.56 - 1.75 (m, 3 H), 1.32 - 1.43 (m, 1 H).

[00302] Another diastereomer ((S)-methyl 2-(benzyloxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate) was transformed in a similar manner to yield (S)-methyl 2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate as clear colorless oil. LC-MS retention time 0.99 min; m/z 231.90 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 5.25 (d, *J*=8.0 Hz, 1 H), 4.29 (dd, *J*=8.4, 7.2 Hz, 1 H), 3.82 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.37 (td, *J*=10.8, 3.3 Hz, 1 H), 3.28 (t, *J*=10.5 Hz, 1 H), 1.96 - 2.08 (m, 1 H), 1.81 (dd, *J*=12.9, 1.6 Hz, 1 H), 1.56 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

Cap-177a and Cap-177b, step d

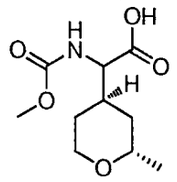


[00303] To a solution of (S)-methyl 2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (126 mg, 0.545 mmol) in THF (4 mL) stirring at rt was added a solution of 1M LiOH (1.090 mL, 1.090 mmol) in water. The reaction was stirred at rt for

3h, neutralized with 1M HCl (1.1 mL) and extracted with EtOAc (3x 10 mL). The organics were dried, filtered and concentrated to yield (S)-2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetic acid (Cap-177a) (125 mg) as a clear colorless oil. LC-MS retention time 0.44 min; m/z 218.00 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 5.28 (d, *J*=8.8 Hz, 1 H), 4.38 (dd, *J*=8.7, 5.6 Hz, 1 H), 3.96 - 4.04 (m, 1 H), 3.91 (d, *J*=11.0 Hz, 1 H), 3.71 (s, 3 H), 3.33 - 3.41 (m, 1 H), 3.24 - 3.32 (m, 1 H), 2.10 - 2.24 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.63 - 1.71 (m, 2 H), 1.35 - 1.49 (m, 1 H).

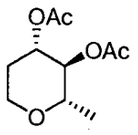
[00304] Another diastereomer ((S)-methyl 2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate) was transformed in a similar manner to yield (S)-2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetic acid (Cap-177b) as clear colorless oil. LC-MS retention time 0.41 min; m/z 217.93 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 6.18 (br. s., 1 H), 5.39 (d, *J*=8.5 Hz, 1 H), 4.27 - 4.37 (m, 1 H), 3.82 - 3.96 (m, 2 H), 3.72 (s, 3 H), 3.42 (td, *J*=10.8, 3.3 Hz, 1 H), 3.35 (t, *J*=10.4 Hz, 1 H), 2.01 - 2.18 (m, 1 H), 1.90 (d, *J*=11.8 Hz, 1 H), 1.59 - 1.76 (m, 2 H), 1.40 - 1.54 (m, 1 H).

Cap-178



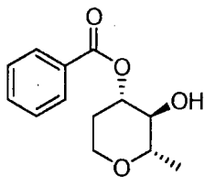
2-(Methoxycarbonylamino)-2-((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)acetic acid

Cap-178, step a



[00305] To a solution of (2S,3S,4S)-2-methyl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (5 g, 23.34 mmol) in 20 mL of MeOH in a hydrogenation tank was added Pd/C (150 mg, 0.141 mmol). The resulting mixture was hydrogenated at 40 psi on Parr Shaker for 1 hour. The mixture was then filtered and the filtrate was concentrated to give Cap-178, step a (5.0 g) as a clear oil, which solidified while standing. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 4.85 - 4.94 (1 H, m), 4.69 (1 H, t, *J*=9.46 Hz), 3.88 - 3.94 (1 H, m), 3.44 (1 H, td, *J*=12.21, 1.83 Hz), 3.36 (1 H, dq, *J*=9.42, 6.12 Hz), 2.03 - 2.08 (1 H, m), 2.02 (3 H, s), 2.00 (3 H, s), 1.70 - 1.80 (1 H, m), 1.16 (3 H, d, *J*=6.10 Hz).

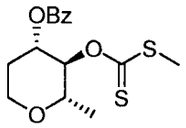
Cap-178, step b



[00306] To a solution of Cap-178, step a (5.0 g, 23 mmol) in 50 mL of MeOH was added several drops of sodium methoxide. After stirring at room temperature for 30 min, sodium methoxide (0.1 mL, 23.12 mmol) was added and the solution was stirred at room temperature overnight. The solvent was then removed under vacuum. The residue was diluted with benzene and concentrated to give the corresponding diol as a yellow solid. The solid was dissolved in 50 mL of pyridine and to this solution at -35 °C was added benzoyl chloride (2.95 mL, 25.4 mmol) dropwise. The resulting mixture was stirred at -35 °C for 1 hour then at room temperature overnight. The mixture was diluted with Et_2O

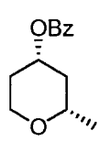
and washed with water. The aqueous layer was extracted with EtOAc (2X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 5%-15% EtOAc/Hex) to give Cap-178, step b (4.5 g) as clear oil which slowly crystallized upon prolonged standing. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{16}NaO_4$ 259.09; found 259.0; ^1H NMR (500 MHz, chloroform-d) δ ppm 8.02 - 8.07 (2 H, m), 7.55 - 7.61 (1 H, m), 7.45 (2 H, t, *J*=7.78 Hz), 5.01 (1 H, ddd, *J*=11.44, 8.70, 5.49 Hz), 3.98 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.54 (1 H, td, *J*=12.36, 2.14 Hz), 3.41 (1 H, t, *J*=9.00 Hz), 3.31 - 3.38 (1 H, m), 2.13 - 2.19 (1 H, m), 1.83 - 1.94 (1 H, m), 1.36 (3 H, d, *J*=5.80 Hz).

Cap-178, step c



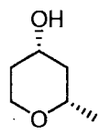
[00307] To a mixture of NaH (1.143 g, 28.6 mmol) (60% in mineral oil) in 6 mL of CS2 was added Cap-178, step b (4.5 g, 19 mmol) in 40 mL of CS_2 dropwise over 15 min. The resulting mixture was stirred at room temperature for 30 min. The mixture turned light orange with some solid. MeI (14.29 mL, 229 mmol) was then added dropwise over 20 min. The mixture was then stirred at room temperature overnight. The reaction was carefully quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 6% EtOAc/Hex) to give Cap-178, step c (3.13 g) as clear oil. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{18}NaO_4S_2$ 349.05; found 349.11; ^1H NMR (500 MHz, chloroform-d) δ ppm 7.94 - 8.00 (2 H, m), 7.50 - 7.58 (1 H, m), 7.41 (2 H, t, *J*=7.78 Hz), 5.96 (1 H, t, *J*=9.46 Hz), 5.28 (1 H, ddd, *J*=11.37, 9.38, 5.49 Hz), 4.02 (1 H, ddd, *J*=11.98, 4.96, 1.68 Hz), 3.54 - 3.68 (2 H, m), 2.48 (3 H, s), 2.31 (1 H, dd), 1.88 - 1.99 (1 H, m), 1.28 (3 H, d).

Cap-178, step d



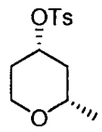
[00308] To a mixture of Cap-178, step c (3.13 g, 9.59 mmol) and AIBN (120 mg, 0.731 mmol) in 40 mL of benzene at 80 °C was added tri-n-butyltin hydride (10.24 mL, 38.4 mmol). The resulting mixture was stirred at reflux temperature for 20 min then cooled to room temperature. The mixture was diluted with diethyl ether and 100 mL of KF (10 g) aqueous solution was added and the mixture was stirred vigorously for 30 min. The two layers were then separated and the aqueous phase was extracted with EtOAc (2X). The organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, deactivated with 3% Et_3N in Hexanes and flushed with 3% Et_3N in Hexanes to remove tributyltin derivative and then eluted with 15% EtOAc/Hex) to give Cap-178, step d (1.9 g) as clear oil. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.98 - 8.07 (2 H, m), 7.52 - 7.58 (1 H, m), 7.43 (2 H, t, *J*=7.63 Hz), 5.08 - 5.17 (1 H, m), 4.06 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.50 - 3.59 (2 H, m), 2.08 - 2.14 (1 H, m), 1.99 - 2.06 (1 H, m), 1.69 - 1.80 (1 H, m), 1.41 - 1.49 (1 H, m), 1.24 (3 H, d, *J*=6.10 Hz).

Cap-178, step e



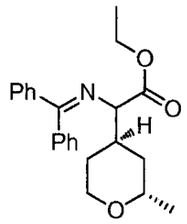
[00309] To a mixture of Cap-178, step d (1.9 g, 8.63 mmol) in 10 mL of MeOH was added sodium methoxide (2 mL, 4.00 mmol) (2 M in methanol). The resulting mixture was stirred at room temperature for 5 hours. The solvent was removed under vacuum. The mixture was neutralized with saturated NH_4Cl solution and extracted with EtOAc (3X). The organic layers were dried with $MgSO_4$ and concentrated to give Cap-178, step e (0.8 g) as clear oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 4.01 (1 H, ddd, *J*=11.80, 5.02, 1.76 Hz), 3.73 - 3.83 (1 H, m), 3.36 - 3.46 (2 H, m), 1.92 - 2.00 (1 H, m), 1.88 (1 H, m), 1.43 - 1.56 (1 H, m), 1.23 (3 H, d), 1.15 - 1.29 (1 H, m).

Cap-178, step f



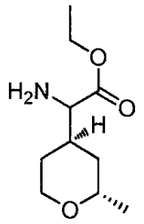
[00310] Tosyl-Cl (2.63 g, 13.77 mmol) was added to a solution of Cap-178, step e (0.8 g, 6.89 mmol) and pyridine (2.23 mL, 27.5 mmol) in 100 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 3 days. 10 mL of water was then added into the reaction mixture and the mixture was stirred at room temperature for an hour. The two layers were separated and the organic phase was washed with water and 1 N HCl aq. solution. The organic phase was dried with $MgSO_4$ and concentrated to give Cap-178, step f (1.75 g) as a light yellow solid. The product was used in the next step without further purification. Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}O_4S$ 271.10; found 270.90; ^1H NMR (500 MHz, chloroform-d) δ ppm 7.79 (2 H, d, *J*=8.24 Hz), 7.34 (2 H, d, *J*=7.93 Hz), 4.53 - 4.62 (1 H, m), 3.94 (1 H, ddd, *J*=12.13, 4.96, 1.83 Hz), 3.29 - 3.41 (2 H, m), 2.45 (3 H, s), 1.90 - 1.97 (1 H, m), 1.79 - 1.85 (1 H, m), 1.64 - 1.75 (1 H, m), 1.38 - 1.48 (1 H, m), 1.17 (3 H, d, *J*=6.10 Hz).

Cap-178, step g



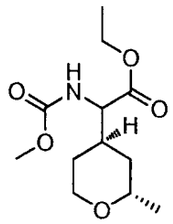
[00311] To a microwave tube was placed ethyl 2-(diphenylmethyleneamino)acetate (1.6 g, 5.92 mmol) and Cap-178, step f (1.6 g, 5.92 mmol). 10 mL of toluene was added. The tube was sealed and LiHMDS (7.1 mL, 7.10 mmol) (1 N in toluene) was added dropwise under N_2. The resulting dark brown solution was heated at 100 °C under microwave radiation for 6 hours. To the mixture was then added water and the mixture was extracted with EtOAc (3X). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated to give a diastereomeric mixture of Cap-3, step g (3.1 g) as an orange oil. The crude mixture was submitted to the next step without separation. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{28}NO_3$ 366.21; found 366.3.

Cap-178, step h



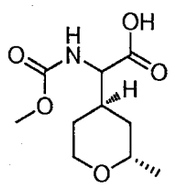
[00312] To a solution of the diastereomeric mixture of ethyl Cap-178, step g in 20 mL of THF was added HCl (30 ml, 60.0 mmol) (2 N aqueous). The resulting mixture was stirred at room temperature for 1 hour. The mixture was extracted with EtOAc and the aqueous layer was concentrated to give an HCl salt of Cap-178, step h (1.9 g) as an orange oil. The salt was used in the next step without further purification. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{20}NO_3$ 202.14; found 202.1.

Cap-178, step i



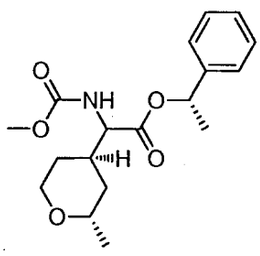
[00313] A solution of 1.9 g Cap-178, step h (HCl salt), DiPEA (4.19 mL, 24.0 mmol) and methyl chloroformate (1.24 mL, 16.0 mmol) in 20 mL of CH_2Cl_2 was stirred at room temperature for 1 hour. The mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (silica gel, 0-20% EtOAc/Hex) to give Cap-178, step i (1.1 g) as a yellow oil. Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{21}NNaO_5$ 282.13; found 282.14; ^1H NMR (400 MHz, chloroform-d) δ ppm 5.16 (1 H, br. s.), 4.43 - 4.58 (1 H, m), 4.17 - 4.28 (2 H, m), 3.89 - 4.03 (1 H, m), 3.72 - 3.78 (2 H, m), 3.67 - 3.72 (3 H, m), 2.07 - 2.19 (1 H, m), 1.35 - 1.77 (4 H, m), 1.30 (3 H, td, *J*=7.09, 2.89 Hz), 1.19 (3 H, d, *J*=6.53 Hz).

Cap-178, step j



[00314] To a mixture of Cap-178, step i (1.1 g, 4.2 mmol) in 5 mL of THF and 2 mL of water was added LiOH (6.36 mL, 12.7 mmol) (2 N aq.). The resulting mixture was stirred at room temperature overnight. The mixture was then neutralized with 1 N HCl aq. and extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated to give Cap-178, step j (0.8 g) as a clear oil. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; found 232.1; ^1H NMR (400 MHz, chloroform-d) δ ppm 5.20 (1 H, d, *J*=8.28 Hz), 4.54 (1 H, t, *J*=8.16 Hz), 3.95 - 4.10 (1 H, m), 3.66 - 3.85 (5 H, m), 2.15 - 2.29 (1 H, m), 1.41 - 1.85 (4 H, m), 1.23 (3 H, dd, *J*=6.53, 1.76 Hz).

Cap-178, step k

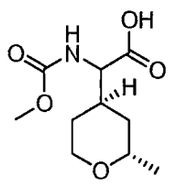


[00315] To a solution of Cap-178, step j (240 mg, 1.04 mmol), (S)-1-phenylethanol (0.141 mL, 1.142 mmol) and EDC (219 mg, 1.14 mmol) in 10 mL of CH_2Cl_2 was added DMAP (13.95 mg, 0.114 mmol). The resulting solution was stirred at room temperature overnight and the solvent was removed under vacuum. The residue was taken up into EtOAc, washed with water, dried with $MgSO_4$ and concentrated. The crude product was purified by chromatography (silica gel, 0-15% EtOAc/Hexanes) to give Cap-178, step k as a mixture of two diastereomers. The mixture was separated by chiral HPLC (CHIRALPAK® AS column, 21 x 250 mm, 10 um) eluting with 90% 0.1%diethylamine/Heptane-10% EtOH at 15 mL/min to give Cap-178, step k stereoisomer 1 (eluted first) and Cap-178, step k stereoisomer 2 (eluted second) as white solids. The stereochemistry of the isomers was not determined.

[00316] Cap-178, step k stereoisomer 1 (130 mg): LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{25}NNaO_5$ 358.16; found 358.16; ^1H NMR (500 MHz, chloroform-d) δ ppm 7.28 -

7.38 (5 H, m), 5.94 (1 H, q, *J*=6.71 Hz), 5.12 (1 H, d, *J*=9.16 Hz), 4.55 (1 H, t, *J*=9.00 Hz), 3.72 - 3.81 (1 H, m), 3.67 (3 H, s), 3.60 - 3.70 (2 H, m), 1.98 - 2.08 (1 H, m), 1.59 (3 H, d, *J*=6.71 Hz), 1.38 - 1.47 (2 H, m), 1.30 (2 H, t, *J*=5.34 Hz), 0.93 (3 H, d, *J*=6.41 Hz).

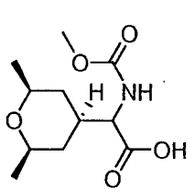
Cap-178, stereoisomer 1



2-(Methoxycarbonylamino)-2-((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)acetic acid

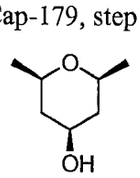
[00317] To a solution of Cap-178, step k stereoisomer 1 ((S)-2-(methoxycarbonylamino)-2-((2S,4R)-2-methyltetrahydro-2H-pyran-4-yl)acetic acid) (150 mg, 0.447 mmol) in 10 mL of EtOH was added Pd/C (20 mg, 0.188 mmol) and the mixture was hydrogenated on Parr shaker at 40 psi overnight. The mixture was then filtered and the filtrate was concentrated to give Cap-178, stereoisomer 1 (100 mg) as a sticky white solid. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; found 232.1; ^1H NMR (500 MHz, chloroform-d) δ ppm 5.14 - 5.27 (1 H, m), 4.51 (1 H, t, *J*=8.39 Hz), 3.90 - 4.07 (1 H, m), 3.60 - 3.83 (5 H, m), 2.06 - 2.27 (1 H, m), 1.45 - 1.77 (4 H, m), 1.21 (3 H, d, *J*=6.41 Hz).

Cap-179



179 stereoisomer 1
179 stereoisomer 2

Cap-179, step a



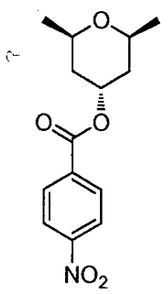
[00318] 2,6-Dimethyl-4H-pyran-4-one (10 g, 81 mmol) was dissolved in ethanol (125 mL) and Pd/C (1 g, 0.94 mmol) was added. The mixture was hydrogenated in a Parr

shaker under H_2 (0.325 g, 161 mmol) (70 psi) at room temperature for 12 hrs. The catalyst was filtered through a pad of CELITE® and washed with ethanol. The filtrate was concentrated in vacuum and he residue was purified via BIOTAGE® (2% to 25 % EtOAc/Hex; 160g column). Two fractions of clear oils were isolated. The first eluting one corresponded to (2R,6S)-2,6-dimethyldihydro-2H-pyran-4(3H)-one (1.8 g, 14.04 mmol, 17.43 % yield) while the second one corresponded to Cap-179, step a (1.8 g).

[00319] (2R,6S)-2,6-Dimethyldihydro-2H-pyran-4(3H)-one data: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 3.69 (2 H, ddd, *J*=11.29, 5.95, 2.29 Hz), 2.24 - 2.36 (2 H, m), 2.08 - 2.23 (2 H, m), 1.18 - 1.34 (6 H, m); ^{13}C NMR (126 MHz, chloroform-d) δ ppm 206.96 (1 C, br. s.), 72.69 (2 C, s), 48.70 (2 C, s), 21.72 (2 C, s).

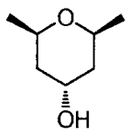
[00320] Cap-179, step a data: ^{1}H NMR (500 MHz, chloroform-d) δ ppm 3.69 - 3.78 (1 H, m), 3.36 - 3.47 (2 H, m), 2.10 (1 H, br. s.), 1.88 (2 H, dd, *J*=12.05, 4.73 Hz), 1.19 (6 H, d, *J*=6.10 Hz), 1.10 (2 H, q, *J*=10.70 Hz); ^{13}C NMR (126 MHz, chloroform-d) δ ppm 71.44 (2 C, s), 67.92 (1 C, s), 42.59 (2 C, s), 21.71 (2 C, s).

Cap-179, step b



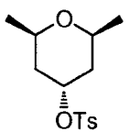
[00321] DEAD (2.311 mL, 14.59 mmol) was added drop wise to a solution of Cap-179, step a (0.38 g, 2.92 mmol), 4-nitrobenzoic acid (2.195 g, 13.14 mmol) and Ph_3P (3.83 g, 14.59 mmol) in benzene (25 mL). Heat evolution was detected and the resulting amber solution was stirred at ambient temperature for 6 h. Solvent was removed under reduced pressure and the residue was purified via BIOTAGE® (0 to 15% EtOAc/Hex; 80g column). A white solid corresponding to Cap-179, step b (0.77 g) was isolated. LC/MS: Anal. Calcd. for $[M]^+$ $C_{14}H_{17}NO_5$: 279.11; found 279.12. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.27 - 8.32 (2 H, m), 8.20 - 8.24 (2 H, m), 5.45 (1 H, quin, *J*=2.82 Hz), 3.92 (2 H, dqd, *J*=11.90, 6.10, 6.10, 6.10, 1.53 Hz), 1.91 (2 H, dd, *J*=14.80, 2.29 Hz), 1.57 (3 H, dt, *J*=14.65, 3.05 Hz), 1.22 (6 H, d, *J*=6.10 Hz).

Cap-179, step c



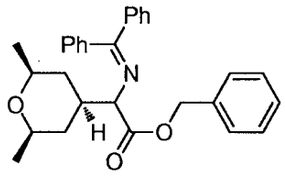
[00322] A solution LiOH (0.330 g, 13.8 mmol) in water (8 mL) was added to a solution of Cap-179, step b (0.77 g, 2.76 mmol) in THF (30 mL) and the resulting mixture was stirred at ambient temperature for 16 h. THF was removed under reduced pressure and the aqueous layer was diluted with more water (20 mL) and extracted with EtOAc (3 X 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. An oily residue with a white solid was recovered. The mixture was triturated with hexanes and the solid was filtered off to yield a clear oil corresponding to Cap-179, step c (0.34 g, 2.61 mmol, 95 % yield). ^1H NMR (500 MHz, chloroform-d) δ ppm 4.21 (1 H, quin, *J*=2.82 Hz), 3.87 - 3.95 (2 H, m), 1.72 (1 H, br. s.), 1.63 (2 H, dd, *J*=14.34, 2.14 Hz), 1.39 - 1.47 (2 H, m), 1.17 (6 H, d, *J*=6.41 Hz).

Cap-179, step d



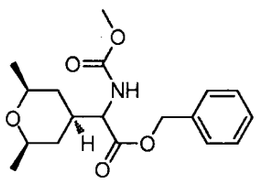
[00323] Tosyl chloride (3.98 g, 20.89 mmol) was added to a solution of Cap-179, step c (1.36 g, 10.5 mmol) and Pyridine (3.38 mL, 41.8 mmol) in CH_2Cl_2 (150 mL) at room temperature and stirred for 24h and then concentrated to a yellow oil. The remaining residue was added to pyridine (20 mL) and water (30 mL) and the resulting mixture was stirred at ambient temperature for 1 1/2 h. The mixture was extracted with Et_2O (75 mL) and the separated organic layer was the washed thoroughly with 1 N aq. HCl (4 X 50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated. A white solid corresponding to Cap-179, step d (2.2 g) was isolated. LC/MS: Anal. Calcd. for $[2M+H]^+$ $C_{28}H_{41}O_8S_2$: 569.22; found 569.3. ^1H NMR (400 MHz, chloroform-d) δ ppm 7.80 (2 H, d, *J*=8.28 Hz), 7.35 (2 H, d, *J*=8.03 Hz), 4.89 (1 H, quin, *J*=2.82 Hz), 3.77 - 3.88 (2 H, m), 2.46 (3 H, s), 1.77 (2 H, dd, *J*=14.93, 2.89 Hz), 1.36 (2 H, ddd, *J*=14.31, 11.54, 2.76 Hz), 1.13 (6 H, d, *J*=6.27 Hz).

Cap-179, step e



[00324] LiHMDS (4.30 mL, 4.30 mmol) was added to a solution of Cap-179, step d (1.02 g, 3.59 mmol) and benzyl 2-(diphenylmethyleneamino)acetate (1.181 g, 3.59 mmol) in toluene (25 mL) at room temperature in a sealed microwave vial and the resulting mixture was then stirred for 5 h at 100 °C under microwave radiation. The reaction was quenched with water (10 mL), extracted with EtOAc, washed with water, dried over MgSO4, filtrated, and concentrated in vacuum. The residue was purified via BIOTAGE® (0% to 6% EtOAc/Hex; 80g column) and a yellow oil corresponding to Cap-179, step e (1.2 g) was isolated. Anal. Calcd. for $[2M+Na]^+$ $C_{58}H_{62}N_2NaO_6$: 905.45; found 905.42. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 7.64 - 7.70 (4 H, m), 7.29 - 7.44 (29 H, m), 7.06 (4 H, dd, *J*=7.65, 1.63 Hz), 5.18 (2 H, d, *J*=2.01 Hz), 3.89 (2 H, d, *J*=6.53 Hz), 3.79 - 3.87 (1 H, m), 3.46 (5 H, dquind, *J*=11.26, 5.87, 5.87, 5.87, 5.87, 1.88 Hz), 2.47 (2 H, s), 2.35 - 2.46 (2 H, m), 1.78 (1 H, dd, *J*=14.81, 3.01 Hz), 1.62 - 1.65 (1 H, m), 1.61 (2 H, s), 1.36 - 1.43 (3 H, m), 1.19 (7 H, d, *J*=6.27 Hz), 1.14 (11 H, dd, *J*=6.15, 2.89 Hz), 0.86 - 0.96 (3 H, m).

Cap-179, step f (stereoisomer 1 and stereoisomer 2)

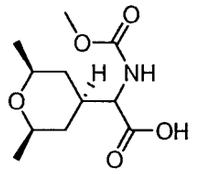


[00325] Cap-179, step d (2.08 g, 4.71 mmol) was dissolved in THF (100 mL) and treated with 2 N HCl (9.42 mL, 18.84 mmol). The resulting clear solution was stirred at ambient temperature for 4 h and then THF was removed under reduced pressure. The remaining aqueous layer was extracted with hexanes (3 X 20 ml) and after diluting with H_2O (20 mL), the aqueous phase was basified with 1 N NaOH to pH = 10 and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO4), filtered and

concentrated under vacuum. The resulting residue was taken up in CH_2Cl_2 (100 mL) and charged with DIEA (2.468 mL, 14.13 mmol) and methyl chloroformate (0.401 mL, 5.18 mmol). The resulting solution was stirred at ambient temperature for 2 h. The reaction mixture was quenched with water (10 mL) and the organic layer was removed under reduced pressure. The aqueous layer was then extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified via BIOTAGE® (10% EtOAc/Hex; 25 g column). A clear colorless oil corresponding to Cap-179, step f (1.05 g) was recovered. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{26}NO_5$: 336.18; found 336.3. ^1H NMR (500 MHz, chloroform-d) δ ppm 7.32 - 7.40 (5 H, m), 5.26 (1 H, d, *J*=8.24 Hz), 5.13 - 5.24 (2 H, m), 4.36 (1 H, dd, *J*=8.85, 4.88 Hz), 3.68 (3 H, s), 3.32 - 3.46 (2 H, m), 2.02 - 2.14 (1 H, m), 1.52 (1 H, d, *J*=12.82 Hz), 1.32 (1 H, d, *J*=12.51 Hz), 1.11 - 1.18 (6 H, m), 0.89 - 1.07 (2 H, m).

[00326] A chiral SFC method was developed to separate the mixture of stereoisomers by using 12% methanol as the modifier on a CHIRALPAK® AD-H column (30 x 250mm, 5μm) (Temp = 35 °C, Pressure = 150 bar, Wavelength = 210 nm, Flow rate = 70 mL/min for 8 min, Solvent A = CO_2, Solvent B = MeOH). The two separated isomers, Cap-179 step f (stereoisomer 1) (first eluting) and Cap-179 step f (stereoisomer 2) (second eluting) showed the same analytical data as the corresponding mixture (see above).

Cap-179



179 stereoisomer-1
179 stereoisomer-2

2-((2R,4R,6S)-2,6-Dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid

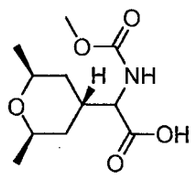
[00327] Cap-179 step f (stereoisomer 1) (0.35 g, 1.044 mmol) was dissolved in MeOH (50 mL) in a Parr bottle and charged with Pd/C (0.111 g, 1.044 mmol). The suspension was then placed in a Parr shaker and the mixture was flushed with N_2 (3X), placed under 40 psi of H_2 (2.104 mg, 1.044 mmol) and shaken at room temperature for 2 h. The catalyst was filtered off through a pad of CELITE® and the solvent was removed under

reduced pressure, to yield an amber solid corresponding to Cap-179 stereoisomer 1 (0.25 g, 1.019 mmol, 98 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.74 (4 H, br. s.), 7.35 (4 H, d, *J*=6.10 Hz), 3.85 (4 H, br. s.), 3.53 (3 H, s), 3.35 (2 H, ddd, *J*=15.95, 9.99, 6.10 Hz), 1.97 (1 H, br. s.), 1.48 (2 H, t, *J*=13.28 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.82 - 1.00 (2 H, m)

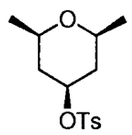
[00328] Cap-179 stereoisomer 2 was obtained according to the procedure used to prepare Cap-179 stereoisomer 1 using Cap-179 step f (stereoisomer 1) as the starting material. Cap-179 stereoisomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.50 (1 H, br. s.), 7.31 (1 H, br. s.), 3.84 (1 H, t, *J*=7.32 Hz), 3.53 (3 H, s), 3.29 - 3.41 (2 H, m), 1.99 (1 H, s), 1.48 (2 H, t, *J*=14.34 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.95 (1 H, q, *J*=12.21 Hz), 0.87 (1 H, q, *J*=11.80 Hz).

Cap-180

Racemic mixture



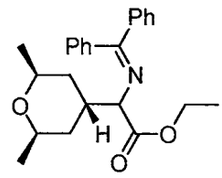
Cap-180, step a



[00329] Tosyl-Cl (4.39 g, 23.0 mmol) was added to a solution of Cap-179, step a (1.50 g, 11.5 mmol) and pyridine (3.73 mL, 46.1 mmol) in CH_2Cl_2 (50 mL) at room temperature and stirred for 2 days. The reaction was diluted with CH_2Cl_2, washed with water, then 1 N HCl. The organic layer was dried ($MgSO_4$) and concentrated to a yellow oil which was purified via BIOTAGE® (5% to 20% EtOAc/Hex; 40g column). A clear oil that solidified under vacuum and corresponding to Cap-180-2a (2.89 g) was isolated. LC/MS: Anal. Calcd. for $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$: 591.21; found 591.3. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.80 (2 H, d, *J*=8.24 Hz), 7.35 (2 H, d, *J*=7.93 Hz), 4.59 (1 H,

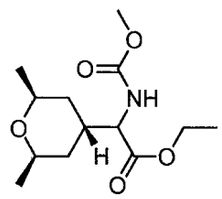
tt, *J*=11.37, 4.96 Hz), 3.36 - 3.46 (2 H, m), 2.46 (3 H, s), 1.91 (2 H, dd, *J*=12.05, 5.04 Hz), 1.37 (2 H, dt, *J*=12.67, 11.52 Hz), 1.19 (6 H, d, *J*=6.10 Hz).

Cap-180, step b



[00330] LiHMDS 1 N (7.09 mL, 7.09 mmol) was added to a solution of Cap-180, step a (1.68 g, 5.91 mmol) and ethyl 2-(diphenylmethyleneamino)acetate (1.579 g, 5.91 mmol) in toluene (30 mL) at room temperature and the resulting mixture was then stirred for 16 h at 85 °C. The reaction was quenched with water (50 mL), extracted with EtOAc, washed with water, dried over $MgSO_4$, filtrated, and concentrated *in vacuo*. The residue was purified via BIOTAGE® (0% to 15% EtOAc/Hex; 40g column). A clear yellowish oil corresponding to Cap-180, step b (mixture of stereoisomers) (0.64 g) was isolated. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{30}NO_3$: 380.22; found 380.03. ^1H NMR (400 MHz, chloroform-d) δ ppm 7.64 - 7.70 (2 H, m), 7.45 - 7.51 (3 H, m), 7.38 - 7.44 (1 H, m), 7.31 - 7.37 (2 H, m), 7.13 - 7.19 (2 H, m), 4.39 (1 H, d, *J*=10.54 Hz), 4.16 - 4.26 (2 H, m), 3.29 - 3.39 (1 H, m), 2.93 - 3.03 (1 H, m), 2.70 (1 H, m, *J*=9.41, 4.14 Hz), 1.42 - 1.49 (2 H, m), 1.31 - 1.37 (1 H, m), 1.29 (4 H, t, *J*=7.15 Hz), 1.04 (6 H, dd, *J*=7.78, 6.27 Hz).

Cap-180, step c

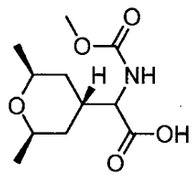


[00331] Cap-180, step b (0.36 g, 0.949 mmol) was dissolved in THF (10 mL) and treated with 2 N HCl (1.897 mL, 3.79 mmol). The resulting clear solution was stirred at ambient temperature for 20 h and THF was removed under reduced pressure. The remaining aqueous layer was extracted with hexanes (3 X 20 mL) and after diluting with H_2O (20 mL), the aqueous phase was basified with 1 N NaOH to pH = 10 and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and

concentrated under vacuum. The resulting residue was taken up in CH_2Cl_2 (10.00 mL) and charged with DIEA (0.497 mL, 2.85 mmol) and methyl chloroformate (0.081 mL, 1.044 mmol). The resulting solution was stirred at ambient temperature for 2 h and the reaction mixture was quenched with water (10 mL) and the organic layer was removed under reduced pressure. Aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. An amber oil corresponding to Cap-180, step c (0.21 g) was recovered and it was used without further purification. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{24}NO_5$: 273.17; found 274.06. ^1H NMR (400 MHz, chloroform-d) δ ppm 5.20 (1 H, d, *J*=8.03 Hz), 4.59 (1 H, t, *J*=10.16 Hz), 4.11 - 4.27 (3 H, m), 3.69 - 3.82 (2 H, m), 3.64 (3 H, s), 1.95 - 2.07 (1 H, m), 1.63 (1 H, d, *J*=13.80 Hz), 1.41 (2 H, dd, *J*=8.03, 4.02 Hz), 1.31 - 1.37 (1 H, m), 1.26 (3 H, t, *J*=7.15 Hz), 1.16 (1 H, d, *J*=6.27 Hz), 1.12 (6 H, dd, *J*=6.15, 3.89 Hz).

Cap-180

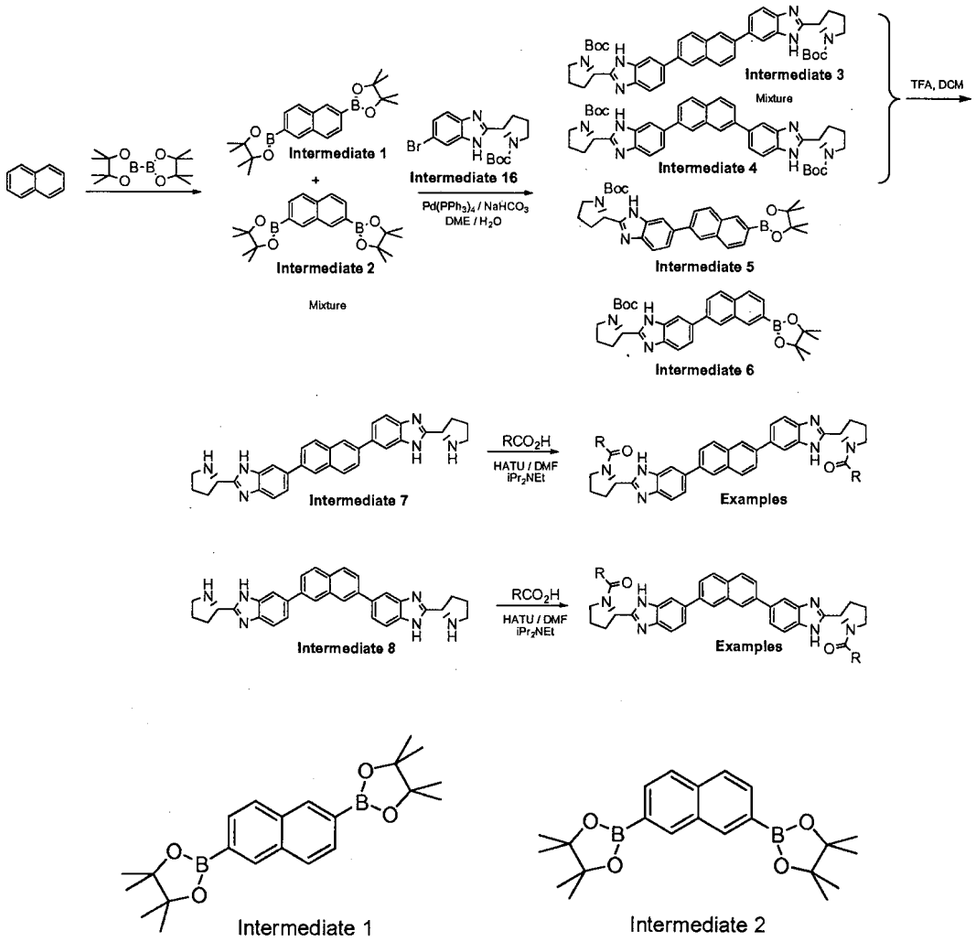
Racemic mixture



[00332] Cap-180, step c (0.32 g, 1.2 mmol) was dissolved in THF (10 mL) and charged with LiOH (0.056 g, 2.342 mmol) in water (3.33 mL) at 0 °C. The resulting solution was stirred at rt for 2 h. THF was removed under reduced pressure and remaining residue was diluted with water (15 mL) and washed with Et2O (2 x 10 mL). The aqueous layer was then acidified with 1N HCl to pH ~ 2 and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to yield Cap-180 (mixture of stereoisomers) (0.2 g) as a white foam. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{20}NO_5$: 246.13; found 246.00. ^1H NMR (400 MHz, chloroform-d) δ ppm 5.14 (1 H, d, *J*=9.03 Hz), 4.65 (1 H, t, *J*=9.91 Hz), 3.63 - 3.89 (5 H, m), 1.99 - 2.13 (1 H, m), 1.56 - 1.73 (2 H, m), 1.48 - 1.55 (1 H, m), 1.35 - 1.48 (1 H, m), 1.27 (1 H, br. s.), 1.17 (6 H, d, *J*=6.02 Hz).

INTERMEDIATES

Scheme 1



Literature ChemComm, 2172-2174 (2005).

Mixture of Intermediate 1

2,6-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene

and Intermediate 2

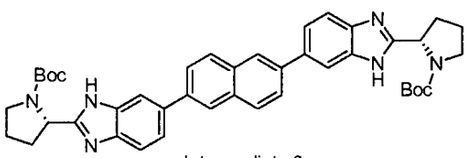
2,7-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene

[00333] To a degassed solution of naphthalene (19.34 g, 151 mmol) and bis(pinacolato)diboron (84 g, 330 mmol) in cyclohexane (500 mL) was added 4,4′-di-*tert*-buthyl-2,2′-dipyridyl (4.05 g, 15.1 mmol) and di-μ-methoxybis(1,5-cyclooctadiene)diirridium (I) (5.0 g, 7.5 mmol). The flask was sealed and heated at 80 °C for 16h then allowed to cool to room temperature. The reaction color turned dark red

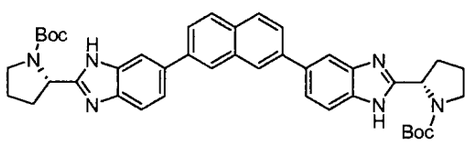
upon heating. The volatile component was removed *in vacuo* and the resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-100% ethyl acetate/ toluene) to afford a mixture of 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene and 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (54.57 g, 95% yield, 1.5:1 ratio) as white solid.

[00334] Intermediate 1: ^{1}H NMR (500 MHz, benzene-d_6) δ ppm 8.70 (s, 2H), 8.16 (d, *J*=8.2 Hz, 2H), 7.75 (d, *J*=8.2 Hz, 2H), 1.15 (s, 24H).

[00335] Intermediate 2: ^{1}H NMR (500 MHz, benzene-d_6) δ ppm 8.77 (s, 2H), 8.22 (d, *J*=8.2 Hz, 2H), 7.66 (d, *J*=8.2 Hz, 2H). 1.15 (s, 24H).



Intermediate 3



Intermediate 4

Mixture of Intermediate 3

(2S,2'S)-*tert*-Butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate

and Intermediate 4

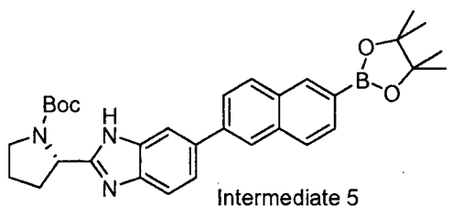
(2S,2'S)-*tert*-Butyl 2,2'-(5,5'-(naphthalene-2,7-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

[00336] To a mixture of 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene and 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (1.5:1) (1.25 g, 3.29 mmol) and (S)-*tert*-butyl 2-(6-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (3.01 g, 8.22 mmol) in 1,2-dimethoxyethane (50 mL) and water (12.5 mL) was added $NaHCO_3$ (1.38 g, 16.4 mmol). The reaction mixture was degassed *in vacuo* and flushed with nitrogen. $Pd(Ph_3P)_4$ (190 mg, 0.164 mmol) was added and the pressure flask was capped and heated with an oil bath at 85 °C for 16 hours. The volatile component was removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were filtered through a pad of diatomaceous earth (CELITE®) and the filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash

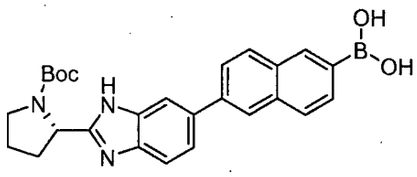
chromatography (sample was dry loaded on silica gel and eluted with 10-100% ethyl acetate/CH_2Cl_2) then flushed with (10% methanol/CH_2Cl_2) to afford a mixture of (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate and (2S,2'S)-*tert*-butyl 2,2'-(5,5'-(naphthalene-2,7-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (622 mg, 27.1% yield) as orange solid which was used without further purification. An aliquot was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide an analytical sample of each intermediate as a TFA salt.

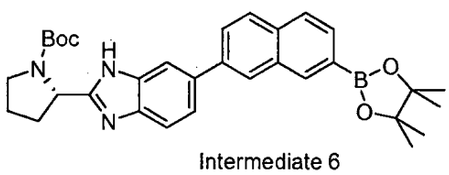
[00337] Analytical data for Intermediate 3: LC-MS retention time 1.46 min; Calcd. for $C_{42}H_{46}N_6O_4$: 698.36 Found m/z 699.26 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.28 (br s, 2H), 8.13 (t, *J*=8.7 Hz, 4H), 8.05 (t, *J*=8.4 Hz, 2H), 7.92 (dd, *J*=14.8, 8.7 Hz, 3H), 5.20 - 5.36 (m, 2H), 3.70 - 3.84 (m, 2H), 3.57 - 3.70 (m, 2H), 2.54 - 2.70 (m, 2H), 2.18 - 2.28 (m, 2H), 2.14 (quin, *J*=6.9 Hz, 4H), 1.50 (s, 9H), 1.23 (s, 9H).

[00338] Analytical data for Intermediate 4: LC-MS retention time 1.52 min; Calcd. for $C_{42}H_{46}N_6O_4$: 698.36 Found m/z 699.24 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of.220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.33 (br s, 2H), 7.98 - 8.17 (m, 6H), 7.83 - 7.98 (m, 4H), 5.18 - 5.35 (m, 2H), 3.71 - 3.83 (m, 2H), 3.57 - 3.70 (m, 2H), 2.63 (br s, 2H), 2.19 - 2.28 (m, 2H), 2.07 - 2.18 (m, 4H), 1.50 (s, 9H), 1.22 (s, 9H).

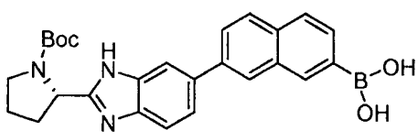


Intermediate 5





Intermediate 6



Boronic acid intermediates

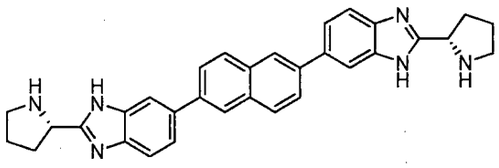
Mixture of Intermediate 5

(S)-*tert*-Butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate trifluoroacetate

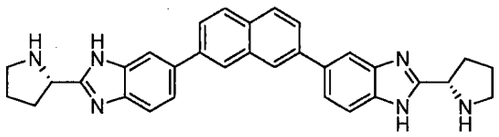
and Intermediate 6

(S)-*tert*-Butyl 2-(6-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate trifluoroacetate

[00339] After flash chromatography purification, the above reaction also provided a mixture of (S)-*tert*-butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate trifluoroacetate and (S)-*tert*-butyl 2-(6-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (658 mg). During the HPLC separation (TFA buffer) the boronic esters partially hydrolyzed to afford the same mixture as boronic acid intermediates. LC-MS retention time 1.34 min (boronic acids) and 2.05 (boronic esters); Calcd. for (boronic acids) $C_{26}H_{28}BN_3O_4$: 457.22 Found m/z 458.14 $[M+H]^+$. For (boronic esters) $[M+H]^+$ $C_{32}H_{38}BN_3O_4$: 539.3 Found m/z 490.16 $[M]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA.



Intermediate 7



Intermediate 8

Intermediate 7

2,6-Bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene

and Intermediate 8

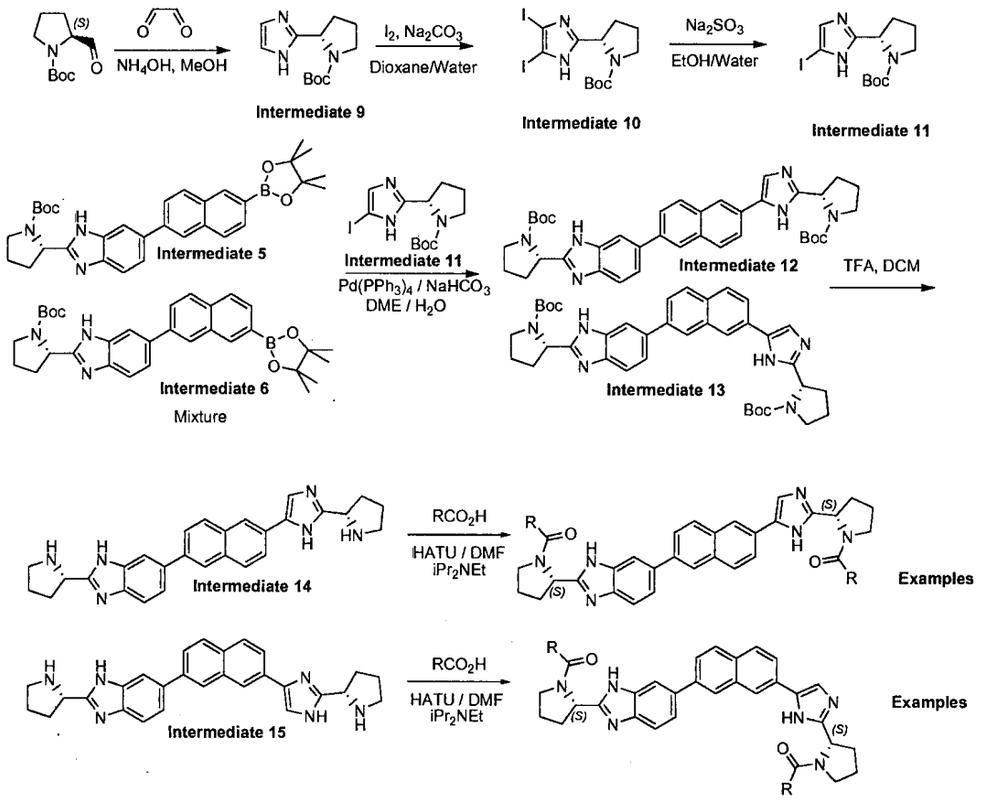
2,7-Bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene

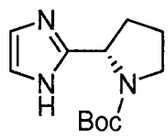
[00340] A mixture of (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate and (2S,2'S)-*tert*-butyl 2,2'-(5,5'-(naphthalene-2,7-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (594 mg, 0.162 mmol) and TFA (2 mL) in CH_2Cl_2 (10 mL) was stirred at ambient conditions for 3 hours. The volatile component was removed *in vacuo* and the crude material was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (434 mg) as yellow solid and a TFA salt of 2,7-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (204.8 mg) as yellow solid.

[00341] Analytical data for Intermediate 7: LC-MS retention time 1.05 min; Calcd. for $C_{32}H_{30}N_6$ 498.25 Found m/z 499.21 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.06 (d, *J*=8.6 Hz, 1H), 8.00 (s, 1H), 7.84 - 7.92 (m, 1H), 7.73 - 7.81 (m, 2H), 5.08 (t, *J*=7.6 Hz, 1H), 3.56 - 3.66 (m, 1H), 3.48 - 3.56 (m, 1H), 2.62 - 2.71 (m, 1H), 2.36 - 2.47 (m, 1H), 2.19 - 2.36 (m, 2H).

[00342] Analytical data for Intermediate 8: LC-MS retention time 1.11 min; Calcd. for $C_{32}H_{30}N_6$ 498.25 Found m/z 499.20 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.23 (s, 2H), 8.01 (m, 4H), 7.82 - 7.89 (m, 2H), 7.69 - 7.82 (m, 4H), 5.08 (t, *J*=7.6 Hz, 2H), 3.57 - 3.66 (m, 2H), 3.48 - 3.57 (m, 2H), 2.60 - 2.73 (m, 2H), 2.37 - 2.48 (m, 2H), 2.19 - 2.36 (m, 4H).

Scheme 2





Intermediate 9

(S)-*tert*-Butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00343] Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a methanol solution of NH_4OH (32 mL) and (S)-Boc-prolinal (8.56 g, 43.0mmol) and the reaction was stirred at ambient temperature for 19 hours. The volatile component was removed *in vacuo* and the residue was purified by a flash chromatography (silica gel, ethyl acetate) followed by a recrystallization (ethyl acetate, room temperature) to provide (S)-*tert*-butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate as a white fluffy solid (4.43g, 18.6 mmol, 43% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35 - 3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). LCMS. RT = 0.87 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; found 238.22. The compound shown to have a 98.9 ee% when analyzed under the chiral HPLC conditions noted below.

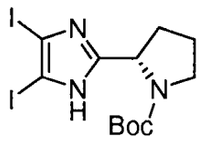
Column: CHIRALPAK® AD, 10 um, 4.6 x 50 mm

Solvent: 1.7% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 256 nm

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

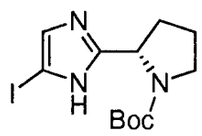


Intermediate 10

(S)-*tert*-Butyl 2-(4,5-diiodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00344] Iodine (16.17 g, 63.7 mmol) was added to a solution of (S)-*tert*-butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate (6.87 g, 29.0 mmol) and sodium carbonate (9.21 g, 87 mmol) in dioxane (72 mL) and water (72 mL) at ambient temperature. The flask was covered with aluminum foil and stirrer for 16 hours. The reaction mixture was diluted with ethyl acetate and a saturated aqueous solution of sodium thiosulfate. The

mixture was stirred for 15 minutes and the phases were separated. The aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford (S)-*tert*-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (12.5 g 88%) as a tan solid. LC-MS retention time 1.40 min; Calcd. for $C_{12}H_{17}I_2N_3O_2$ 488.94 Found m/z 489.96 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^1H NMR (500 MHz, MeOD) δ ppm 4.72 - 4.84 (m, 1H), 3.58 - 3.70 (m, 1H), 3.43 - 3.54 (m, 1H), 2.36 (br s, 1H), 1.88 - 2.08 (m, 3H), 1.47 (br s, 3H), 1.27 (br s, 6H).

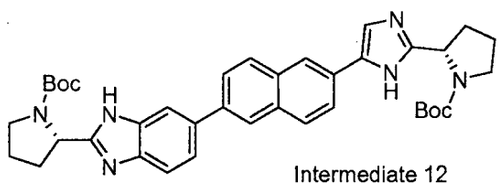


Intermediate 11

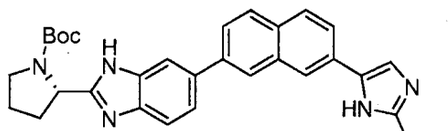
(S)-*tert*-Butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00345] Sodium sulfite (10.31 g, 82 mmol) was added to a solution of (S)-*tert*-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (4.0 g, 8.2 mmol) in ethanol (75 mL) and water (75 mL). The suspension was heated with an oil bath at 100 °C for 4 hours and at 90 °C for 16h. The reaction was diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted several times with ethyl acetate. The combined organic phases were dried (brine, Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by a flash chromatography (sample was dry loaded on silica gel and eluted with, 0 to 40% ethyl acetate/CH_2Cl_2) to afford (S)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (2.17 g, 73.1%) as a white solid. LC-MS retention time 0.930 min; Calcd. for $C_{12}H_{18}IN_3O_2$ 363.04 Found m/z 364.06 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow

rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.52-7.64 (m, 1H), 4.95 - 5.10 (m, 1H), 3.57 - 3.70 (m, 1H), 3.47 - 3.57 (m, 1H), 2.37 - 2.55 (m, 1H), 1.94 - 2.10 (m, 3H), 1.46 (s, 4H), 1.27 (s, 5H).



Intermediate 12



Intermediate 13

Mixture of Intermediate 12

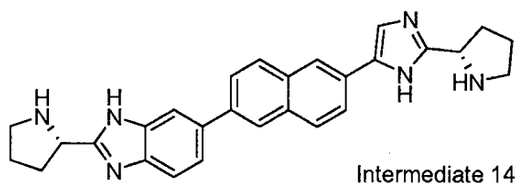
(S)-*tert*-Butyl 2-(5-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

and Intermediate 13

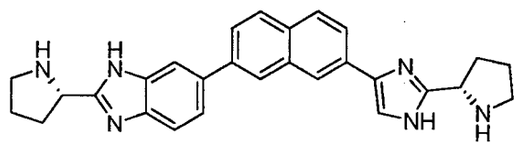
(S)-*tert*-Butyl 2-(5-(7-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00346] To a mixture of (S)-*tert*-butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate trifluoroacetate and (S)-*tert*-butyl 2-(6-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate trifluoroacetate (560 mg, 0.980 mmol) and (S)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (463 mg, 1.27 mmol) in 1,2-dimethoxyethane (11.2 mL) and water (2.8 mL) was added $NaHCO_3$ (412 mg, 4.90 mmol). The reaction mixture was degassed *in vacuo* for 5 minutes and was flushed with nitrogen. $Pd(Ph_3P)_4$ (57 mg, 0.049 mmol) was added and the pressure flask was capped and heated with an oil bath at 100 °C for 16 hours. The volatile component was removed *in vacuo*. The residue was partitioned between

ethyl acetate and water and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 50-100% ethyl acetate/hexanes) to afford a partially purified mixture of products which was further purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a mixture of a TFA salt of (S)-*tert*-butyl 2-(5-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and a TFA salt of (S)-*tert*-butyl 2-(5-(7-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (74 mg). LC-MS retention time 1.32 min; Calcd. for $[M+H]^+$ $C_{38}H_{44}N_6O_4$ 648.34 Found m/z 649.20 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile / 10% water / 0.1% TFA. The mixture was used without further purification.



Intermediate 14



Intermediate 15

Intermediate 14

2-((S)-Pyrrolidin-2-yl)-6-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazole

and Intermediate 15

2-((S)-Pyrrolidin-2-yl)-6-(7-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-1H-benzo[d]imidazole

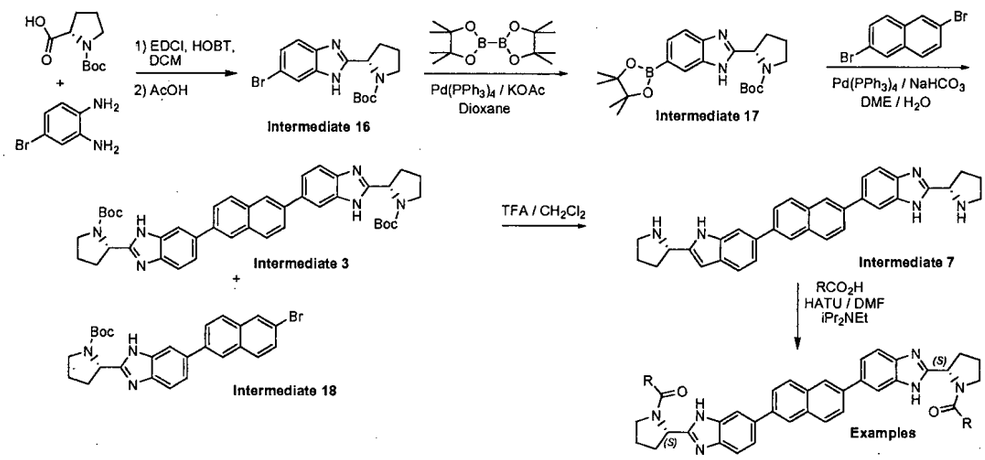
[00347] A mixture of (S)-*tert*-butyl 2-(5-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-*tert*-butyl 2-(5-(7-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate as TFA salts (74 mg) and TFA (2 mL) in CH_2Cl_2 (10 mL) was stirred at ambient conditions for 4 hours. The volatile component was removed *in vacuo*. The crude material was purified by a reverse phase HPLC (0 to 50% water/acetonitrile/TFA) to provide a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazole (32 mg, 31%) as yellow oil and a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(7-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-1H-benzo[d]imidazole (16 mg) as yellow oil.

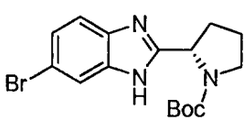
[00348] Analytical data for Intermediate 14: LC-MS retention time 0.081 min; Calcd. for $C_{38}H_{28}N_6$ 448.24 Found m/z 449.20 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.17 (s, 1H), 8.03 (d, *J*=3.7 Hz, 1H), 8.01 (s, 2H), 7.92 - 7.97 (m, 1H), 7.87 7.92 (m, 1H), 7.75 - 7.80 (m, 3H), 5.11 (t, *J*=7.8 Hz, 1H), 4.99 (t, *J*=7.9 Hz, 1H), 3.49 - 3.69 (m, 4H), 2.56 - 2.76 (m, 2H), 2.41 - 2.52 (m, 2H), 2.21 - 2.41 (m, 4H).

[00349] Analytical data for Intermediate 15: LC-MS retention time 0.87 min; Calcd. for $C_{38}H_{28}N_6$ 448.24 Found m/z 449.21 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water /

0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.39 (s, 1H), 8.19 (s, 1H), 7.97 - 8.04 (m, 3H), 7.91 (d, *J*=8.6 Hz, 1H), 7.87 (d, *J*=8.6 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 2H), 5.12 (t, *J*=7.6 Hz, 1H), 5.04 (t, *J*=8.1 Hz, 1H), 3.50 - 3.68 (m, 4H), 2.60 - 2.74 (m, 2H), 2.41 - 2.55 (m, 2H), 2.21 - 2.41 (m, 4H).

Scheme 3



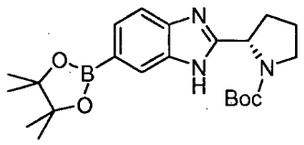


Intermediate 16

(S)-*tert*-Butyl 2-(6-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

[00350] EDCI·HCl (16.9 g, 88.0 mmol) was added to a mixture of 4-bromobenzene-1,2-diamine (15.0 g, 80.0 mmol), N-Boc-L-proline (18.13 g, 84.0 mmol) and 1-hydroxybenzotriazole (12.28 g, 80.0 mmol) in CH_2Cl_2 (500 mL) and stirred at ambient conditions for 16 h. The mixture was then diluted with water. The resulting white precipitate was filtered away and the layers were separated. The organic layer was washed with water, dried (brine; Na_2SO_4), filtered and concentrated *in vacuo* to provide a brown foam. Acetic acid (300 mL) was added to the foam and the mixture was heated at 85 °C (bath temperature) for 5h. The volatile component was removed *in vacuo* and the residue was dissolved in EtOAc, washed with water and the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant crude material was submitted

to flash chromatography (silica gel; 0-37% EtOAc/CH_2Cl_2). The partially pure material was re-submitted to flash chromatography (silica gel; 20-35% EtOAc/ CH_2Cl_2) to provide (S)-*tert*-butyl 2-(6-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (17.98 g, 61.2 % yield) as yellow foam. LC-MS retention time 1.23 min; Calcd. for $C_{16}H_{20}BrN_3O_2$: 365.07 Found m/z 368.07 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.59 - 7.75 (m., 1H), 7.38 - 7.53 (m, 1H), 7.31 - 7.38 (m, 1H), 5.04-5.09 (m, 0.3H), 4.94 - 5.00 (m, 0.7H), 3.68 - 3.76 (m, 1H), 3.50 - 3.59 (m, 1H), 2.34 - 2.51 (m., 1H), 1.95 - 2.12 (m., 3H), 1.47 (br s, 3H), 1.15 (s, 6H).

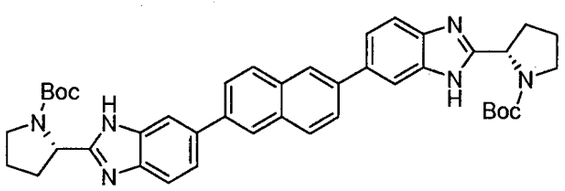


Intermediate 17

(S)-*tert*-Butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

[00351] To a flask containing a mixture of (S)-*tert*-butyl 2-(6-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (4.5 g, 12 mmol) and bis(pinacolato)diboron (6.55 g, 25.8 mmol) in 1,4-dioxane (50 mL) was added potassium acetate (3.01 g, 30.7 mmol). The reaction flask was degassed *in vacuo* for 5 minutes and then purged with nitrogen. The catalyst $Pd(Ph_3P)_4$ (710 mg, 0.614 mmol) was added and the flask was capped and heated with an oil bath at 85 °C (bath temperature) for 16h. The reaction mixture was concentrated *in vacuo*. The crude material was partitioned between CH_2Cl_2 and a saturated $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried (brine, Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography

(sample was dry loaded on silica gel and eluted with 10-50% ethyl acetate/ CH_2Cl_2) to provide (S)-*tert*-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (2.80 g, 55% yield) as white solid. LC-MS retention time 1.493 min; Calcd. for $C_{22}H_{32}BN_3O_4$: 413.25 Found m/z 414.23 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.81 - 8.08 (m, 1H), 7.40 - 7.68 (m., 2H), 4.95 - 5.13 (m, 1H), 3.68 - .3.79 (br s, 1H), 3.48 - 3.60 (br s, 1H), 2.35 - 2.52 (br s, 1H), 1.95-2.15 (m, 3H), 1.46 (s, 3H), 1.37 (s, 12H), 1.13 (s, 6H).

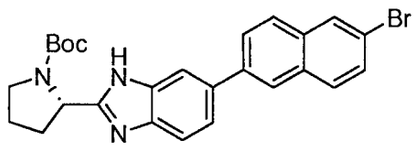


Intermediate 3

tert-Butyl 2-(5-(6-(2-(1-(*tert*-butoxycarbonyl)-2-pyrrolidinyl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate

[00352] To a mixture of (S)-*tert*-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.29 g, 33.1 mmol) and 2,6-dibromonaphthalene (446 mg, 1.56 mmol) in 1,2-dimethoxyethane (20 mL) and water (6 mL) was added $NaHCO_3$ (787 mg, 9.36 mmol). The reaction mixture was degassed *in vacuo* for 10 minutes and was flushed with nitrogen. The catalyst $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol) was added and the flask was capped and heated with an oil bath at 100 °C for 16 hours. The volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water and the layers were separated. The aqueous phase was extracted several times with CH_2Cl_2 and the combined organic phases were dried (brine, Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-70%

ethyl acetate / CH_2Cl_2) to afford *tert*-butyl 2-(5-(6-(2-(1-(*tert*-butoxycarbonyl)-2-pyrrolidinyl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (605 mg) as yellow solid. LC-MS retention time 1.46 min; Calcd. for $C_{42}H_{46}N_6O_4$: 698.36 Found m/z 699.26 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA ^{1}H NMR (500 MHz, MeOD) δ ppm 8.28 (br s, 2H), 8.13 (t, *J*=8.7 Hz, 4H), 8.05 (t, *J*=8.4 Hz, 2H), 7.92 (dd, *J*=14.8, 8.7 Hz, 4H), 5.20 - 5.36 (m, 2H), 3.70 - 3.84 (m, 2H), 3.57 - 3.70 (m, 2H), 2.54 - 2.70 (m, 2H), 2.18 - 2.28 (m, 2H), 2.14 (quin, *J*=6.9 Hz, 4H), 1.50 (s, 9H), 1.23 (s, 9H).

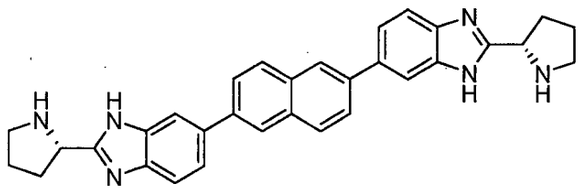


Intermediate 18

tert-Butyl (2S)-2-(5-(6-bromo-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate

[00353] The above reaction also provided *tert*-butyl (2S)-2-(5-(6-bromo-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (519 mg) as yellow solid. LC-MS retention time 1.88 min; Calcd. for $[M+H]^+$ $C_{26}H_{26}BrN_3O_2$: 491.12 Found m/z 494.04 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.21 (d, *J*=8.6 Hz, 1H), 8.05 - 8.14 (m, 2H), 7.93 - 8.05 (m, 2H), 7.82 - 7.93 (m, 3H), 7.57 - 7.67 (m,

1H), 5.28 (br s, 1H), 3.98 (s, 1H), 3.70 - 3.80 (m, 1H), 3.57 - 3.70 (m, 1H), 2.54 - 2.71 (m, 1H), 2.17 - 2.29 (m, 1H), 2.09 - 2.17 (m, 2H), 1.49 (s, 4H), 1.22 (s, 5H).

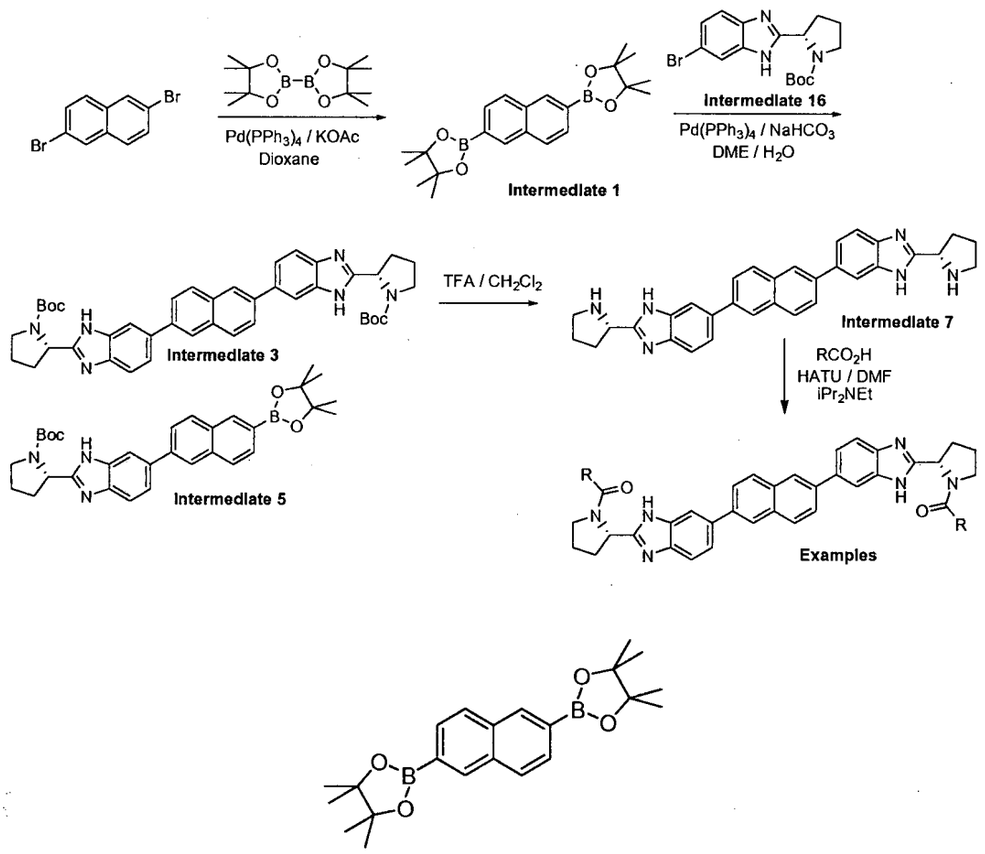


Intermediate 7

5,5'-(2,6-Naphthalenediyl)bis(2-(2-pyrrolidinyl)-1H-benzimidazole)

[00354] A mixture of *tert*-butyl 2-(5-(6-(2-(1-(*tert*-butoxycarbonyl)-2-pyrrolidinyl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (591 mg. 0.844 mmol) and TFA (2mL) in CH_2Cl_2 (10 mL) was stirred at ambient conditions for 2 hours. The volatile component was removed *in vacuo* and the resulting material was loaded onto a MCX column, flushed with methanol, released with 2.0 M NH_3/methanol elution) and concentrated to provide 5,5'-(2,6-naphthalenediyl)bis(2-(2-pyrrolidinyl)-1H-benzimidazole) (419 mg) as tan solid. LC-MS retention time 1.02 min; Calcd. for $C_{33}H_{31}N_5$: 498.25 Found m/z 499.25 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^1H NMR (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.06 (d, *J*=8.6 Hz, 1H), 8.00 (s, 1H), 7.84 - 7.92 (m, 1H), 7.73 - 7.81 (m, 2H), 5.08 (t, *J*=7.6 Hz, 1H), 3.56 - 3.66 (m, 1H), 3.48 - 3.56 (m, 1H), 2.62 - 2.71 (m, 1H), 2.36 - 2.47 (m, 1H), 2.19 - 2.36 (m, 2H).

Scheme 4

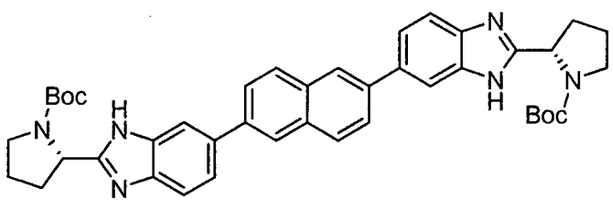


Intermediate 1

2,6-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene

[00355] A pressure flask containing a mixture of 2,6-dibromonaphthalene (8.0 g, 28 mmol), bis(pinacolato)diboron (21.3 g, 84.0 mmol), potassium acetate (3.01 g, 30.7 mmol) and 1,4-dioxane (50 mL) was degassed *in vacuo* for 5 minutes and purged with nitrogen. The catalyst $Pd(Ph_3P)_4$ (710 mg, 0.614 mmol) was added. The flask was capped and heated with an oil bath at 85 °C (bath temperature) for 16 hours. The reaction mixture was concentrated *in vacuo* and the crude material was partitioned between CH_2Cl_2 and a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 50-100% CH_2Cl_2/Hexanes) to provide 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene contaminated with

bis(pinacolato)diboron. The solid was dissolved into CH_2Cl_2 and methanol was added until precipitation was observed. The precipitate was collected by filtration to afford 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (5.1g, 48 % yield) as white solid. ^{1}H NMR (500 MHz, benzene-d_6) δ ppm 8.70 (s, 2H), 8.16 (d, *J*=8.2 Hz, 2H), 7.75 (d, *J*=8.2 Hz, 2H), 1.15 (s, 24H).

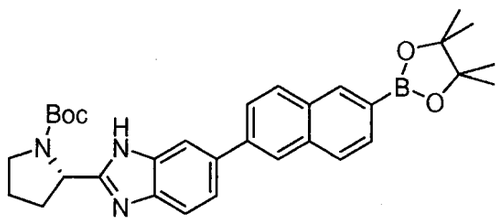


Intermediate 3

(2S,2'S)-*tert*-Butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate

[00356] To a mixture of 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (2.0 g, 5.3 mmol) and (S)-*tert*-butyl 2-(6-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (2.89 g, 7.89 mmol) in 1,2-dimethoxyethane (42.1 mL) and water (10.5 mL) was added $NaHCO_3$ (2.21 g, 26.3 mmol). The reaction mixture was degassed *in vacuo* and was flushed with nitrogen. The catalyst $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol) was added. The flask was capped and heated with an oil bath at 100 °C for 16 hours. The volatile component was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were filtered through a pad of diatomaceous earth (CELITE®) and the filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-100% ethyl acetate/ hexanes) to afford (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate (761 mg, 21% yield) as orange solid. LC-MS retention time 1.46 min; Calcd. for $C_{42}H_{46}N_6O_4$: 698.36 Found m/z 699.26 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA ^{1}H NMR (500 MHz, MeOD) δ ppm 8.28 (br s, 2H), 8.13 (t, *J*=8.7 Hz, 4H), 8.05 (t, *J*=8.4 Hz, 2H), 7.92 (dd, *J*=14.8, 8.7 Hz, 4H), 5.20 - 5.36 (m, 2H), 3.70 - 3.84 (m, 2H), 3.57 - 3.70 (m, 2H), 2.54 - 2.70 (m, 2H), 2.18 - 2.28 (m, 2H), 2.09 - 2.19 (m, 4H), 1.50 (s, 9H), 1.23 (s, 9H).

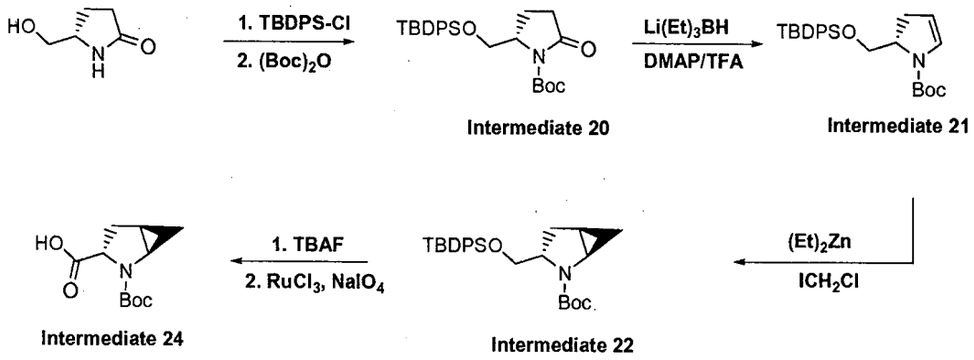


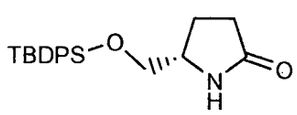
Intermediate 5

(S)-*tert*-Butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

[00357] The above reaction also provided (S)-*tert*-butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.58 g, 56% yield) as tan solid. LC-MS retention time 1.46 min; Calcd. for $C_{32}H_{38}BN_3O_4$: 539.3 Found m/z 540.24 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA.

Scheme 5

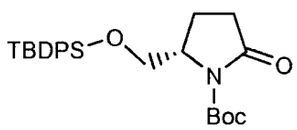




Intermediate 19

(S)-5-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidin-2-one

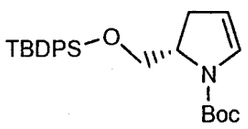
[00358] To a solution of (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (10 g, 87 mmol) in CH_2Cl_2 (50 mL) was added *tert*-butylchlorodiphenylsilane (25.6 g, 93 mmol), Et_3N (12.1 mL, 87 mmol) and DMAP (1.06 g, 8.7 mmol). The mixture was stirred at room temperature until the starting pyrrolidinone was completely consumed and then diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated *in vacuo* and the crude material was submitted to flash chromatography (silica gel; 30 to 100% of EtOAc/hexanes) to afford (S)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-2-one (22.7 g, 74 % yield) as a colorless oil. LC/MS $(M+H)^+ = 354.58$. ^1H NMR (400 MHz, DMSO-d_6) δ 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).



Intermediate 20

(S)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate

[00359] Di-*tert*-butyl dicarbonate (38.5 g, 177 mmol) was added in portions as a solid over 10 min to a solution of (S)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-2-one (31.2 g, 88.3 mmol), Et_3N (8.93 g, 88 mmol) and DMAP (1.08 g, 8.83 mmol) in CH_2Cl_2 (200 mL) and the reaction mixture was stirred for 18 h at 24 °C. Most of the volatile material was removed *in vacuo* and the crude material was purified by silica gel chromatography (20% EtOAc/hexanes to 50% EtOAc/hexanes) to afford (S)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (32.65 g, 82 % yield) as a white solid. LC/MS $(M\text{-}Boc+H)^+ = 354.58$. ^1H NMR (400 MHz, DMSO-d_6) δ 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).

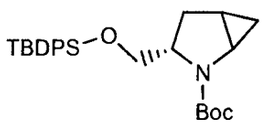


Intermediate 21

(S)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate

[00360] A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with (S)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (10.05 g, 22.16 mmol) and toluene (36 mL) and lowered into -55 °C cooling bath. When the internal temperature of the mixture reached -50 °C, lithium triethylborohydride (23 mL of 1.0 M/THF, 23 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. The reaction mixture was diluted with toluene (15 mL), cooled with an ice-water bath and treated slowly with water (55 mL) over 5 min. The phases were separated and the organic layer washed with water (50 mL, 2x) and concentrated *in vacuo*. The crude

material was purified by flash chromatography (silica gel; 5% EtOAc/hexanes) to afford (S)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate (7.947 g, 82% yield) as a colorless viscous oil. LC/MS: $[M+Na]^+ = 460.19$. 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 MeOH/water; B = 0.1% TFA in 9:1 MeOH/water) over 2 min and hold for 1 min; detection at 220 nm; PHENOMENEX® Luna 3.0X50 mm S10 column. ^{1}H NMR (400 MHz, DMSO-d_6) δ 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, 0.5H), 3.69 (br s, 1.5H), 2.90-2.58 (br m, 2H), 1.40/1.26 (overlapping br s, 9H), 0.98 (s, 9H).

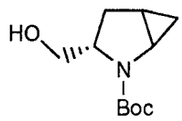


Intermediate 22

(3S)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyloxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00361] Diethylzinc (19 mL of ~1.1 M in toluene, 21 mmol) was added dropwise over 15 min to a cooled (-30 °C) toluene (27 mL) solution of (S)-*tert*-butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate (3.94 g, 9.0 mmol). Chloroiodomethane (stabilized over copper; 3.0 mL, 41 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. The reaction mixture was filtered through a filter paper and the white cake was washed with 50 mL of toluene. The organic phase of the filtrate was separated and washed with water (40 mL, 2x), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified using by silica gel chromatography (350 g silica gel; sample was loaded with 7% EtOAc/hexanes; eluted with 7-20% EtOAc/hexanes) to afford (3S)-*tert*-butyl 3-((*tert*-butyldiphenylsilyloxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (3.69 g, 90.7%) as a mixture of *cis/trans* isomers. [Note: the exact *cis/trans*-isomer ratio was not

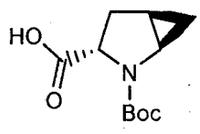
determined at this stage]. LC/MS: $[M+Na]^+ = 474.14$. Rt = 2.39 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 MeOH/water; B = 0.1% TFA in 9:1 MeOH/water) over 2 min and hold for 1 min; detection at 220 nm; PHENOMENEX® Luna 3.0X50 mm S10 column. ^{1}H NMR (400 MHz, DMSO-d_6) δ 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).



Intermediate 23

(3S)-*tert*-Butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00362] TBAF (7.27 mL of 1.0 M in THF, 7.27 mmol) was added dropwise over 5 min to a THF (30 mL) solution of (3S)-*tert*-butyl 3-((*tert*-butyldiphenylsilyloxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (mixture of *cis/trans* isomers) (3.13 g, 6.93 mmol) and the mixture was stirred at ambient temperature for 4.75 h. After the addition of saturated NH_4Cl solution (5 mL), most of the volatile material was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (70 mL) and 50% saturated NH_4Cl solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (30 mL) and the combined organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* and then exposed to high vacuum overnight. The crude material was purified using a flash chromatography (silica gel; 40-50% EtOAc/hexanes) to afford (3S)-*tert*-butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.39 g, 94% yield) as a mixture of *cis/trans* isomers and a colorless oil. [Note: the exact *cis/trans* isomer ratio was not determined at this stage.] LC/MS $(M+Na)^+ = 236.20$. ^{1}H NMR (400 MHz, DMSO-d_6, δ = 2.5 ppm) δ 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).



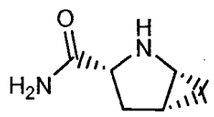
Intermediate 24

(1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid

[00363] A semi-solution of $NaIO_4$ (6.46 g, 30.2 mmol) in water (31 mL) was added to a solution of (3S)-*tert*-butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (mixture of *cis/trans* isomers) (2.15 g, 10.08 mmol) in CH_3CN (20 mL) and CCl_4 (20 mL). $RuCl_3$ (0.044 g, 0.212 mmol) was added immediately and the heterogeneous reaction mixture was stirred vigorously for 75 min. The reaction mixture was diluted with water (60 mL) and extracted with CH_2Cl_2 (50 mL, 3x). The combined organic phases was treated with 1 mL MeOH, allowed to stand for about 5 min and then filtered through a pad of diatomaceous earth (CELITE®). The pad was washed with CH_2Cl_2 (50 mL) and the filtrate was concentrated *in vacuo* to afford a light charcoal-colored solid. The crude material was dissolved in EtOAc (~10 mL) with heating and allowed to stand at ambient temperature with seeding. About 15 min into the cooling phase, a rapid crystal formation was observed. About 1 h later, hexanes (~6 mL) was added and the mixture refrigerated overnight (it did not appear that additional material precipitated out). The mixture was filtered and washed with ice/water-cooled hexanes/EtOAc (2:1 ratio; 20 mL) and dried under high vacuum to afford the first crop of (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (off-white crystals, 1.222 g). The mother liquor was concentrated *in vacuo* and the residue dissolved in ~3 mL of EtOAc with heating, allowed to stand at ambient temperature for 1 h and then 3 mL hexanes was added and stored in a refrigerator for ~15 h. A second crop of (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid was retrieved similarly (grey crystals, 0.133 g), for a combined yield of 59%. LC/MS $[M+Na]^+$ = 250.22. 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 at 220 nm; PHENOMENEX® Luna 3.0X50 mm S10 column. MP (dec.) for the first crop = 147.5-149.5 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 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

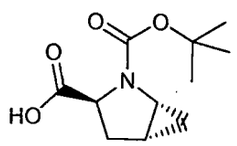
overlapped s, 9H), 0.71 (m, 1H), 0.45 (m, 1H). 13C-NMR (100.6 MHz, DMSO-d_6) 172.96, 172.60, 154.45, 153.68, 78.74, 59.88, 59.58, 36.91, 31.97, 31.17, 27.77, 27.52, 14.86, 14.53, 13.69. Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13;H, 7.54; N, 6.16. Found (for first crop): C, 58.24;H, 7.84; N, 6.07. Optical rotation (10 mg/mL in $CHCl_3$): [α] D = -216 and -212 for the first and second crop, respectively.

An alternative synthesis for Intermediate 24:



· MSA

[00364] (1R,3R,5R)-2-Azabicyclo[3.1.0]hexane-3-carboxamide (.CH_3SO_3H) was prepared according to the procedure described for the synthesis of its stereoisomer in patent WO 2004/052850.



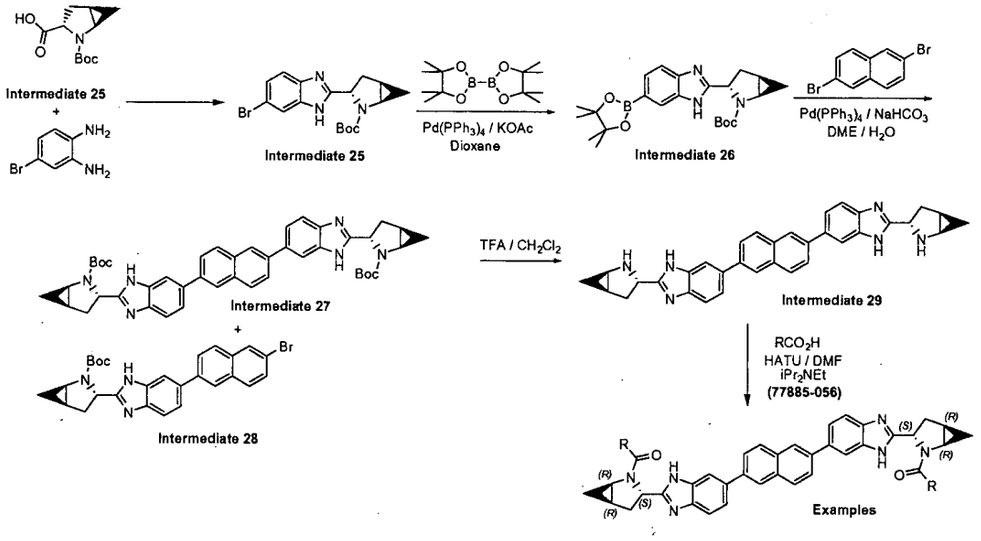
Intermediate 24

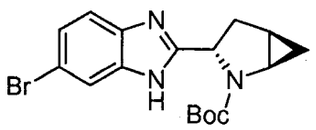
(1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid

[00365] A 1 L round bottom flask equipped with a nitrogen inlet, overhead agitator, thermocouple and heating mantle was charged with 50 g (225 mmol) (1R,3R,5R)-2-Azabicyclo[3.1.0]hexane-3-carboxamide (.CH_3SO_3H) and 250 mL isopropanol. The resulting slurry was then charged with 252 mL of 23 wt% NaOEt in EtOH (2.68 M, 675 mmol, 3.0 equiv) and stirred at 50 °C for ca. 1h. The mixture was charged with 12.2 mL (675 mmol, 3 equiv) of water and heated to 60 °C. The resulting slurry was allowed to stir at 60 °C for ca. 18h. The slurry was cooled to rt and charged with 250 mL water and 98.2 g (450 mmol, 2.0 equiv) di-*t*-butyldicarbonate. Ethanol and isopropanol were removed *via* vacuum distillation and the aqueous mixture cooled to 0 °C. The mixture was neutralized with 76 ml (456 mmol) 6M aqueous HCl while maintaining an internal temperature < 5 °C. The product was extracted with 500 mL MTBE and the rich organic layer was washed with 100 mL water. The clear solution was concentrated down to 150

mL *via* vacuum distillation and the resulting slurry was charged with 600 mL heptane while maintaining an internal temperature > 45 °C. The slurry was cooled to rt over ca. 30 min and allowed to stir at rt for ca. 2h. The product was filtered, washed with 250 mL 4:1 heptane:MTBE and dried under vacuum at 70 °C to give 40.5 g (178 mmol, 79% yield, 99.8 AP at 205 nm) of (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 4.02-3.80 (m, 1H), 3.45-3.15 (m, 1H), 2.40-2.19 (m, 1H), 2.19-2.0 (m, 1H), 1.70-1.50 (m, 1H), 1.50-1.20 (m, 9H), 0.83-0.60 (m, 1H), 0.33-0.55 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 173.2, 155.0, 154.3, 79.4, 60.5, 60.2, 37.6, 32.6, 31.8, 28.4, 28.2, 15.6, 15.2, 14.4; HRMS calcd for $C_{11}H_{18}NO_4$ (M + H; ESI$^+$): 228.1236. Found: 228.1234.

Scheme 6

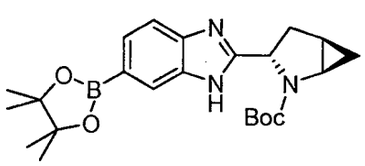




Intermediate 25

(1R,3S,5R)-*tert*-Butyl 3-(6-bromo-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

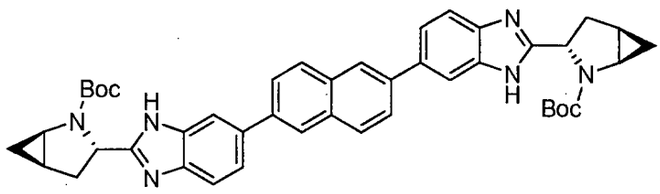
[00366] EDCI·HCl (2.65 g, 13.8 mmol) was added to a mixture of 4-bromobenzene-1,2-diamine 2.35 g, 12.6 mmol), (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (3.00 g, 13.2 mmol) and 1-hydroxybenzotriazole (1.93 g, 12.6 mmol) in CH_2Cl_2 (80 mL) and stirred at ambient conditions for 16 h. The mixture was then diluted with CH_2Cl_2, washed with water, dried (brine; $MgSO_4$), filtered and concentrated *in vacuo* to provide a brown foam. Acetic acid (80 mL) was added to the foam and the mixture was heated at 75 °C (bath temperature) for 5h. The volatile component was removed *in vacuo* and the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution and the organic phase was dried (brine; $MgSO_4$), filtered and concentrated *in vacuo*. The resultant crude material was submitted to flash chromatography (silica gel; 50-100% EtOAc/hexanes) to provide (1R,3S,5R)-*tert*-butyl 3-(6-bromo-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (3.01 g, 7.96 mmol, 63.3 % yield) as a light orange foam, which was used without further purification. The reaction also yielded 847 mg of same product with lower purity. An aliquot of the collected material was purified further by preparative HPLC (C-18/ 30-100% CH_3CN-water+ 0.1 % NH_4OAc) to achieve an analytical sample. LC-MS retention time 1.248 min; Calcd. for $C_{17}H_{21}BrN_3O_2$: 378.08 Found m/z 380.05 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 7.67 (br s, 1H), 7.43 (br s, 1H), 7.34 (d, *J*=8.6 Hz, 1H), 4.75 (br s, 1H), 3.62 (br s, 1H), 2.50 - 2.57 - 2.31 (m, 1H), 2.31 (dt, *J*=13.2, 6.7 Hz, 1H), 1.66 - 1.85 (m, 1H), 1.45 (br s, 3H), 1.11 (br s, 6H), 0.87 (dt, *J*=8.6, 5.8 Hz, 1H), 0.66 (br s, 1H).



Intermediate 26

(1R,3S,5R)-*tert*-Butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00367] To a pressure flask containing a mixture of (1R,3S,5R)-*tert*-butyl 3-(6-bromo-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (2.0 g, 5.3 mmol) and bis(pinacolato)diboron (2.69 g, 10.6 mmol) in 1,4-dioxane (50 mL) was added potassium acetate (0.78 g, 7.9 mmol). The reaction flask was degassed *in vacuo* for 10 min and purged with nitrogen. $Pd(Ph_3P)_4$ (305 mg, 0.264 mmol) was added to the reaction mixture and the flask was capped and heated with an oil bath at 85 °C (bath temperature) for 16 hours. The reaction mixture was concentrated *in vacuo* and the crude material was partitioned 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 (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 20-100% ethyl acetate/hexanes) to provide (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.74g, 77% yield) as white foam. An aliquot of the collected material was further purified by preparative HPLC (C-18/ 30-100% CH_3CN-water+ 0.1 % NH_4OAc). LC-MS retention time 1.78 min; Calcd. for $C_{23}H_{32}BN_{32}$ 425.25 Found m/z 426.21 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0 X 50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mmol ammonium acetate and Solvent B was 95% acetonitrile/ 5% water / 10 mmol ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode ^1H NMR (500 MHz, MeOD) δ ppm 7.94 (s, 1H), 7.61 (d, *J*=7.9 Hz, 1H), 7.41 - 7.56 (m, 1H), 4.83 (br s, 1H), 3.64 (d, *J*=1.2 Hz, 1H), 2.51 - 2.70 (m, 1H), 2.33 (dt, *J*=13.4, 6.6 Hz, 1H), 1.67 - 1.84 (m, *J*=8.5, 6.10, 5.8, 5.8 Hz, 1H), 1.39 - 1.59 (br s, 3H), 1.37 (s, 12H), 1.10 (br s, 6H), 0.88 (dt, *J*=8.2, 5.8 Hz, 1H), 0.66 (br s, 1H).

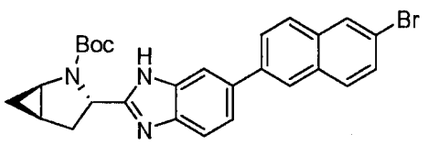


Intermediate 27

(1R,1'R,3S,3'S,5R,5'R)-*tert*-Butyl 3,3'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate)

[00368] To a mixture of (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.50 g, 3.53 mmol) and 2,6-dibromonaphthalene (403 mg, 1.41 mmol) in 1,2-dimethoxyethane (21.7 mL) and water (6.50 mL) was added $NaHCO_3$ (356 mg, 4.23 mmol). The reaction mixture was degassed *in vacuo* for 10 minutes and flushed with nitrogen. $Pd(Ph_3P)_4$ (82 mg, 0.071 mmol) was added and the reaction mixture was heated with an oil bath at 100 °C for 16 hours and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water (30 mL) and the aqueous phase was extracted several times with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-70% ethyl acetate/ CH_2Cl_2) to afford (1R,1'R,3S,3'S,5R,5'R)-*tert*-butyl 3,3'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate) (377 mg) as yellow solid. LC-MS retention time 1.49 min; Calcd. for $C_{44}H_{46}N_6O_4$: 722.36 Found m/z 723.26 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 8.26 (s, 2H), 8.12 (d, *J*=8.5 Hz, 2H), 8.09 (s, 2H), 8.00 (m, *J*=8.6 Hz, 2H), 7.93 (m, *J*=8.6 Hz, 2H), 7.86 (d, *J*=8.6 Hz, 2H), 5.01 (br s, 2H), 3.68

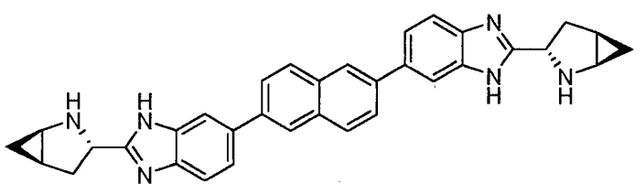
(br s, 2H), 2.76 (dd, *J*=13.3, 9.3 Hz, 2H), 2.42 - 2.54 (m, 2H), 1.87 (br s, 2H), 1.49 (br s, 9H), 1.19 (br s, 9H), 0.94 (dt, *J*=8.3, 6.1 Hz, 2H), 0.79 (br s, 2H).



Intermediate 28

(1R,3S,5R)-*tert*-Butyl 3-(6-(6-bromonaphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00369] The above reaction also provided (1R,3S,5R)-*tert*-butyl 3-(6-(6-bromonaphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (418 mg) as yellow solid. LC-MS retention time 1.90 min; Calcd. for $C_{27}H_{26}BrN_3O_2$: 503.12 Found m/z 506.05 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.93 - 8.00 (m, 2H), 7.86 - 7.93 (m, 2H), 7.84 (d, *J*=8.6 Hz, 1H), 7.63 (dd, *J*=8.6, 1.8 Hz, 1H), 5.00 (br s, 1H), 3.68 (br s, 1H), 2.75 (dd, *J*=13.4, 9.2 Hz, 1H), 2.41 - 2.54 (m, 1H), 1.87 (br s, 1H), 1.49 (br s, 5H), 1.17 (br s, 4H), 0.87 - 0.98 (m, 1H), 0.79 (br s, 1H).

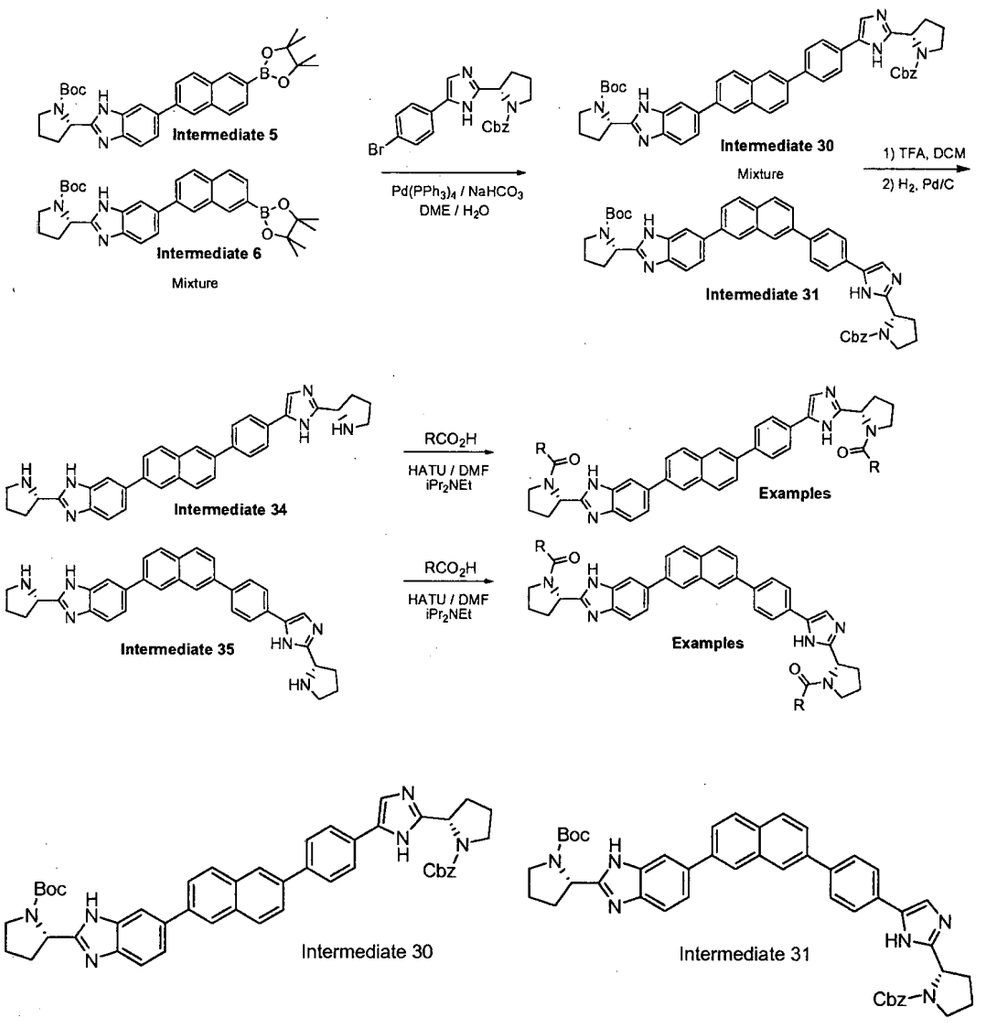


Intermediate 29

2,6-Bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalene

[00370] A mixture of (1R,1'R,3S,3'S,5R,5'R)-*tert*-butyl 3,3'-(6,6'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate) (360 mg. 0.498 mmol) and TFA (2mL) in CH_2Cl_2 (10 mL) was stirred at ambient conditions for 3 hours. The volatile component was removed *in vacuo* and the resulting material was loaded onto an MCX column, flushed with methanol, eluted with 2.0 M NH_3/methanol and concentrated to provide 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalene as yellow solid (253 mg). LC-MS retention time 1.07 min; Calcd. for $C_{34}H_{30}N_6$: 522.25 Found m/z 523.19 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.17 (s, 2H), 8.06 (d, *J*=8.2 Hz, 2H), 8.00 (s, 2H), 7.88 (d, *J*=8.6 Hz, 2H), 7.71 - 7.81 (m, 4H), 4.84 (dd, *J*=10.8, 7.5 Hz, 2H), 3.47 - 3.53 (m, 2H), 2.80 (dd, *J*=12.8, 7.6 Hz, 2H), 2.54 - 2.63 (m, 2H), 2.04 - 2.11 (m, 2H), 1.20 - 1.27 (m, 2H), 1.02 (q, *J*=7.7 Hz, 2H).

Scheme 7



Mixture of Intermediate 30

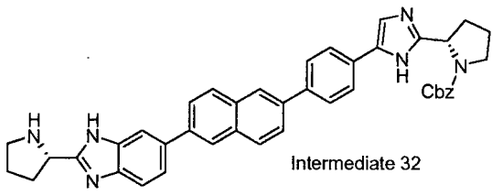
(S)-Benzyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate bistrifluoroacetate

and Intermediate 31

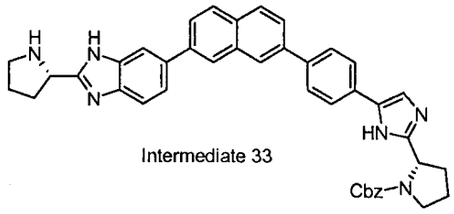
(S)-Benzyl 2-(5-(4-(7-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate bistrifluoroacetate

[00371] To a mixture of a TFA salt of (S)-*tert*-butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

and a TFA salt of (S)-*tert*-butyl 2-(6-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (190 mg), (S)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (Patent applications: WO 2008/021928, WO 2008/021936 and WO 2008/021927) (213 mg, 0.499 mmol), in 1,2-dimethoxyethane (10.0 mL) and water (2.0 mL) was added $NaHCO_3$ (140 mg, 1.663 mmol). The reaction mixture was degassed *in vacuo* for 5 minutes and was flushed with nitrogen. $Pd(Ph_3P)_4$ (19 mg, 0.017 mmol) was added and the pressure flask was capped and heated with an oil bath at 85 °C for 16 hours. The volatile component was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-5% methanol/CH_2Cl_2) to afford partially purified products. The residue was further purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a mixture of a TFA salt of (S)-benzyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and a TFA salt of (S)-benzyl 2-(5-(4-(7-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (381 mg) which was used without further purification. LC-MS retention time 1.54 min; Calcd. for $C_{47}H_{46}N_6O_4$ 758.36 Found m/z 759.37 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA.



Intermediate 32



Intermediate 33

Mixture of Intermediate 32

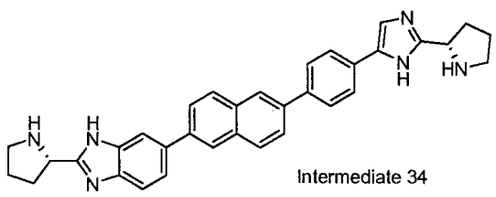
(S)-Benzyl 2-(5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

and Intermediate 33

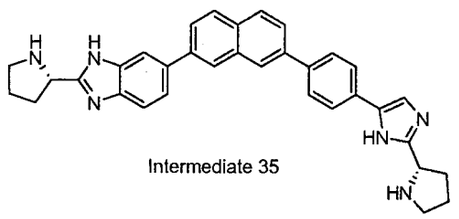
(S)-Benzyl 2-(5-(4-(7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00372] A mixture of a TFA salt of (S)-benzyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and a TFA salt of (S)-benzyl 2-(5-(4-(7-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (381 mg) and TFA (2 mL) in CH_2Cl_2 (10 mL) was stirred at ambient conditions for 4 hours. The volatile component was removed *in vacuo* and the crude material was purified by a reverse phase HPLC (0 to 50% water/acetonitrile/NH_4OAc) to provide a mixture of (S)-benzyl 2-(5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-benzyl 2-(5-(4-(7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (70 mg, 21% yield) as yellow oil. LC-MS retention time 2.87 min; Calcd. for $C_{42}H_{38}N_6O_2$ 658.31 Found m/z 659.47 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 80% Solvent A / 20% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% acetonitrile / 95% water / 10 mmol NH_4OAc and Solvent B was 95% acetonitrile/ 5% water / 10 mmol NH_4OAc. ^1H NMR (Mixture of compounds, 500 MHz, MeOD) δ ppm 8.07 - 8.24 (m, 4H), 7.91 - 8.03 (m, 6H), 7.73 - 7.89 (m, 12H), 7.66 - 7.73 (m, 4H), 7.27 - 7.46 (m, 6H),

7.09 - 7.18 (m, 4H), 6.97 - 7.04 (m, 2H), 5.01 - 5.21 (m, 5H), 4.83 - 5.01 (m, 2H), 3.72 - 3.82 (m, 2H), 3.53 - 3.65 (m, 2H), 3.42 - 3.52 (m, 2H), 3.35 - 3.42 (m, 4H), 2.48 - 2.62 (m, 2H), 2.28 - 2.47 (m, 4H), 2.04 - 2.24 (m, 8H).



Intermediate 34



Intermediate 35

Intermediate 34

2-((S)-Pyrrolidin-2-yl)-6-(6-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-benzo[d]imidazole tetratrifluoroacetate

and Intermediate 35

2-((S)-Pyrrolidin-2-yl)-6-(7-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-benzo[d]imidazole tetratrifluoroacetate

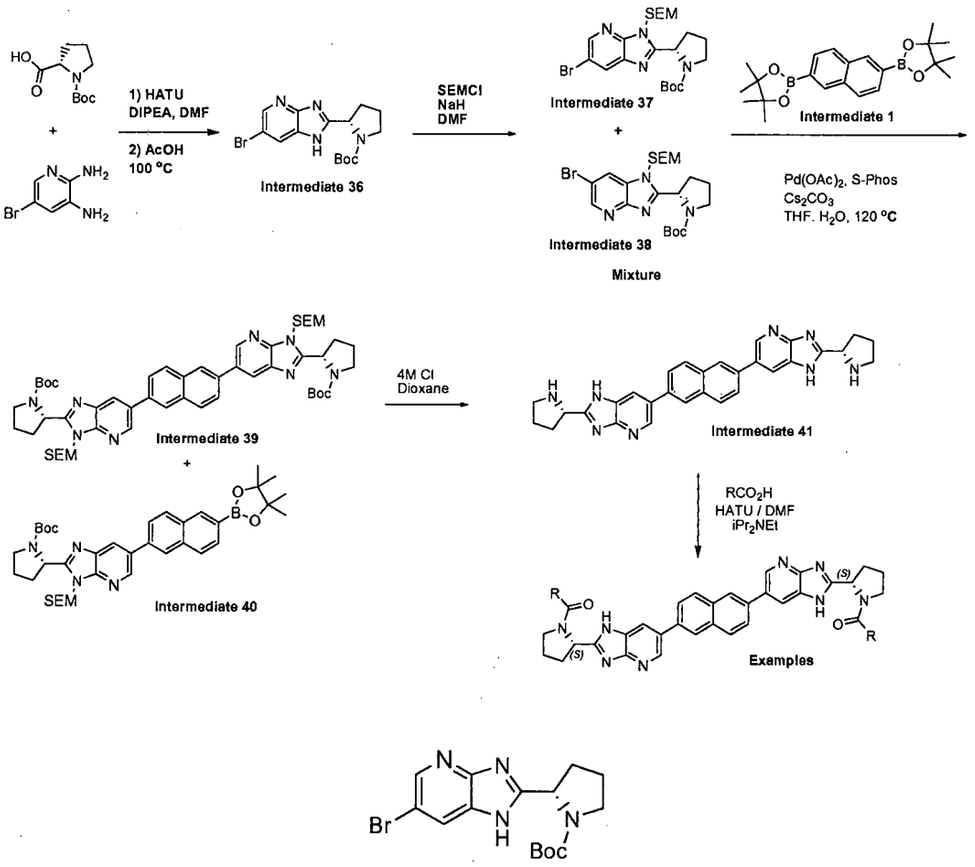
[00373] To a solution of a mixture of (S)-benzyl 2-(5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-benzyl 2-(5-(4-(7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (70 mg. 0.057 mmol) and potassium carbonate (K_2CO_3) in methanol (5 mL) was added a slurry of palladium on carbon (10%, 11 mg) in methanol (2 mL) at ambient temperature. The reactor was vacuum purged and backfilled with hydrogen. The reaction was stirred for 16h under a balloon of hydrogen. The mixture was filtered through a pad of diatomaceous earth (CELITE®) under vacuum and the filtrate was evaporated in *vacuo*. The crude material was purified by a reverse phase HPLC (0 to 50% water/acetonitrile/TFA) to provide a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(6-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-benzo[d]imidazole (50 mg) as white solid and a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(7-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-benzo[d]imidazole (24 mg) as white solid.

[00374] Analytical data for Intermediate 34: LC-MS retention time 1.06 min; Calcd. for $C_{34}H_{32}N_6$ 524.27 Found m/z 525.26 $[M+H]^+$. LC data was recorded on a Shimadzu

LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 80% Solvent A / 20% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.19 (d, *J*=10.4 Hz, 2H), 8.02 - 8.10 (m, 3H), 7.84 - 7.96 (m, 7H), 7.77 - 7.83 (m, 2H), 5.14 (t, *J*=7.8 Hz, 1H), 5.06 - 5.11 (m, 1H), 3.52 - 3.67 (m, 4H), 2.61 - 2.74 (m, 2H), 2.43 - 2.56 (m, 2H), 2.30 - 2.42 (m, 2H), 2.18 - 2.30 (m, 2H).

[00375] Analytical data for Intermediate 35: LC-MS retention time 1.13 min; Calcd. for $C_{34}H_{32}N_6$ 524.27 Found m/z 525.24 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 80% Solvent A / 20% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.27 (d, *J*=7.0 Hz, 2H), 7.99 - 8.06 (m, 3H), 7.90 - 7.96 (m, 4H), 7.87 (td, *J*=8.2, 1.7 Hz, 2H), 7.76 - 7.85 (m, 3H), 5.13 (t, *J*=7.8 Hz, 1H), 5.03 - 5.08 (m, 1H), 3.51 - 3.67 (m, 4H), 2.61 - 2.74 (m, 2H), 2.42 - 2.54 (m, 2H), 2.20 - 2.40 (m, 4H).

Scheme 8

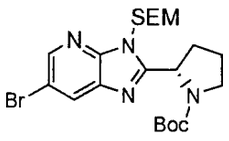


Intermediate 36

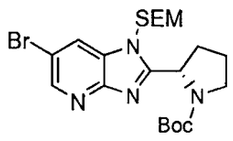
(S)-*tert*-Butyl 2-(6-bromo-1H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate

[00376] HATU (3.64 g, 9.57 mmol) was added to a stirred solution of 5-bromopyridine-2,3-diamine (1.64 g, 8.70 mmol) and (S)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.87 g, 8.70 mmol) in DMF (50 mL) and DIPEA (3.19 mL, 18.3 mmol). The reaction mixture was stirred at room temperature for 3d, diluted with water (400 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The crude material was partially purified by flash chromatography (110 g SiO_2, 1-4% MeOH/DCM) to yield 3.36 g of solidified foam. The material was dissolved into AcOH (35.0 mL) and heated at 100 °C for 8h. The reaction was cooled to room temperature, concentrated and purified by flash chromatography (loaded with DCM, 80g SiO_2, 20-40% EtOAc/Hexanes) to yield (S)-*tert*-butyl 2-(6-bromo-1H-imidazo[4,5-b]pyridin-2-

yl)pyrrolidine-1-carboxylate (1.73 g) as yellow solid. LC-MS retention time 1.33 min; m/z 365, 367 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.40 (br s, 1H), 8.09 (br s, 1H), 5.12 - 4.96 (m, 1H), 3.77 - 3.67 (m, 1H), 3.62 - 3.51 (m, 1H), 2.56 - 2.38 (m, 1H), 2.15 - 1.90 (m, 3H), 1.46 (s, 3.5H), 1.16 (s, 5.5H).



Intermediate 37



Intermediate 38

Mixture of Intermediate 37

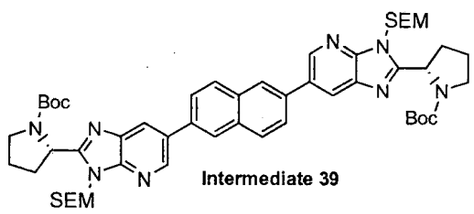
(S)-*tert*-Butyl 2-(6-bromo-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate

and Intermediate 38

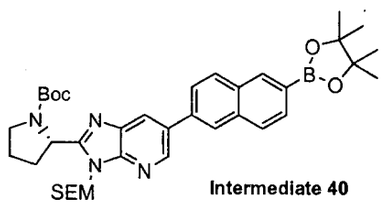
(S)-*tert*-Butyl 2-(6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate

[00377] A 60% dispersion of NaH (0.120 g, 3.00 mmol) was added to a stirred solution of (S)-*tert*-butyl 2-(6-bromo-1H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.7 mmol) in DMF (25 mL) and the reaction was stirred for 1.5h at room temperature. Then SEM-Cl (0.483 mL, 2.72 mmol) was added and the reaction was stirred 16h. The reaction was diluted with water (~ 30 mL) and EtOAc (~35 mL), the layers were separated and the organic layer was washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated. The residual crude yellow oil was purified by flash chromatography (80g SiO_2, 20-30% EtOAc/hexanes) to yield a mixture of (S)-*tert*-butyl 2-(6-bromo-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridin-2-

yl)pyrrolidine-1-carboxylate and (S)-*tert*-butyl 2-(6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate (838 mg) as a yellow oil. The mixture was used w/o further purification. LC-MS retention time 2.54 min; m/z 497,499 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 39



Intermediate 40

Intermediate 39

(2S,2'S)-*tert*-Butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridine-6,2-diyl))dipyrrolidine-1-carboxylate

and Intermediate 40

(S)-*tert*-Butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate

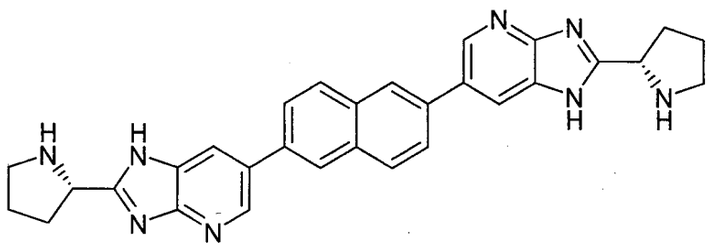
[00378] In a microwave vial, 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (57 mg, 0.150 mmol), a mixture of (S)-*tert*-butyl 2-(6-bromo-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate and (S)-*tert*-butyl 2-(6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate (112 mg), cesium carbonate (147 mg, 0.450 mmol) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (12.3 mg, 0.030 mmol)

were dissolved into THF (3 mL) and water (0.3 mL). An additional 1.5 mL of THF was added and the reaction was sparged with bubbling nitrogen until ~2 mL had evaporated away. To the clear solution was added palladium (II) acetate (3.37 mg, 0.015 mmol). The vial was flushed with nitrogen, sealed and then heated with microwave irradiation at 120 °C for 30 min. The reaction was diluted with EtOAc (~ 3 mL) and washed with water (2 mL) and brine (2 mL). The reaction was dried ($MgSO_4$), filtered and concentrated to a yellow oil which was purified by flash chromatography (12 g SiO_2, 25-75% EtOAc/hexanes) to yield (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridine-6,2-diyl))dipyrrolidine-1-carboxylate (74 mg) as a clear colorless oil (mixture of SEM regioisomers) and (S)-*tert*-butyl 2-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridin-2-yl)pyrrolidine-1-carboxylate (32 mg) as a colorless oil (mixture of SEM regioisomers). Each was used without further purification.

[00379] Analytical data for Intermediate 39: LC-MS retention time 3.42 min; m/z 961.9 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) (mixture of SEM regioisomers) δ ppm 8.84 - 8.75 (m, 2H), 8.39 - 8.31 (m, 2H), 8.26 - 8.18 (m, 2H), 8.11 (br s, 2H), 7.92 - 7.84 (m, 2H), 5.94 - 5.83 (m, 3H), 5.79 (d, J = 11.0 Hz, 1H), 5.34 - 5.25 (m, 2H), 3.86 - 3.57 (m, 8H), 2.61 - 2.39 (m, 2H), 2.34 - 1.99 (m, 6H), 1.45 (s, 8H), 1.17 (s, 10H), 1.10 - 0.87 (m, 4H), -0.02 (s, 18H).

[00380] Analytical data for Intermediate 40: LC-MS retention time 3.15 min; m/z 671.5 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A /

100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. (mixture of SEM regioisomers) δ ppm 8.82 - 8.75 (m, 1H), 8.39 - 8.29 (m, 2H), 8.21 - 8.15 (m, 1H), 8.07 - 8.01 (m, 1H), 8.11 (br s, 2H), 7.98 - 7.93 (m, 1H), 7.89- 7.80 (m, 2H), 5.94 - 5.85 (m, 1.5H), 5.79 (d, J = 11.3 Hz, 0.5H), 5.33 - 5.24 (m, 1H), 3.85 - 3.56 (m, 4H), 2.62 - 2.39 (m, 1H), 2.33 - 1.99 (m, 1H), 1.49 - 0.87 (m, 23H), -0.02 (s, 9H).



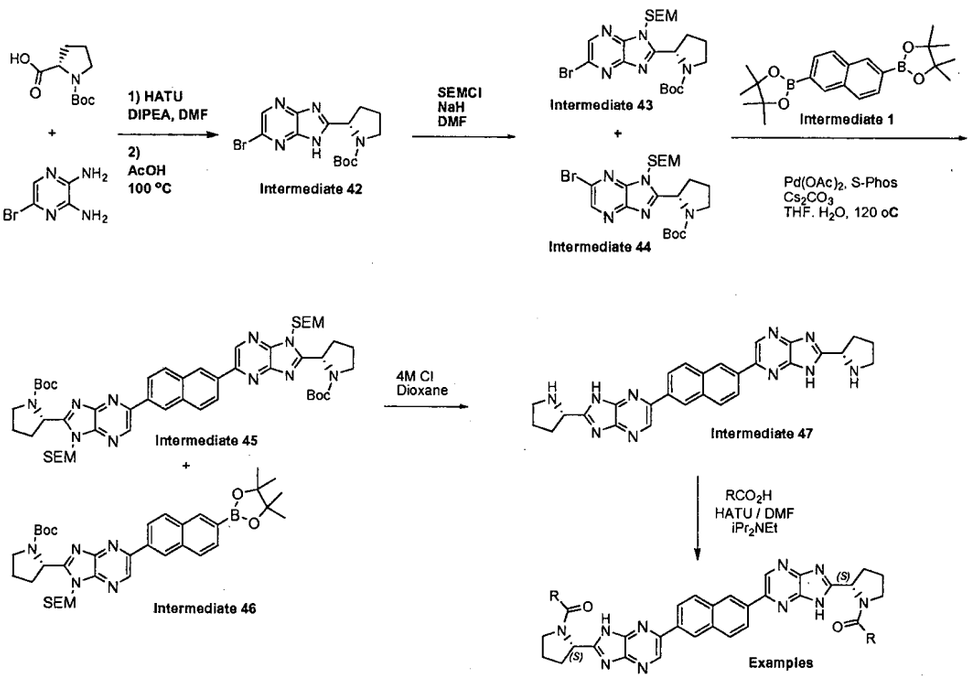
Intermediate 41

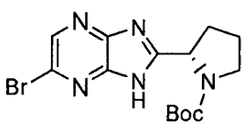
2,6-Bis(2-((S)-pyrrolidin-2-yl)-3H-imidazo[4,5-b]pyridin-6-yl)naphthalene

[00381] 4M Hydrogen chloride(2.0 mL, 8.0 mmol) in dioxane was added to a stirred solution of (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(naphthalene-2,6-diyl)bis(3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridine-6,2-diyl))dipyrrolidine-1-carboxylate (74 mg, 0.077 mmol) (mixture of SEM regioisomers) in methanol (1 mL). The reaction was stirred at room temperature for 16h and then concentrated to dryness to yield a hydrochloride salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-3H-imidazo[4,5-b]pyridin-6-yl)naphthalene (51.1 mg) as yellow solid which was used without further purification. LC-MS retention time 0.83 min; m/z 501.13 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% trifluoroacetic acid and Solvent B was 10% water / 90% acetonitrile / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, D_2O) δ ppm 8.76 (s, 2H), 8.54 (s, 2H), 8.07 -

7.97 (m, 4H), 7.86- 7.78 (m, 2H), 5.26 - 5.16 (m, 2H), 3.98 - 3.65 (m, 8H), 2.79 - 2.63 (m, 2H), 2.46 - 2.25 (m, 6H).

Scheme 9



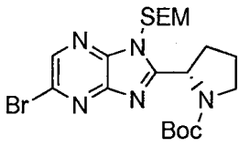


Intermediate 42

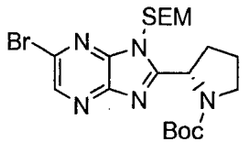
(S)-*tert*-Butyl 2-(6-bromo-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate

[00382] HATU (5.05 g, 13.3 mmol) was added to a stirred solution of 5-bromopyrazine-2,3-diamine (2.28 g, 12.1 mmol) and (S)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (2.60 g, 12.0 mmol) in DMF (50 mL) and DIPEA (4.42 mL, 25.3 mmol). The reaction mixture was stirred at room temperature for 3d and then at 90 °C for 1d. The reaction mixture was diluted with water (350 mL) and extracted with EtOAc (200 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The crude material was partially purified by flash chromatography (110 g SiO_2, 1-4% MeOH/DCM) to yield 1.9 g of solidified foam.

The material was dissolved into AcOH (35.0 mL) and heated at 95 °C for 8h. The reaction was cooled to room temperature, concentrated and purified by flash chromatography (loaded with DCM, 80g SiO_2, 20-30% EtOAc/Hexanes) to yield (S)-*tert*-butyl 2-(6-bromo-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate (760 mg, 2.06 mmol, 17% yield) as yellow solidified foam. LC-MS retention time 1.28 min; m/z 366, 368 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.50 - 8.43 (m, 1H), 5.11 - 4.99 (m, 1H), 3.77 - 3.68 (m, 1H), 3.62 - 3.51 (m, 1H), 2.57 - 2.40 (m, 1H), 2.19 - 1.95 (m, 3H), 1.46 (s, 3.5H), 1.17 (s, 5.5H).



Intermediate 43



Intermediate 44

Intermediate 43

(S)-*tert*-Butyl 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate

and Intermediate 44

(S)-*tert*-Butyl 2-(6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate

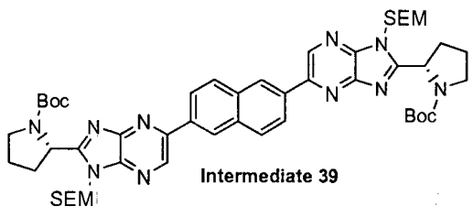
[00383] A 60% dispersion of NaH (75mg, 1.9 mmol) was added to a stirred solution of (S)-*tert*-butyl 2-(6-bromo-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate (627 mg, 1.70 mmol) in DMF (15 mL) and the reaction was stirred for 1.5h at room temperature. Then SEM-Cl (0.30 mL, 1.7 mmol) was added and the reaction was stirred overnight. The reaction was diluted with water (~ 30 mL) and EtOAc (~35 mL), the

layers were separated and the organic layer was washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated. The crude yellow oil was purified by flash chromatography (40g SiO_2, 20-30% EtOAc/hexanes) to yield (S)-*tert*-butyl 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate (421 mg) as a clear colorless oil and (S)-*tert*-butyl 2-(6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate (345 mg) as a clear colorless oil. The absolute regiochemistry of the SEM group was not established unambiguously, the names (and structures) may be exchanged in these intermediates.

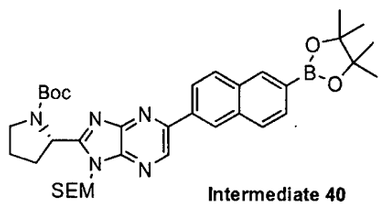
[00384] Analytical data for Intermediate 43: LC-MS retention time 2.43 min; m/z 496, 498 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.52 (s, 0.5H), 8.49 (s, 0.5H), 5.90 - 5.72 (m, 2H), 5.32 - 5.25 (m, 1H), 3.82 - 3.54 (m 4H), 2.59 - 2.41 (m, 1H), 2.32 - 1.98 (m, 3H), 1.43 (s, 4.5H), 1.15 (s, 4.5H), 1.07 - 0.85 (m, 2H), -0.02 (s, 9H).

[00385] Analytical data for Intermediate 44: LC-MS retention time 2.41 min; m/z 496, 498 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.61 (s, 0.5H), 8.58 (s, 0.5H), 5.88 - 5.71(m, 2H), 5.28 (dd, *J*=

8.5, 4.5 Hz, 1H), 3.82 - 3.54 (m 4H), 2.59 - 2.41 (m, 1H), 2.32 - 1.98 (m, 3H), 1.43 (s, 4.5H), 1.15 (s, 4.5H), 1.09 - 0.85 (m, 2H), -0.02 (s, 9H).



Intermediate 39



Intermediate 40

Intermediate 45

(2S,2'S)-*tert*-Butyl 2,2'-(5,5'-(naphthalene-2,6-diyl)bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazine-5,2-diyl))dipyrrolidine-1-carboxylate

and Intermediate 46

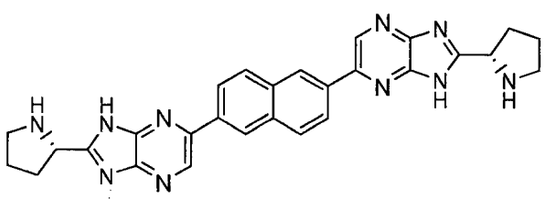
(S)-*tert*-Butyl 2-(5-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate

[00386] In a microwave vial, 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (149 mg, 0.393 mmol), (S)-*tert*-butyl 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate (294 mg, 0.590 mmol) (or a SEM regioisomer), cesium carbonate (384 mg, 1.18 mmol) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (32.3 mg, 0.079 mmol) were dissolved into THF (4 mL) and water (0.4 mL). An additional 1.5 mL of THF was added and the reaction was sparged with bubbling nitrogen until the 1.5 mL had evaporated away. To the clear solution was added palladium(II) acetate (8.83 mg, 0.039 mmol). The vial was flushed with nitrogen, sealed and then heated with microwave irradiation at 120 °C for 30 min. The reaction was diluted with EtOAc (~ 3 mL) and washed with water (2 mL) and brine (2 mL). The reaction was dried ($MgSO_4$), filtered and concentrated to a yellow oil which was purified by flash chromatography(12 g SiO_2, 25-75% EtOAc/hexanes) to yield (2S,2'S)-*tert*-butyl 2,2'-(5,5'-(naphthalene-2,6-diyl)bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazine-5,2-diyl))dipyrrolidine-1-carboxylate (or a SEM regioisomer) (210 mg) as a yellow solidified foam and (S)-*tert*-butyl 2-(5-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazin-2-yl)pyrrolidine-1-carboxylate (or a SEM regioisomer) (53.5 mg) as a colorless oil.

[00387] Analytical date for Intermediate 45: LC-MS retention time 3.27 min; m/z 963.89 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) (mixture of SEM regioisomers) δ ppm 9.29 - 9.15 (m 2H), 8.79 - 8.66 (m, 2H), 8.43 - 8.29 (m, 2H), 8.20 - 7.98 (m, 2H), 6.03 - 5.84 (m, 4H), 5.34 (dd, J = 8.3, 4.3 Hz, 2H), 3.87 - 3.70 (m, 6H), 3.68 - 3.58 (m, 2H), 2.63 - 2.43 (m, 2H), 2.36 - 1.14 (m, 4H), 2.14 - 1.99 (m, 2H), 1.46 (s, 8H), 1.17 (s, 10H), 1.35- 0.85 (m, 4H), -0.02 (s, 18H).

[00388] Analytical date for Intermediate 45: LC-MS retention time 3.07 min; m/z 672.52 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

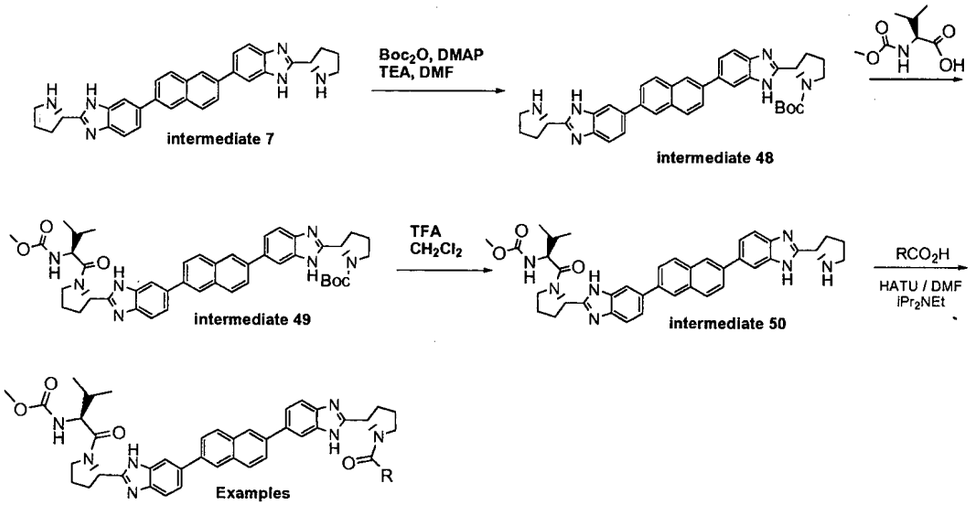


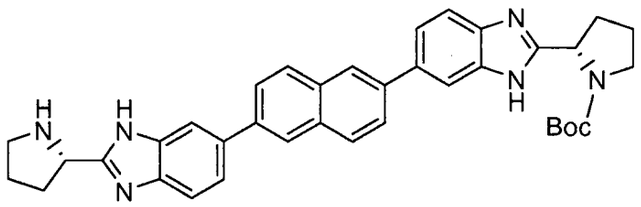
Intermediate 47

2,6-Bis(2-((S)-pyrrolidin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)naphthalene

[00389] 4M Hydrogen chloride (6.0 mL, 24 mmol) in dioxane was added to a stirred solution of (2S,2'S)-*tert*-butyl 2,2'-(5,5'-(naphthalene-2,6-diyl)bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyrazine-5,2-diyl))dipyrrolidine-1-carboxylate (210 mg, 0.218 mmol) (absolute regiochemistry of the SEM was not established) in methanol (3 mL). The reaction was stirred at room temperature for 16h and concentrated to dryness to yield a hydrochloride salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)naphthalene (143 mg) as orange solid which was used without further purification. LC-MS retention time 0.90 min; m/z 503.21 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% trifluoroacetic acid and Solvent B was 10% water / 90% acetonitrile / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, D_2O) δ ppm 8.59 (s, 2H), 7.94 (s, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 5.23 - 5.16 (m, 2H), 3.98 - 3.66 (m, 8H), 2.78 - 2.64 (m, 2H), 2.47- 2.28 (m, 6H).

Scheme 10

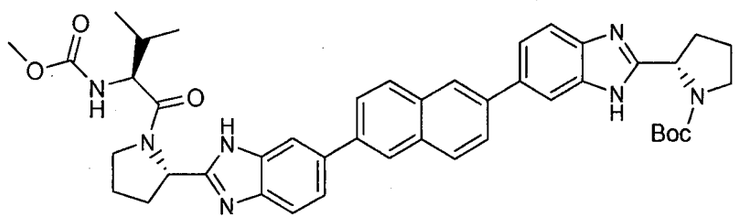




Intermediate 48

tert-Butyl (2S)-2-(5-(6-(2-((2S)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate

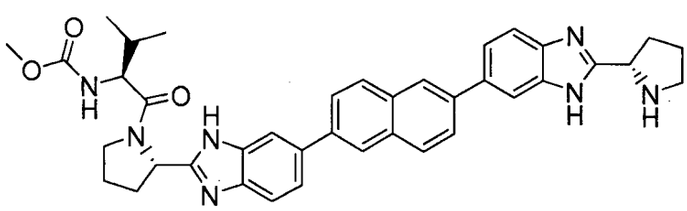
[00390] To a solution of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (885 mg, 1.78 mmol), DMAP (10.8 mg, 0.089 mmol) and triethylamine (1.2 mL, 8.9 mmol) in DMF (30 mL) at room temp was added in one portion di-*tert*-butyl dicarbonate (387 mg, 1.78 mmol). The reaction mixture was stirred overnight at room temperature and purified on a BIOTAGE® (dry loaded to a 80g silica gel cartridge and eluted with a gradient of 0 to 50 % DCM in MeOH), to yield *tert*-butyl (2S)-2-(5-(6-(2-((2S)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (500 mg, 0.835 mmol, 47.1 % yield) as orange solid. LC-MS retention time 1.207 min; m/z 599.25 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.27 (d, *J*=3.1 Hz, 1H), 8.23 (s, 1H), 8.04 - 8.17 (m, 4H), 8.03 (s, 1H), 7.88 - 7.97 (m, 3H), 7.75 - 7.83 (m, 2H), 5.28 - 5.35 (m, 1H), 5.11 (t, *J*=7.8 Hz, 1H), 3.75 - 3.83 (m, 1H), 3.60 - 3.72 (m, 2H), 3.51 - 3.59 (m, 1H), 2.60 - 2.74 (m, 2H), 2.40 - 2.50 (m, 1H), 2.21 - 2.38 (m, 3H), 2.10 - 2.20 (m, 2H), 1.52 (s, 4H), 1.25 (s, 4H).



Intermediate 49

tert-Butyl (2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate

[00391] To a solution of *tert*-butyl (2S)-2-(5-(6-(2-((2S)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (400 mg, 0.668 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (176 mg, 1.00 mmol) and DIEA (0.583 mL, 3.34 mmol) in DMF (10 mL) was added HATU (381 mg, 1.00 mmol). The reaction mixture was stirred 2h at room temperature and then purified by prep HPLC (using a Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 0 to 50 % ACN -Water + 0.1 % TFA) to yield a TFA salt of *tert*-butyl (2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (445 mg) as yellow solid. LC-MS retention time 1.317 min; m/z 756.28 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

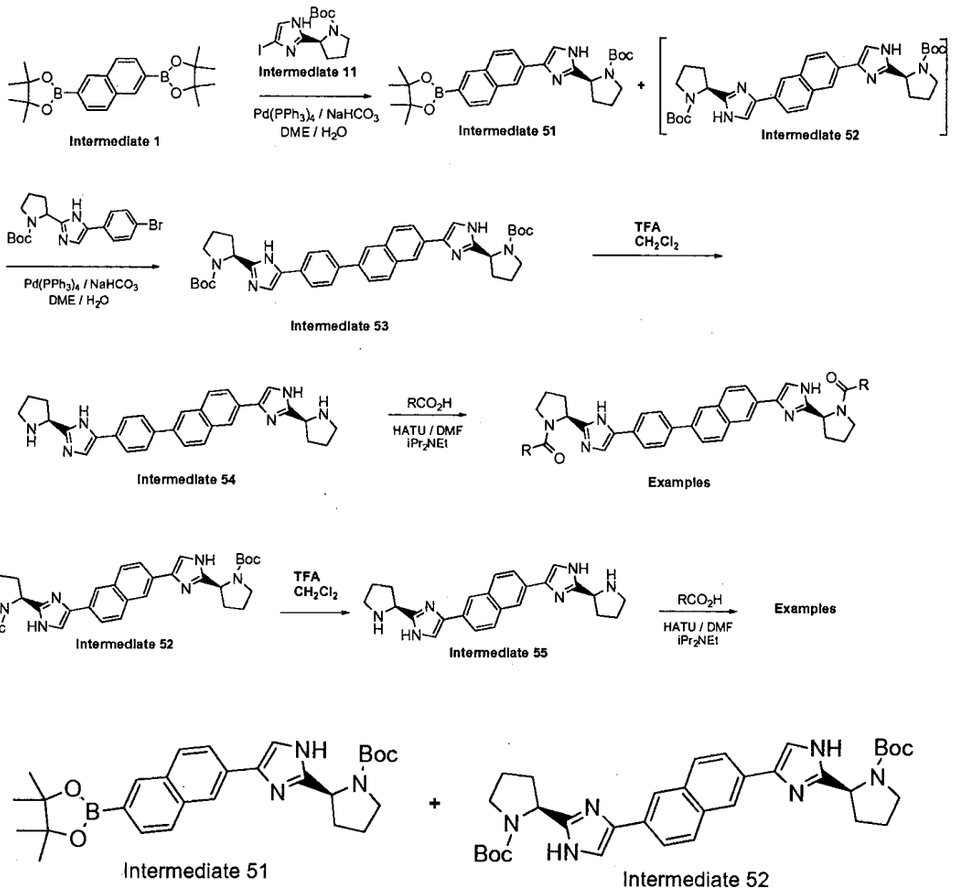


Intermediate 50

Methyl ((1S)-2-methyl-1-(((2S)-2-(5-(6-(2-((2S)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[00392] To a solution of a TFA salt of *tert*-butyl (2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinecarboxylate (445 mg) in DCM (10 mL) at room temp was added TFA (1 mL, 13 mmol). The mixture was stirred at rt for 3h, concentrated, and the residue was diluted in MeOH, loaded onto a Strata XC MCX cartridge and washed with methanol. The compound was release from the cartridge by eluting with a solution of 2M ammonia in methanol and then evaporated under reduced pressure to give methyl ((1S)-2-methyl-1-(((2S)-2-(5-(6-(2-((2S)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (275 mg) as orange solid LC-MS retention time 1.120 min; m/z 656.27 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 8.26 (br s, 1H), 8.22 (br s, 1H), 8.08 - 8.16 (m, 3H), 8.04 - 8.08 (m, 1H), 8.03 (s, 1H), 7.86 - 7.96 (m, 3H), 7.73 - 7.82 (m, 2H), 5.88 - 5.93 (m, 0.1H), 5.37 - 5.44 (m, 0.9H), 5.07 - 5.15 (m, 1H), 4.28 - 4.33 (m, 1H), 4.12 - 4.19 (m, 0.8H), 4.06 - 4.10 (m, 0.2H), 3.94 - 4.02 (m, 1H), 3.59 - 3.75 (m, 4H), 3.50 - 3.59 (m, 1H), 2.63 - 2.74 (m, 2H), 2.41 - 2.47 (m, 1H), 2.23 - 2.40 (m, 5H), 2.06 - 2.16 (m, 1H), 1.00 - 1.04 (m, 0.4H), 0.94 - 1.00 (m, 3H), 0.88 - 0.93 (m, 2.6H).

Scheme 11



Intermediate 51

(S)-*tert*-Butyl 2-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

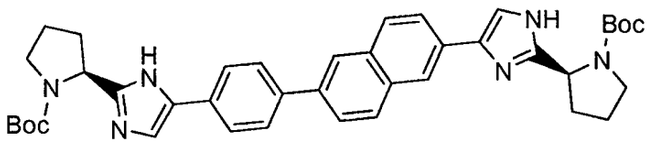
and Intermediate 52

(2S,2'S)-*tert*-Butyl 2,2'-(4,4'-(naphthalene-2,6-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

[00393] A 100 mL pressure vessel equipped with a magnetic stir bar was charged with 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (2.00 g, 5.26 mmol), (S)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (2.10 g, 5.79 mmol) and $Pd(Ph_3P)_4$ (0.058 g, 0.05 mmol) in DME (47.8 mL) and water (4.8 mL). The solution was degassed under vacuum for 5 min and the reactor was back filled with nitrogen. The vessel was sealed and the reaction mixture was heated overnight at 120 °C. The reaction was cooled to room temperature and the volatiles were removed under. The residue was

partitioned between water and EtOAc and the water layer was extracted with additional EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified with a BIOTAGE® (dry loaded onto a 90g silica gel cartridge and eluted with a gradient of 0 to 30 % EtOAc in DCM) and repurified with a BIOTAGE® (dry loaded onto a 80g silica gel cartridge and eluted with a gradient of 0 to 50 % EtOAc in DCM) to yield (S)-*tert*-butyl 2-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (949 mg) as a yellow solid. The material (contaminated with (2S,2'S)-*tert*-butyl 2,2'-(4,4'-(naphthalene-2,6-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate) was used in the next step without further purification. LC-MS retention time 1.760 min; m/z 490.21 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

[00394] The preparative HPLC from the next reaction yielded (2S,2'S)-*tert*-butyl 2,2'-(4,4'-(naphthalene-2,6-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (92 mg, 0.111 mmol, 11 % yield) as yellow solid LC-MS retention time 1.113 min; m/z 599.24 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 8.35 (br s, 2H), 8.13 (br s, 2H), 8.08 (br s, 1H), 8.00 (br s, 1H), 7.95 (m, 2H), 5.18 (br s, 2H), 3.68 - 3.78 (m, 2H), 3.62 (br s, 2H), 2.51 - 2.68 (m, 2H), 2.21 (br s, 2H), 2.06 - 2.15 (m, 4H), 1.50 (br s, 9H), 1.31 (br s, 9H).

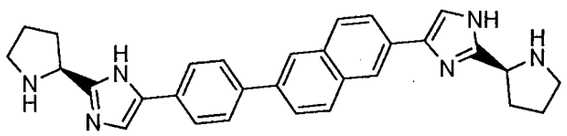


Intermediate 53

(S)-*tert*-Butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00395] A 100 mL pressure vessel equipped with a magnetic stir bar was charged with (S)-*tert*-butyl 2-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (500 mg, 1.02 mmol), (S)-*tert*-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (601 mg, 1.53 mmol) and $Pd(Ph_3P)_4$ (58 mg, 0.05 mmol) in DME (10 mL) and water (1.0 mL). The solution was degassed under vacuum for 5 min and the reactor was back filled with nitrogen. The mixture was heated for 8h at 120 °C, additional $Pd(Ph_3P)_4$ (57.8 mg, 0.05 mmol) was added and the mixture was degassed and stirred overnight at 130 °C. The reaction was cooled to room temperature and the volatiles were removed under vacuum. The residue was partitioned between water and EtOAc and the water layer was extracted with additional EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified on a BIOTAGE® (dry loaded onto a 90g silica gel cartridge and eluted with a gradient of 5 to 100 % EtOAc in DCM) and then repurified by prep HPLC (using a Waters Sunfire C18 column 30 X 100 mm 5u eluted MeOH -Water + 0.1 % TFA) to yield a TFA salt of (S)-*tert*-butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (50 mg). LC-MS retention time 1.278 min; m/z 675.70 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 8.31 (d,

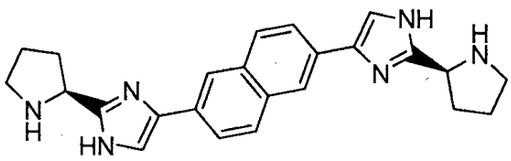
J=15.9 Hz, 2H), 8.14 - 8.18 (m, 1H), 8.10 (d, *J*=8.85 Hz, 1H), 8.05 (s, 0.6H), 7.96 - 8.03 (m, 4H), 7.85 - 7.94 (m, 3.4H), 5.11 - 5.23 (m, 2H), 3.69 - 3.77 (m, 2H), 3.62 (br s, 2H), 2.51 - 2.67 (m, 2H), 2.16 - 2.26 (m, 2H), 2.05 - 2.16 (m, 4H), 1.51 (s, 9H), 1.32 (s, 9H).



Intermediate 54

2-((2S)-2-Pyrrolidinyl)-4-(4-(6-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole

[00396] To a solution of a TFA salt of (S)-*tert*-butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (50 mg) in DCM (10 mL) was added TFA (2.0 mL, 26 mmol) in one portion. The mixture was agitated at room temperature for 2h. The reaction was concentrated under vacuum to yield a TFA salt of 2-((S)-pyrrolidin-2-yl)-5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole (51.5 mg) as orange solid, which was used without further purification. LC-MS retention time 0.978 min; m/z 475.19 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. HPLC-MS (TFA) 78457-087 using a Waters Sunfire C18 column 4.6 X 50 mm 5u showed the reaction was complete peak found at RT = 0.978 min. MH+ = 475.19. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.34 (s, 1H), 8.20 (s, 1H), 8.03 (dd, *J*=14.2, 8.7 Hz, 2H), 7.84 - 7.96 (m, 7H), 7.79 - 7.84 (m, 1 H,) 4.99 - 5.11 (m, 2H), 3.48 - 3.63 (m, 4H), 2.57 - 2.70 (m, 2H), 2.41 - 2.55 (m, 2H), 2.29 - 2.41 (m, 2H), 2.15 - 2.29 (m, 2H).

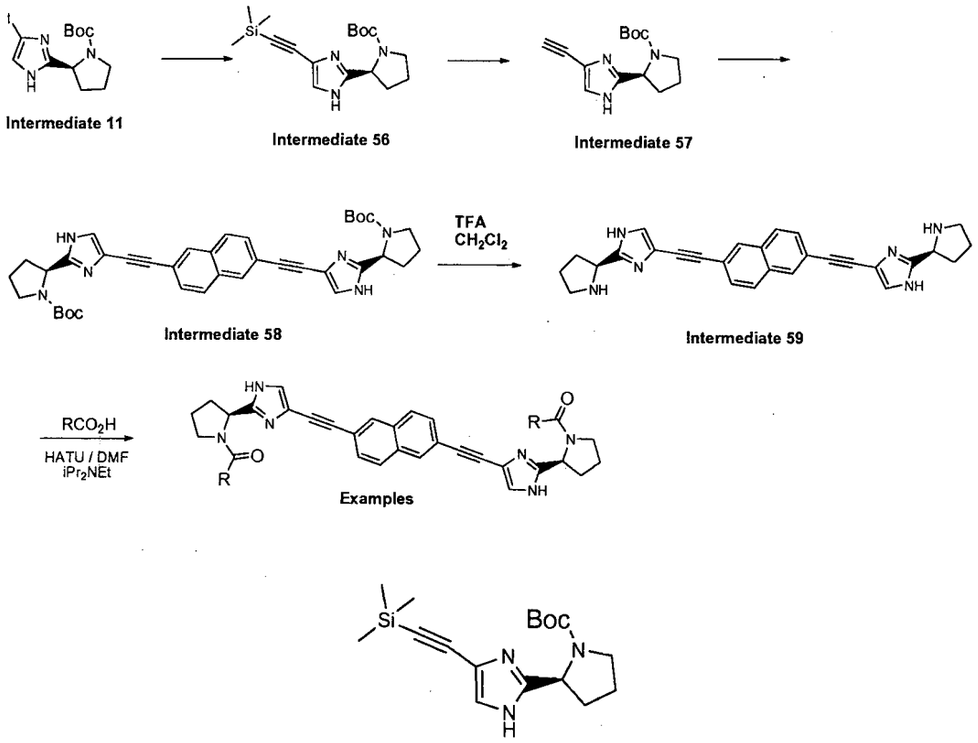


Intermediate 55

4,4′-(2,6-Naphthalenediyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)

[00397] To a solution of a TFA salt of (2S,2′S)-*tert*-butyl 2,2′-(4,4′-(naphthalene-2,6-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (82 mg) in DCM (2 mL) at room temperature was added TFA (2.0 mL, 26 mmol) in one portion. The mixture was stirred for 3h at room temperature, purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 5 to 90 % MeOH -Water + 0.1 % TFA) and repurified by prep HPLC (PHENOMENEX® Luna C18 column 30 X 100 mm 10u eluted with a gradient of 10 to 90 % methanol -Water + 0.1 % TFA) to yield a TFA salt of 4,4′-(2,6-naphthalenediyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) (68 mg) as tan solid. LC-MS retention time 0.978 min; m/z 399.18 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.31 (s, 2H), 7.95 - 8.00 (m, 2H), 7.91 - 7.95 (m, 2H), 7.85 (s, 2H), 5.03 (t, *J*=8.2 Hz, 2H), 3.49 - 3.62 (m, 4H), 2.59 - 2.67 (m, 2H), 2.42 - 2.52 (m, 2H), 2.31 - 2.40 (m, 2H), 2.17 - 2.28 (m, 2H).

Scheme 12

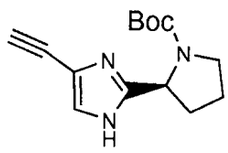


Intermediate 56

(S)-*tert*-Butyl 2-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00398] (S)-*tert*-Butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (750 mg, 2.07 mmol) and copper(I) iodide (79 mg, 0.41 mmol) were dissolved into DMF (20 mL) and triethylamine(1.439 mL, 10.33 mmol). The reaction solution was vacuum flushed for 10 minutes (aspirator vacuum, flushed with nitrogen) and then ethynyltrimethylsilane (1.2 mL, 8.3 mmol) and finally $Pd(PPh_3)_4$ (119 mg, 0.103 mmol) were added. The flask was flushed with nitrogen, seal and heated at 50 °C overnight. The reaction was concentrated to a crude black tar, dissolved into DCM and purified via BIOTAGE® Horizon (80g SiO_2, 20-40% EtOAc/hexanes) to yield (S)-*tert*-butyl 2-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (546 mg, 1.64 mmol, 79 % yield) as a yellow solid. This material was used without further purification. LC-MS retention time 1.393 min; m/z 332.33 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent

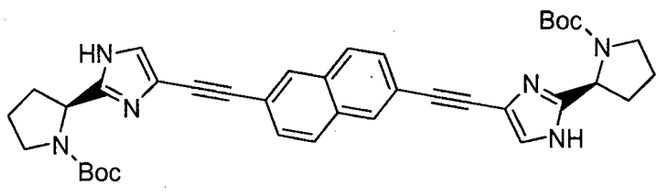
B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 - 7.13 (m, 1H), 4.92 - 4.85 (m, 1H), 3.43 - 3.31 (m, 2H), 3.04 - 2.83 (m, 1H), 2.20 - 1.88 (m, 3H), 1.51 (s, 3H), 1.49 (s, 6H), 0.25 (s, 3H), 0.23 (s, 6H).



Intermediate 57

(S)-*tert*-Butyl 2-(5-ethynyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

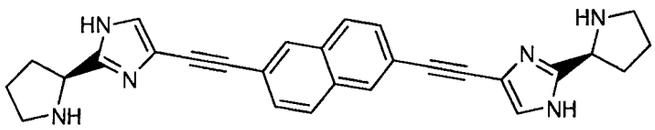
[00399] (S)-*tert*-Butyl 2-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (537 mg, 1.61 mmol) was dissolved into MeOH (20 mL) and then potassium carbonate (22 mg, 0.16 mmol) was added and the reaction was stirred at rt for 3h. The reaction was concentrated, dissolved into dichloromethane, loaded onto a SiO_2 column and purified by BIOTAGE® Horizon (30-50% EtOAc/hexanes) to yield (S)-*tert*-butyl 2-(5-ethynyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (346 mg, 1.32 mmol, 82 % yield) as an off-white solid. LC-MS retention time 0.878 min; m/z 260.35 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.21 - 7.17 (m, 1H), 4.92 - 4.87 (m, 1H), 3.43 - 3.30 (m, 2H), 3.05 (s, 1H), 3.03 - 2.85 (m, 1H), 2.20 - 1.88 (m, 3H), 1.60 -1.45 (m, 9H).



Intermediate 58

tert-Butyl (2S)-2-(4-((6-((2-((2S)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)ethynyl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

[00400] (S)-*tert*-Butyl 2-(5-ethynyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (340 mg, 1.30 mmol), 2,6-dibromonaphthalene (744 mg, 2.60 mmol) and copper(I) iodide (12.39 mg, 0.065 mmol) were slurried into DMF (10 mL) and triethylamine (0.54 mL, 3.9 mmol). The solution was vacuum flushed with nitrogen (5X), treated with $Pd(PPh_3)_4$ (75 mg, 0.065 mmol) and then vacuum flushed with nitrogen (2X). The cloudy yellow solution was stirred under nitrogen at rt for 3 h. The reaction was concentrated to a yellow-orange semi-solid, slurried into DMF/MeOH (~1:1), filtered and purified in five injections by prep HPLC (acetonitrile/water with 10 mM ammonium acetate, 15-100%). The fractions containing the desired product were combined and concentrated to yield *tert*-butyl (2S)-2-(4-((6-((2-((2S)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)ethynyl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate (70 mg, 0.11 mmol, 18 % yield) as a light yellow solid. LC-MS retention time 1.448 min; m/z 647.45 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.70 (br s, 2H), 7.98 (s, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.30 - 7.25 (m, 2H, under solvent peak), 4.95 (dd, J = 7.3, 3.3 Hz, 2H), 3.46 - 3.37 (m, 4H), 3.08 - 2.91 (m, 2H), 2.24 - 2.08 (m, 4H), 2.03 - 1.92 (m, 2H), 1.51 (s, 18H).

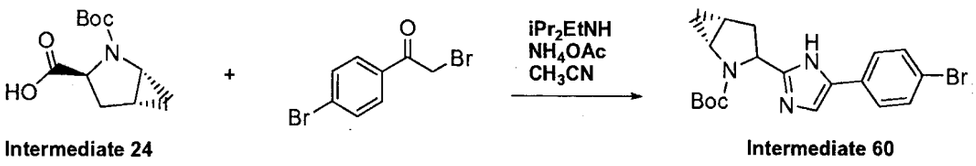


Intermediate 59

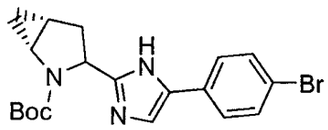
4,4′-(2,6-Naphthalenediyldi-2,1-ethynediyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)

[00401] (2S,2′S)-*tert*-Butyl 2,2′-(5,5′-(naphthalene-2,6-diylbis(ethyne-2,1-diyl))bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (32 mg, 0.049 mmol) was dissolved into dichloroethane (2 mL) and then TFA (1 mL, 13 mmol) was added. The solution was stirred at rt for 1h. The reaction was concentrated to dryness to yield a TFA salt of 4,4′-(2,6-naphthalenediyldi-2,1-ethynediyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) (41.6 mg) as tan solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.05 (s, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.52 (s, 2H), 4.89 - 4.84 (m, 2H), 3.56 - 3.44 (m, 4H), 2.59 - 2.50 (m, 2H), 2.42 - 2.24 (m, 4H), 2.26 - 2.14 (m, 2H).

Scheme 13



Intermediate 24 **Intermediate 60**



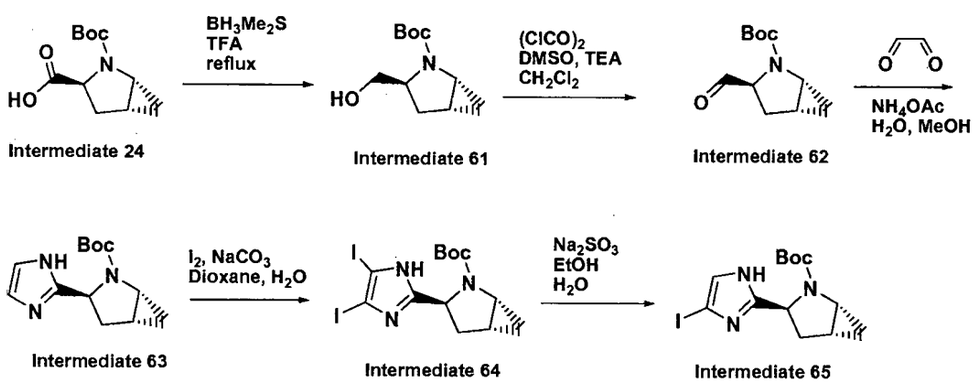
Intermediate 60

(1R,5R)-*tert*-Butyl 3-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00402] Hunig's Base (7.69 mL, 44.0 mmol) was added to a stirred solution of 2-bromo-1-(4-bromophenyl)ethanone (12.23 g, 44.0 mmol) and (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (10 g, 44 mmol) in dry MeCN (400 mL). The mixture was stirred for 16h at RT. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine, dried (sodium sulfate), filtered and concentrated. In a

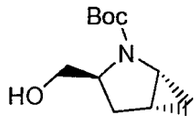
pressure vessel the residue was taken up in xylene (400 mL) and ammonium acetate (33.9 g, 440 mmol) was added. The vessel was sealed and heated at 140 °C for 2h. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution (pH = 9), brine, dried over sodium sulfate and concentrated. The crude product, as a reddish orange foam, was dissolved in methylene chloride and placed onto a 300g Thompson silica gel cartridge (eluted with 20% B to 100% B for 4000 mL where Solvent B = ethyl acetate and Solvent A = hexanes) to yield (1R,3S,5R)-*tert*-butyl 3-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (16.67 g, 39.1 mmol, 88.8 % yield) as a golden-brown foam. LC-MS retention time 1.762 min; m/z 403.94 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna S10 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.62 (br d, J = 8.6 Hz, 2H), 7.50 (br d, J = 8.6 Hz, 2H), 7.37 (s, 1H), 4.66 (br s, 1H), 3.58 (br s, 1H), 2.56 - 2.47 (m, 1H), 2.36 - 2.27 (m, 1H), 1.75 - 1.67 (m, 1H), 0.97 (br s, 9H), 0.88 - 0.81 (m, 1H), 0.64 - 0.57 (m, 1H).

Scheme 14



Intermediate 24 | Intermediate 61 | Intermediate 62

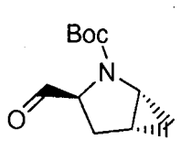
Intermediate 63 | Intermediate 64 | Intermediate 65



Intermediate 61

(1R,3S,5R)-*tert*-Butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

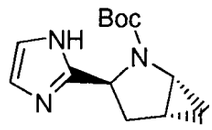
[00403] To a solution of (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (9.85 g, 43.3 mmol) in THF (200 mL) at 0 °C was added dropwise borane-methyl sulfide complex (282 mL, 563 mmol) over 30 min. The ice bath was removed, the mixture was stirred for 1h and then heated at reflux for 2h. The mixture was cooled to 0 °C, slowly quenched with methanol (~200 mL) and concentrated under vacuum. The residue was dissolved in DCM and washed with water (emulsion), 1N HCl, sat $NaHCO_3$ aq, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to yield (1R,3S,5R)-*tert*-butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (8.43 g, 39.5 mmol, 91 % yield) as colorless oil. LC-MS retention time 1.398 min; m/z 236.20 $[M+Na]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 90% methanol/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 3.72 - 3.79 (m, 1H), 3.52 - 3.64 (m, 3H), 3.15 - 3.24 (m, 1H), 2.00 - 2.08 (m, 1H), 1.62 - 1.72 (m, 1H), 1.54 - 1.62 (m, 1H), 1.45 - 1.51 (m, 9H), 0.84 (br s, 1H), 0.36 (td, *J*=5.0, 2.4 Hz, 1H).



Intermediate 62

(1R,3S,5R)-*tert*-Butyl 3-formyl-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00404] To a solution of (1R,3S,5R)-*tert*-butyl 3-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (4.85 g, 22.74 mmol) in DCM (125 mL) at 0 °C was added Dess-Martin periodinane (11.57 g, 27.3 mmol). The reaction was warmed up to RT and stirred for 3h. The reaction was poured into a saturated aq solution of $NaHCO_3$ then ca ~20g of $Na_2S_2O_3$ was added and stirred for 1h. The layers were separated and the aqueous layer was extracted several times with DCM. The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 40% EtOAc/hexanes to afford (1R,3S,5R)-*tert*-butyl 3-formyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (4.47 g, 21.2 mmol, 93 % yield) as colorless oil. LC-MS retention time 0.813 min; m/z no ionization (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 9.48 (br s, 1H), 3.67 - 3.97 (m, 1H), 3.33 - 3.59 (m, 1H), 2.10 - 2.31 (m, 2H), 1.56 - 1.67 (m, 1H), 1.47 (br s, 9H), 0.80 (br s, 1H), 0.55 (br s, 1H).

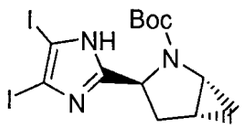


Intermediate 63

(1R,3S,5R)-*tert*-Butyl 3-(1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00405] Ammonium hydroxide (16.40 mL, 421 mmol) was added dropwise to a stirred solution of (1R,3S,5R)-*tert*-butyl 3-formyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (4.4 g) in methanol (15 mL) at 0 °C. The reaction was allowed to warm to room temp and stirred for 45 min. Then, oxalaldehyde 40% H_2O (5.32 mL, 46.3 mmol) was added dropwise and the reaction mixture was stirred overnight. The reaction color turned brown over time. The reaction was diluted with brine and concentrated to remove the volatile

solvent. The remaining aqueous layer was then extracted several times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 evaporated under vacuum. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 70% EtOAc/hexanes to afford (1R,3S,5R)-*tert*-butyl 3-(1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (3.71 g, 14.9 mmol, 71 % yield) as white solid. LC-MS retention time 0.772 min; m/z 250.20 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 10.43 (br s, 1H), 6.99 (s, 2H), 4.86 (dd, *J*=9.0, 5.0 Hz, 1H), 3.35 (br s, 1H), 3.20 (br s, 1H), 2.28 - 2.38 (m, 1H), 1.71 - 1.80 (m, 1H), 1.49 (s, 9H), 0.83 - 0.90 (m, 1H), 0.45 (br s, 1H).

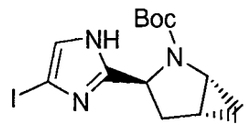


Intermediate 64

(1R,3S,5R)-*tert*-Butyl 3-(4,5-diiodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00406] Iodine (I_2, 12.43 g, 49.0 mmol) was added to a solution of 3-(1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (5.55 g, 22.3 mmol) and sodium carbonate (7.08 g, 66.8 mmol) in dioxane (56 mL) and water (56 mL) and the reaction mixture was stirred in the dark for 16 h at room temperature. The reaction mixture was diluted with EtOAc and washed an aqueous saturated solution of sodium thiosulfate. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 100% EtOAc/hexanes to afford (1R,3S,5R)-*tert*-butyl 3-(4,5-diiodo-1H-imidazol-2-yl)-2-

azabicyclo[3.1.0]hexane-2-carboxylate (8.3 g, 16 mmol, 71 % yield) as white solid. LC-MS retention time 1.455 min; m/z 502.07 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 4.51 (br s, 1H), 3.56 (br s, 1H), 2.40 - 2.54 (m, 1H), 2.18 - 2.27 (m, 1H), 1.65 - 1.73 (m, 1H), 1.20 - 1.40 (br s, 9H), 0.82 (dt, *J*=8.6, 5.8 Hz, 1H), 0.58 (br s, 1H).



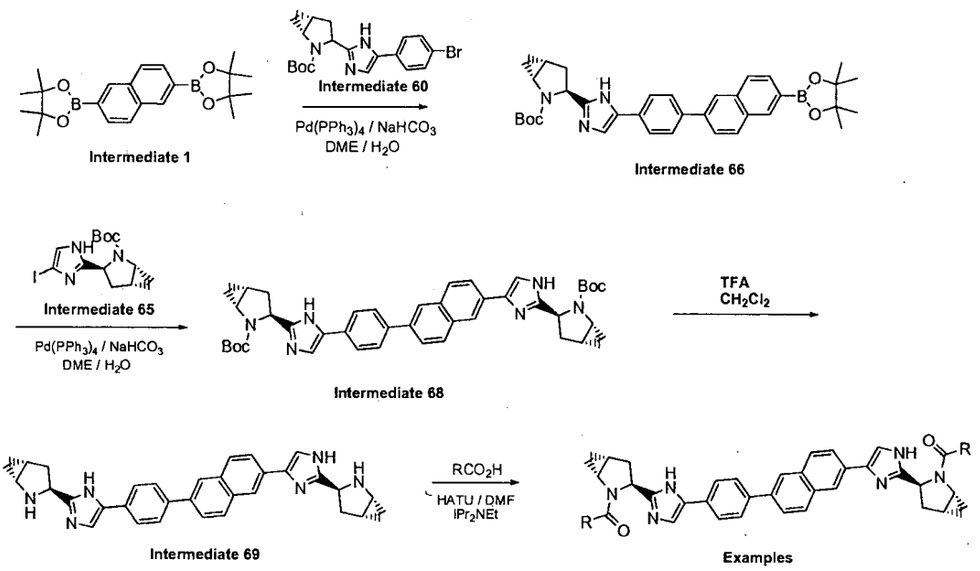
Intermediate 65

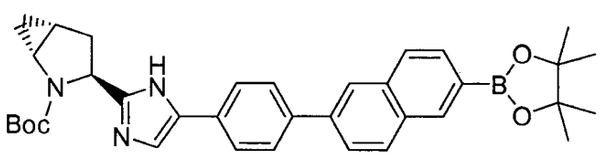
(1R,3S,5R)-*tert*-Butyl 3-(4-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00407] A 250 mL pressure flask equipped with a stir bar was charge with a solution of (1R,3S,5R)-*tert*-butyl 3-(4,5-diiodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (8.3 g, 17 mmol) in EtOH (83 mL) and water (83 mL). Then, sodium sulfite (20.88 g, 166 mmol) was added and the mixture was heated at 90 °C for 16h. The reaction mixture was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 15% EtOAc/DCM to afford (1R,3S,5R)-*tert*-butyl 3-(4-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (3.84 g, 10.2 mmol, 62 % yield) as yellow solid along with the fully reduced product (1R,3S,5R)-*tert*-butyl 3-(1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (550 mg, 2.21 mmol, 13 % yield). LC-MS retention time 0.932 min; m/z 376.22 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow

rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 7.12 (br s, 1H), 4.59 (br s, 1H), 3.44 - 3.64 (br s, 1H), 2.40 - 2.52 (m, 1H), 2.17 - 2.30 (m, 1H), 1.65 - 1.73 (m, 1H), 1.27 (br s, 9H), 0.84 (dt, *J*=8.5, 5.7 Hz, 1H), 0.58 (br s, 1H).

Scheme 15





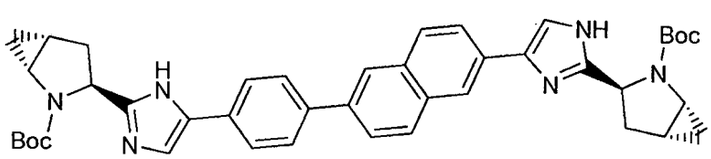
Intermediate 66

(1R,3S,5R)-*tert*-Butyl 3-(5-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

and Intermediate 67

(1R,1′R,3S,3′S,5R,5′R)-*tert*-Butyl 3,3′-(5,5′-(4,4′-(naphthalene-2,6-diyl)bis(4,1-phenylene))bis(1H-imidazole-5,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate)

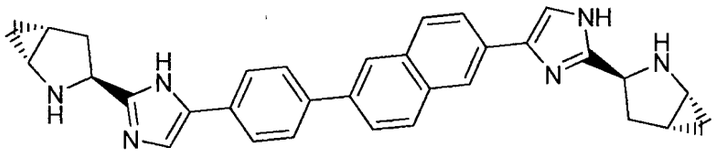
[00408] A solution of 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (1.0 g, 2.6 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.06 g, 2.63 mmol), Na_2CO_3 (0.837 g, 7.89 mmol) in DME (20 mL) and water (2 mL) was degassed under vacuum for 10 min. The mixture was heated at 80 °C and then $Pd(Ph_3P)_4$ (0.152 g, 0.132 mmol) was added under a stream of nitrogen. The reactor was sealed and the heating was pursued further at 120 °C for 16h. The DME was removed *in vacuo* and the crude material was partitioned between EtOAc/H_2O. The layers were separated and the aqueous layer was extracted several times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 5% MeOH/DCM to afford the partially pure target product contaminated with reaction side products. The impure product was purified again by flash column chromatography (BIOTAGE®), eluting with a gradient of 50 to 100% EtOAc/hexanes, then the column was flushed with 10% MeOH/DCM to afford (1R,3S,5R)-*tert*-butyl 3-(5-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (606 mg) as yellow foam. LC-MS retention time 1.608 min; m/z 578.4 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, chloroform-d, Partial NMR) δ ppm 4.89 (br s, 1H), 3.20 - 3.66 (m, 1H), 2.33 - 2.50 (m, 1H), 1.76 - 1.86 (m, 1H), 1.52 (br s, 9H), 1.24 - 1.32 (m, 12H), 0.87 - 0.93 (m, 1H), 0.51 (br s, 1H).



Intermediate 68

(1R,3S,5R)-*tert*-Butyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00409] A solution of (1R,3S,5R)-*tert*-butyl 3-(5-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (568 mg), (1R,3S,5R)-*tert*-butyl 3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (369 mg, 0.983 mmol), Na_2CO_3 (313 mg, 2.95 mmol) in DME (10 mL) and water (2 mL) was degassed under vacuum for 10 min. The mixture was heated at 80 °C and then $Pd(Ph_3P)_4$ (114 mg, 0.098 mmol) was added under a stream of nitrogen. The reactor was sealed and the heating was pursued further at 130 °C overnight. The DME was removed *in vacuo* and the crude material was partitioned between EtOAc/H_2O. The layers were separated and the aqueous layer was extracted several times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 20 to 100 % EtOAc/hexanes, then 5% MeOH/DCM to afford the partially pure (1R,3S,5R)-*tert*-butyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (277 mg). LC-MS retention time 1.578 min; m/z 699.56 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.62 - 7.69 (m, 6H), 7.53 - 7.59 (m, 4H), 6.95 (s, 2H), 4.67 (br s, 2H), 3.46 - 3.56(m, 2H), 2.50 - 2.59 (m, 0.5H), 2.32 - 2.49 (m, 2H), 2.27 (br s, 1.5H), 1.65 - 1.78 (m, 2H), 1.28 (br. s, 18H), 0.80 - 0.88 (m, 2H), 0.53 - 0.66 (m, 2H).

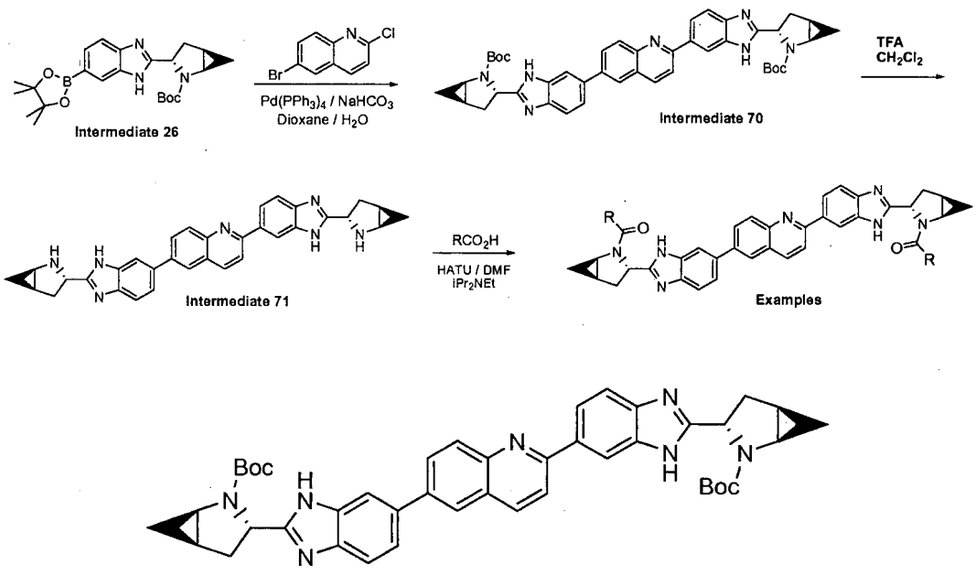


Intermediate 69

(1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00410] To a solution of (1R,3S,5R)-*tert*-butyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (275 mg) in DCM (10 mL) was added TFA (2 mL, 26.0 mmol). The mixture was stirred for 2h at room temperature. The volatiles were removed under vacuum and the crude residue was purified by a reverse phase HPLC (water/MeOH/TFA) to afford a TFA salt of (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (106 mg) as tan solid. LC-MS retention time 1.153 min; m/z 499.36 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.19 (s, 1H), 7.99 - 8.05 (m, 2H), 7.85 - 7.95 (m, 6H), 7.83 (s, 1H), 7.76 (s, 1H), 4.78 (q, *J*=9.4 Hz, 2H), 3.47 - 3.54 (m, 2H), 2.65 - 2.74 (m, 4H), 2.02 - 2.12 (m, 2H), 1.18 - 1.25 (m, 2H), 0.97 - 1.05 (m, 2H).

Scheme 16

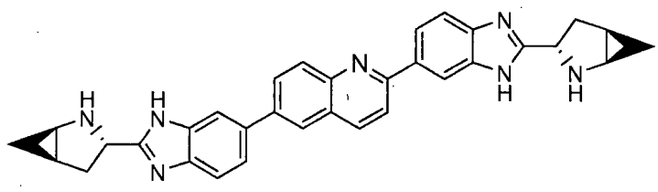


Intermediate 70

tert-Butyl (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-6-quinolinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00411] To a degassed solution of 6-bromo-2-chloroquinoline (30 mg, 0.12 mmol), Na_2CO_3 (39.3 mg, 0.371 mmol) and (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (116 mg, 0.272 mmol) in dioxane (1 mL) and H_2O (0.2 mL) was added $Pd(Ph_3P)_4$ (14.3 mg, 0.012 mmol) and the mixture was stirred at 110 °C for 2 h. The reaction mixture was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of *tert*-butyl (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-6-quinolinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (60.6 mg, 0.057 mmol, 46.3 % yield) as a yellow solid. LC-MS retention time 2.05 min; m/z 724 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 8.68 (1H, d, *J*=8.5 Hz), 8.60 (1H, s), 8.44 (1H, dd, *J*=8.5, 1.5 Hz), 8.39 (1H, d, *J*=1.3 Hz), 8.33 (1H, d, *J*=8.8 Hz), 8.23 - 8.29 (1H, m), 8.25

(1H, d, *J*=8.5 Hz), 8.19 (1H, s), 8.08 (1H, d, *J*=9.0 Hz), 7.96 (1H, d, *J*=9.0 Hz), 7.93 (1H, d, *J*=9.5 Hz), 5.02 - 5.12 (2H, m), 3.70 (2H, br s), 2.74 - 2.85 (2H, m), 2.45 - 2.57 (2H, m), 1.84 - 1.96 (2H, m), 1.05 - 1.68 (18H, m), 0.89 - 1.01 (2H, m), 0.77 - 0.86 (2H, m).

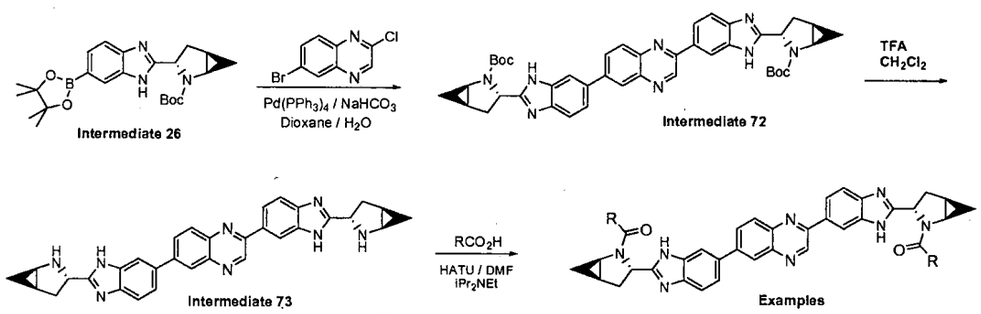


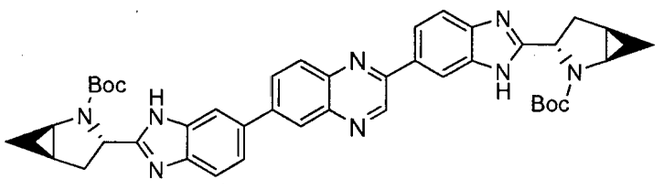
Intermediate 71

2,6-Bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoline

[00412] A TFA salt of *tert*-butyl (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-6-quinolinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (51 mg, 0.054 mmol) was mixed with a dioxane solution of HCl (0.5 mL, 2.00 mmol), and stirred at rt for 2 h. The volatiles were removed to yield an HCl salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoline (53 mg) as yellow solid. LC-MS retention time 1.20 min; m/z 524 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).

Scheme 17

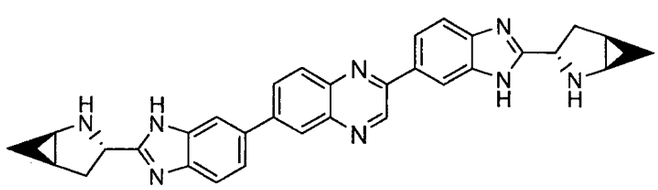




Intermediate 72

tert-Butyl (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-6-quinoxalinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00413] $Pd(Ph_3P)_4$ (14.24 mg, 0.012 mmol) was added to a degassed solution of 6-bromo-2-chloroquinoxaline (30 mg, 0.123 mmol), $NaHCO_3$ (31.1 mg, 0.370 mmol) and (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (131 mg, 0.308 mmol) in dioxane (1.0 mL) and H_2O (0.2 mL) and the mixture was stirred at 100 °C for 2h, then at 110 °C for 2 h. The reaction was diluted with MeOH, filtered and the filtrate was purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of *tert*-butyl (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-6-quinoxalinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (67.6 mg) as a yellow solid. LC-MS retention time 2.13 min; m/z 725 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 9.60 (1H, s), 8.71 (1H, s), 8.56 (1H, dd, *J*=8.8, 1.5 Hz), 8.45 (1H, d, *J*=1.5 Hz), 8.26 - 8.35 (2H, m), 8.21 (1H, s), 8.06 - 8.11 (1H, m), 7.91 - 7.99 (2H, m), 5.02 - 5.13 (2H, m), 3.70 (2H, br s), 2.79 (2H, dd, *J*=13.4, 9.2 Hz), 2.43 - 2.57 (2H, m), 1.83 - 1.96 (2H, m), 1.07 - 1.65 (18H, m), 0.95 (2H, m), 0.77 - 0.85 (2H, m).

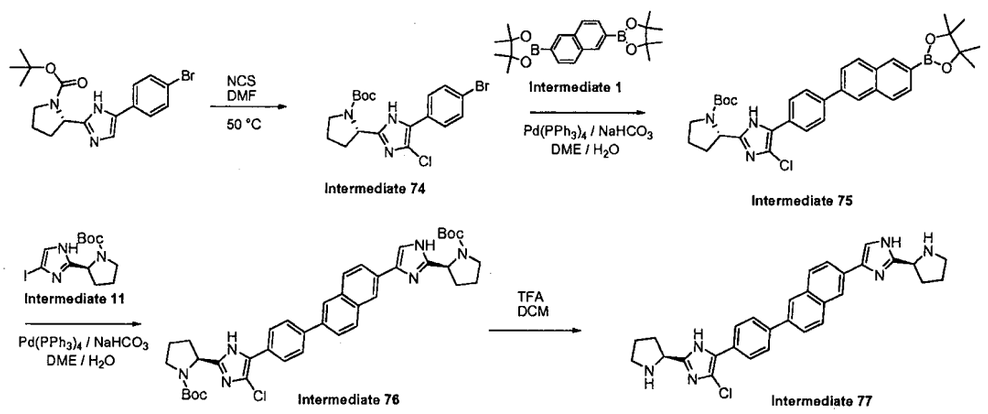


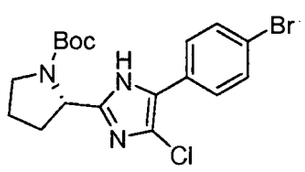
Intermediate 73

2,6-Bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxaline

[00414] TFA (0.25 mL, 3.24 mmol) was added to a solution of a TFA salt of *tert*-butyl (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-6-quinoxalinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (65 mg) in DCM (0.5 mL) and the mixture was stirred at rt for 16 h. The volatiles were removed and the residue was triturated with Et_2O. The resulting solid was collected via filtration funnel and rinsed with Et_2O to yield a TFA salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxaline (60 mg) as yellow solid. LC-MS retention time 1.51 min; m/z 525 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 9.52 (1H, s), 8.58 (1H, s), 8.36 (1H, s), 8.22 - 8.33 (2H, m), 8.30 (1H, d, *J*=9.5 Hz), 8.08 (1H, s), 7.76 - 7.94 (2H, m), 7.83 (1H, d, *J*=9.5 Hz), 4.80 - 5.05 (2H, m), 3.45 - 3.61 (2H, m), 2.70 - 2.92 (2H, m), 2.50 - 2.67 (2H, m), 2.00 - 2.18 (2H, m), 1.26 (2H, br s), 1.04 (2H, br s).

Scheme 18

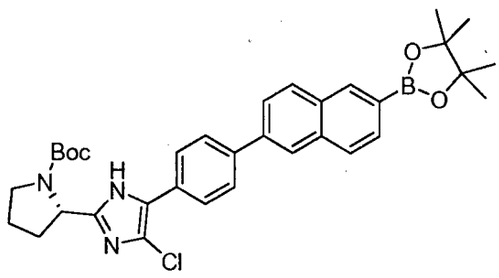




Intermediate 74

(S)-*tert*-Butyl 2-(5-(4-bromophenyl)-4-chloro-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00415] NCS (0.51 g, 3.82 mmol) was added to a solution of *tert*-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.55 mmol) in DMF (25 mL) and the mixture was heated at 50 °C overnight. The volatiles were removed under vacuum. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 10 % EtOAc/DCM to afford the partially pure (S)-*tert*-butyl 2-(5-(4-bromophenyl)-4-chloro-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.04 g) as yellow foam. LC-MS retention time 1.99 min; m/z 427.12 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.63 (s, 4H), 4.74 - 4.81 (m, 1H), 3.64 - 3.72 (m, 1H), 3.45 - 3.55 (m, 1H), 2.27 - 2.42 (m, 1H), 2.00 - 2.15 (m, 2H), 1.90 - 2.00 (m, 1H), 1.48 (m, 3H), 1.27 (m, 6H).

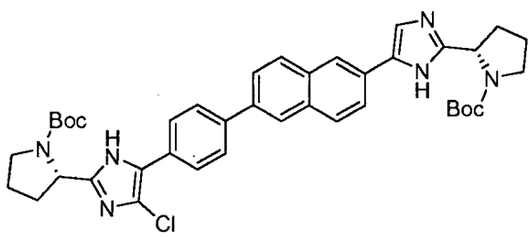


Intermediate 75

(S)-*tert*-Butyl 2-(4-chloro-5-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00416] A solution of (S)-*tert*-butyl 2-(5-(4-bromophenyl)-4-chloro-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.04 g, 2.44 mmol) and 2,6-bis(4,4,5,5-tetramethyl-1,3,2-

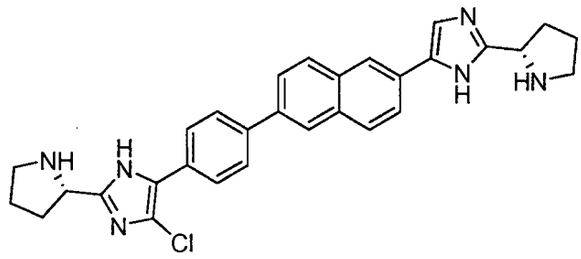
dioxaborolan-2-yl)naphthalene (0.926 g, 2.44 mmol) in DME (10 mL) and water (2 mL) was degassed under vacuum for 10 min. The mixture was heated at ca ~80 °C, $Pd(Ph_3P)_4$ (0.282 g, 0.244 mmol) was added under a stream of nitrogen and the reactor was sealed. The heating was pursued further to 130 °C for 8 h. Additional $Pd(PPh_3)_4$ (100 mg) was added and the heating was pursued overnight. The DME was removed *in vacuo* and the crude material was partitioned between EtOAc/H_2O. The layers were separated and the aqueous layer was extracted several times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 100 % EtOAc/hexanes to afford the partially pure (S)-*tert*-butyl 2-(4-chloro-5-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate contaminated with triphenylphosphine (292 mg). A small aliquot was purified further by a reverse phase HPLC (water/acetonitrile/TFA) to afford the pure title material. The remaining material was used in subsequent step without further purification. LC-MS retention time 2.227 min; m/z 598.46 (MH-) LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 10 mM ammonium acetate and Solvent B was 10% H_2O / 90% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD, TFA salt, partial NMR) δ ppm 3.71 (br s, 2H), 3.55 (br s, 2H), 2.45 (br s, 1H), 2.07 - 2.17 (m, 2H), 1.97 - 2.06 (m, 1H), 1.50 (s, 3H), 1.43 (m, 6H), 1.31 (br s, 6H).



Intermediate 76

(S)-*tert*-Butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-4-chloro-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

[00417] A solution of (S)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (163 mg, 0.450 mmol), (S)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (163 mg, 0.450 mmol), sodium bicarbonate (113 mg, 1.350 mmol) in a solvent mixture of DME (10 mL) and water (2 mL) was degassed under vacuum for 10 min. The mixture was heated at 80 °C then $Pd(Ph_3P)_4$ (52.0 mg, 0.045 mmol) was added and the reactor was flushed with nitrogen and sealed. The heating was pursued further to 120 °C for 16 h. The flask was cooled to room temperature, the DME was removed *in vacuo* and the crude material was partitioned between DCM/H_2O. The layers were separated and the aqueous layer was extracted several times with DCM. The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 0 to 100 % EtOAc/hexanes to afford the partially pure (S)-*tert*-butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-4-chloro-1H-imidazol-2-yl)pyrrolidine-1-carboxylate contaminated with triphenylphosphine (77 mg). LC-MS retention time 1.830 min; m/z 709.43 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d Partial NMR) δ ppm 5.00 (d, *J*=4.5 Hz, 2H), 3.38 - 3.52 (m, 4H), 3.10 (br. s, 1H), 2.91 (br s, 1H), 2.09 - 2.33 (m, 4H), 1.93 - 2.05 (m, 2H), 1.54 (s, 18H).

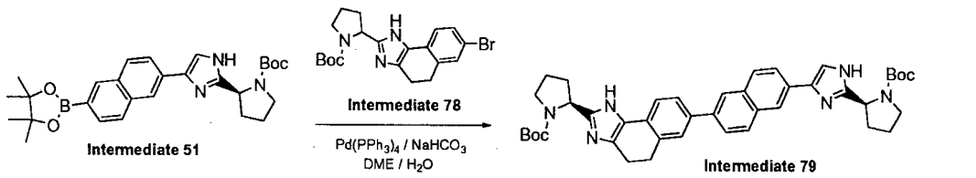


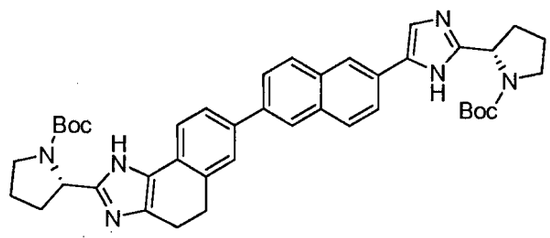
Intermediate 77

4-Chloro-2-((S)-pyrrolidin-2-yl)-5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole

[00418] TFA (2 mL) was added to a solution of (S)-*tert*-butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-4-chloro-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (75 mg) in DCM (10 mL) and the mixture was stirred for 2h at room temperature. The solvents were removed *in vacuo* and the residue was taken up in a solvent mixture of 1:1 methanol/CH_2Cl_2 and filtered through an MCX cartridge (Strata XC). The cartridge was washed with methanol and the compound was eluted with a solution of NH_3 in methanol (2M). The appropriate fractions were concentrated *in vacuo* to afford 4-chloro-2-((S)-pyrrolidin-2-yl)-5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole (40 mg, 0.079 mmol) as yellow solid. LC-MS retention time 1.353 min; m/z 509.32 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD, partially soluble only) δ ppm 8.20 (s, 1H), 8.09 (s, 1H), 7.88 - 7.96 (m, 2H), 7.76 - 7.88 (m, 6H), 7.51 (s, 1H), 4.50 (t, *J*=7.28 Hz, 1H), 4.35 (t, *J*=7.15 Hz, 1H), 3.03 - 3.31 (partially masked by methanol, m, 4H), 2.24 - 2.42 (m, 2H), 1.88 - 2.21 (m, 6H).

Scheme 19



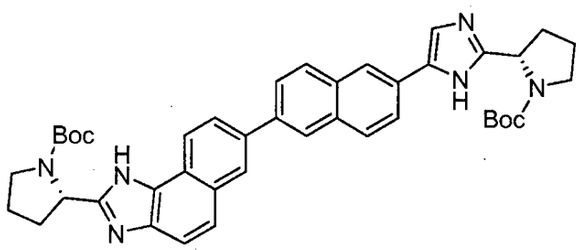


Intermediate 79

(S)-*tert*-Butyl 2-(7-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

[00419] A solution of (S)-*tert*-butyl 2-(5-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (402 mg, 0.821 mmol), (S)-*tert*-butyl 2-(7-bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (344 mg, 0.821 mmol) and sodium bicarbonate (207 mg, 2.46 mmol) in DME (14 mL) and water (1.8 mL) was degassed under vacuum for 10 min. The mixture was heated at 80 °C at which time the flask was opened and $Pd(Ph_3P)_4$ (76 mg, 0.066 mmol) was added. The flask was flushed with nitrogen, sealed and heated at 120 °C for 16 h. The flask was cooled to room temp., the DME was removed *in vacuo* and the crude material was partitioned between DCM and H_2O. The layers were separated and the aqueous layer was extracted several times with DCM. The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 20 to 100% EtOAc/Hexanes and then 0 to 10 % methanol/DCM to afford (S)-*tert*-butyl 2-(7-(6-(2-

((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (183 mg). LC-MS retention time 1.543 min; m/z 701.47 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

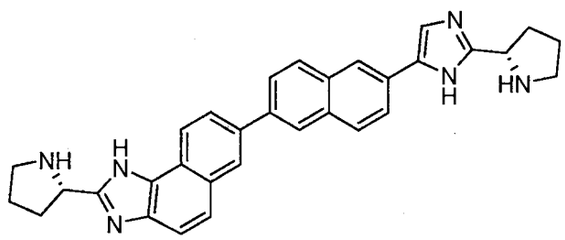


Intermediate 80

(S)-*tert*-Butyl 2-(7-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

[00420] Manganese(IV) oxide (1.53 g, 17.6 mmol) was added to a solution of (S)-*tert*-butyl 2-(7-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (183 mg, 0.196 mmol) in DCM (5 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was filtered through a pad of diatomaceous earth (CELITE®) and washed with a solution of methanol/DCM 1:1. The volatiles were removed under vacuum using a rotavap to afford (S)-*tert*-butyl 2-(7-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (163 mg) as tan solid. LC-MS retention time 1.523 min; m/z 699.53 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0%

Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



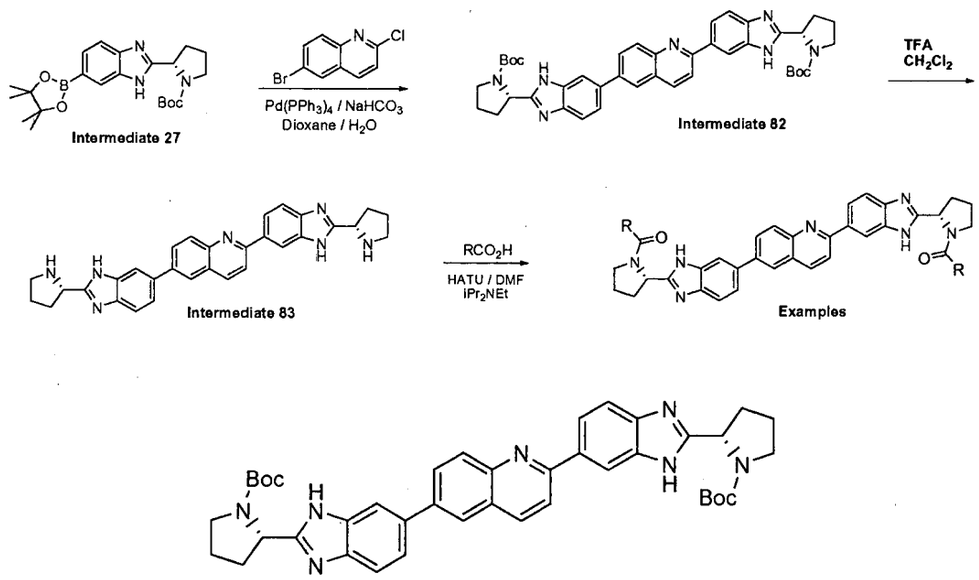
Intermediate 81

2-((S)-Pyrrolidin-2-yl)-7-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-naphtho[1,2-d]imidazole

[00421] TFA (2 mL, 26.0 mmol) was added in one portion to a stirred solution of (S)-*tert*-butyl 2-(7-(6-(2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (137 mg) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred for 2h at room temp. and then the solvents were removed *in vacuo*. The residue was taken up in 50% methanol/CH_2Cl_2 and filtered through an MCX cartridge (Strata XC). The cartridge was washed with methanol and the compound was eluted with a solution of NH_3 in methanol (2M). The appropriate fractions were concentrated *in vacuo* to afford 2-((S)-pyrrolidin-2-yl)-7-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-naphtho[1,2-d]imidazole (98 mg, 0.20 mmol) as orange solid. LC-MS retention time 1.245 min; m/z 499.30 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.59 (d, *J*=8.5 Hz, 1H), 8.43 (d, *J*=1.5 Hz, 1H), 8.36 (s, 1H), 8.31 (s, 1H), 8.13 (dd, *J*=8.6, 1.8 Hz, 1H),

8.01 - 8.10 (m, 3H), 7.90 - 7.98 (m, 2H), 7.87 (s, 1H), 7.80 (d, *J*=8.6 Hz, 1H), 5.18 (t, *J*=7.9 Hz, 1H), 5.05 (t, *J*=8.1 Hz, 1H), 3.63 - 3.72 (m, 1H), 3.52 - 3.63 (m, 3H), 2.61 - 2.77 (m, 2H), 2.45 - 2.58 (m, 2H), 2.33 - 2.43 (m, 2H), 2.20 - 2.33 (m, 2H).

Scheme 20

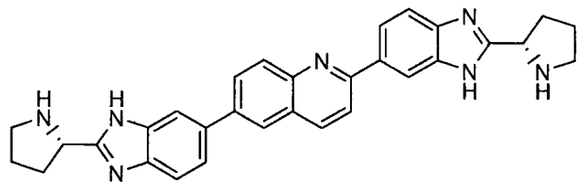


Intermediate 82

(2S,2'S)-*tert*-Butyl 2,2'-(6,6'-(quinoline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate

[00422] $Pd(Ph_3P)_4$ (19.06 mg, 0.016 mmol) was added to a stirred and degassed solution of 6-bromo-2-chloroquinoline (40 mg, 0.165 mmol), (S)-*tert*-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate (150 mg, 0.363 mmol) and $NaHCO_3$ (41.6 mg, 0.495 mmol) in dioxane (1 mL) and H_2O (0.2 mL). The reaction mixture was then heated at 110 °C for 2h., cooled to rt, diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(quinoline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate (73 mg) as a yellow solid. LC-MS retention time 2.02 min; m/z 700 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm

8.63 - 8.74 (1H, m), 8.60 (1H, s), 8.44 (1H, dd, *J*=8.7, 1.6 Hz), 8.38 (1H, br s), 8.32 (1H, d, *J*=8.8 Hz), 8.25 (2H, d, *J*=8.8 Hz), 8.14 - 8.21 (1H, m), 8.04 - 8.12 (1H, m), 7.90 - 8.00 (2H, m), 5.24 - 5.36 (2H, m), 3.73 - 3.83 (2H, m), 3.59 - 3.72 (2H, m), 2.57 - 2.74 (2H, m), 2.20 - 2.33 (2H, m), 2.09 - 2.20 (4H, m), 1.50 (9H, br s), 1.23 (9H, br s).

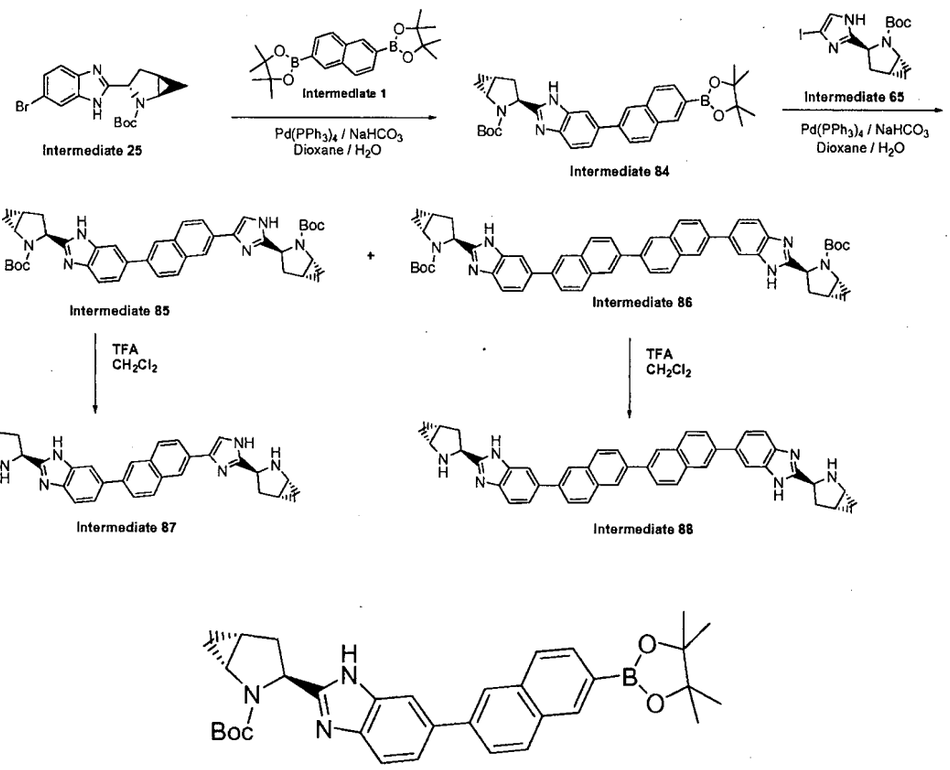


Intermediate 83

2,6-Bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)quinoline

[00423] TFA (0.25 mL, 3.24 mmol) was added to a solution of a TFA salt of (2S,2'S)-*tert*-butyl 2,2'-(6,6'-(quinoline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate (65 mg) in DCM (0.5 mL) and the mixture was stirred at rt for 2h. The volatiles were removed under vacuum and the residue was triturated with Et_2O. The resulting solid was collected via filtration and rinsed with Et_2O to yield a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)quinoline (61 mg) as yellow solid. LC-MS retention time 1.12 min; m/z 500 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 8.89 (1H, d, *J*=8.8 Hz), 8.48 (1H, d, *J*=1.3 Hz), 8.45 (1H, s), 8.34 - 8.41 (2H, m), 8.31 (1H, d, *J*=8.8 Hz), 8.12 (1H, dd, *J*=8.5, 1.8 Hz), 8.09 (1H, s), 7.89 (1H, d, *J*=8.5 Hz), 7.77 - 7.85 (2H, m), 5.05 - 5.19 (2H, m), 3.44 - 3.72 (4H, m), 2.61 - 2.75 (2H, m), 2.19 - 2.49 (6H, m).

Scheme 21

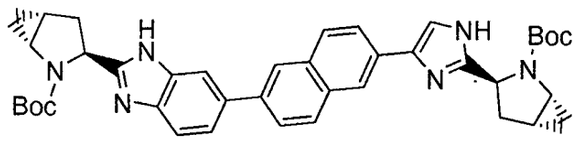


Intermediate 84

(1R,3S,5R)-*tert*-Butyl 3-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00424] $Pd(Ph_3P)_4$ (0.382 g, 0.330 mmol) was added to a degassed solution of 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene (2.51 g, 6.61 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-bromo-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (2.5 g, 6.6 mmol) and sodium carbonate (2.78 g, 33.0 mmol) in DME (52.9 mL) and water (13.2 mL) at 80 °C. The reaction was backfilled with nitrogen, sealed and heated at 100 °C overnight. The volatiles were removed under vacuum and the residue was taken in EtOAc, washed with water, and the water layer was extracted with EtOAc. The combined organic layers were filtered through a pad of diatomaceous earth (CELITE®) and dried over Na_2SO_4, concentrated and purified on a BIOTAGE® (dry loaded on silica gel, charged to a 90g silica gel cartridge and eluted with a gradient of 0 to 70 % ethyl acetate in hexanes, then flushed with 10% MeOH/ DCM) to yield (1R,3S,5R)-*tert*-butyl 3-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-

yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.8 g, 3.3 mmol, 49 % yield) as yellowish solid. LC-MS retention time 1.905 min; m/z 552.47 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

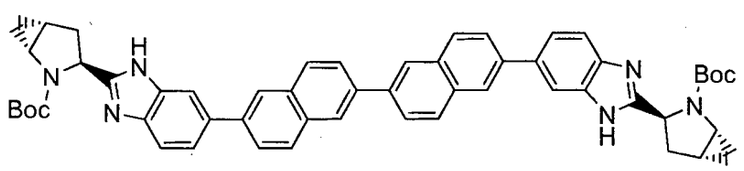


Intermediate 85

tert-Butyl (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00425] A 200 mL pressure round bottom flask equipped with a magnetic stir bar was charged with (1R,3S,5R)-*tert*-butyl 3-(5-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (795 mg, 1.44 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (538 mg, 1.43 mmol) and sodium bicarbonate (502 mg, 5.97 mmol) in DME (9.5 mL) and water (2.4 mL). The solution was degassed under vacuum for 5 min and the reactor was back filled with N_2. Then, $Pd(Ph_3P)_4$ (110 mg, 0.096 mmol) was added under a stream of N_2 and the reactor was sealed and the heated overnight at 120 °C. The reaction was cooled to room temperature and the volatiles were removed under vacuum. The residue was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc. The combined organics were filtered through a pad of diatomaceous earth (CELITE®), dried over Na_2SO_4 and the volatiles were removed under vacuum. The residue was purified by flash column chromatography (BIOTAGE®), eluting with a gradient of 50 to 100% EtOAc/Hexanes

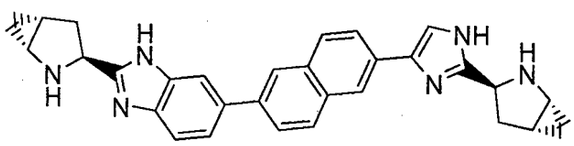
and then 10 % methanol/DCM to afford the partially pure target product contaminated with starting material, reduced starting material and other reaction side products. The residue was further purified by prep HPLC (ACN/water, 0.1%TFA) to yield a TFA salt of *tert*-butyl (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (200.5 mg). A side product was also collected form the same reaction mixture which was identified as a TFA salt (1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-2,2'-binaphthalen-6-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (108 mg) LC-MS retention time 1.497 min; m/z 673.52 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.31 (s, 1H), 8.09 - 8.20 (m, 3H), 7.96 - 8.08 (m, 2H), 7.87 - 7.94 (m, 2H), 5.07 (t, *J*=8.2 Hz, 1H), 4.91 (m, 1H), 3.69 (br s, 2H), 2.70 - 2.84 (m, 2H), 2.48 (br s, 2H), 1.81 - 1.94 (m, 2H), 1.51 (br s, 1H), 1.51 (br s, 9H), 1.31 (br s, 5H), 1.21 (br s, 4H), 0.89 - 0.99 (m, 2H), 0.82 (br s, 1H), 0.77 (br s, 1H).



Intermediate 86

(1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-2,2'-binaphthalen-6-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00426] Side product obtained as TFA salt (108 mg) after purification of the reaction mixture from Intermediate 85 synthesis. LC-MS retention time 1.882 min; m/z 849.84 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.36 (s, 2H), 8.28 (s, 2H), 8.11 - 8.19 (m, 6H), 8.03 - 8.09 (m, 4H), 7.87 - 7.96 (m, 4H), 5.07 (t, *J*=8.2 Hz, 2H), 3.71 (br s, 2H), 2.75 - 2.85 (m, 2H), 2.51 (br s, 2H), 1.86 - 1.94 (m, 2H), 1.52 (m, 10H), 1.22 (br s, 8H), 0.97 (ddd, *J*=8.4, 6.0, 5.8 Hz, 2H), 0.83 (br s, 2H).

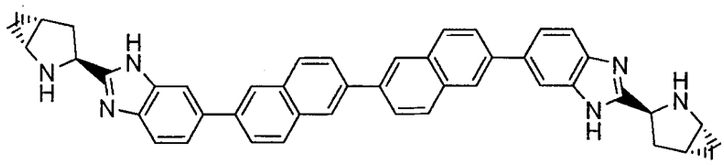


Intermediate 87

6-(6-(2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazole

[00427] 4M HCl in dioxane (10 mL, 40.0 mmol) was added to a stirred solution of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-5-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (151 mg) in DCM (3 mL). Precipitate formed immediately. The suspension was agitated for 30 min. The volatile components were evaporated under vacuum. The crude residue was taken in DCM (3 mL) and TFA (2 mL) was added. The solution was agitated for 1h. The volatile components were evaporated under reduced pressure. The residue was taken into MeOH and filtered through a Strata XC MCX cartridge. The cartridge was washed with methanol and the compound was release from the cartridge by eluting with a solution of 2M of ammonia/methanol. The ammonia/methanol filtrate was evaporated under reduced pressure to yield 6-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-

yl)naphthalen-2-yl)-2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazole (79 mg, 0.17 mmol) as yellow solid. LC-MS retention time 1.130 min; m/z 473.35 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.19 (s, 1H), 8.07 (s, 1H), 7.92 (dd, *J*=8.6, 5.8 Hz, 2H), 7.88 (s, 1H), 7.82 (dd, *J*=5.8, 1.5 Hz, 2H), 7.61 - 7.66 (m, 2H), 7.51 (s, 1H), 4.24 - 4.35 (m, 2H), 3.11 (td, *J*=6.1, 2.4 Hz, 1H), 3.06 (td, *J*=6.0, 2.6 Hz, 1H), 2.40 - 2.53 (m, 2H), 2.18 - 2.33 (m, 2H), 1.69 - 1.76 (m, 1H), 1.62 - 1.69 (m, 1H), 0.88 (ddd, *J*=6.6, 4.3, 2.6 Hz, 1H), 0.79 - 0.84 (m, 1H), 0.61 - 0.68 (m, 1H), 0.55 - 0.60 (m, 1H).



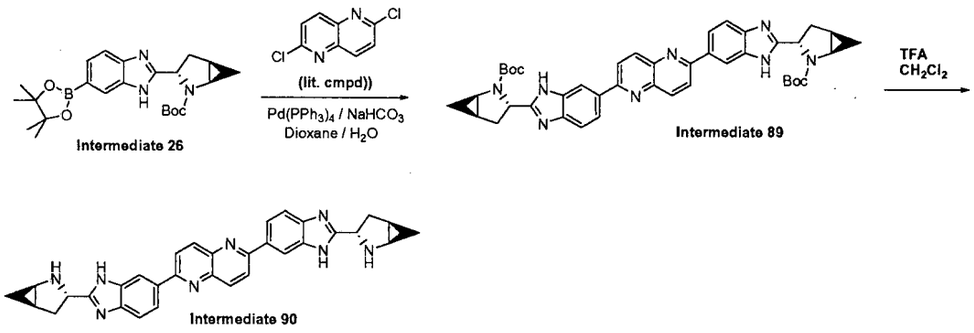
Intermediate 88

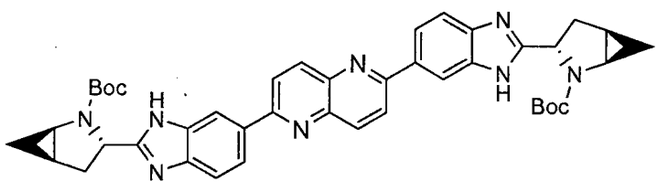
6,6′-Bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-5-yl)-2,2′-binaphthyl

[00428] TFA (2.0 mL, 26 mmol) was added to a solution of a TFA salt (1R,3S,5R)-3-(5-(6′-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-2,2′-binaphthalen-6-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (108 mg) in DCM (5 mL) and the reaction mixture was stirred for 2h at rt. The reaction mixture was then concentrated to yield a TFA salt of 6,6′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-5-yl)-2,2′-binaphthyl (22 mg) as tan solid. LC-MS retention time 1.722 min; m/z 649.54 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at

a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.33 (br s, 2H), 8.22 (br s, 2H), 8.09 - 8.15 (m, 4H), 8.01 - 8.07 (m, 4H), 7.89 - 7.95 (m, 2H), 7.77 - 7.87 (m, 4H), 4.85 - 4.98 (m, 2H), 3.51 - 3.57 (m, 2H), 2.79 - 2.87 (m, 2H), 2.59 - 2.68 (m, 2H), 2.07 - 2.14 (m, 2H), 1.23 - 1.30 (m, 2H), 1.01 - 1.09 (m, 2H).

Scheme 22



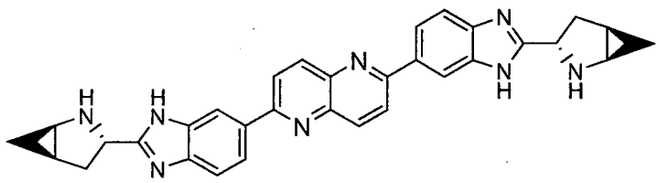


Intermediate 89

tert-Butyl (1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-1,5-naphthyridin-2-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00429] Tetrakis(triphenylphosphine)palladium(0) (17.4 mg, 0.015 mmol) was added to a solution of 2,6-dichloro-1,5-naphthyridine (30 mg, 0.151 mmol), sodium bicarbonate (38.0 mg, 0.452 mmol) and (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (141 mg, 0.332 mmol) in dioxane (1.0 mL) and H_2O (0.2 mL) and the mixture was heated

and stirred at 110 °C for 2 h. The reaction was diluted with MeOH, filtered, concentrated and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield *tert*-butyl (1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-1,5-naphthyridin-2-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (22.3 mg, 0.030 mmol) as a white solid. LC-MS retention time 2.11 min; m/z 725 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).



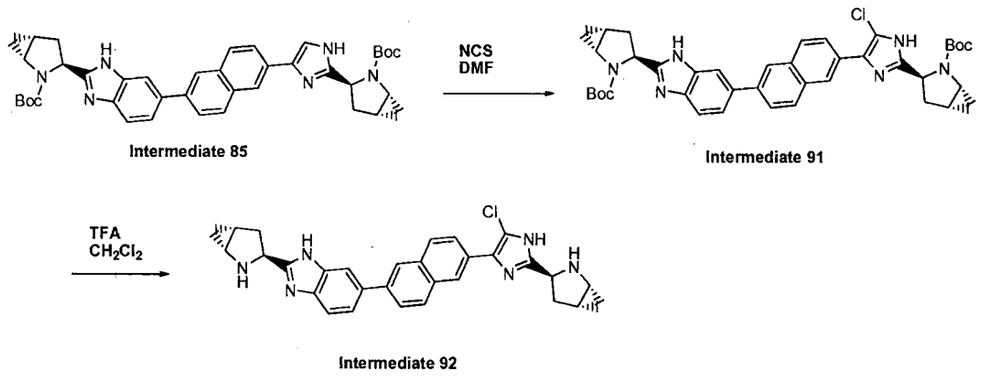
Intermediate 90

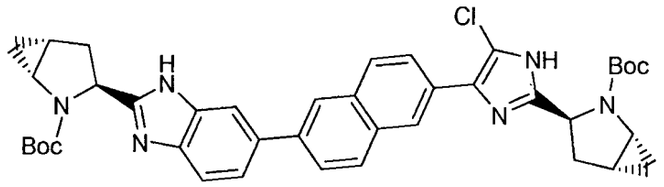
2,6-Bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-1,5-naphthyridine

[00430] TFA (0.25 mL, 3.2 mmol) was added to a solution of *tert*-butyl (1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-1,5-naphthyridin-2-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (20 mg, 0.028 mmol) in DCM (0.5 mL) and the mixture was stirred at rt for 16h. The volatile were removed under vacuum and the residue was triturated with Et_2O. The resulting solid was collected via filtration and rinsed with Et_2O to yield a TFA salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-1,5-naphthyridine (26 mg, 0.022 mmol, 78 % yield) as a yellow solid. LC-MS retention time 1.41 min; m/z 525 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 8.61 (2H, d, *J*=8.8 Hz), 8.51 (2H, s), 8.40 (2H, d, *J*=9.0 Hz), 8.23 (2H, dd, *J*=8.5, 1.5 Hz), 7.81 (2H, d, *J*=8.5 Hz), 4.74 - 4.97 (2H, m), 3.47 - 3.57 (2H, m),

2.78 - 2.88 (2H, m), 2.52 - 2.65 (2H, m), 2.04 - 2.15 (2H, m), 1.22 - 1.33 (2H, m), 0.99 - 1.11 (2H, m).

Scheme 23



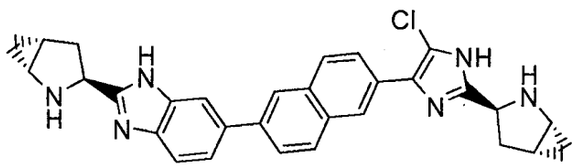


Intermediate 91

tert-Butyl (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-5-chloro-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00431] NCS (20 mg, 0.15 mmol) was added portionwise to a stirring solution of *tert*-butyl (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (183 mg, 0.272 mmol) in DMF (5 mL) at rt. The reaction mixture was then heated at 50 °C for 3h. The reaction was cooled to 0 °C, additional NCS (15 mg, 0.112 mmol) was added, and the mixture was stirred for 2h at 50 °C. The reaction was diluted with water (2 mL) and methanol (2 mL), the volatiles were removed and the crude product was purified by prep HPLC (TFA) to yield a TFA salt of *tert*-butyl (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-5-chloro-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (140.4 mg) as orange solid. LC-MS

retention time 1.822 min; m/z 707.54 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm 5 µm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.27 (d, *J*=2.8 Hz, 2H), 8.03 - 8.18 (m, 4H), 7.87 - 7.98 (m, 3H), 5.04 - 5.10 (m, 1H), 4.63 (d, *J*=7.6 Hz, 1H), 3.71 (br s, 1H), 3.63 (br s, 1H), 2.74 - 2.87 (m, 1H), 2.59 (dd, *J*=13.3, 8.7 Hz, 1H), 2.51 (br s, 1H), 2.41 (ddd, *J*=13.6, 6.7, 6.6 Hz, 1H), 1.86 - 1.95 (m, 1H), 1.78 (br s, 1H), 1.12 - 1.63 (m, 18H), 0.97 (ddd, *J*=8.7, 6.0, 5.8 Hz, 1H), 0.79 - 0.91 (m, 2H), 0.66 (br s, 1H).



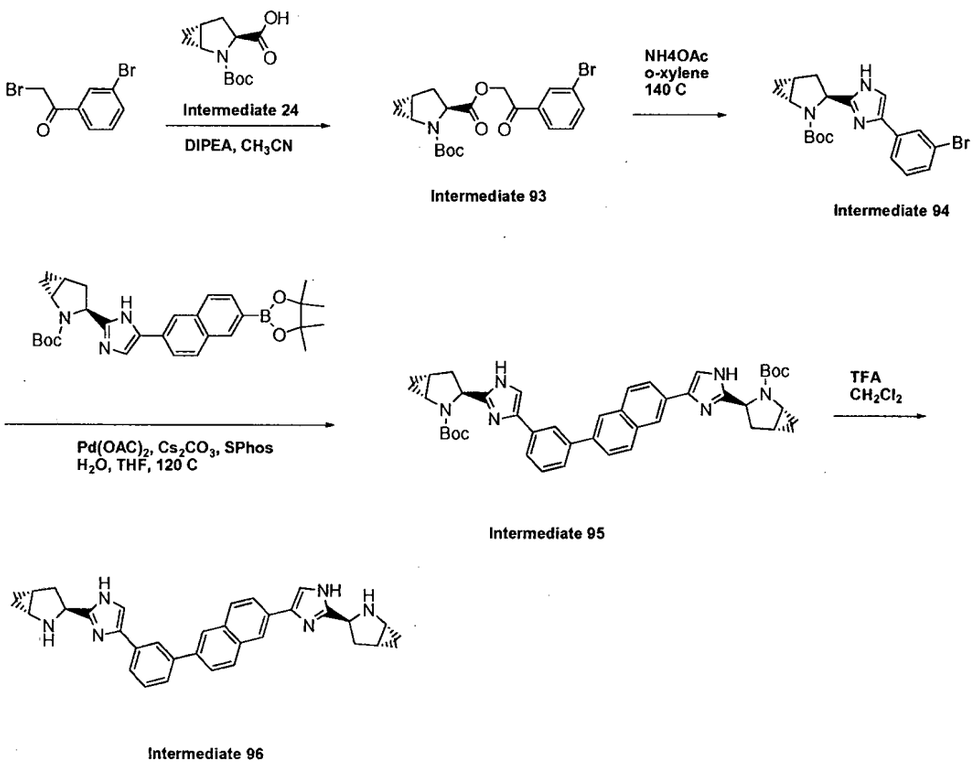
Intermediate 92

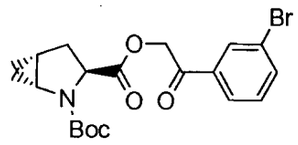
2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hex-3-yl)-5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-4-chloro-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazole

[00432] TFA (2 mL, 26.0 mmol) was added to a solution of a TFA salt of *tert*-butyl (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-5-chloro-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (131 mg, 0.140 mmol) in DCM (10 mL) and the mixture was stirred for 3h at rt. The volatiles were removed under vacuum and the residue was taken into MeOH and filtered through a Strata XC MCX cartridge. The cartridge was washed with methanol and the compound was release from the cartridge by eluting with a solution of 2M of ammonia/methanol. The ammonia/methanol filtrate was evaporated under reduced pressure to yield 2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-4-chloro-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazole (55 mg, 0.11 mmol) as tan solid. LC-MS retention time

1.375 min; m/z 507.33 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm 5 µm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.26 (s, 1H), 8.19 (s, 1H), 8.00 - 8.09 (m, 3H), 7.92 (ddd, *J*=12.1, 8.6, 1.8 Hz, 2H), 7.85 (dd, *J*=8.6, 1.5 Hz, 1H), 7.81 (d, *J*=8.6 Hz, 1H), 4.96 (dd, *J*=11.0, 7.6 Hz, 1H), 4.64 (app t, *J*=9.3 Hz, 1H), 3.53 - 3.59 (m, 1H), 3.44 - 3.50 (m, 1H), 2.82 (dd, *J*=13.0, 7.5 Hz, 1H), 2.61 - 2.74 (m, 3H), 2.03 - 2.15 (m, 2H), 1.24 - 1.30 (m, 1H), 1.18 - 1.24 (m, 1H), 0.96 - 1.09 (m, 2H).

Scheme 24

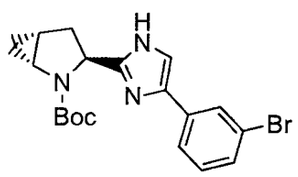




Intermediate 93

(1R,3S,5R)-3-(2-(3-Bromophenyl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

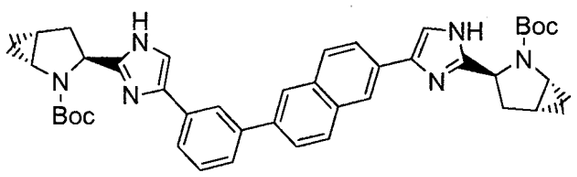
[00433] DIPEA (2.79 mL, 16.0 mmol) was added to a stirring slurry of (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (2.00 g, 8.80 mmol) and 2-bromo-1-(3-bromophenyl)ethanone (2.22 g, 8.00 mmol) in acetonitrile (25 mL) (the solution became clear and amber colored) and the reaction mixture was stirred overnight. The reaction was concentrated and purified via BIOTAGE® (80g SiO_2, 10-25% EtOAc/hexanes) to yield (1R,3S,5R)-3-(2-(3-bromophenyl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (3.37 g, 7.94 mmol) as a viscous light yellow oil. LC-MS retention time 1.853 min; m/z 423 and 425.98 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a waters XTERRA® MS 7u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (d, J = 1.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.0, 7.8 Hz, 1H), 5.58 - 5.10 (m, 2H), 4.23 (br s, 1H), 3.62 - 3.39 (m, 1H), 2.58 (dt, J = 13.3, 6.5 Hz, 1H), 2.46 (dd, J = 13.3, 9.5 Hz, 1H), 1.73 - 1.51 (m, 1H), 1.47 (s, 9H), 0.85 (br s, 1H), 0.51 (s, 1H).



Intermediate 94

(1R,3S,5R)-*tert*-Butyl 3-(4-(3-bromophenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00434] In a 350 mL high pressure vessel ammonium acetate (5.94 g, 77 mmol) was added to a solution of (1R,3S,5R)-3-(2-(3-bromophenyl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (3.33 g, 7.85 mmol) in xylene (75 mL) and stirred under nitrogen for 5 minutes. The vessel was sealed and then placed into an oil bath which had been heated to 140 °C (reaction became dark brown) and the reaction was held at 140 °C for 11h. Additional ammonium acetate (3.0g) was added and the reaction was stirred at 145 °C for 8 hrs, cooled to rt and stirred (>90% conversion by LCMS). The reaction was concentrated under high vacuum to a brown oil which was partitioned between DCM (~ 200 mL) and 1/2 sat. sodium bicarbonate (~200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude orange solidified foam was purified on a BIOTAGE® Horizon (20-50% EtOAc/hexanes, 160 g SiO_2) to yield (1R,3S,5R)-*tert*-butyl 3-(4-(3-bromophenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (2.03 g, 5.02 mmol) as a yellow solidified foam. LC-MS retention time 2.450 min; m/z 404 and 406.06 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (s, 1H), 7.65 (d, J = 6.5 Hz, 1H), 7.42 - 7.32 (m 2H), 7.26 (t, J = 7.8 Hz, 1H), 4.72 - 4.61 (m, 1H), 3.62 - 3.53 (m, 1H), 2.51 (dd, J = 13.0, 7.8 Hz, 1H), 2.36 - 2.26 (m, 1H), 1.75 - 1.66 (m, 1H), 1.29 (br s, 9H), 0.84 (dt, J = 8.0, 5.7 Hz, 1H), 0.63 - 0.57 (m, 1H).

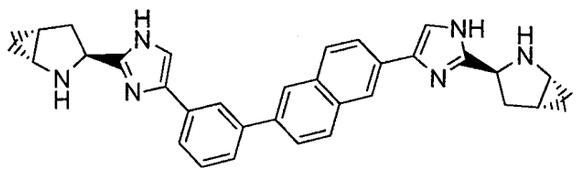


Intermediate 95

tert-Butyl (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00435] A solution of (1R,3S,5R)-*tert*-butyl 3-(5-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (220 mg, 0.395 mmol) (prepared in the same manner as Intermediate 51 from Intermediate 55), (1R,3S,5R)-*tert*-butyl 3-(4-(3-bromophenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (192 mg, 0.474 mmol) and cesium carbonate (386 mg, 1.185 mmol) in THF (4 mL) and water (4 mL) in a 100 mL pressure flask was degassed under vacuum for 5 min and then backfilled with nitrogen. Palladium (II) acetate (8.9 mg, 0.039 mmol) was added and the mixture was heated for 4h at 120 °C. The reaction mixture was cooled to RT, diluted with water and extracted with EtOAC and DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified on a BIOTAGE® system (90g silica gel cartridge, eluted with a gradient of 0 to 100 % EtOAc in hexanes) to yield *tert*-butyl (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (142 mg, 0.203 mmol) as a yellow solid. LC-MS retention time 1.585 min; m/z 699.57 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm 5um column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.33 (d, *J*=1.2 Hz, 1H), 8.31 (s, 1H), 8.20 - 8.24 (m, 1H), 8.14 - 8.20 (m, 1H), 8.10 -

8.14 (m, 1H), 7.97 - 8.07 (m, 3H), 7.94 (d, *J*=7.9 Hz, 1H), 7.87 - 7.92 (m, 1H), 7.77 - 7.82 (m, 1H), 7.67 - 7.74 (m, 1H), 4.84 - 4.96 (m, 2H), 3.67 (br s, 2H), 2.69 - 2.80 (m, 2H), 2.47 (br s, 2H), 1.82 - 1.91 (m, 2H), 1.19 - 1.63 (m, 18H), 0.89 - 0.97 (m, 2H), 0.77 (br s, 2H).

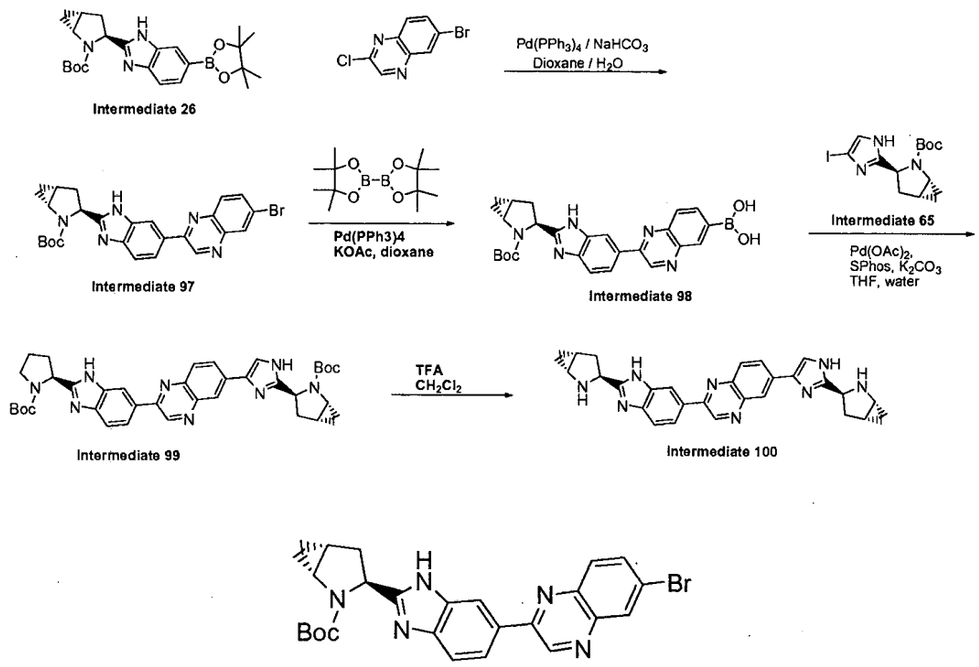


Intermediate 96

(1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-Azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00436] TFA (2 mL, 26.0 mmol) was added to a solution of *tert*-butyl (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (130 mg, 0.20 mmol) in DCM (2 mL) and the mixture was stirred for 2h at RT. The volatiles were removed under vacuum and the crude product was purified by prep HPLC (methanol/water, 0.1%TFA) to yield a TFA salt of (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (103 mg) as a tan solid. LC-MS retention time 1.303 min; m/z 499.13 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm 5 μM column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.22 (d, *J*=12.5 Hz, 2H), 8.02 (dd, *J*=8.6, 5.8 Hz, 2H), 7.90 - 7.97 (m, 2H), 7.75 - 7.82 (m, 4H), 7.58 (t, *J*=7.8 Hz, 1H), 4.74 - 4.78 (m, 2H), 3.46 - 3.53 (m, 2H), 2.64 - 2.74 (m, 4H), 2.04 - 2.12 (m, 2H), 1.19 - 1.26 (m, 2H), 1.02 (ddd, *J*=14.2, 7.3, 7.2 Hz, 2H).

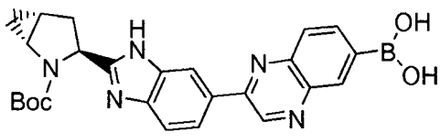
Scheme 25



Intermediate 97

(1R,3S,5R)-*tert*-Butyl 3-(6-(6-bromoquinoxalin-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

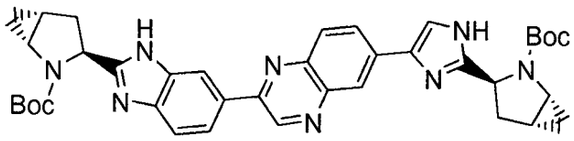
[00437] $Pd(Ph_3P)_4$ (28.5 mg, 0.025 mmol) was added to a degassed solution of 6-bromo-2-chloroquinoxaline (60 mg, 0.246 mmol), (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (115 mg, 0.271 mmol) and sodium bicarbonate (62.1 mg, 0.739 mmol) in dioxane (1 mL) and H_2O (0.2 mL) and the mixture was stirred at 110 °C for 2 h and then at 120 °C for 2 h. The reaction was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield (1R,3S,5R)-*tert*-butyl 3-(6-(6-bromoquinoxalin-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (102.2 mg, 0.202 mmol, 82 % yield) as bright yellow solid. LC-MS retention time 2.31 min; m/z 506 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).



Intermediate 98

2-(2-((1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-6-ylboronic acid

[00438] $Pd(Ph_3P)_4$ (23.28 mg, 0.020 mmol) was added to a degassed solution of (1R,3S,5R)-*tert*-butyl 3-(6-(6-bromoquinoxalin-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (102 mg, 0.201 mmol), KOAc (49.4 mg, 0.504 mmol) and bis(pinacolato)diboron (113 mg, 0.443 mmol) in dioxane (2 mL) and the reaction was stirred at 83 °C for 16 h. The reaction mixture was partitioned between EtOAc (20 mL) and sat. NH_4Cl (aq.) (5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to an orange oil, which was purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield 2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-6-ylboronic acid (57 mg, 0.121 mmol, 60.0 % yield) as orange solid. LC-MS retention time 1.94 min; m/z 472 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).

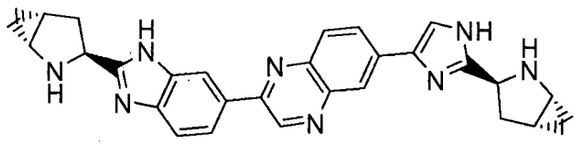


Intermediate 99

tert-Butyl (1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-6-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00439] $Pd(OAc)_2$ (2.67 mg, 0.012 mmol) was added to a degassed solution of 2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-6-ylboronic acid (56 mg, 0.119 mmol), (1R,3S,5R)-

tert-butyl 3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (66.9 mg, 0.178 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (9.76 mg, 0.024 mmol) and K_2CO_3 (49.3 mg, 0.356 mmol) in THF (1 mL) and water (0.25 mL) and the mixture was stirred at 120 °C for 2 h. The reaction was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield (1R,3S,5R)-*tert*-butyl 3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-6-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (32 mg, 0.047 mmol) as yellow solid. LC-MS retention time 1.89 min; m/z 675 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% water/ 5% methanol/10 mM ammonium acetate. Solvent B = 5% water/ 95% methanol/10 mM ammonium acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 9.44 (s, 1H), 8.45 (br s, 1H), 8.39 (s, 1H), 8.23 (d, *J*=8.8 Hz, 1H), 8.18 (d, *J*=8.5 Hz, 1H), 8.13 (d, *J*=8.8 Hz, 1H), 7.69 - 7.76 (m, 1H), 7.64 (s, 1H), 4.69 - 4.78 (m, 1H), 4.49 - 4.57 (m, 1H), 3.56 - 3.70 (m, 2H), 2.50 - 2.73 (m, 2H), 2.31 - 2.47 (m, 2H), 1.67 - 1.86 (m, 2H), 1.31 (br s, 18H), 0.82 - 0.95 (m, 2H), 0.54 - 0.75 (m, 2H).



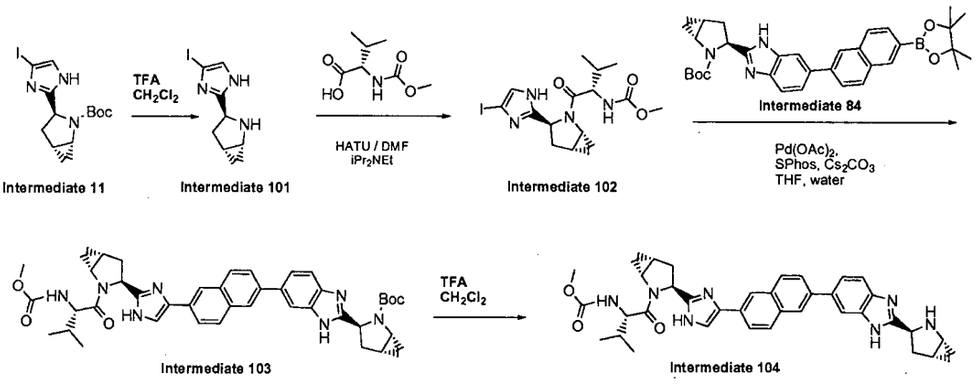
Intermediate 100

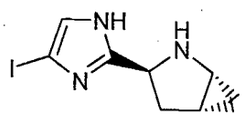
2-(2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)quinoxaline

[00440] TFA (0.25 mL, 3.24 mmol) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-(2-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-6-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (30 mg, 0.044 mmol) in DCM (0.5 mL) and the mixture was stirred at rt for 16 h. The volatiles were removed under vacuum and the residue was triturated with Et_2O to yield a TFA salt of 2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)quinoxaline (32.7 mg) as yellow solid. LC-MS retention time 1.33 min; m/z 475 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90%

water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.47 (s, 1H), 8.54 (s, 1H), 8.50 (s, 1H), 8.31 (dd, *J*=8.8, 1.8 Hz, 1H), 8.26 (dd, *J*=8.5, 1.3 Hz, 1H), 8.15 (d, *J*=8.8 Hz, 1H), 7.83 (s, 1H), 7.82 (d, *J*=8.8 Hz, 1H), 4.85 - 4.97 (m, 1H), 4.67 (dd, *J*=10.8, 7.5 Hz, 1H), 3.45 - 3.57 (m, 2H), 2.77 - 2.86 (m, 1H), 2.65 - 2.74 (m, 1H), 2.52 - 2.65 (m, 2H), 2.02 - 2.15 (m, 2H), 1.18 - 1.30 (m, 2H), 0.95 - 1.09 (m, 2H).

Scheme 26



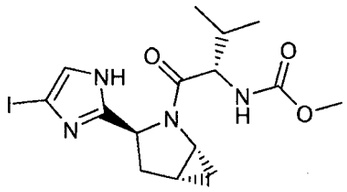


Intermediate 101

(1R,3S,5R)-3-(4-Iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00441] TFA (1 mL, 12.98 mmol) was added dropwise to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (450 mg, 1.20 mmol) in DCM (5 mL) at room temperature. The mixture was stirred for 2h at room temperature, then, the volatiles were removed and the residue was taken in MeOH (5 mL) and filtered through a Strata XC MCX cartridge. The cartridge was washed with methanol (30 mL) and the compound was release from the cartridge by eluting with a solution of 2M of ammonia/methanol (40 mL) and concentrated to give (1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (283 mg, 1.03 mmol, 86 % yield) as white solid. LC-MS retention time 0.448 min; m/z 275.94 (MH+). LC data was recorded

on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.17 (s, 1H), 4.20 (dd, *J*=10.4, 7.3 Hz, 1H), 3.08 (td, *J*=6.2, 2.6 Hz, 1H), 2.38 (dd, *J*=12.5, 7.3 Hz, 1H), 2.19 (ddd, *J*=12.7, 10.5, 4.9 Hz, 1H), 1.68 - 1.74 (m, 1H), 0.85 (ddd, *J*=6.6, 4.4, 2.8 Hz, 1H), 0.61 - 0.67 (m, 1H).

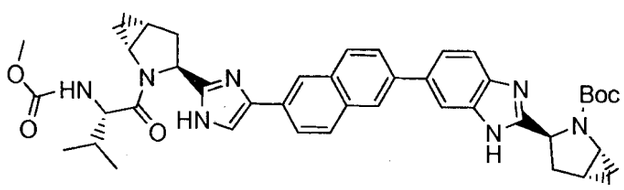


Intermediate 102

Methyl (S)-1-((1R,3S,5R)-3-(4-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00442] HATU (464 mg, 1.22 mmol) was added to a solution of (1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (280 mg, 1.02 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (214 mg, 1.22 mmol) and DIEA (1.8 mL, 10 mmol) in DMF (3 mL). The reaction mixture was stirred 2h at room temperature and then diluted with MeOH (5 mL) and water (5 mL). The volatiles were removed under vacuum and the residue was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-100 ethyl acetate/ hexanes) to afford methyl (S)-1-((1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (500 mg, 0.925 mmol, 91 % yield) as yellowish oil. LC-MS retention time 0.850 min; m/z 432.97 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and

an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.09 (s, 1H), 5.09 (dd, *J*=8.9, 4.6 Hz, 1H), 4.47 - 4.60 (m, 1H), 3.67 (s, 3H), 3.59 -3.62 (m, 1H), 2.39 - 2.49 (m, 1H), 2.29 - 2.39 (m, 1H), 2.12 (dq, *J*=13.6, 6.8 Hz, 1H), 1.95 - 2.06 (m, 1H), 1.11 (dt, *J*=8.6, 5.5 Hz, 1H), 0.94 - 1.02 (m, 3H), 0.91 (d, *J*=6.7 Hz, 3H), 0.76 (br s, 1H).

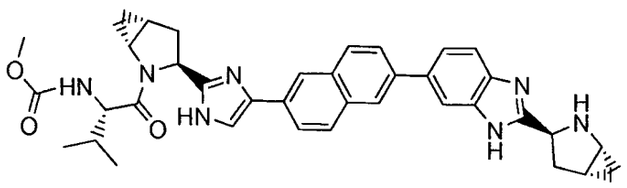


Intermediate 103

(1R,3S,5R)-*tert*-Butyl 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00443] A solution of (1R,3S,5R)-*tert*-butyl 3-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (573 mg, 1.04 mmol), methyl (S)-1-((1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (374 mg, 0.87 mmol), dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (SPHOS, 71.0 mg, 0.173 mmol) and cesium carbonate (846 mg, 2.60 mmol) in THF (7.9 mL) and water (0.8 mL) was degassed at 0 °C under vacuum for 5 min and the reactor was then back filled with nitrogen. Palladium(II) acetate (19.4 mg, 0.087 mmol) was added and the reaction mixture was heated at 100 °C for 3h. water was added to the cooled solution and the reaction was further diluted with EtOAc (15 mL). The phases were separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried over Na_2SO_4, filtered through a pad of diatomaceous earth (CELITE®) and the volatiles were removed under reduced pressure. The residue was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 20-100% ethyl acetate/ hexanes then 5% MeOH/DCM) to afford (1R,3S,5R)-*tert*-butyl 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-

azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (246 mg, 0.337 mmol, 39.0 % yield). LC-MS retention time 1.448 min; m/z 730.21 (MH+).LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.32 (br s, 1H), 8.30 (s, 1H), 8.03 - 8.19 (m, 4H), 7.96 - 8.03 (m, 1H), 8.01 (s, 1H), 7.85 - 7.96 (m, 2H), 5.18 (dd, *J*=9.0, 7.0 Hz, 1H), 5.09 (dd, *J*=8.9, 7.6 Hz, 1H), 4.58 (d, *J*=6.5 Hz, 1H), 3.81 - 3.89 (m, 1H), 3.65 - 3.75 (m, 1H), 3.69 (s, 3H), 2.68 - 2.86 (m, 2H), 2.52 (dt, *J*=13.6, 6.8 Hz, 2H), 2.15 - 2.29 (m, 1H), 2.06 - 2.15 (m, 1H), 1.85 - 1.95 (m, 1H), 1.51 (br s, 4H), 1.41 (d, *J*=16.3 Hz, 1H), 1.27 (s, 1H), 1.20 (br s, 3H), 1.12 (ddd, *J*=8.7, 6.0, 5.9 Hz, 1H), 1.04 (d, *J*=6.8 Hz, 3H), 0.87 - 1.00 (m, 5H), 0.83 (br s, 1H).



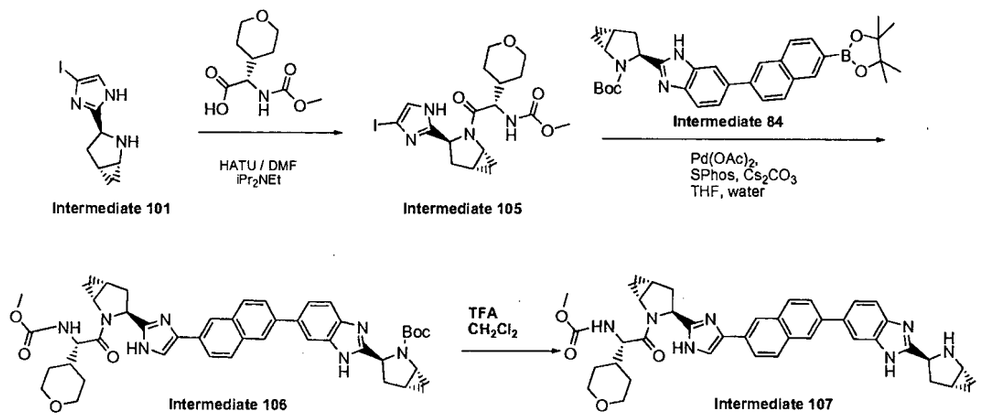
Intermediate 104

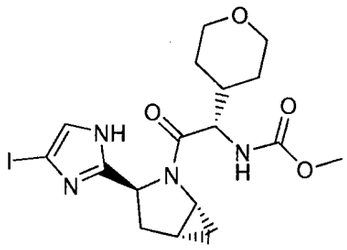
Methyl (S)-1-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00444] TFA (2 mL,) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (226 mg, 0.310 mmol) in DCM (5 mL) and the reaction was stirred for 2h at room temperature. The solution was concentrated under vacuum and the residue was taken in MeOH (10 mL) and filtered through a Strata XC MCX cartridge and washed with methanol (25 mL). The compound was released from

the cartridge by washing the column with a solution of 2M of ammonia/methanol (10 mL) and concentrated under reduced pressure to give a methyl (S)-1-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (131 mg, 0.208 mmol) as tan solid. LC-MS retention time 1.235 min; m/z 630.17 (MH+).LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.16 (s, 1H), 8.07 (s, 1H), 7.92 (dd, *J*=8.3, 6.3 Hz, 2H), 7.87 (s, 1H), 7.78 - 7.85 (m, 2H), 7.60 - 7.69 (m, 2H), 7.44 (s, 1H), 5.20 (dd, *J*=8.8, 4.8 Hz, 1H), 4.62 (d, *J*=6.8 Hz, 1H), 4.28 (dd, *J*=9.8, 7.8 Hz, 1H), 3.66 - 3.76 (m, 4H), 3.35 - 3.41 (m, 2H), 3.03 (td, *J*=6.0, 2.5 Hz, 1H), 2.40 - 2.59 (m, 3H), 2.12 - 2.25 (m, 2H), 1.99 - 2.09 (m, 1H), 1.59 - 1.68 (m, 1H), 1.10 - 1.18 (m, 1H), 1.00 - 1.08 (m, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 - 1.04 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.76 - 0.84 (m, 2H), 0.50 - 0.59 (m, 1H).

Scheme 27



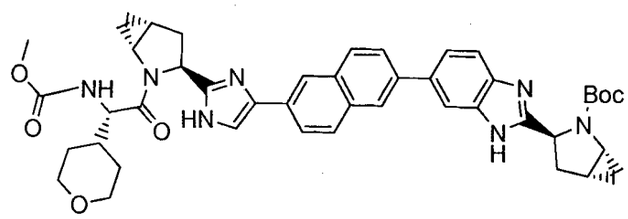


Intermediate 105

Methyl (S)-2-((1R,3S,5R)-3-(4-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate

[00445] HATU (846 mg, 2.23 mmol) was added to a solution of (1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (510 mg, 1.85 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (483 mg, 2.23 mmol) and DIEA (3.24 mL, 18.5 mmol) in DMF (5 mL) and the reaction was stirred 2h at room temperature. The reaction mixture was diluted with MeOH (5 mL) and water (5 mL). The volatiles were removed under vacuum and the residue was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 0-100% ethyl acetate/ hexanes then 10% MeOH/DCM) to afford the methyl (S)-2-((1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate (370 mg, 0.780 mmol, 42.1 % yield) as white foam. Impure material was further purified on reverse phase HPLC (water/methanol, 0.1%TFA) to afford the TFA salt of methyl (S)-2-((1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate, (387 mg) as colorless oil. LC-MS retention time 0.690 min; m/z 474.95 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 7.58 (s, 1H), 5.04 (dd, *J*=9.2, 6.7 Hz, 1H), 4.56 (d, *J*=7.8 Hz, 1H), 3.96 (td, *J*=11.7, 3.1 Hz, 2H), 3.74 - 3.81 (m, 1H), 3.65 - 3.73 (m, 3H), 3.35 - 3.44 (m, 2H), 2.61 (dd, *J*=13.6, 9.3 Hz, 1H), 2.37 (ddd, *J*=13.6, 6.7, 6.5 Hz,

1H), 1.96 - 2.09 (m, 2H), 1.37 - 1.62 (m, 4H), 1.06 (dt, *J*=8.8, 5.9 Hz, 1H), 0.84 (td, *J*=5.6, 2.4 Hz, 1H).

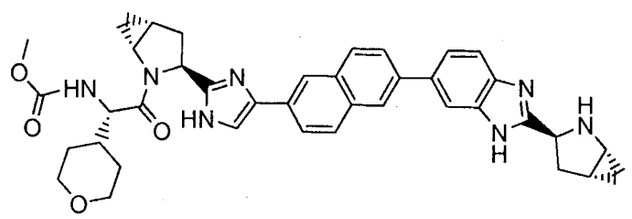


Intermediate 106

(1R,3S,5R)-*tert*-Butyl 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00446] A slurry of (1R,3S,5R)-*tert*-butyl 3-(6-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (407 mg, 0.738 mmol), a TFA salt of methyl (S)-2-((1R,3S,5R)-3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate (350 mg), dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (60.6 mg, 0.148 mmol) and cesium carbonate (721 mg, 2.21 mmol) in THF (6.7mL) and water (0.7 mL) was degassed at 0 °C under vacuum for 5 min and then the reactor was back filled with nitrogen. Palladium(II) acetate (16.6 mg, 0.074 mmol) was added and the mixture was heated at 100 °C for 3h. The volatiles were removed under vacuum and the mixture was diluted with water (20 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was purified with flash chromatography (sample was dry loaded on silica gel and eluted with 20-100% ethyl acetate/ hexanes, then 10% MeOH/DCM). The residue was purified again by on reverse phase HPLC (water/methanol, 0.1%TFA) to afford the TFA salt of (1R,3S,5R)-*tert*-butyl 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (231 mg) as yellow solid. LC-MS retention time 1.395 min; m/z 772.31 (MH+). LC data was recorded on a Shimadzu LC-10AS

liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.09 - 8.18 (m, 3H), 8.05 (dd, *J*=8.7, 1.7 Hz, 1H), 7.97 - 8.02 (m, 2H), 7.91 (d, *J*=8.6 Hz, 1H), 7.88 (dd, *J*=8.7, 1.7 Hz, 1H), 5.16 (dd, *J*=9.2, 7.0 Hz, 1H), 5.01 - 5.09 (m, 1H), 4.62 (d, *J*=7.6 Hz, 1H), 3.91 - 4.02 (m, 3H), 3.83 - 3.89 (m, 1H), 3.70 (br s, 4H), 3.35 - 3.45 (m, 2H), 2.68 - 2.83 (m, 2H), 2.45 - 2.57 (m, 2H), 2.04 - 2.16 (m, 2H), 1.90 (br s, 1H), 1.43 - 1.61 (m, 8H), 1.14 - 1.31 (m, 4H), 1.07 - 1.13 (m, 1H), 0.97 (dt, *J*=8.8, 5.8 Hz, 1H), 0.91 (br s, 1H), 0.82 (br s, 1H).



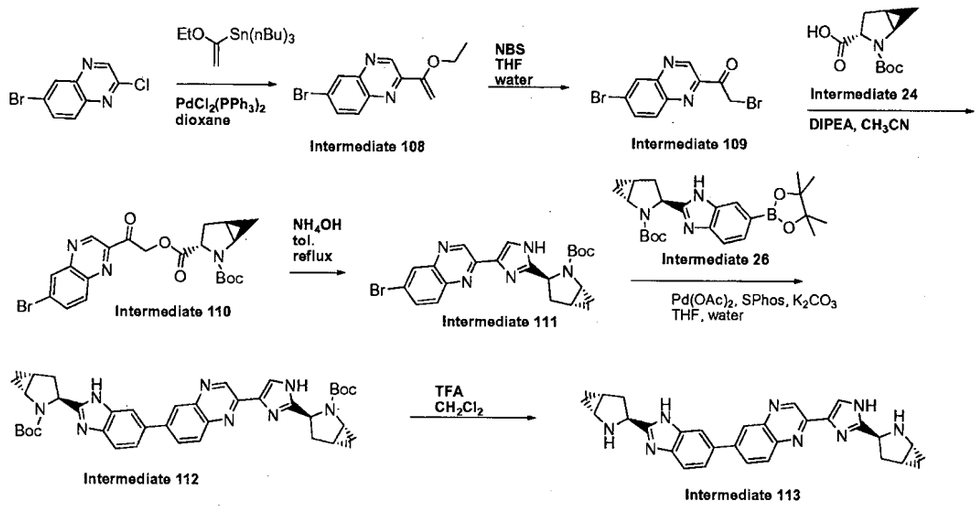
Intermediate 107

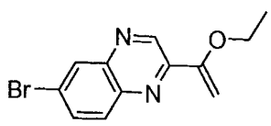
Methyl (S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate

[00447] TFA (2 mL, 26.0 mmol) was added to a solution of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (150 mg) in DCM and the mixture was stirred for 2h at rt. The volatiles were removed under vacuum and the residue was taken in MeOH (15 mL), filtered through a Strata XC MCX cartridge (1g) and washed with methanol. The compound was release from the cartridge by washing the column with a solution of 2M of ammonia/methanol (20 mL) and concentrated to give methyl (S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-

azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate (100 mg, 0.149 mmol) as white solid. LC-MS retention time 1.772 min; m/z 670.36 (M-H+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 10 mM ammonium acetate and solvent and Solvent B was 10% water / 90% methanol / 10 mM ammonium acetate and solvent. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.28 (s, 1H), 8.24 (s, 1H), 8.13 (d, *J*=8.9 Hz, 1H), 8.05 - 8.10 (m, 1H), 8.03 (s, 1H), 7.96 - 8.00 (m, 2H), 7.84 (dd, *J*=8.7, 1.7 Hz, 1H), 7.75 - 7.82 (m, 2H), 5.16 (dd, *J*=9.2, 7.3 Hz, 1H), 4.84 - 4.88 (partially shaded by MeOD, m, 1H), 4.62 (d, *J*=7.6 Hz, 1H), 3.91 - 4.01 (m, 2H), 3.84 - 3.89 (m, 1H), 3.66 - 3.76 (m, 3H), 3.51 - 3.56 (m, 1H), 3.35 - 3.46 (m, 2H), 2.82 (dd, *J*=12.8, 7.3 Hz, 1H), 2.73 (dd, *J*=13.7, 9.2 Hz, 1H), 2.61 (td, *J*=12.0, 4.7 Hz, 1H), 2.53 (ddd, *J*=13.8, 6.8, 6.6 Hz, 1H), 2.06 - 2.16 (m, 3H), 1.58 - 1.64 (m, 1H), 1.44 - 1.57 (m, 3H), 1.23 - 1.30 (m, 1H), 1.08 - 1.16 (m, 1H), 1.05 (q, *J*=7.8 Hz, 1H), 0.88 - 0.93 (m, 1H).

Scheme 28

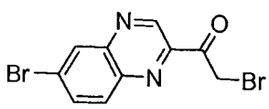




Intermediate 108

6-Bromo-2-(1-ethoxyvinyl)quinoxaline

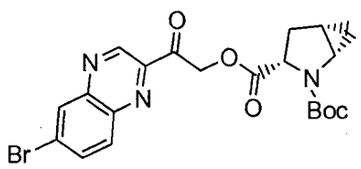
[00448] Dichlorobis(triphenylphosphine)-palladium(II) (17.30 mg, 0.025 mmol) was added to a solution of 6-bromo-2-chloroquinoxaline (60 mg, 0.246 mmol) and tributyl(1-ethoxyvinyl)stannane (107 mg, 0.296 mmol) in dioxane (1.5 mL) and the mixture was stirred at 110 °C for 2 h. The reaction was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield 6-bromo-2-(1-ethoxyvinyl)quinoxaline (36 mg, 0.129 mmol, 52.3 % yield) as white solid. LC-MS retention time 2.76 min; m/z 279 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).



Intermediate 109

2-Bromo-1-(6-bromoquinoxalin-2-yl)ethanone

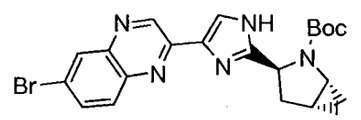
[00449] NBS (55.1 mg, 0.310 mmol) was added to a solution of 6-bromo-2-(1-ethoxyvinyl)quinoxaline (72 mg, 0.26 mmol) in THF (2 mL) and water (0.500 mL) and the mixture was stirred at rt for 2 h. The reaction was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield 2-bromo-1-(6-bromoquinoxalin-2-yl)ethanone (50 mg, 0.15 mmol, 59 % yield) as white solid. LC-MS retention time 2.40 min; m/z 329 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).



Intermediate 110

(1S,3S,5S)-3-(2-(6-Bromoquinoxalin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

[00450] DIPEA (0.040 mL, 0.227 mmol) was added to a solution of 2-bromo-1-(6-bromoquinoxalin-2-yl)ethanone (50 mg, 0.152 mmol) and (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (37.9 mg, 0.167 mmol) in acetonitrile (1.5 mL) and the mixture was stirred at rt for 16 h. The solvent was evaporated and the residue was partitioned between EtOAc (20 mL) / aq. sat. $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to yield crude (1R,3S,5R)-3-(2-(6-bromoquinoxalin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (63 mg) as orange solid. LC-MS retention time 2.74 min; m/z 476 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).

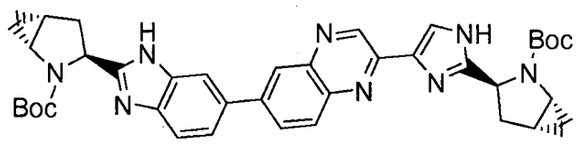


Intermediate 111

(1R,3S,5R)-*tert*-Butyl 3-(4-(6-bromoquinoxalin-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00451] NH_4OAc (102 mg, 1.323 mmol) was added to a solution of (1R,3S,5R)-3-(2-(6-bromoquinoxalin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (63 mg, 0.13 mmol) in toluene (3 mL) and the mixture was stirred at 120 °C for 4 h. Additional NH_4OAc (102 mg, 1.323 mmol) was added and the reaction was further heated at 120 °C for 4h. The reaction was diluted with EtOAc (20 mL) and aq. sat. $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and then purified by flash silica chromatography (eluted with 1:2 EtOAc/hexane) to yield

(1R,3S,5R)-*tert*-butyl 3-(4-(6-bromoquinoxalin-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (25 mg, 0.055 mmol) as red orange solid. LC-MS retention time 2.07 min; m/z 456 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).

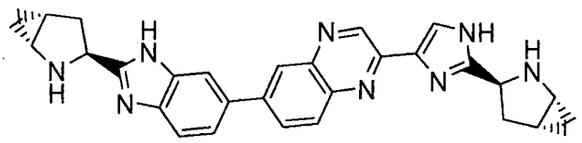


Intermediate 112

(1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00452] $Pd(OAc)_2$ (1.230 mg, 5.48 μmol) was added to a degassed suspension of (1R,3S,5R)-*tert*-butyl 3-(4-(6-bromoquinoxalin-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (25 mg, 0.055 mmol), K_2CO_3 (22.71 mg, 0.164 mmol), dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (4.50 mg, 10.96 μmol) and (1R,3S,5R)-*tert*-butyl 3-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (30.3 mg, 0.071 mmol) in THF (1 mL) and water (0.250 mL) and the mixture was stirred at 110 °C for 2 h. The reaction was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield (1R,3S,5R)-*tert*-butyl 3-(5-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (12 mg, 0.018 mmol, 33 % yield) as yellow solid. LC-MS retention time 1.90 min; m/z 675 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% water/ 5% methanol/10 mM ammonium acetate. Solvent B = 5% water/ 95% methanol/10 mM ammonium acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 9.38 (s, 1H), 8.28 (d, *J*=2.0 Hz, 1H), 8.16 - 8.22 (m, 1H), 8.10 - 8.15 (m, 1H), 7.95 (s, 2H), 7.66 - 7.76 (m, 2H), 3.54 -

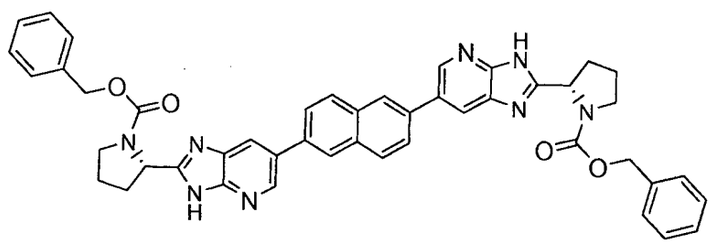
3.73 (m, 2H), 2.52 - 2.69 (m, 2H), 2.33 - 2.47 (m, 2H), 1.71 - 1.84 (m, 2H), 1.08 - 1.57 (m, 20H), 0.83 - 0.95 (m, 2H), 0.60 - 0.74 (m, 2H).



Intermediate 113

6-(2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)quinoxaline

[00453] TFA (0.25 mL, 3.24 mmol) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxalin-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (10 mg, 0.015 mmol) in DCM (0.5 mL) and the mixture was stirred at rt for 16 h. The volatiles were removed under vacuum and the residue was triturated with Et_2O. The resulting solid was rinsed with Et_2O to yield a TFA salt of 6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)quinoxaline (10.5 mg) as yellow solid. LC-MS retention time 1.32 min; m/z 475 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).



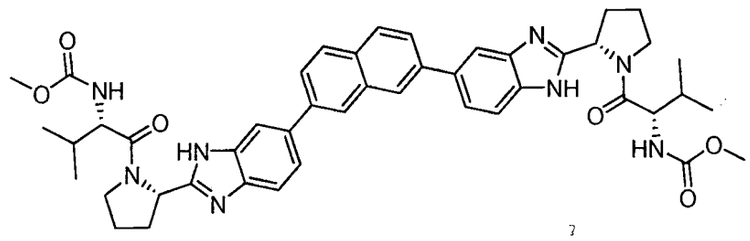
Intermediate 114

Benzyl (2S)-2-(6-(6-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyridin-6-yl)-2-naphthyl)-3H-imidazo[4,5-b]pyridin-2-yl)-1-pyrrolidinecarboxylate

[00454] Prepared in a similar manner as Intermediate 39 using (S)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid as a starting material rather than (S)-1-

(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid and the intermediates were not SEM protected. Prepared benzyl (2S)-2-(6-(6-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyridin-6-yl)-2-naphthyl)-3H-imidazo[4,5-b]pyridin-2-yl)-1-pyrrolidinecarboxylate (20.8 mg) as a white solid. LC-MS retention time 1.742 min; m/z 769.41 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

EXAMPLES

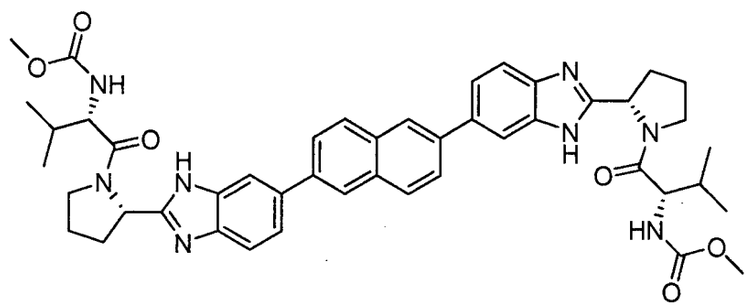


Example 1

Methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00455] HATU (59 mg, 0.15 mmol) was added to a mixture of a TFA salt of 2,7-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (37 mg), diisopropylethylamine (68 μL, 0.40 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (27 mg, 0.15 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient conditions for 2.5 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL) and stirred for 15 min. The volatile component was removed *in vacuo* and the residue was purified twice by a reverse phase HPLC

(water/acetonitrile/TFA) and reverse phase HPLC (water/acetonitrile/NH_4OAc) to provide the desired product which was suspended in methanol and TFA. The volatiles were removed *in vacuo* to afford a TFA salt of methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (11.3 mg) as tan solid. LC-MS retention time 1.34 min; Calcd. for $C_{46}H_{52}N_8O_6$ 812.4 Found m/z 813.42 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.03 - 8.10 (m, 4H), 7.96 - 8.02 (m, Hz, 2H), 7.89 (dd, *J*=8.6, 1.5 Hz, 2H), 7.85 (m, 2H), 5.36 (t, *J*=7.0 Hz, 2H), 4.22 - 4.32 (m, 2H), 4.09 - 4.19 (m, 2H), 3.89 - 4.00 (m, 2H), 3.63 - 3.74 (m, 6H), 2.56 - 2.70 (m, 2H), 2.31 - 2.40 (m, 2H), 2.19 - 2.31 (m, 4H), 2.08 (dd, *J*=13.6, 6.9 Hz, 2H), 0.95 (d, *J*=7.0 Hz, 6H), 0.89 (d, *J*=6.7 Hz, 6H).

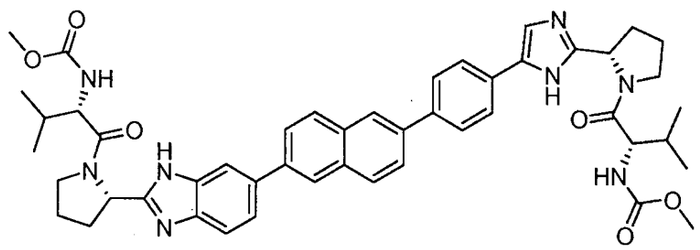


Example 2

Methyl ((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00456] HATU (82 mg, 0.217 mmol) was added to a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (69 mg), diisopropylethylamine (126 μL, 0.723 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (51 mg,

0.29 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient conditions for 2.5 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then the volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of methyl ((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (47 mg) as tan solid. LC-MS retention time 1.30 min; Calcd. for $C_{46}H_{52}N_8O_6$: 812.40 Found m/z 813.42 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.25 (s, 2H), 8.07 - 8.16 (m, 4H), 8.02 (m, *J*=8.6 Hz, 2H), 7.91 (m, *J*=8.6 Hz, 2H), 7.87 (d, *J*=8.6 Hz, 2H), 5.37 (t, *J*=7.2 Hz, 2H), 4.28 (d, *J*=7.0 Hz, 2H), 4.09 - 4.18 (m, 2H), 3.90 - 4.01 (m, 2H), 3.63 - 3.73 (m, 6H), 2.57 - 2.70 (m, 2H), 2.32 - 2.45 (m, 2H), 2.19 - 2.32 (m, 4H), 2.09 (dq, *J*=13.6, 6.9 Hz, 2H), 0.95 (d, *J*=6.7 Hz, 6H), 0.89 (d, *J*=6.7 Hz, 6H).

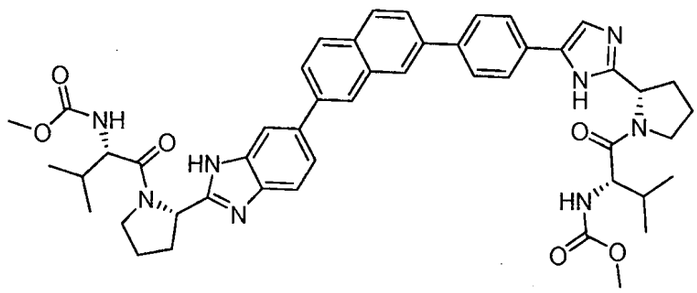


Example 3

Methyl ((1S)-1-(((2S)-2-(4-(4-(6-(2-(1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00457] HATU (39 mg, 0.10 mmol) was added to a mixture of a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(6-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-benzo[d]imidazole (50 mg), diisopropylethylamine (89 μL, 0.51 mmol) and (S)-2-

(methoxycarbonylamino)-3-methylbutanoic acid (27 mg, 0.15 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient conditions for 2.5 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(4-(6-(2-(1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (31.4 mg) as tan solid. LC-MS retention time 1.37 min; Calcd. for $C_{48}H_{54}N_8O_6$ 838.42 Found m/z 839.36 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.23 - 8.28 (m, 2H), 8.08 - 8.15 (m, 3H), 8.02 (d, *J*=8.6 Hz, 1H), 7.95 - 8.00 (m, 2H), 7.85 - 7.95 (m, 6H), 5.40 (t, *J*=7.2 Hz, 1H), 5.29 (t, *J*=7.5 Hz, 1H), 4.29 (dd, *J*=19.4, 7.2 Hz, 2H), 4.10 - 4.19 (m, 2H), 3.96 - 4.03 (m, 1H), 3.87 - 3.96 (m, 1H), 3.69 (m, 6H), 2.55 - 2.73 (m, 2H), 2.04 - 2.42 (m, 8H), 0.89 - 1.05 (m, 12H).

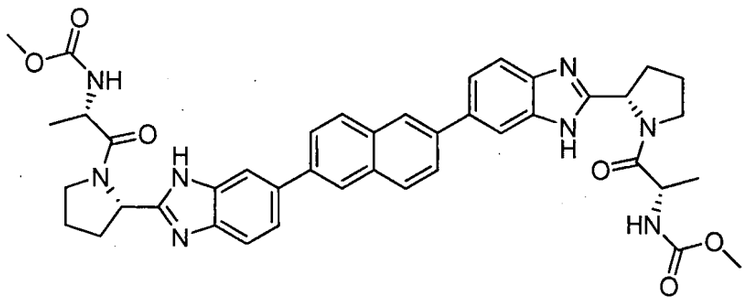


Example 4

Methyl ((1S)-1-(((2S)-2-(4-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00458] HATU (29 mg, 0.076 mmol) was added to a mixture of a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(7-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-

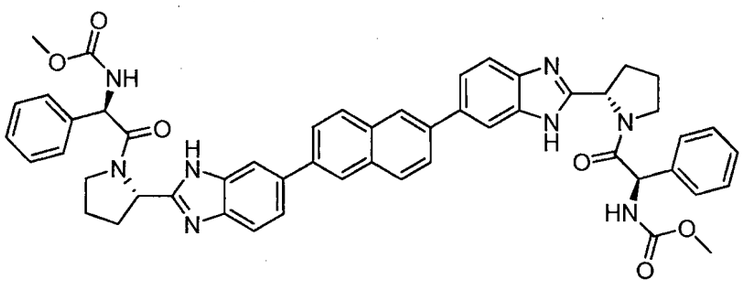
yl)-1H-benzo[d]imidazole (25 mg), diisopropylethylamine (45 μL, 0.26 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (13 mg, 0.76 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient conditions for 2.5 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (14.2 mg) as yellow solid. LC-MS retention time 1.40 min; Calcd. for $C_{48}H_{54}N_8O_6$ 838.42 Found m/z 839.36 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.33 (br s, 2H), 8.13 (s, 1H), 8.03 - 8.10 (m, 3H), 8.00 (d, *J*=8.2 Hz, 2H), 7.86 - 7.94 (m, 6H), 5.40 (t, *J*=7.2 Hz, 1H), 5.29 (t, *J*=7.6 Hz, 1H), 4.31 (d, *J*=7.3 Hz, 1H), 4.27 (d, *J*=7.3 Hz, 1H), 4.10 - 4.20 (m, 2H), 3.85 - 4.10 (m, 2H), 3.69 (s, 6H), 2.55 - 2.74 (m, 2H), 2.03 - 2.37 (m, 8H), 0.85 - 1.05 (m, 12H).



Example 5

Methyl ((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

[00459] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg), (S)-2-(methoxycarbonylamino)propanoic acid (28.8 mg, 0.196 mmol) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) to afford a TFA salt of methyl ((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate (35.9 mg) as white solid. LC-MS retention time 1.12 min; Calcd. for $C_{42}H_{44}N_8O_6$ 756.34 Found m/z 757.20 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.22 - 8.30 (m, 2H), 8.08 - 8.18 (m, 4H), 7.99 - 8.07 (m, 2H), 7.83 - 7.96 (m, 4H), 5.44 (dd, *J*=8.6, 5.2 Hz, 2H), 4.56 (q, *J*=6.9 Hz, 2H), 4.0 - 4.09 (m, 2H), 3.94 - 4.02 (m, 2H), 3.61 - 3.75 (m, 6H), 2.58 - 2.72 (m, 2H), 2.21 - 2.38 (m, 6H), 1.32 - 1.45 (m, 6H).

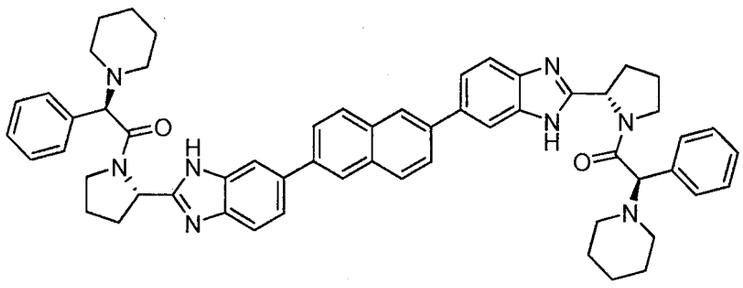


Example 6

Dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

[00460] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg), (R)-2-

(methoxycarbonylamino)-2-phenylacetic acid (41.0 mg, 0.196 mmol) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate (32.3 mg) as white solid. LC-MS retention time 1.43 min; Calcd. for $C_{52}H_{48}N_8O_6$ 880.37 Found m/z 881.23 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.25 - 8.35 (m, 2H), 8.12 - 8.21 (m, 4H), 8.05 - 8.12 (m, 2H), 7.90 - 8.00 (m, 4H), 7.38 - 7.54 (m, 10H), 5.62 (s, 2H), 5.38 - 5.53 (m, 2H), 4.04 - 4.18 (m, 2H), 3.67 (s, 6H), 2.34 - 2.41 (m, 2H), 2.46 - 2.58 (m, 2H), 2.15 - 2.35 (m, 4H), 2.02 - 2.13 (m, 2H).

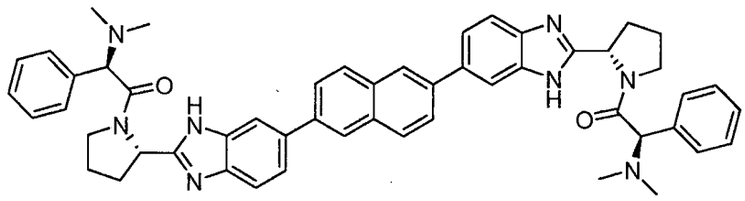


Example 7

5,5′-(2,6-Naphthalenediyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-benzimidazole)

[00461] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg), (R)-2-phenyl-2-(piperidin-1-yl)acetic acid (43.0 mg, 0.196 mmol) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with

MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford 5,5′-(2,6-naphthalenediyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-benzimidazole) (44.3 mg) as white solid. LC-MS retention time 1.18 min; Calcd. for $[M+H]^+$ $C_{58}H_{50}N_8O_2$ 900.48 Found m/z 451.33 $[1/2\ M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA.

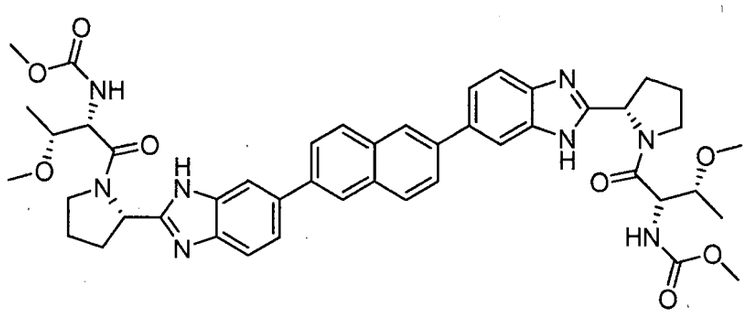


Example 8

(1R)-2-((2S)-2-(5-(6-(2-((2S)-1-((2R)-2-(Dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine

[00462] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg, 0.065 mmol), (R)-2-(dimethylamino)-2-phenylacetic acid (35.1 mg) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford (1R)-2-((2S)-2-(5-(6-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine (44.3 mg) as off-white solid. LC-MS retention time 1.07 min; Calcd. for $C_{52}H_{52}N_8O_2$ 820.42 Found m/z 821.29 $[M+H]^+$. LC data was recorded on a Shimadzu

LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.20 - 8.24 (m, 2H), 8.13 - 8.20 (m, 2H), 8.07 - 8.13 (m, 2H), 7.89 - 8.05 (m, 4H), 7.60 - 7.70 (m, 10H), 5.55 - 5.59 (m, 2H), 5.52 (dd, *J*=8.7, 3.8 Hz, 2H), 4.11 - 4.19 (m, 2H), 2.42 - 3.18 (m, 13H), 2.17 - 2.36 (m, 5H), 1.98 - 2.08 (m, 4H).

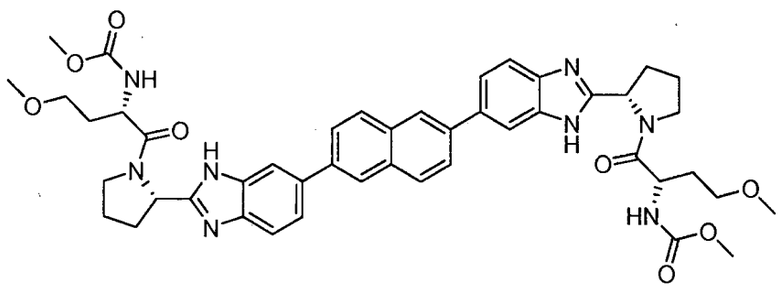


Example 9

Methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[00463] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg), (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (37.4 mg, 0.196 mmol) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (9.3 mg) as white solid. LC-MS retention time 1.22 min; Calcd. for $[M+H]^+$ $C_{46}H_{52}N_8O_8$ 844.39 Found m/z

845.25 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.10 - 8.21 (m, 2H), 7.99 - 8.08 (m, 2H), 7.83 - 7.96 (m, 4H), 7.58 - 7.77 (m, 4H), 5.70 - 5.75 (m, 0.4H), 5.35 (dd, *J*=7.9, 4.9 Hz, 1.6H), 4.58 - 4.61 (m, 0.2H), 4.51 (d, *J*=4.9 Hz, 1.5H), 4.37 - 4.43 (m, 0.3H), 3.89 - 4.08 (m, 3H), 3.61 - 3.78 (m, 7H), 3.38 - 3.45 (m, 2H), 3.23 - 3.31 (m, 5H), 1.93 - 2.57 (m, 9H), 1.10 - 1.28 (m, 6H).

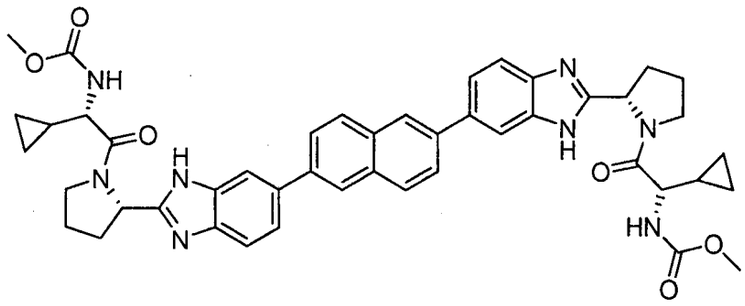


Example 10

Methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

[00464] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg), (S)-4-methoxy-2-(methoxycarbonylamino)butanoic acid (37.4 mg, 0.196 mmol) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) to afford a TFA salt of methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (28.6 mg) as yellow solid. LC-MS retention time 1.18 min; Calcd. for $[M+H]^+$ $C_{46}H_{52}N_8O_8$ 844.39

Found m/z 845.22 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.23 - 8.30 (m, 2H), 8.09 - 8.18 (m, 4H), 8.00 - 8.09 (m, 2H), 7.84 - 7.97 (m, 4H), 5.84 -5.90 (m, 0.2H), 5.44 (dd, *J*=8.2, 4.9 Hz, 1.8H), 4.65 (dd, *J*=9.2, 4.0 Hz, 1.8H), 4.38 - 4.45 (m, 0.2H), 3.91 - 4.11 (m, 4H), 3.66 - 3.78 (m, 6H), 3.39 - 3.55 (m, 4H), 3.27 - 3.38 (m, 7H), 2.59 - 2.75 (m, 2H), 2.25 - 2.40 (m, 5H), 2.16 (dddd, *J*=14.3, 7.0, 6.8, 4.3 Hz, 2H), 1.74 - 1.93 (m, 2H).

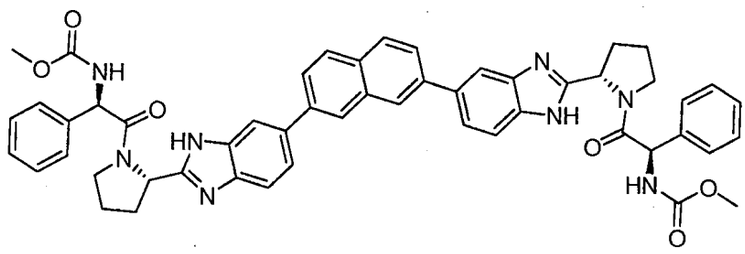


Example 11

Dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate

[00465] HATU (74.5 mg, 0.196 mmol) was added to a stirring solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (40 mg, 0.065 mmol), (S)-2-cyclopropyl-2-(methoxycarbonylamino)acetic acid (33.9 mg, 0.196 mmol) and DIEA (0.114 mL, 0.653 mmol) in DMF (2 mL). The reaction was stirred 9h at room temperature, diluted with MeOH (2 mL) and water (2 mL), concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) to afford a TFA salt of dimethyl (1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(naphthalene-2,6-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclopropyl-2-oxoethane-2,1-diyl)dicarbamate (34.9 mg, 0.038 mmol, 58 % yield) as white solid. LC-MS retention time 1.23 min; Calcd. for $C_{46}H_{48}N_8O_6$ 808.37 Found m/z 809.22 $[M+H]^+$. LC data was

recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.20 - 8.29 (m, 2H), 8.07 - 8.16 (m, 4H), 7.98 - 8.07 (m, 2H), 7.84 - 7.95 (m, 4H), 5.37 - 5.48 (m, 2H), 4.03 - 4.13 (m, 2H), 3.87 - 4.03 (m, 4H), 3.64 - 3.74 (m, 6H), 2.65 - 2.74 (m, 2H), 2.20 - 2.40 (m, 6H), 1.09 - 1.22 (m, 2H), 0.47 - 0.67 (m, 6H), 0.30 - 0.46 (m, 2H).

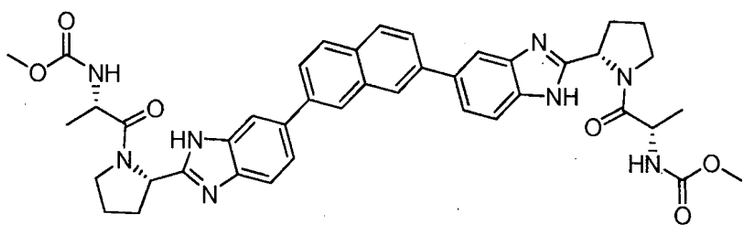


Example 12

Dimethyl (2,7-naphthalenediylbis(1H-benzimidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

[00466] HATU (56.2 mg, 0.148 mmol) was added to a stirred solution of a TFA salt of 2-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (47 mg), (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (30.9 mg, 0.148 mmol) and DIEA (0.086 mL, 0.49 mmol) in DMF (2 mL). The reaction was stirred 4 h at room temperature, diluted with MeOH (2 mL) and water (2 mL) concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) to afford a TFA salt of dimethyl (1R,1′R)-2,2′-((2S,2′S)-2,2′-(5,5′-(naphthalene-2,7-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-phenylethane-2,1-diyl)dicarbamate (38 mg) as light yellow solid. LC-MS retention time 1.45 min; Calcd. for $C_{52}H_{48}N_8O_6$ 880.37 Found m/z 881.26 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions

employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.31 - 8.39 (m, 2H), 8.03 - 8.17 (m, 6H), 7.84 - 8.00 (m, 4H), 7.33 - 7.53 (m, 10H), 5.55 - 5.63 (m, 2H), 5.40 - 5.54 (m, 2H), 4.01 - 4.17 (m, 2H), 3.67 (s, 6H), 3.27 - 4.41 (m, 2H), 2.44 - 2.75 (m, 2H), 2.01 - 2.33 (m, 6H).

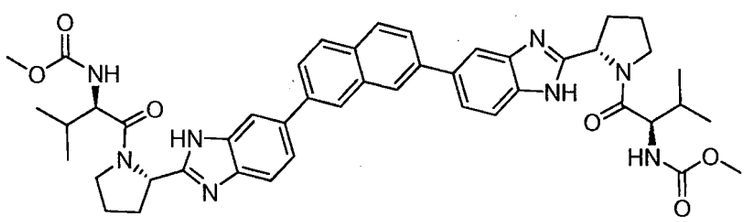


Example 13

Methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

[00467] HATU (56.2 mg, 0.148 mmol) was added to a stirred solution of a TFA salt of 2-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (47 mg), (S)-2-(methoxycarbonylamino)propanoic acid (21.7mg, 0.148 mmol) and DIEA (0.086 mL, 0.49 mmol) in DMF (2 mL). The reaction was stirred 5h at room temperature, diluted with MeOH (2 mL) and water (2 mL) concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate (20.9 mg) as white solid. LC-MS retention time 1.16 min; Calcd. for $C_{42}H_{44}N_8O_6$ 756.34 Found m/z 757.27 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.16 - 8.24 (m, 2H), 7.87 - 8.02 (m, 4H), 7.80 - 7.87 (m, 2H), 7.60 - 7.75 (m, 4H), 5.42 - 5.46 (m, 0.3H), 5.34 (dd, *J*=7.9, 4.0 Hz, 1.7H), 4.55 (q, *J*=7.0 Hz, 1.7H), 4.31 - 4.37 (m, 0.3H), 3.80 - 3.98 (m, 4H), 3.67 (s, 5H), 3.47 (s, 1H), 2.39 - 2.55 (m, 2H), 2.04 - 2.36 (m, 4H), 1.92 - 2.01 (m, 2H), 1.31 - 1.42 (m, 6H).

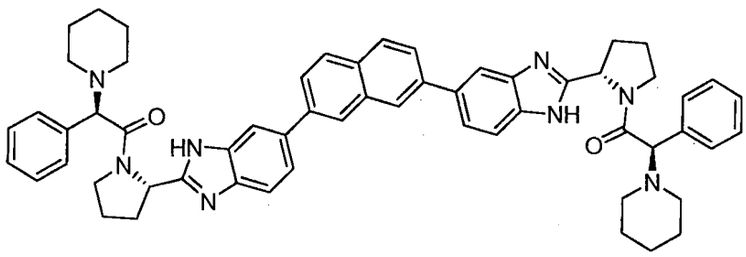


Example 14

Methyl ((1R)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00468] HATU (56.2 mg, 0.148 mmol) was added to a stirred solution of a TFA salt of 2-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (47 mg), (R)-2-(methoxycarbonylamino)-3-methylbutanoic acid (25.9 mg, 0.148 mmol) and DIEA (0.086 mL, 0.49 mmol) in DMF (2 mL). The reaction was stirred 5h at room temperature, diluted with MeOH (2 mL) and water (2 mL) concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford a TFA salt of methyl ((1R)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (25 mg) as beige solid. LC-MS retention time 1.36 min; Calcd. for $C_{46}H_{52}N_8O_6$ 812.40 Found m/z 813.36 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0%

Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.33 (s, 2H), 8.07 - 8.13 (m, 4H), 8.05 (dd, *J*=8.5, 1.2 Hz, 2H), 7.84 - 7.96 (m, 4H), 5.49 (dd, *J*=8.6, 3.7 Hz, 2H), 4.36 (d, *J*=7.3 Hz, 2H), 4.15 - 4.23 (m, 2H), 3.83 - 3.97 (m, 2H), 3.72 (s, 6H), 2.58 - 2.71 (m, 2H), 2.21 - 2.38 (m, 6H), 2.05 - 2.18 (m, 2H), 1.07 (d, *J*=6.7 Hz, 6H), 1.04 (d, *J*=6.7 Hz, 6H).

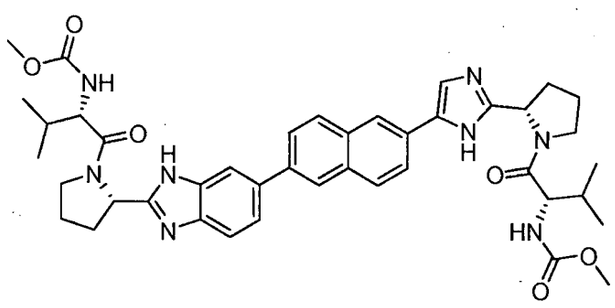


Example 15

5,5′-(2,7-Naphthalenediyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-benzimidazole)

[00469] HATU (56.2 mg, 0.148 mmol) was added to a stirred solution of a TFA salt of 2-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-7-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (47 mg), (R)-2-phenyl-2-(piperidin-1-yl)acetic acid (32.4 mg, 0.148 mmol) and DIEA (0.086 mL, 0.49 mmol) in DMF (2 mL). The reaction was stirred 5h at room temperature, diluted with MeOH (2 mL) and water (2 mL) concentrated to remove the volatiles and purified by preparative HPLC (acetonitrile/water with 0.1% TFA) and then by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to afford 5,5′-(2,7-naphthalenediyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-benzimidazole) (16.4 mg) as white solid. LC-MS retention time 1.21 min; Calcd. for $[M+H]^+$ $C_{58}H_{60}N_8O_6$ 900.48 Found m/z 451.43 1/2$[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90%

acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.18 - 8.28 (m, 2H), 7.96 - 8.05 (m, 2.2H), 7.92 (d, *J*=1.0 Hz, 1.5H), 7.80 - 7.90 (m, 2.2H), 7.65 - 7.76 (m, 3.8H), 7.55 - 7.64 (m, 3.2H), 7.46 - 7.55 (m, 4.5H), 6.85 - 6.97 (m, 1.6H), 6.76-6.83 (m, 1H), 5.65 - 5.70 (m, 0.5H), 5.28 (dd, *J*=7.5, 3.3 Hz, 1.5H), 4.48 (br s, 0.5H), 4.02 - 4.12 (m, 1.5H), 3.90 - 3.98 (m, 0.5H), 3.74 - 3.84 (m, 0.5H), 3.25 - 3.40 (m, 3H), 2.51 - 2.93 (m, 8H), 1.89 - 2.33 (m, 8H), 1.62 - 1.75 (m, 8H), 1.47 - 1.59 (m 4H).

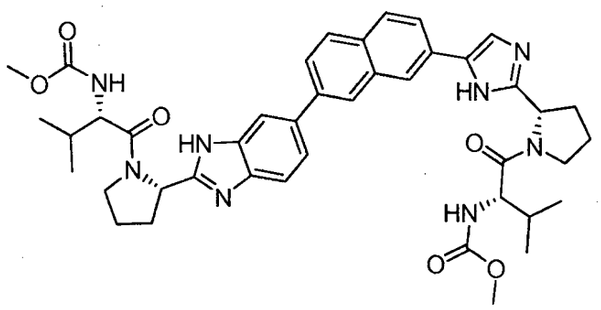


Example 16

Methyl ((1S)-1-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00470] HATU (40 mg, 0.11 mmol) was added to a mixture of a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-benzo[d]imidazole (32 mg), diisopropylethylamine (62 μL, 0.35 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (19 mg, 0.106 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient conditions for 9 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). The volatile component was removed *in vacuo* and the residue was purified by reverse phase HPLC (once with water/acetonitrile 10 mM ammonium acetate and twice with water/ acetonitrile 0.1% TFA) to provide a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (21 mg) as white solid. LC-MS retention time 1.17 min; Calcd. for $C_{42}H_{50}N_8O_6$ 762.39 Found m/z 763.34 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow

rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.27 (s, 1H), 8.15 (d, *J*=8.9 Hz, 1H), 8.10 (d, *J*=8.9 Hz, 1H), 8.07 (s, 1H), 7.94 - 8.01 (m, 3H), 7.82 - 7.89 (m, 2H), 5.38 (t, *J*=7.2 Hz, 1H), 5.31 (t, *J*=7.6 Hz, 1H), 4.28 (dd, *J*=14.5, 7.2 Hz, 2H), 4.15 (br s, 2H), 3.86 - 4.01 (m, 2H), 3.69 (s, 6H), 2.55 - 2.69 (m, 2H), 2.19 - 2.39 (m, 6H), 2.04 - 2.15 (m, 2H), 0.86 - 1.05 (m, 12H).

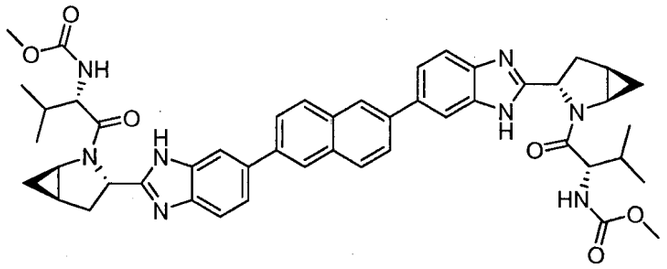


Example 17

Methyl ((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00471] HATU (20 mg, 0.053 mmol) was added to a mixture of a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(7-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-1H-benzo[d]imidazole (16 mg), diisopropylethylamine (31 μL, 0.18 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (9.3 mg, 0.053 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient for 9 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile 0.1% TFA) to provide a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (7.9 mg) as white solid. LC-MS retention time 1.20 min; Calcd. for $C_{42}H_{50}N_8O_6$ 762.39 Found m/z 763.35 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-

10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.35 (s, 1H), 8.25 (s, 1H), 8.09 (dd, *J*=8.4, 3.2 Hz, 2H), 8.04 (s, 1H), 7.89 - 8.00 (m, 3H), 7.77 - 7.87 (m, 2H), 5.37 (t, *J*=7.0 Hz, 1H), 5.30 (t, J= 7.3 Hz, 1H), 4.28 (dd, *J*=15.4, 7.2 Hz, 2H), 4.08 - 4.20 (m, 2H), 3.86 - 4.01 (m, 2H), 3.69 (s, 6H), 2.56-2.68 (m, 3H), 2.39 - 2.02 (m, 7H), 0.87 - 1.04 (m, 12H).

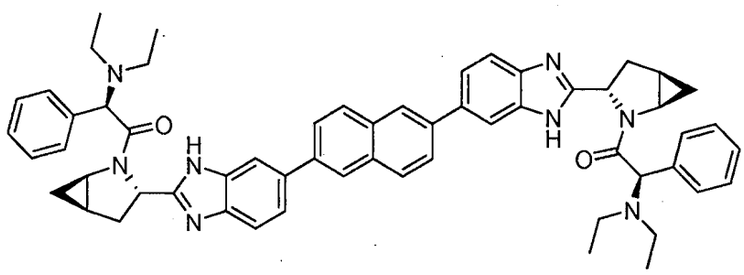


Example 18

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00472] HATU (218 mg, 0.574 mmol) was added to a mixture of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (100 mg), diisopropylethylamine (334 μL, 1.91 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (101 mg, 0.574 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient for 4 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then, the volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile 0.1%TFA) to provide a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (85 mg) as yellow solid.. LC-MS retention time

1.33 min; Calcd. for $C_{48}H_{52}N_8O_6$: 836.4 Found m/z 837.32 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 8.22 (s, 2H), 8.05 - 8.13 (m, 4H), 7.96 - 8.02 (m, 2H), 7.82 - 7.92 (m, 4H), 5.22 - 5.32 (m, 2H), 4.59 (d, *J*=6.4 Hz, 2H), 3.86 (t, *J*=6.0 Hz, 2H), 3.60 - 3.75 (m, 6H), 2.66 - 2.79 (m, 2H), 2.54 (m, 2H), 2.16 - 2.26 (m, 2H), 2.02 - 2.16 (m, 2H), 1.10 - 1.16 (m, 2H), 0.98 - 1.05 (m, 6H), 0.94 - 0.97 (m, 2H), 0.91 (d, *J*=6.7 Hz, 6H).

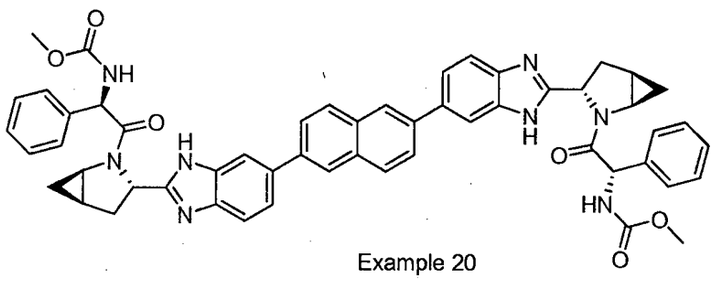


Example 19

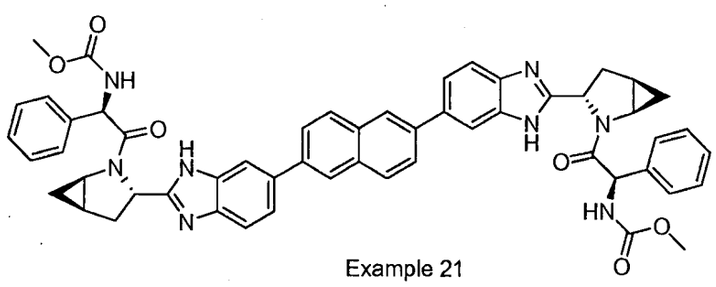
(1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2R)-2-(Diethylamino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-N,N-diethyl-2-oxo-1-phenylethanamine

[00473] HATU (109 mg, 0.287 mmol) was added to a mixture of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (50 mg), diisopropylethylamine (0.167 mL, 0.957 mmol) and (R)-2-(diethylamino)-2-phenylacetic acid, HCl (70.0 mg, 0.287 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient for 5 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then, the volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile 0.1%TFA) then by reverse phase HPLC (water/acetonitrile 10 mM ammonium acetate) and finally by reverse

phase HPLC (water/acetonitrile 0.1%TFA) to provide a TFA salt of (1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2R)-2-(diethylamino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-6-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-N,N-diethyl-2-oxo-1-phenylethanamine (25.2 mg) as white powder. LC-MS retention time 1.15 min; Calcd. for $[M+H]^+$ $C_{58}H_{60}N_8O_2$: 900.48 Found m/z 451.46 $[1/2\ M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.27 (s, 2H), 8.08 - 8.17 (m, 4H), 7.96 (td, *J*=8.7, 1.5 Hz, 4H), 7.87 (d, *J*=8.6 Hz, 2H), 7.68 - 7.72 (m, 4H), 7.57 - 7.68 (m, 6H), 5.79 (s, 2H), 5.23 (dd, *J*=9.0, 6.3 Hz, 2H), 3.95 - 4.05 (m, 2H), 3.25 - 3.48 (m, 4H), 3.06 (br s, 4H), 2.43 - 2.61 (m, 4H), 2.01 - 2.11 (m, 2H), 1.31 (t, *J*=6.9 Hz, 12H), 0.62 (ddd, *J*=8.7, 6.0, 5.8 Hz, 2H), -0.21 (td, *J*=5.7, 2.4 Hz, 2H).



Example 20



Example 21

Example 20

Methyl ((1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate

and Example 21

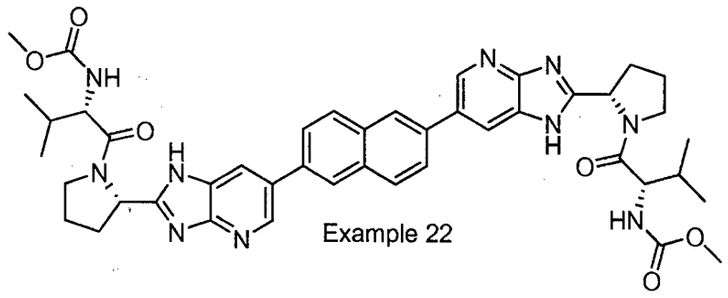
Dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

[00474] HATU (109 mg, 0.287 mmol) was added to a mixture of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (50 mg), diisopropylethylamine (0.167 mL, 0.957 mmol) and (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (60.0 mg, 0.287 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient for 5 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then, the volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile 0.1%TFA) then by reverse phase HPLC (water/acetonitrile 10 mM ammonium acetate) and finally by reverse phase HPLC (water/acetonitrile 0.1%TFA) to provide a TFA salt of methyl ((1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate (6.9 mg) as white solid and a TFA salt of dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate (12.5 mg) as white solid.

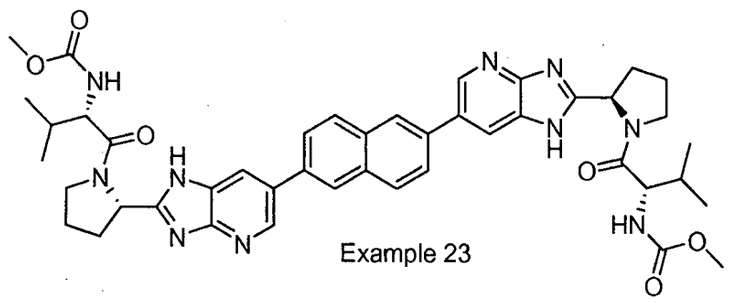
[00475] Analytical data for Example 20: LC-MS retention time 1.46 min; Calcd. for $C_{54}H_{48}N_8O_6$: 904.37 Found m/z 453.35 $[1/2\ M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.28 (d, *J*=4.6 Hz, 2H), 8.15 (d, *J*=8.6 Hz,

2H), 8.12 (s, 1H), 8.07 (s, 1H), 8.03 (t, *J*=8.9 Hz, 2H), 7.92 - 7.98 (m, 2H), 7.90 (d, *J*=8.6 Hz, 1H), 7.85 (d, *J*=8.6 Hz, 1H), 7.48 - 7.54 (m, 2H), 7.37 - 7.48 (m, 8H), 5.85 (s, 1H), 5.78 (s, 1H), 5.39 (dd, *J*=9.0, 6.3 Hz, 1H), 5.29 (dd, *J*=9.2, 5.8 Hz, 1H), 3.91 - 3.97 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.52 - 3.61 (m, 1H), 2.73 (dd, *J*=13.7, 9.2 Hz, 1H), 2.46 - 2.65 (m, 3H), 2.06 - 2.14 (m, 1H), 1.98 - 2.06 (m, 1H), 1.23 - 1.30 (m, 1H), 1.10 (br s, 1H), 0.66 - 0.72 (m, 1H), 0.01 - 0.10 (m, 1H).

[00476] Analytical data for Example 21: LC-MS retention time 1.48 min; Calcd. for $[M+H]^+$ $C_{54}H_{48}N_8O_6$: 904.37 Found m/z 453.35 $[1/2\ M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (s, 2H), 8.16 (d, *J*=8.6 Hz, 2H), 8.11 (s, 2H), 8.01 - 8.06 (m, 2H), 7.95 (d, *J*=8.6 Hz, 2H), 7.90 (m, *J*=8.6 Hz, 2H), 7.48 - 7.55 (m, 4H), 7.36 - 7.48 (m, 6H), 5.85 (s, 2H), 5.29 (dd, *J*=9.2, 5.8 Hz, 2H), 3.92 - 3.97 (m, 2H), 3.66 (s, 6H), 2.55 - 2.66 (m, 2H), 2.51 (ddd, *J*=13.3, 6.6, 6.4 Hz, 2H), 1.97 - 2.07 (m, 2H), 0.63 - 0.74 (m, 2H), -0.02 - 0.10 (m, 2H).



Example 22



Example 23

Example 22

Methyl ((1S)-1-(((2S)-2-(6-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyridin-6-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyridin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

and Example 23

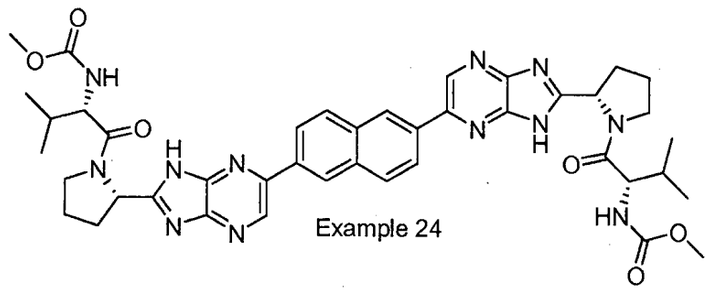
Methyl ((1S)-1-(((2R)-2-(6-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyridin-6-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyridin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00477] HATU (63.5 mg, 0.167 mmol) was added to a stirred slurry of a hydrochloride salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-3H-imidazo[4,5-b]pyridin-6-yl)naphthalene (45 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (29.3 mg, 0.167 mmol) in DMF (1 mL) and DIPEA (0.122 mL, 0.696 mmol). The reaction mixture was stirred at room temperature for 16h, diluted with MeOH, filtered and purified by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to provide methyl ((1S)-1-(((2S)-2-(6-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyridin-6-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyridin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (19.2 mg) as white solid and methyl ((1S)-1-(((2R)-2-(6-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyridin-6-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyridin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (16.5 mg) as white solid (uncertain if pyrrolidine stereocenter racemized during this step or in a previous step). Resolution of 2,6-bis(2-((S)-pyrrolidin-2-yl)-3H-imidazo[4,5-b]pyridin-6-yl)naphthalene by chiral HPLC showed a broad peak, but individual diastereomers could not be resolved under the attempted conditions.

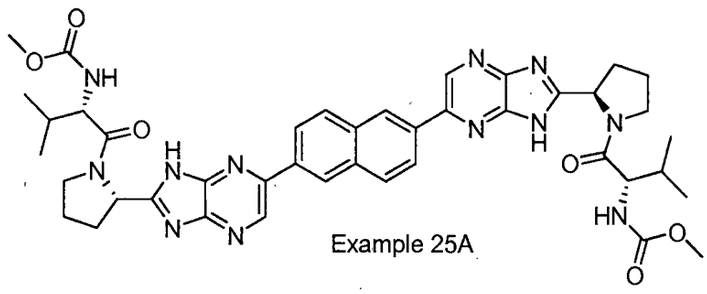
[00478] Analytical data for Example 22: LC-MS retention time 1.407 min; m/z 815.60 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped

with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.82 - 8.71 (m, 2H), 8.32 - 8.18 (m, 4H), 8.14 - 8.07 (m, 2H), 7.92 - 7.84 (m, 2H), 5.37 - 5.29 (m, 2H), 4.30 (d, J = 7.3 Hz, 2H), 4.13 - 4.04 (m, 2H), 4.02 - 3.92 (m, 2H), 3.68 (s, 6H), 2.54 - 1.98 (m, 10H), 1.03 - 0.89 (m, 12H).

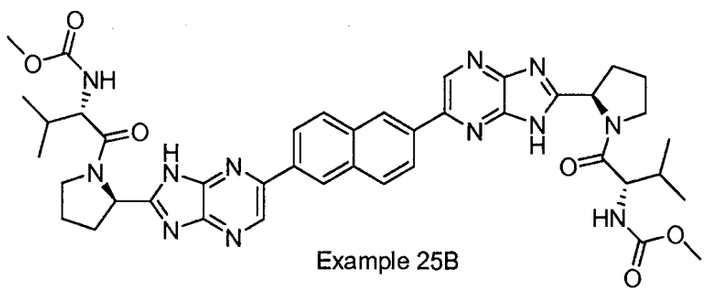
[00479] Analytical data for Example 23: LC-MS retention time 1.442 min; m/z 815.59 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.89 - 8.66 (m, 2H), 8.36 - 8.20 (m, 4H), 8.15 - 8.10 (m, 2H), 7.94 - 7.86 (m, 2H), 5.44 - 5.29 (m, 2H), 4.34 (d, J = 7.6 Hz, 1H), 4.30 (d, J = 7.6 Hz, 1H), 4.21 - 3.80 (m, 4H), 3.74 (s, 3H), 3.68 (s, 3H), 2.69 - 1.95 (m, 10H), 1.09 - 0.41 (m, 12H).



Example 24



Example 25A



Example 25B

Example 24

Methyl ((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyrazin-5-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyrazin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

and Example 25A

Methyl ((1S)-1-(((2S)-2-(5-(6-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyrazin-5-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyrazin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

and Example 25B

Methyl ((1S)-1-(((2R)-2-(5-(6-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyrazin-5-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyrazin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00480] HATU (63 mg, 0.17 mmol) was added to a stirred slurry of an HCl salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)naphthalene (45 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (29 mg, 0.17 mmol) in DMF (1 mL) and DIPEA (0.12 mL, 0.69 mmol). The reaction mixture was stirred at room temperature for 16h diluted with MeOH, filtered and purified by preparative HPLC (acetonitrile/water with 10 mM ammonium acetate) to yield methyl ((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-

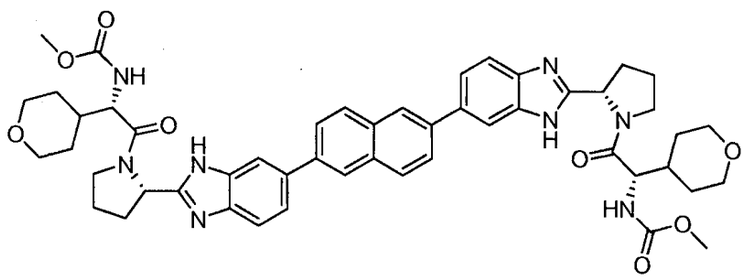
imidazo[4,5-b]pyrazin-5-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyrazin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (11.2 mg) as yellow solid, methyl ((1S)-1-(((2S)-2-(5-(6-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyrazin-5-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyrazin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (17.3 mg) as yellow solid and methyl ((1S)-1-(((2R)-2-(5-(6-(2-((2R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazo[4,5-b]pyrazin-5-yl)-2-naphthyl)-1H-imidazo[4,5-b]pyrazin-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (6.7 mg) as yellow solid (uncertain if pyrrolidine stereocenter racemized during this step or in a previous step). Resolution of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazo[4,5-b]pyrazin-5-yl)naphthalene by chiral HPLC showed a broad peak, but individual diastereomers could not be resolved under the attempted conditions.

[00481] Analytical data for Example 24: LC-MS retention time 1.420 min; m/z 817.59 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 9.14 - 9.06 (m, 2H), 8.71 - 8.64 (m, 2H), 8.37 - 8.29 (m, 2H), 8.18 - 8.11 (m, 2H), 5.59 - 5.30 (m, 2H), 4.30 (d, J = 7.3 Hz, 2H), 4.13 - 3.96 (m, 4H), 3.78 - 3.64 (m, 6H), 2.57 - 2.01 (m, 10H), 1.07 - 0.92 (m, 12H).

[00482] Analytical data for Example 25A: LC-MS retention time 1.507 min; m/z 817.56 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was

determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 9.14 - 9.02 (m, 2H), 8.69 - 8.60 (m, 2H), 8.36 - 8.27 (m, 2H), 8.15 - 8.08 (m, 2H), 5.41 - 5.36 (m, 1H), 5.34 - 5.29 (m, 1H), 4.35 (d, J = 7.9 Hz, 1H), 4.31 (d, J = 7.3 Hz, 1H), 4.24 - 3.81 (m, 4H), 3.78 (s, 3H), 3.68 (s, 3H), 2.62 - 1.97 (m, 10H), 1.09 - 0.46 (m, 12H).

[00483] Analytical data for Example 25B: LC-MS retention time 1.562 min; m/z 817.58 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% acetonitrile / 95% water / 10 mM ammonium acetate and Solvent B was 5% water / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

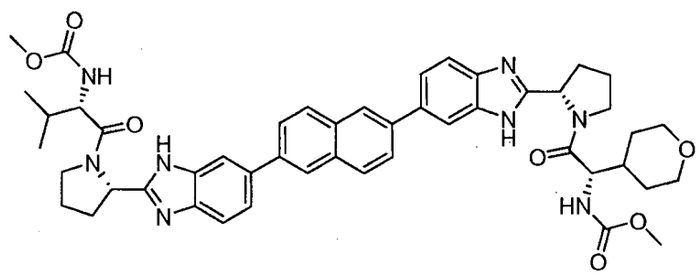


Example 26

Dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate

[00484] HATU (114 mg, 0.301 mmol) was added to a stirred solution of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (50 mg), diisopropylethylamine (175 µL, 1.0 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (65 mg, 0.30 mmol) in DMF (5 mL) and the resulting mixture was stirred at ambient conditions for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then, the volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of dimethyl (2,6-naphthalenediylbis(1H-

benzimidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate (51.5 mg) as pale yellow solid. LC-MS retention time 1.117 min; m/z 897.31 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt 500 MHz, MeOD) δ ppm 8.27 (br s, 2H), 8.10 - 8.18 (m, 4H), 8.01 - 8.07 (m, 2H), 7.86 - 7.96 (m, 4H), 5.88 - 5.93 (m, 0.2H), 5.39 (t, *J*=7.0 Hz, 1.8H), 4.33 - 4.38 (m, 2H), 4.12 - 4.22 (m, 2H), 3.89 - 4.05 (m, 7H), 3.70 (s, 6H), 3.35 - 3.45 (m, 2H), 2.60 - 2.75 (m, 2H), 2.14 - 2.47 (m, 6.5H), 1.94 - 2.12 (m, 2.5H), 1.32 - 1.69 (m, 8H).

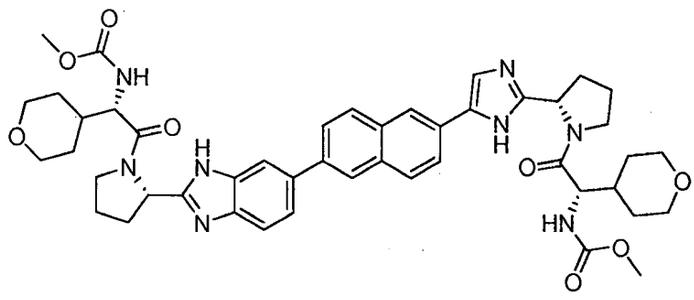


Example 27

Methyl ((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00485] HATU (87 mg, 0.23 mmol) was added to a stirred solution of methyl ((1S)-2-methyl-1-(((2S)-2-(5-(6-(2-((2S)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (50 mg), diisopropylethylamine (133 μL, 0.76 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (50 mg, 0.23 mmol) in DMF (3 mL) and the resulting mixture was stirred at ambient conditions for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then the volatile component was

removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of methyl ((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (36 mg) as yellow solid. LC-MS retention time 1.177 min; m/z 855.30 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.22 - 8.30 (m, 1.8H), 8.20 (br s, 0.2H), 8.07 - 8.17 (m, 4H), 8.00 - 8.06 (m, 1.8H), 7.98 (br s, 0.2H), 7.85 - 7.95 (m, 4H), 5.86 (m, 0.1H), 5.35 - 5.44 (m, 1.8H), 5.25 - 5.31 (m, 0.1H), 4.36 (d, *J*=7.6 Hz, 0.5H), 4.31 (d, *J*=6.7 Hz, 1H), 4.15 (br s, 1.5H), 3.87 - 4.05 (m, 4H), 3.69 (br s, 6H), 3.34 - 3.47 (m, 1H), 2.96 - 3.23 (m, 2H), 2.61 - 2.77 (m, 2.5H), 2.21 - 2.47 (m, 6H), 1.95 - 2.16 (m, 2H), 1.33 - 1.69 (m, 3.5H), 1.00 - 1.05 (m, 0.3H), 0.94 - 0.99 (m, 3H), 0.91 (d, *J*=6.7 Hz, 2.7H).

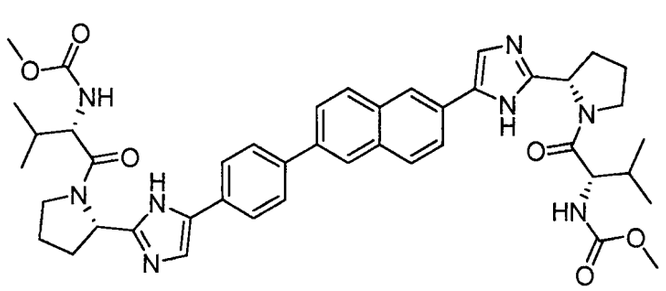


Example 28

Methyl ((1S)-2-((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00486] HATU (36.6 mg, 0.096 mmol) was added to a stirred solution of a TFA salt of 2-((S)-pyrrolidin-2-yl)-6-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-

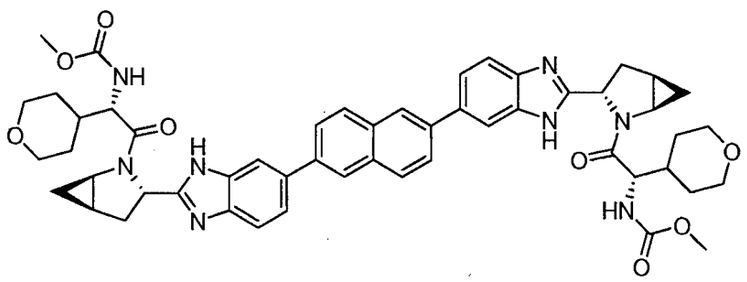
1H-benzo[d]imidazole (29 mg), diisopropylethylamine (56 µL, 0.32 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (21 mg, 0.10 mmol) in DMF (2 mL) and the resulting mixture was stirred at ambient conditions for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). Then the volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/acetonitrile/TFA) to provide a TFA salt of methyl ((1S)-2-((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (16.3 mg) as yellow solid. LC-MS retention time 1.023 min; m/z 847.31 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=12.5 Hz, 2H), 8.15 (d, *J*=8.6 Hz, 1H), 8.10 (d, *J*=8.5 Hz, 1H), 8.07 (s, 1H), 7.92 - 8.01 (m, 3H), 7.81 - 7.90 (m, 2H), 5.37 (dd, *J*=7.9, 6.1 Hz, 1H), 5.30 (t, *J*=7.5 Hz, 1H), 4.28 - 4.39 (m, 2H), 4.12 - 4.22 (m, 2H), 3.88 - 4.04 (m, 7H), 3.65 - 3.77 (m, 6H), 3.38 - 3.45 (m, 1H), 2.56 - 2.69 (m, 2H), 2.20 - 2.40 (m, 6.5H), 2.01 (br s, 2.5H), 1.57 - 1.69 (m, 2.5H), 1.35 - 1.53 (m, 6.5H).



Example 29

Methyl ((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00487] HATU (57.6 mg, 0.152 mmol) was added to a stirred solution of a TFA salt of 2-((S)-pyrrolidin-2-yl)-5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole (47 mg), diisopropylethylamine (88 μL, 0.51 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (26.5 mg, 0.152 mmol) in DMF (4 mL) and the resulting mixture was stirred at ambient conditions for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/methanol/TFA), repurified by a reverse phase HPLC (water/acetonitrile/ammonium acetate) and finally repurified by a reverse phase HPLC (water/methanol/TFA) to provide a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (33.3 mg) as yellow solid. LC-MS retention time 1.237 min; m/z 789.29 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=8.9 Hz, 2H), 8.15 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.9 Hz, 1H), 7.95 - 8.03 (m, 4H), 7.93 (s, 1H), 7.84 - 7.91 (m, 3H), 5.69 - 5.72 (m, 0.2H), 5.24 - 5.35 (m, 1.8H), 4.27 (dd, *J*=7.2, 2.6 Hz, 2H), 4.09 - 4.19 (m, 2H), 3.85 - 3.97 (m, 2H), 3.67 - 3.76 (m, 6H), 2.55 - 2.68 (m, 2H), 2.27 - 2.38 (m, 2H), 2.14 - 2.27 (m, 4H), 2.02 - 2.14 (m, 2H), 0.86 - 1.06 (m, 12H).

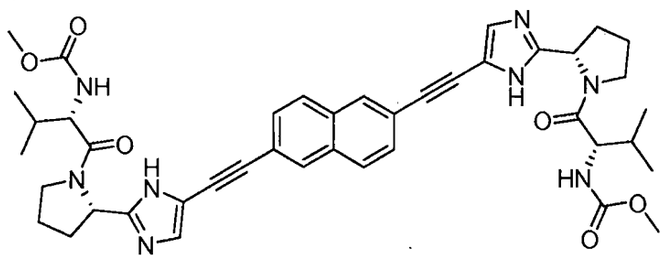


Example 30

Dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate

[00488] HATU (54.6 mg, 0.144 mmol) was added to a stirred solution of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalene (25 mg), diisopropylethylamine (84 μL, 0.48 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (31.2 mg, 0.144 mmol) in DMF (5 mL) and the resulting mixture was stirred at ambient conditions for 4 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL). The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (water/methanol/TFA), repurified by a reverse phase HPLC (water/acetonitrile/ammonium acetate) and finally repurified by a reverse phase HPLC (water/methanol/TFA) to provide a TFA salt of dimethyl (2,6-naphthalenediylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate (8.2 mg) as off-white solid. LC-MS retention time 1.220 min; m/z 461.3 [1/2 $M+H^+$]. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min and an analysis time of 4 min where Solvent A was 10% acetonitrile / 90% water / 0.1% TFA and Solvent B was 90% acetonitrile/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.28 (br s, 2H), 8.07 - 8.18 (m, 4H), 8.00 - 8.07 (m, 2H), 7.84 - 7.96 (m, 4H), 5.23 - 5.31 (m, 2H), 4.59 - 4.67 (m, 2H), 3.85 - 4.01 (m, 6H), 3.70 (s, 6H), 3.28 -

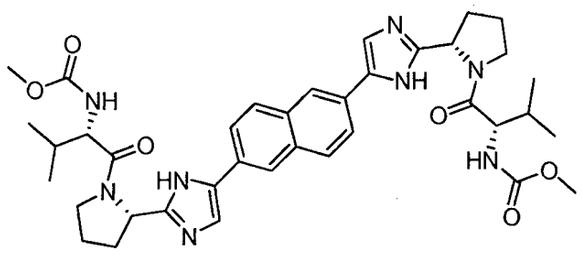
3.44 (m, 4H), 2.71 - 2.80 (m, 2H), 2.58 (ddd, *J*=13.2, 6.5, 6.3 Hz, 2H), 2.03 - 2.20 (m, 4H), 1.41 - 1.65 (m, 8H), 1.13 (br s, 2H), 0.97 (br s, 2H).



Example 31

Methyl ((1S)-1-(((2S)-2-(4-((6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

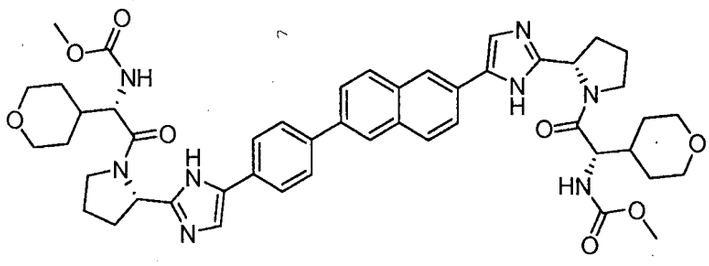
[00489] HATU (47.6 mg, 0.125 mmol) was added to a TFA salt of 2,6-bis((2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)ethynyl)naphthalene (38 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (22 mg, 0.13 mmol) in DMF (0.7 mL) and TEA (0.047 mL, 0.33 mmol) and the clear yellow solution was at rt ON. The reaction was diluted with MeOH (1mL), filtered and purified by prep HPLC 15-100% MeOH/water / TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((2S)-2-(4-((6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (37.1 mg) as light yellow solid. LC-MS retention time 2.530 min; m/z 759.61 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 32

Methyl ((1S)-1-(((2S)-2-(4-((6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00490] A TFA salt of 4,4′-(2,6-naphthalenediyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) (21 mg, 0.025 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (12.9 mg) were dissolved into DMF (3 mL) and DIEA (0.043 mL, 0.246 mmol). Then HATU (28.0 mg, 0.074 mmol) was added and the reaction mixture was stirred at room temperature for 2h. The volatiles were removed under vacuum and the crude product was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 0 to 90 % MeOH -Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-1-(((2S)-2-(4-((6-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (10.4 mg) as off white solid. LC-MS retention time 1.158 min; m/z 713.60 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.11 (d, *J*=8.6 Hz, 2H), 7.94 - 8.03 (m, 2H), 7.84 - 7.94 (m, 2H), 5.29 (t, *J*=7.3 Hz, 2H), 4.26 (d, *J*=7.02 Hz, 2H), 4.14 (t, *J*=10.2 Hz, 2H), 3.85 - 3.96 (m, 2H), 3.68 (s, 6H), 2.53 - 2.67 (m, 2H), 2.31 (d, *J*=10.4 Hz, 2H), 2.16 - 2.28 (m, 4H), 2.03 - 2.15 (m, 2H), 0.88 - 1.08 (m, 12H).

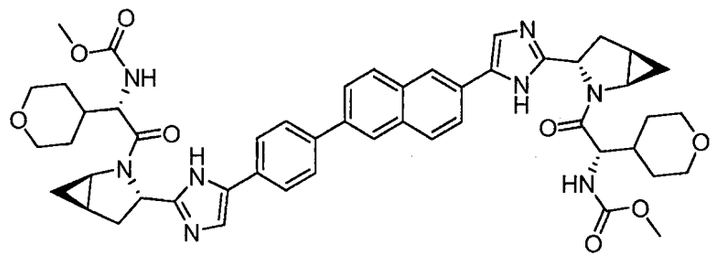


Example 33

Methyl ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00491] HATU (120 mg, 0.316 mmol) was added to a stirred solution of a TFA salt of 2-((2S)-2-pyrrolidinyl)-4-(4-(6-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (50 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (68.7 mg, 0.316 mmol) in DMF (5 mL) and DIEA (0.18 mL, 1.1 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 10 to 90 % MeOH -Water + 0.1 % TFA) and then repurified by prep HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of to % ACN -Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (96 mg) as yellow solid. LC-MS retention time 1.207 min; m/z 873.63 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 5 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=7.9 Hz, 2H), 8.14 (d, *J*=8.9 Hz, 1H), 8.06 - 8.11 (m, 1H), 7.94 - 8.03 (m, 4H), 7.90 - 7.94 (m, 1H), 7.80 - 7.90 (m, 3H), 5.74 (br s,

0.2H), 5.23 - 5.35 (m, 1.8H), 4.32 (dd, *J*=8.1, 4.7 Hz, 2H), 4.16 (d, *J*=2.8 Hz, 2H), 3.94 (dd, *J*=9.5, 7.3 Hz, 6H), 3.69 (s, 6H), 3.31 - 3.48 (m, 4H), 2.55 - 2.68 (m, 2H), 2.16 - 2.35 (m, 6H), 1.92 - 2.10 (m, 2H), 1.63 (d, *J*=12.8 Hz, 2H), 1.34 - 1.54 (m, 6H).

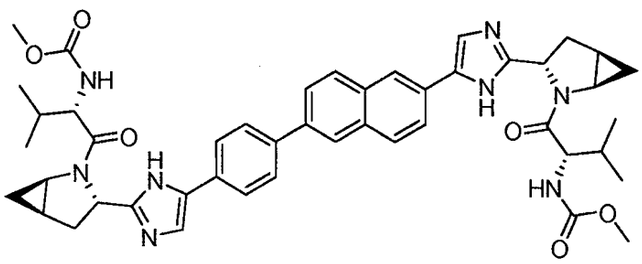


Example 34

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00492] HATU (57 mg, 0.150 mmol) was added to a stirred solution of (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (25 mg, 0.050 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (33 mg) in DMF (3 mL) and DIEA (0.078 mL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 10 to 100 % MeOH -Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (27 mg) as pale yellow solid. LC-MS retention time 1.280 min; m/z 897.65 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min

where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.28 - 8.32 (m, 2H), 8.14 (d, *J*=8.6 Hz, 1H), 8.07 - 8.11 (m, 1H), 7.95 - 8.02 (m, 4H), 7.84 - 7.93 (m, 4H), 5.12 - 5.23 (m, 2H), 4.62 (dd, *J*=7.6, 4.0 Hz, 2H), 3.92 - 4.00 (m, 4H), 3.83 - 3.89 (m, 2H), 3.72 - 3.78 (m, 2H), 3.70 (s, 6H), 3.35 - 3.46 (masked with methanol, m, 4H), 2.68 - 2.77 (m, 2H), 2.47 - 2.57 (m, 2H), 2.00 - 2.15 (m, 4H), 1.42 - 1.65 (m, 6H), 1.06 - 1.17 (m, 2H), 0.84 - 0.93 (m, 2H).

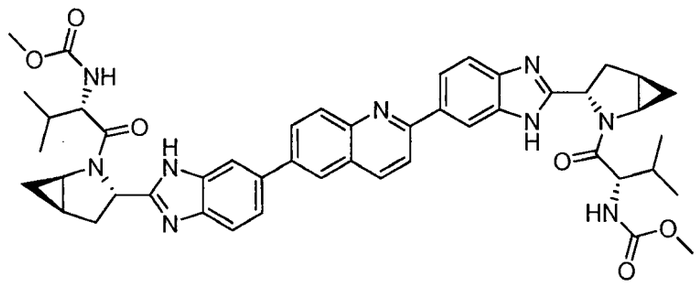


Example 35

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00493] HATU (57 mg, 0.150 mmol) was added to a stirred solution of (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (25 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (26 mg, 0.15 mmol) in DMF (3 mL) and DIEA (0.070 mL, 0.40 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 10 to 100 % MeOH - Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (34.8 mg) as pale yellow

solid. LC-MS retention time 1.402 min; m/z 813.69 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=7.9 Hz, 2H), 8.14 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 7.95 - 8.01 (m, 4H), 7.92 (s, 1H), 7.84 - 7.90 (m, 3H), 5.16 (ddd, *J*=11.6, 9.2, 7.0 Hz, 2H), 4.58 (dd, *J*=6.4, 2.1 Hz, 2H), 3.81 - 3.88 (m, 2H), 3.66 - 3.75 (m, 6H), 2.67 - 2.77 (m, 2H), 2.46 - 2.57 (m, 2H), 2.21 (dq, *J*=12.9, 6.5 Hz, 2H), 2.06 - 2.14 (m, 2H), 1.08 - 1.18 (m, 2H), 1.04 (d, *J*=6.7 Hz, 6H), 0.95 (d, *J*=6.7 Hz, 6H), 0.91 (br s, 2H).

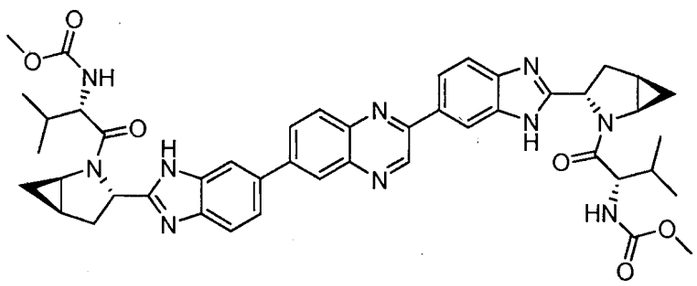


Example 36

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinolinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00494] HATU (32.7 mg, 0.086 mmol) was added to a solution of a hydrochloride salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoline (25 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (15 mg, 0.086 mmol) in DMF (1 mL) and DIPEA (0.059 mL, 0.34 mmol) and the mixture was stirred at rt for 16 h. The reaction was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (2S,2'S)-1,1'-

((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinoline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (8.3 mg) as a yellow solid. LC-MS retention time 1.88 min; m/z 838 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 8.64 - 8.80 (1H, m), 8.49 - 8.62 (1H, m), 7.45 - 8.48 (9H, m), 5.21 - 5.52 (2H, m), 4.50 - 4.68 (2H, m), 3.82 - 4.13 (2H, m), 3.70 - 3.79 (2H, m), 3.68, 3.66 (6H, s, s), 2.48 - 2.83 (3H, m), 2.02 - 2.28 (3H, m), 1.09 - 1.30 (2H, m), 0.83 - 1.08 (14H, m).

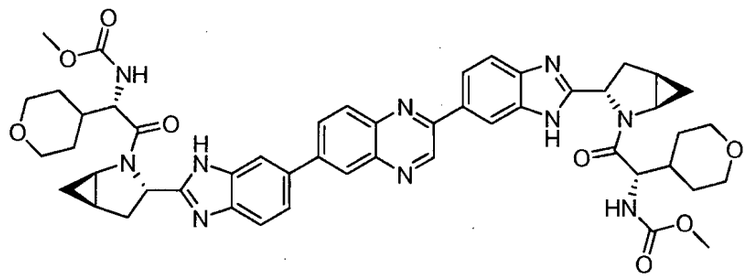


Example 37

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinoxalinyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00495] HATU (25 mg, 0.066 mmol) was added to a solution of a TFA salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxaline (28 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (11.5 mg, 0.066 mmol) in DMF (0.5 mL) and DIPEA (0.045 mL, 0.26 mmol) and the mixture was stirred at rt for 2h. The reaction was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (2S,2'S)-1,1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinoxaline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (27 mg) as a yellow solid. LC-MS retention time 1.94 min; m/z 839 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90%

water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (TFA salt, 400 MHz, MeOD) δ ppm 9.56 (s, 1H), 8.67 (s, 1H), 8.52 (d, *J*=8.8 Hz, 1H), 8.40 (s, 1H), 8.26 (d, *J*=8.8 Hz, 1H), 8.24 (d, *J*=8.8 Hz, 1H), 8.17 (s, 1H), 8.05 (d, *J*=8.5 Hz, 1H), 7.93 (d, *J*=8.5 Hz, 1H), 7.90 (d, *J*=8.8 Hz, 1H), 5.30 (app dd, *J*=9.0, 6.8 Hz, 2H), 4.60 (app d, *J*=6.0 Hz, 2H), 3.93 - 3.84 (m, 2H), 3.68 (s, 6H), 2.80 - 2.70 (m, 2H), 2.63 - 2.51 (m, 2H), 2.29 - 2.09 (m, 4H), 1.21 - 1.11 (m, 2H), 1.03 (d, *J*=6.8 Hz, 6H), 1.00 - 0.90 (m, 2H), 0.93 (d, *J*=6.5 Hz, 6H).

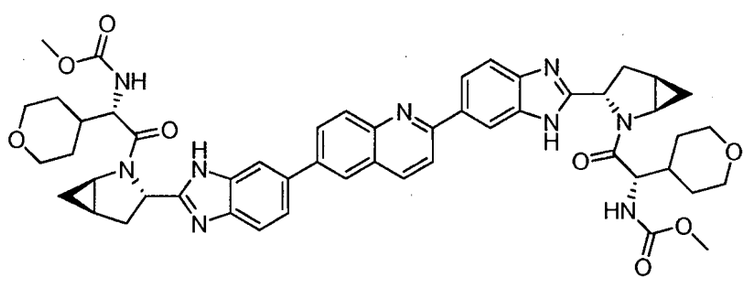


Example 38

Dimethyl (2,6-quinoxalinediylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate

[00496] HATU (25.9 mg, 0.068 mmol) was added to a solution of a TFA salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoxaline (29 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (14.8 mg, 0.068 mmol) in DMF (0.5 mL) and DIPEA (0.046 mL, 0.27 mmol) and the mixture was stirred at rt for 16 h. The reaction was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(6,6′-(quinoxaline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)dicarbamate (32.5 mg) as a yellow solid. LC-MS retention time 1.74 min; m/z 462 $[1/2\ M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (TFA salt, 400 MHz, MeOD) δ ppm 9.53 (s, 1H), 8.70 (s,

1H), 8.55 (dd, *J*=8.8, 1.5 Hz, 1H), 8.44 (d, *J*=1.8 Hz, 1H), 8.31 (d, *J*=8.8 Hz, 1H), 8.27 (dd, *J*=8.8, 1.8 Hz, 1H), 8.19 (br s, 1H), 8.08 (dd, *J*=8.8, 1.5 Hz, 1H), 7.96 (d, *J*=8.8 Hz, 1H), 7.92 (d, *J*=8.8 Hz, 1H), 5.28 (app dd, *J*=8.8, 6.8 Hz, 2H), 4.63 (app d, *J*=7.3 Hz, 2H), 3.99 - 3.86 (m, 6H), 3.69 (s, 6H), 3.44 - 3.29 (m, 4H), 2.81 - 2.71 (m, 2H), 2.63 - 2.52 (m, 2H), 2.20 - 2.03 (m, 4H), 1.68 - 1.37 (m, 8H), 1.17 - 1.08 (m, 2H), 0.99 - 0.92 (m, 2H).

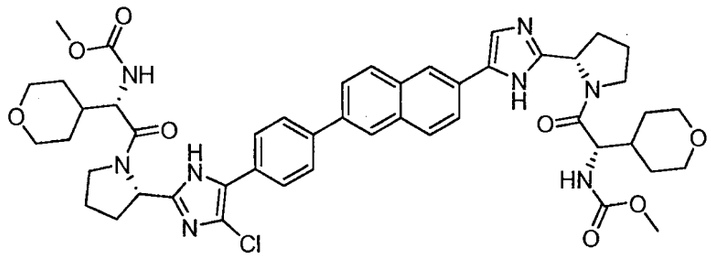


Example 39

Dimethyl (2,6-quinolinediylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate

[00497] HATU (34.0 mg, 0.089 mmol) was added to a solution of a hydrochloride salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)quinoline (26 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (19.4 mg, 0.089 mmol) in DMF (0.5 mL) and DIPEA (0.061 mL, 0.350 mmol) and the mixture was stirred at rt for 16 h. The reaction was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinoline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)dicarbamate (6.0 mg) as a yellow solid. LC-MS retention time 1.65 min; m/z 462 $[1/2\ M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 8.70 (1H, d, *J*=8.5 Hz), 8.57 (1H, s), 8.23 - 8.45 (5H, m), 8.17 (1H, s), 8.01 - 8.12 (1H, m), 7.88 - 7.97 (2H, m), 5.27 (2H, t, *J*=7.8 Hz), 4.33 - 4.68 (2H, m), 3.84 - 4.02 (6H, m),

3.69 (6H, s), 3.35 - 3.47 (4H, m), 2.67 - 2.81 (2H, m), 2.49 - 2.64 (2H, m), 1.91 - 2.21 (4H, m), 1.35 - 1.71 (8H, m), 1.07 - 1.17 (2H, m), 0.85 - 1.00 (2H, m).

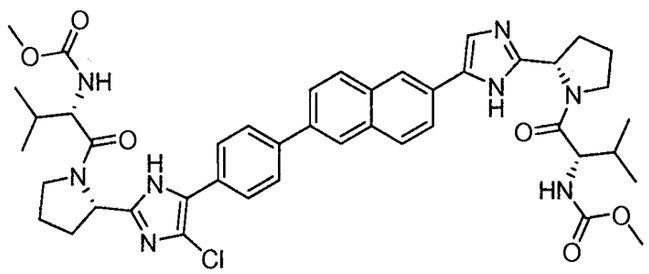


Example 40

Methyl ((1S)-2-((2S)-2-(4-chloro-5-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00498] HATU (45 mg, 0.118 mmol) was added to a solution of 4-chloro-2-((S)-pyrrolidin-2-yl)-5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole (20 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (25.6 mg, 0.118 mmol) in DMF (3 mL) and DIEA (0.070 mL, 0.40 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 10 to 100 % MeOH -Water + 0.1 % TFA) and then repurified by HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 10 to 100 % ACN -Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-2-((2S)-2-(4-chloro-5-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (12.9 mg) as yellow solid. LC-MS retention time 1.595 min; m/z 907.39 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a

hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.20 - 8.28 (m, 2H), 8.09 - 8.12 (m, 1H), 8.02 - 8.08 (m, 1H), 7.91 - 8.00 (m, 3H), 7.87 - 7.91 (m, 2H), 7.80 - 7.87 (m, 2H), 5.28 (t, *J*=7.5 Hz, 1H), 5.06 - 5.14 (m, 1H), 4.25 - 4.35 (m, 2H), 4.11 - 4.19 (m, 1H), 4.00 - 4.07 (m, 1H), 3.85 - 4.00 (m, 6H), 3.63 - 3.69 (m, 6H), 3.32 - 3.43 (m, 4H), 2.57- 2.64(m, 1H), 2.34 - 2.40 (m, 1H), 2.26 - 2.32 (m, 2H), 2.12 - 2.25 (m, 4H), 1.95 - 2.09 (m, 2H), 1.34 - 1.64(m, 8H).

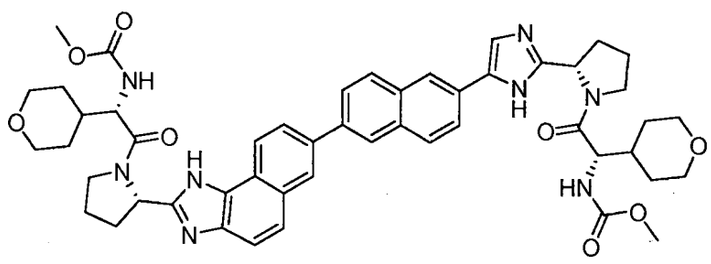


Example 41

Methyl ((1S)-1-(((2S)-2-(4-(6-(4-(4-chloro-2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00499] HATU (45 mg, 0.118 mmol) was added to a solution of 4-chloro-2-((S)-pyrrolidin-2-yl)-5-(4-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole (20 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (20.7 mg, 0.118 mmol) in DMF (3 mL) and DIEA (0.070 mL, 0.40 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 10 to 100 % MeOH -Water + 0.1 % TFA) and then repurified by HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 10 to 100 % ACN -Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(6-(4-(4-chloro-2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-1-

pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (3.6 mg) as yellow solid. LC-MS retention time 1.715 min; m/z 823.49 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.24 - 8.29 (m, 1H), 8.22 (s, 1H), 8.08 - 8.15 (m, 1H), 8.03 - 8.08 (m, 1H), 7.81 - 8.01 (m, 7H), 5.31 (t, *J*=7.5 Hz, 1H), 5.12 (app t, *J*=7.5 Hz, 1H), 4.21 - 4.32 (m, 2H), 4.08 - 4.19 (m, 1H), 3.99 - 4.08 (m, 1H), 3.85 - 3.96 (m, 2H), 3.57 - 3.74 (m, 6H), 2.56 - 2.67 (m, 1H), 2.35 - 2.46 (m, 1H), 2.28 - 2.35 (m, 2H), 2.20 - 2.26 (m, 2H), 2.05 - 2.19 (m, 4H), 0.90 - 1.09 (m, 12H).

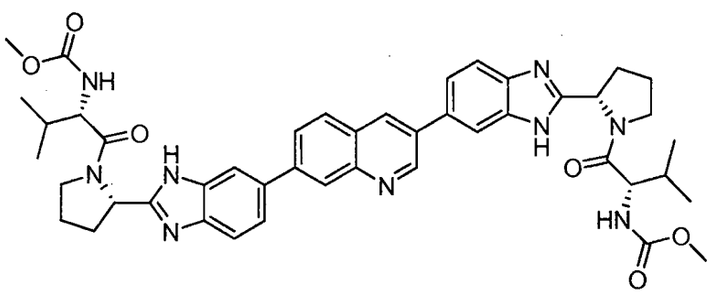


Example 42

Methyl ((1S)-2-((1R,3S,5R)-3-(7-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00500] HATU (103 mg, 0.271 mmol) was added to a solution of 2-((S)-pyrrolidin-2-yl)-7-(6-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)-1H-naphtho[1,2-d]imidazole (45 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (58.8 mg, 0.271 mmol) in DMF (3 mL) and DIEA (0.16 mL, 0.90 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100

mm 5u eluted with a gradient of 10 to 100 % MeOH -Water + 0.1 % TFA) and then repurified by HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 0 to 90 % ACN -Water + 0.1 % TFA) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(7-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (8.7 mg) as white solid. LC-MS retention time 1.307 min; m/z 897.67 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.51 - 8.57 (m, 2H), 8.40 (s, 1H), 8.30 (s, 1H), 8.23 (d, *J*=10.1 Hz, 1H), 8.18 (d, *J*=8.6 Hz, 1H), 8.05 - 8.15 (m, 3H), 8.00 (s, 1H), 7.87 (dd, *J*=8.6, 1.8 Hz, 1H), 7.79 - 7.85 (m, 1H), 5.43 (t, *J*=7.3 Hz, 1H), 5.30 (t, *J*=7.3 Hz, 1H), 4.28 - 4.40 (m, 2H), 4.19 (br s, 2H), 3.88 - 4.07 (m, 6H), 3.70 (d, *J*=1.5 Hz, 6H), 3.26 - 3.45 (overlap with methanol, m, 4H), 2.57 - 2.71 (m, 2H), 2.30 - 2.42 (m, 3H), 2.20 - 2.29 (m, 3H), 1.93 - 2.10 (m, 2H), 1.58 - 1.68 (m., 2H), 1.34 - 1.58 (m, 6H).

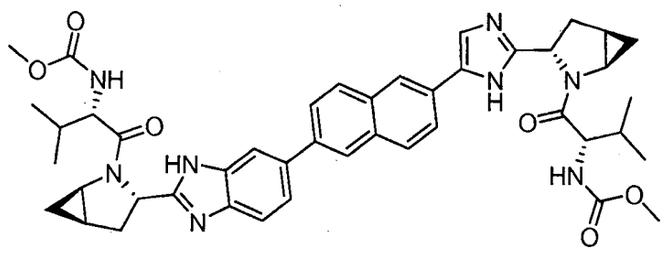


Example 43

Methyl ((1S)-2-((1R,3S,5R)-3-(7-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-

3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00501] HATU (24.5 mg, 0.065 mmol) was added to a solution of a TFA salt of 2,6-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)quinoline (30 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (11.3 mg, 0.065 mmol) in DMF (1 mL) and DIPEA (0.044 mL, 0.252 mmol) and the mixture was stirred at rt for 2 h. The reaction was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(6,6'-(quinoline-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (34 mg) as a yellow solid. LC-MS retention time 1.82 min; m/z 814 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 8.71 (1H, d, *J*=8.8 Hz), 8.57 (1H, s), 8.21 - 8.43 (5H, m), 8.18 (1H, s), 8.04 (1H, dd, *J*=8.5, 1.5 Hz), 7.88 - 7.96 (2H, m), 5.40 (2H, t, *J*=7.03 Hz), 4.31 (2H, d, *J*=6.8 Hz), 4.09 - 4.21 (2H, m), 3.91 - 4.06 (2H, m), 3.68 (6H, s), 2.58 - 2.73 (2H, m), 2.20 - 2.49 (6H, m), 2.02 - 2.19 (2H, m), 0.96 (6H, dd, *J*=6.8, 1.8 Hz), 0.90 (6H, dd, *J*=6.7, 1.6 Hz).

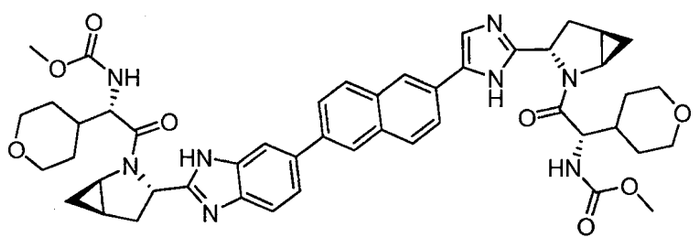


Example 44

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00502] HATU (82 mg, 0.22 mmol) was added to a solution of 6-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazole (34 mg), (S)-2-

(methoxycarbonylamino)-3-methylbutanoic acid (37.8 mg, 0.216 mmol) and DIEA (0.13 mL, 0.72 mmol) in DMF (3 mL) and the reaction was stirred 2h at room temperature. The reaction mixture was diluted with MeOH (2 ml) and water (2 mL). The volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 10 to 80 % ACN-Water + 0.1 % TFA) to afford a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (49.8 mg) as pale yellow solid. LC-MS retention time 1.357 min; m/z 787.65 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=10.7 Hz, 2H), 8.07 - 8.19 (m, 3H), 7.94 - 8.05 (m, 3H), 7.84 - 7.92 (m, 2H), 5.29 (dd, *J*=9.2, 6.7 Hz, 1H), 5.18 (dd, *J*=9.2, 7.0 Hz, 1H), 4.59 (dd, *J*=12.4, 6.6 Hz, 2H), 3.81 - 3.91 (m, 2H), 3.69 (s, 6H), 2.67 - 2.80 (m, 2H), 2.48 - 2.61 (m, 2H), 2.07 - 2.27 (m, 4H), 1.09 - 1.19 (m, 2H), 0.99 - 1.06 (m, 6H), 0.88 - 1.00 (m, 8H).

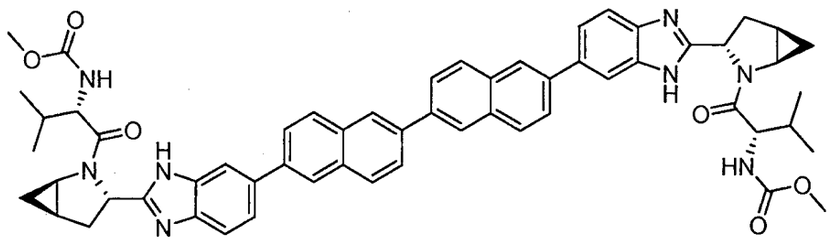


Example 45

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-

3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00503] HATU (82 mg, 0.216 mmol) was added to a solution of 6-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)-2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazole (34 mg), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (46.9 mg, 0.216 mmol) and DIEA (0.13 mL, 0.72 mmol) in DMF (3 mL) and the reaction was stirred for 2h at room temperature. The reaction mixture was diluted with MeOH (2 ml) and water (2 mL). The volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 10 to 80 % ACN-Water + 0.1 % TFA) to afford a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (38 mg) as pale yellow solid. LC-MS retention time 1.240 min; m/z 871.66 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.30 (d, *J*=6.1 Hz, 2H), 8.08 - 8.18 (m, 3H), 8.04 (dd, *J*=8.6, 1.5 Hz, 1H), 7.95 - 8.01 (m, 2H), 7.85 - 7.92 (m, 2H), 5.27 (dd, *J*=9.2, 6.7 Hz, 1H), 5.16 (dd, *J*=9.2, 7.0 Hz, 1H), 4.59 - 4.66 (m, 2H), 3.84 - 4.01 (m, 6H), 3.70 (s, 6H), 3.35 - 3.45 (m, 4H), 2.69 - 2.80 (m, 2H), 2.48 - 2.61 (m, 2H), 2.03 - 2.20 (m, 4H), 1.57 - 1.65 (m, 2H), 1.40 - 1.56 (m, 6H), 1.07 - 1.17 (m, 2H), 0.97 (br s, 1H), 0.91 (br s, 1H).

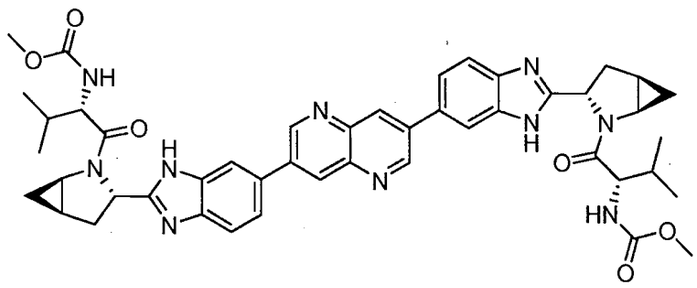


Example 46

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2,2'-binaphthalen-6-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00504] HATU (22.7 mg, 0.060 mmol) was added to a solution of a TFA salt of 6,6'-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-5-yl)-2,2'-binaphthyl (22 mg), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (10.5 mg, 0.060 mmol) and DIEA (0.035 mL, 0.20 mmol) in DMF (3 mL) and the reaction was stirred at rt for 2h. The reaction mixture was diluted with MeOH (2 ml) and water (2 mL) and the volatiles were removed under vacuum. The residue was purified by prep HPLC (Waters Sunfire C18 column 30 X 100 mm 5u eluted with a gradient of 10 to 80 % MeOH-Water + 0.1 % TFA) to afford a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2,2'-binaphthalen-6-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (15.6 mg) as tan solid. LC-MS retention time 1.765 min; m/z 482.68 (1/2 M+H+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.36 (s, 2H), 8.27 (s, 2H), 8.12 - 8.18 (m, 4H), 8.11 (s, 2H), 8.05 (app t, *J*=8.6 Hz, 4H), 7.91 - 7.96 (m, 2H), 7.86 - 7.91 (m, 2H), 5.29 (dd, *J*=9.2, 6.7 Hz, 2H), 4.61 (d, *J*=6.4 Hz, 2H), 3.85 - 3.91 (m,

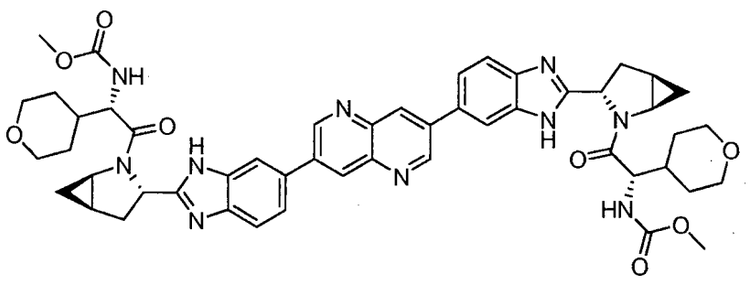
2H), 3.70 (s, 6H), 2.72 - 2.80 (m, 2H), 2.53 - 2.62 (m, 2H), 2.12 - 2.26 (m, 4H), 1.13 - 1.21 (m, 2H), 1.04 (d, *J*=6.7 Hz, 6H), 0.99 (br s, 2H), 0.95 (d, *J*=6.7 Hz, 6H).



Example 47

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-1,5-naphthyridin-2-yl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

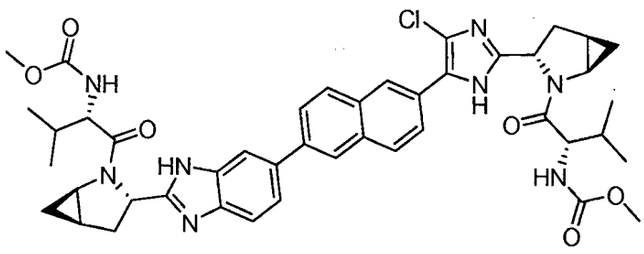
[00505] HATU (8.7 mg, 0.023 mmol) was added to a solution of a TFA salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-1,5-naphthyridine (12 mg, 9.93 μmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (4.2 mg) in DMF (0.5 mL) and DIPEA (0.017 mL, 0.099 mmol) and the mixture was stirred at rt for 16h. The reaction was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (2S,2′S)-1,1′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(6,6′-(1,5-naphthyridine-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (5.6 mg) as yellow solid. LC-MS retention time 1.91 min; m/z 420 $[1/2\ M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 8.59 - 8.67 (4H, m), 8.48 (2H, dd, *J*=8.8, 1.3 Hz), 8.44 (2H, d, *J*=8.8 Hz), 7.92 (2H, d, *J*=8.5 Hz), 5.29 (2H, dd, *J*=9.2, 6.7 Hz), 4.60 (2H, d, *J*=6.5 Hz), 3.84 - 3.92 (2H, m), 3.68 (6H, s), 2.69 - 2.80 (2H, m), 2.51 - 2.62 (2H, m), 2.07 - 2.27 (4H, m), 1.10 - 1.21 (2H, m), 1.02 (6H, d, *J*=6.8 Hz), 0.95 - 1.00 (2H, m), 0.93 (6H, d, *J*=6.8 Hz).



Example 48

Dimethyl (1,5-naphthyridine-2,6-diylbis(1H-benzimidazole-5,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate

[00506] HATU (8.68 mg, 0.023 mmol) was added to a solution of a TFA salt of 2,6-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-1,5-naphthyridine (12 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (5.0 mg, 0.023 mmol) in DMF (0.5 mL) and DIPEA (0.016 mL, 0.089 mmol) and the mixture was stirred at rt for 3 h. The reaction was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(1,5-naphthyridine-2,6-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)dicarbamate (11 mg) as yellow solid. LC-MS retention time 1.73 min; m/z 462 $[1/2\ M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 8.61 - 8.68 (4H, m), 8.50 (2H, dd, *J*=8.8, 1.51 Hz), 8.45 (2H, d, *J*=8.8 Hz), 7.93 (2H, d, *J*=8.8 Hz), 5.28 (2H, dd, *J*=9.3, 6.8 Hz), 4.64 (2H, d, *J*=7.5 Hz), 3.84 - 4.02 (6H, m), 3.69 (6H, s), 3.35 - 3.46 (4H, m), 2.75 (2H, dd, *J*=13.7, 9.2 Hz), 2.58 (2H, d, *J*=6.8 Hz), 1.99 - 2.22 (4H, m), 1.36 - 1.69 (8H, m), 1.07 - 1.19 (2H, m), 0.96 (2H, m).

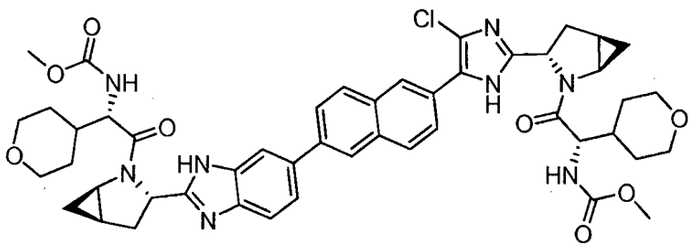


Example 49

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00507] HATU (76 mg, 0.20 mmol) was added to a solution of 2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-4-chloro-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazole (34 mg), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (35.2 mg, 0.201 mmol) and DIEA (0.12 mL, 0.67 mmol) in DMF (3 mL) and the resulting mixture was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL) and the volatile component was removed *in vacuo*. The residue was purified by a reverse phase preparative HPLC (water/methanol, 0.1%TFA) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (41.3 mg) as yellow solid. LC-MS retention time 1.717 min; m/z 821.58 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm 5mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.24 (d, *J*=1.8 Hz, 2H), 8.01 - 8.13 (m, 4H), 7.84 - 7.98 (m, 3H), 5.29 (dd, *J*=9.2, 6.7 Hz, 1H), 5.09 (t, *J*=7.2 Hz, 1H), 4.60 (t, *J*=7.2 Hz, 2H), 3.86 - 3.91 (m, 1H), 3.71 - 3.76

(m, 1H), 3.69 (s, 3H), 3.68 (m, 3H), 2.77 (dd, *J*=13.6, 9.3 Hz, 1H), 2.57 (ddd, *J*=13.6, 6.7, 6.6 Hz, 1H), 2.44 - 2.53 (m, 2H), 2.11 - 2.26 (m, 3H), 1.99 - 2.10 (m, 1H), 1.10 - 1.22 (m, 2H), 0.89 - 1.09 (m, 13H), 0.80 - 0.84 (m, 1H).

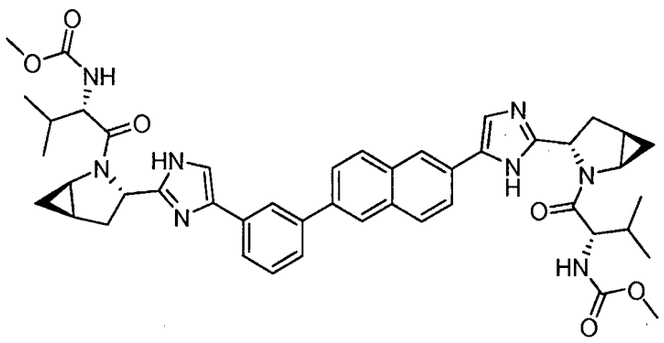


Example 50

Methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00508] HATU (45.0 mg, 0.118 mmol) was added to a solution of 2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-4-chloro-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazole (20 mg, 0.039 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (25.7 mg) and DIEA (0.069 mL, 0.39 mmol) in DMF (3 mL) and the resulting mixture was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL) and the volatile component was removed *in vacuo*. The residue was purified by a reverse phase preparative HPLC (water/methanol, 0.1%TFA) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (28.1 mg) as pale yellow solid. LC-MS retention time 1.597 min; m/z 905.67 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm 5mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol /

90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.24 (s, 2H), 8.02 - 8.13 (m, 4H), 7.86 - 7.97 (m, 3H), 5.27 (dd, *J*=9.2, 7.0 Hz, 1H), 5.08 (t, *J*=7.2 Hz, 1H), 4.65 (t, *J*=7.3 Hz, 2H), 3.88 - 4.02 (m, 5H), 3.75 - 3.83 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.36 - 3.49 (m, 4H), 2.77 (dd, *J*=13.7, 9.5 Hz, 1H), 2.57 (ddd, *J*=13.7, 6.7, 6.4 Hz, 1H), 2.46 - 2.53 (m, 2H), 2.00 - 2.20 (m, 4H), 1.55 - 1.69 (m, 4H), 1.40 - 1.70 (m, 4H), 1.08 - 1.20 (m, 2H), 0.94 - 1.00 (m, 1H), 0.80 - 0.84 (m, 1H).

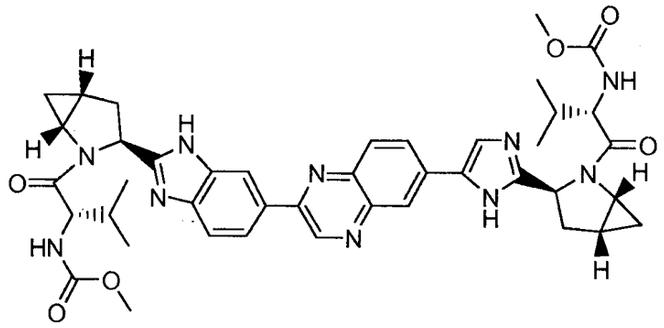


Example 51

Methyl ((1S)-1-(((1S,3R,5S)-3-(4-(6-(3-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00509] HATU (47.8 mg, 0.126 mmol) was added to a mixture of a TFA salt of (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (40 mg), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (22 mg, 0.13 mmol) and DIEA (0.073 mL, 0.42 mmol) in DMF (3 mL) and the resulting mixture was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with methanol (2 mL) and water (2 mL) and the volatile component was removed *in vacuo*. The residue was partially purified by a reverse phase HPLC (water/methanol, 0.1%TFA) and then repurified by reverse phase HPLC (water/acetonitrile, 0.1%TFA) to yield a TFA salt of methyl ((1S)-1-(((1S,3R,5S)-3-(4-(6-(3-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-

imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (45 mg) as a white solid. LC-MS retention time 1.458 min; m/z 813.30 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 10 mM ammonium acetate and Solvent B was 10% water / 90% methanol / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.30 (d, *J*=4.6 Hz, 2H), 8.18 (s, 1H), 8.14 (d, *J*=8.9 Hz, 1H), 8.10 (d, *J*=8.9 Hz, 1H), 7.98 - 8.02 (m, 2H), 7.98 (s, 1H), 7.93 (d, *J*=8.2 Hz, 1H), 7.88 (dd, *J*=8.7, 1.7 Hz, 1H), 7.77 (d, *J*=8.2 Hz, 1H), 7.69 (t, *J*=7.8 Hz, 1H), 5.13 - 5.20 (m, 2H), 4.57 (t, *J*=6.1 Hz, 2H), 3.80 - 3.88 (m, 2H), 3.69 (d, *J*=6.1 Hz, 6H), 2.67 - 2.77 (m, 2H), 2.51 (dq, *J*=13.7, 6.8 Hz, 2H), 2.15 - 2.25 (m, 2H), 2.10 (dq, *J*=13.8, 6.8 Hz, 2H), 1.08 - 1.18 (m, 2H), 1.03 (dd, *J*=6.7, 4.6 Hz, 6H), 0.95 (dd, *J*=6.7, 3.4 Hz, 6H), 0.92 (dd, *J*=5.3, 2.0 Hz, 2H).

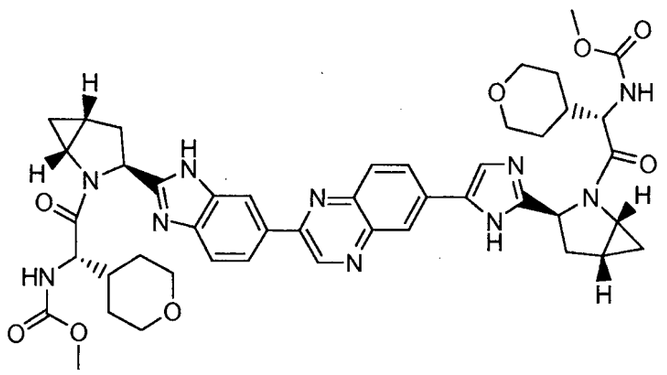


Example 52

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-6-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00510] HATU (13.16 mg, 0.035 mmol) was added to a solution of a TFA salt of 2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-6-(2-

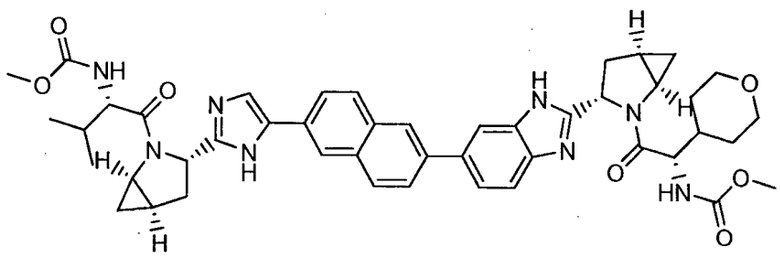
((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)quinoxaline (14 mg, 0.015 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (6.1 mg) in DMF (0.5 mL) and DIPEA (0.024 mL, 0.135 mmol) and the mixture was stirred at rt for 16 h. The reaction was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-6-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (11.8 mg,) as a yellow solid. LC-MS retention time 1.77 min; m/z 789 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.59 (s, 1H), 8.67 (s, 1H), 8.51 (d, *J*=8.8 Hz, 1H), 8.46 (d, *J*=1.8 Hz, 1H), 8.27 (d, *J*=8.8 Hz, 1H), 8.19 (dd, *J*=8.8, 2.0 Hz, 1H), 8.11 (s, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 5.29 (dd, *J*=9.2, 6.7 Hz, 1H), 5.17 (dd, *J*=9.2, 7.2 Hz, 1H), 4.58 (dd, *J*=13.2, 6.7 Hz, 2H), 3.78 - 3.92 (m, 2H), 3.68 (s, 6H), 2.67 - 2.79 (m, 2H), 2.45 - 2.62 (m, 2H), 2.03 - 2.27 (m, 4H), 1.07 - 1.21 (m, 2H), 1.03 (d, *J*=6.8 Hz, 6H), 0.93 - 1.00 (m, 2H), 0.93 (dd, *J*=6.3, 5.8 Hz, 6H).



Example 53

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-6-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

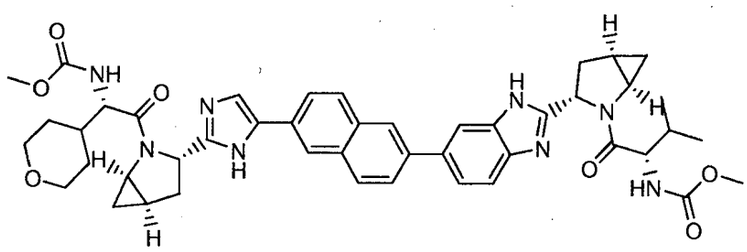
[00511] HATU (15.0 mg, 0.040 mmol) was added to a solution of a TFA salt of 2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)quinoxaline (16 mg) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (8.6 mg, 0.040 mmol) in DMF (0.5 mL) and DIPEA (0.027 mL, 0.16 mmol) and the mixture was stirred at rt for 16 h. The reaction was diluted with MeOH, and purified by prep HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield methyl ((1S)-2-((1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-6-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (14.5 mg) as yellow solid. LC-MS retention time 1.58 min; m/z 873 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 9.34 (s, 1H), 8.36 (s, 1H), 8.28 (d, *J*=1.0 Hz, 1H), 8.08 - 8.19 (m, 2H), 8.03 (d, *J*=8.8 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.54 (s, 1H), 5.27 (t, *J*=6.9 Hz, 1H), 5.18 (dd, *J*=8.9, 4.9 Hz, 1H), 4.69 (d, *J*=5.5 Hz, 2H), 3.87 - 4.03 (m, 4H), 3.73 - 3.85 (m, 2H), 3.68 (s, 6H), 3.32 - 3.47 (m, 4H), 2.50 - 2.61 (m, 3H), 2.40 - 2.49 (m, 1H), 1.99 - 2.16 (m, 4H), 1.51 - 1.72 (m, 6H), 1.38 - 1.51 (m, 2H), 1.09 - 1.22 (m, 2H), 0.76 - 0.92 (m, 2H).



Example 54

Methyl ((1S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00512] HATU (157 mg, 0.413 mmol) was added to a solution of methyl (S)-1-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (130 mg), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (90 mg, 0.41 mmol) and DIEA (0.36 mL, 2.1 mmol) in DMF (4 mL) and the reaction was stirred 2h at room temperature. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL). The volatiles were removed under vacuum. The material was purified on reverse phase HPLC (water/methanol, 0.1%TFA) to afford a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (194 mg) as yellow solid. LC-MS retention time 1.307 min; m/z 829.27 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 1H), 8.29 (s, 1H), 8.16 (d, *J*=8.5 Hz, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 1H), 8.02 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.00 (s, 1H), 7.98 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.27 (dd, *J*=9.2, 6.7 Hz, 1H), 5.18 (dd, *J*=9.2, 7.0 Hz, 1H), 4.62 - 4.67 (m, 1H), 4.58 (d, *J*=6.4 Hz, 1H), 3.87 - 4.01 (m, 3H), 3.82 - 3.87 (m, 1H), 3.70 (m, 6H), 3.36 - 3.44 (m, 2H), 2.74 (td, *J*=13.3, 9.5 Hz, 2H), 2.48 - 2.62 (m, 2H), 2.04 - 2.24 (m, 4H), 1.40 - 1.60 (m, 4H), 1.09 - 1.19 (m, 2H), 1.04 (d, *J*=6.7 Hz, 3H), 0.89 - 0.99 (m, 5H).

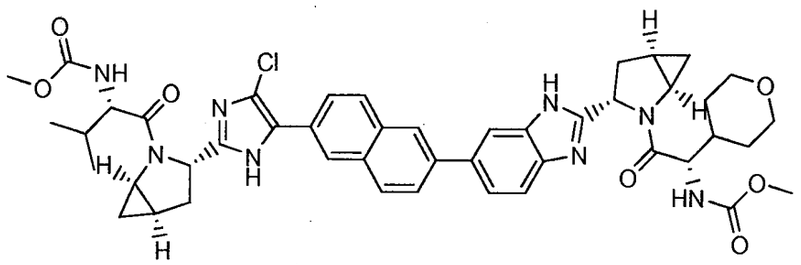


Example 55

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00513] HATU (100 mg, 0.263 mmol) was added to a solution of methyl (S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethylcarbamate (118 mg), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (46.2 mg, 0.263 mmol) and DIEA (0.31 mL, 1.8 mmol) in DMF (4 mL) and the reaction was stirred 2h at room temperature. The reaction mixture was diluted with MeOH (2 mL) and water (2 mL). The volatiles were removed under vacuum using a rotavap and the residue was purified on reverse phase HPLC (water/methanol, 0.1%TFA) to afford the a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (55.3 mg). LC-MS retention time 1.320 min; m/z 829.42 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 1H) 8.29 (s, 1H), 8.08 - 8.18 (m, 3H), 8.04 (dd, *J*=8.9, 1.5 Hz, 1H), 7.95 - 8.00 (m, 2H), 7.90 (d, *J*=8.6 Hz, 1H), 7.87 (dd, *J*=8.6, 1.8

Hz, 1H), 5.29 (dd, *J*=9.3, 6.9 Hz, 1H), 5.17 (dd, *J*=9.2, 7.0 Hz, 1H), 4.62 (dd, *J*=9.2, 7.3 Hz, 2H), 3.96 (td, *J*=10.8, 2.9 Hz, 2H), 3.83 - 3.92 (m, 2H), 3.64 - 3.77 (m, 6H), 3.35 - 3.46 (m, 2H), 2.74 (ddd, *J*=19.3, 13.5, 9.3 Hz, 2H), 2.48 - 2.62 (m, 2H), 2.06 - 2.26 (m, 4H), 1.45 - 1.63 (m, 4H), 1.06 - 1.22 (m, 2H), 1.03 (d, *J*=6.7 Hz, 3H), 0.96 - 1.01 (m, 1H), 0.93 (d, *J*=6.7 Hz, 3H), 0.88 - 091 (m, 1H).

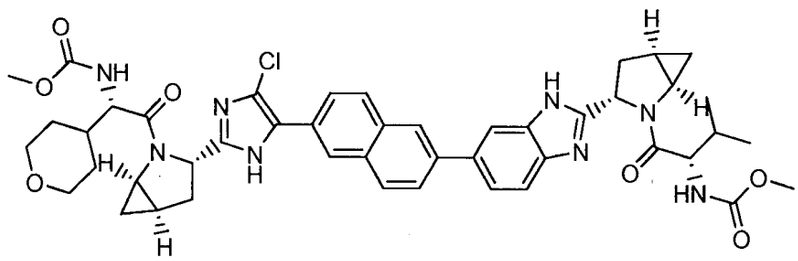


Example 56

Methyl ((1S)-2-((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00514] NCS (14.98 mg, 0.112 mmol) was added to a solution of methyl ((1S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (93 mg) in DMF and the reaction mixture was heated at 50 °C (oil bath temp) for 2h. The crude reaction mixture was purified on reverse phase HPLC (water/methanol, 0.1%TFA) to afford a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (102.8 mg). LC-MS retention time 1.648 min; m/z 863.32 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of

1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.22 (br s, 2H), 8.10 (s, 1H), 8.00 - 8.06 (m, 3H), 7.85 - 7.94 (m, 3H), 5.28 (dd, *J*=9.2, 7.0 Hz, 1H), 5.09 (t, *J*=7.2 Hz, 1H), 4.65 (d, *J*=7.3 Hz, 1H), 4.59 (d, *J*=7.0 Hz, 1H), 3.89 - 3.99 (m, 3H), 3.66 - 3.77 (m, 7H), 3.35 - 3.44 (m, 2H), 2.77 (dd, *J*=13.6, 9.3 Hz, 1H), 2.57 (ddd, *J*=13.8, 6.8, 6.6 Hz, 1H), 2.47 - 2.52 (m, 2H), 2.02 - 2.22 (m, 4H), 1.44 - 1.63 (m, 4H), 1.13 (dt, *J*=8.6, 5.8 Hz, 2H), 1.05 (d, *J*=7.0 Hz, 3H), 0.92 - 1.02 (m, 4H), 0.83 (d, *J*=1.8 Hz, 1H).

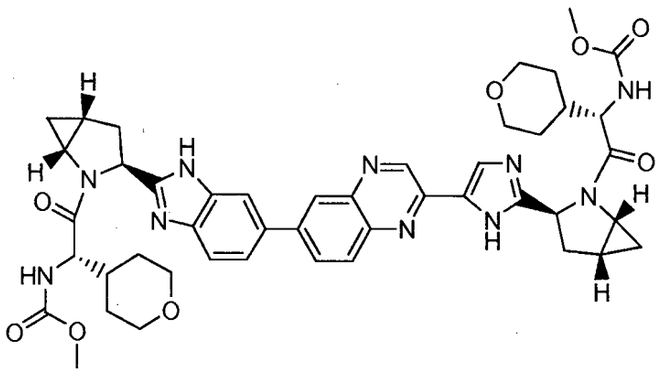


Example 57

Methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00515] NCS (10.31 mg, 0.077 mmol) was added to a solution of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (64 mg) in DMF (2 mL) and the reaction mixture was heated at 50 °C for 2h. The crude reaction mixture was purified on reverse phase HPLC (water/methanol, 0.1%TFA) and repurified on reverse phase HPLC (water/ACN, 0.1%TFA) to afford the TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)-1H-benzimidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (44.7 mg) as tan solid. LC-MS retention time

1.63 min; m/z 863.39 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire C18 4.6 x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 10% water / 90% methanol / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.24 (br s, 2H), 8.02 - 8.12 (m, 4H), 7.86 - 7.95 (m, 3H), 5.28 (dd, *J*=9.2, 6.7 Hz, 1H), 5.08 (t apparent, *J*=7.0 Hz, 1H), 4.65 (d, *J*=7.6 Hz, 1H), 4.60 (d, *J*=6.7 Hz, 1H), 3.93 - 4.01 (m, 2H), 3.86 - 3.91 (m, 1H), 3.75 - 3.81 (m, 1H), 3.65 - 3.74 (m, 6H), 3.36 - 3.46 (m, 2H), 2.77 (dd, *J*=13.7, 9.2 Hz, 1H), 2.57 (ddd, *J*=13.7, 6.7, 6.4 Hz, 1H), 2.49 (dd, *J*=7.8, 3.2 Hz, 2H), 2.12 - 2.25 (m, 2H), 2.00 - 2.12 (m, 2H), 1.54 - 1.67 (m, 3H), 1.41 - 1.51 (m, 1H), 1.09 - 1.19 (m, 2H), 0.97 - 1.06 (m, 4H), 0.94 (d, *J*=6.7 Hz, 3H), 0.82 (br s, 1H).

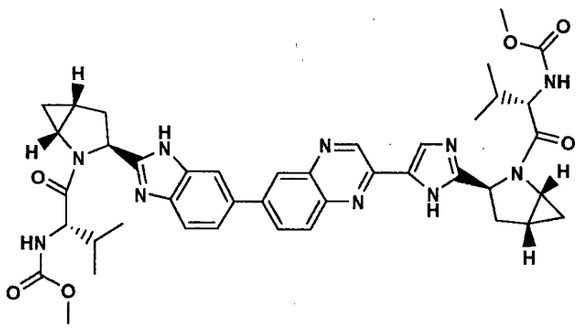


Example 58

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00516] HATU (5.64 mg, 0.015 mmol) was added to a solution of a TFA salt of 6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)quinoxaline (6.0 mg) and

(S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (3.2 mg) in DMF (0.5 mL) and DIPEA (10.13 μL, 0.058 mmol) and the mixture was stirred at rt for 16 h. The solvent was removed and the residue was purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (5.5 mg) as a yellow solid. LC-MS retention time 1.60 min; m/z 873 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% water/ 5% methanol/10 mM ammonium acetate. Solvent B = 5% water/ 95% methanol/10 mM ammonium acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.42 (s, 1H), 8.41 - 8.50 (m, 2H), 8.30 (d, *J*=1.3 Hz, 2H), 8.19 (d, *J*=1.0 Hz, 1H), 8.07 (dd, *J*=8.5, 1.5 Hz, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 5.13 - 5.33 (m, 3H), 4.57 - 4.70 (m, 1H), 3.81 - 4.04 (m, 6H), 3.62 - 3.77 (m, 6H), 3.34 - 3.46 (m, 4H), 2.65 - 2.82 (m, 2H), 2.45 - 2.61 (m, 2H), 2.01 - 2.22 (m, 4H), 1.40 - 1.65 (m, 8H), 1.03 - 1.17 (m, 2H), 0.83 - 0.98 (m, 2H).

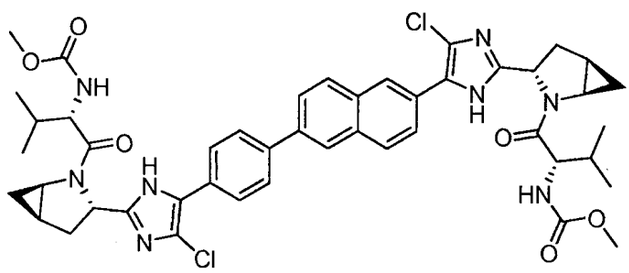


Example 59

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

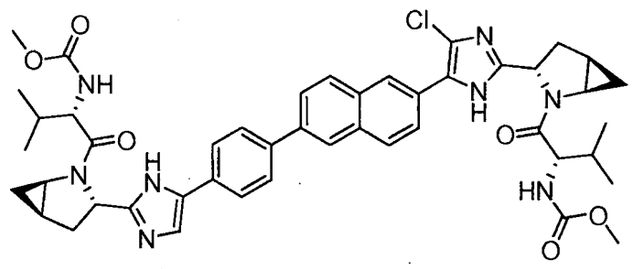
[00517] HATU (5.64 mg, 0.015 mmol) was added to a solution of a TFA salt of 6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-benzo[d]imidazol-6-yl)-2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)quinoxaline (6.0 mg) and

(S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (2.60 mg, 0.015 mmol) in DMF (0.5 mL) and DIPEA (10.13 μL, 0.058 mmol) and the mixture was stirred at rt for 16 h. The solvent was removed and the residue was purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-benzimidazol-5-yl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (3.6 mg) as yellow solid. LC-MS retention time 1.75 min; m/z 789 $[M+H]^+$. (Column PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% water:10% methanol: 0.1% TFA. Solvent B = 10% water:90% methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 9.42 (s, 1H), 8.41 - 8.48 (m, 2H), 8.30 (d, *J*=1.3 Hz, 2H), 8.18 (d, *J*=1.0 Hz, 1H), 8.06 (dd, *J*=8.7, 1.6 Hz, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 5.24 - 5.33 (m, 1H), 5.16 - 5.24 (m, 1H), 4.52 - 4.63 (m, 2H), 3.78 - 3.91 (m, 2H), 3.68 (d, *J*=1.0 Hz, 6H), 2.65 - 2.79 (m, 2H), 2.46 - 2.61 (m, 2H), 2.05 - 2.26 (m, 4H), 1.07 - 1.20 (m, 2H), 0.99 - 1.06 (m, 6H), 0.94 - 1.01 (m, 2H), 0.92 (dd, *J*=6.8, 3.3 Hz, 6H).



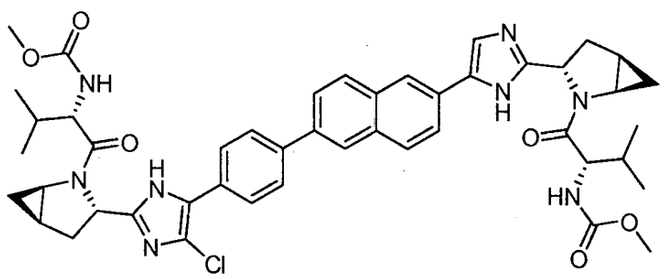
Example 60

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate



Example 62

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate



Example 63

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00518] NCS (13.0 mg, 0.097 mmol) was added to a solution of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (79 mg) in DMF (2 mL) at room temperature and the mixture was heated at 50 °C for 16 h. The crude product was purified by prep HPLC (TFA) using a Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 30 to 90 % MeOH -Water + 0.1 % TFA to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-

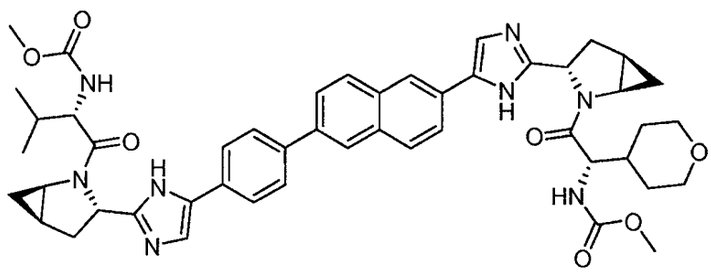
yl)carbonyl)-2-methylpropyl)carbamate (20.2 mg) as yellow solid and a mixture of the two monochloride products which were separated by SFC on a CHIRALPAK® IB column and then repurified individually by prep HPLC (TFA) using a Waters Sunfire C18 column 30 X 150 mm 5u eluted with a gradient of 25 to 100 % MeOH -Water + 0.1 % TFA to yield a TFA of methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (11.1 mg) as a yellow solid and a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (11.4 mg) as a yellow solid.

[00519] For Example 60: LC-MS retention time 2.133 min; m/z 883.35 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.22 (s, 2H), 8.07 (d, J=8.5 Hz, 1H), 8.03 (d, J=8.9 Hz, 1H), 7.83 - 7.95 (m, 6H), 5.08 (td, J=9.1, 6.0 Hz, 2H), 4.59 (dd, J=6.7, 1.8 Hz, 2H), 3.71 - 3.79 (m, 2H), 3.68 (s, 6H), 2.44 - 2.57 (m, 4H), 2.13 - 2.25 (m, 2H), 2.00 - 2.10 (m, 2H), 1.09 - 1.16 (m, 2H), 1.05 (dd, J=6.7, 1.5 Hz, 6H), 0.91 - 1.02 (m, 6H), 0.79 - 0.87 (m, 2H).

[00520] For Example 62: LC-MS retention time 1.745 min; m/z 847.33 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90%

MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.23 (s, 2H), 8.02 - 8.09 (m, 2H), 7.98 (d, *J*=8.2 Hz, 2H), 7.89 - 7.94 (m, 3H), 7.86 (d, *J*=8.6 Hz, 2H), 5.15 (dd, *J*=9.2, 7.0 Hz, 1H), 5.09 (t, *J*=7.0 Hz, 1H), 4.58 (t, *J*=6.7 Hz, 2H), 3.84 (t, *J*=4.7 Hz, 1H), 3.71 - 3.77 (m, 1H), 3.69 (d, *J*=3.1 Hz, 6H), 2.72 (dd, *J*=13.7, 9.5 Hz, 1H), 2.45 - 2.54 (m, 3H), 2.14 - 2.24 (m, 2H), 2.00 - 2.14 (m, 2H), 1.09 - 1.18 (m, 2H), 1.00 - 1.08 (m, 6H), 0.96 (t, *J*=7.6 Hz, 6H), 0.92 (br s, 1H), 0.83 (br s, 1H).

[00521] For Example 63: LC-MS retention time 1.753 min; m/z 847.32 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.26 (d, *J*=7.0 Hz, 2H), 8.13 (d, *J*=8.9 Hz, 1H), 8.04 - 8.10 (m, 1H), 7.95 - 8.01 (m, 2H), 7.89 - 7.95 (m, 2H), 7.82 - 7.89 (m, 3H), 5.17 (dd, *J*=9.2, 7.0 Hz, 1H), 5.07 (t, *J*=7.2 Hz, 1H), 4.58 (d, *J*=6.4 Hz, 2H), 3.81 - 3.88 (m, 1H), 3.71 - 3.76 (m, 1H), 3.69 (d, *J*=4.6 Hz, 6H), 2.73 (dd, *J*=13.4, 9.5 Hz, 1H), 2.44 - 2.56 (m, 3H), 2.14 - 2.25 (m, 2H), 2.08 - 2.14 (m, 1H), 1.09 - 1.18 (m, 2H,) 1.00 - 1.08 (m, 6H), 0.96 (t, *J*=6.4 Hz, 6H), 0.92 (br s, 1H) 0.78 - 0.85 (m, 1H).



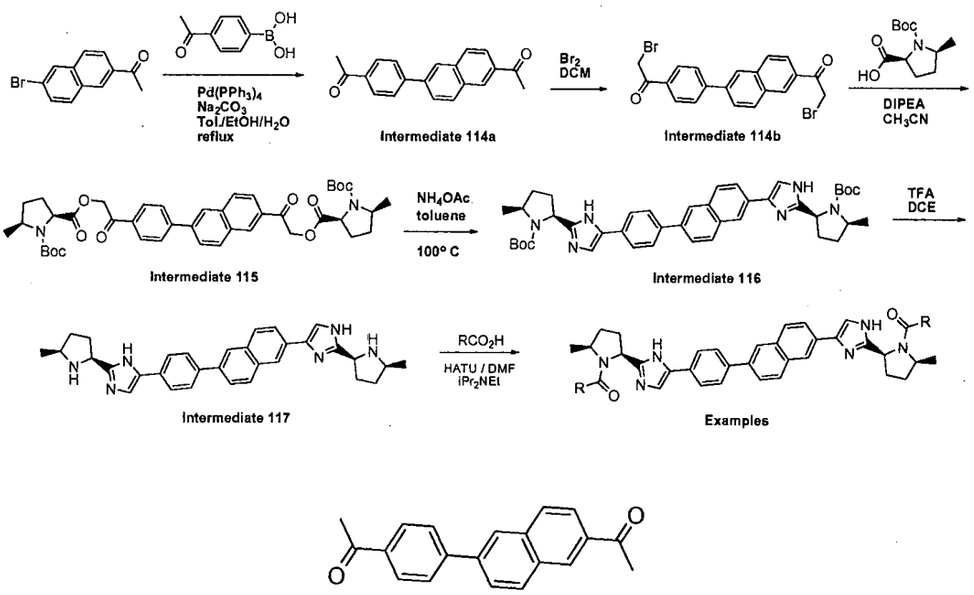
Example 61

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-

imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00522] The reaction of Intermediate 105 and the appropriate boronic acid (prepared in a similar manner as Intermediate 66 using the appropriate starting materials) via a coupling reaction similar to the preparation of Intermediate 106 yielded a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (91 mg) as a pale yellow solid. LC-MS retention time 1.362 min; m/z 855.31 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Sunfire 5u C18 4.6x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% TFA and Solvent B was 10% H_2O / 90% MeOH / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 8.01 - 7.94 (m, 4H), 7.93 - 7.91 (m, 1H), 7.90 - 7.83 (m, 3H), 5.19 - 5.12 (m, 2H), 4.62 (d, *J*= 7.6 Hz, 1H), 4.58 (d, *J*= 6.4 Hz, 1H), 3.99 - 3.91 (m, 2H), 3.89 - 3.80 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.46 - 3.35 (m, 2H), 2.76 - 2.67 (m, 2H), 2.57 - 2.46 (m, 2H), 2.25 - 2.16 (m, 1H), 2.15 - 2.05 (m, 3H), 1.65 - 1.40 (m, 4H), 1.16 - 1.07 (m, 2H), 1.04 (d, *J*= 6.7 Hz, 3H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.93 - 0.87 (m, 2H).

Scheme 29

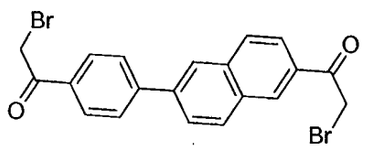


Intermediate 114a

1-(4-(6-Acetylnaphthalen-2-yl)phenyl)ethanone

[00523] A solution of sodium carbonate (5.43 g, 51.3 mmol) in water (35 mL) was added to a stirred solution of 1-(6-bromonaphthalen-2-yl)ethanone (2.554 g, 10.25 mmol) and 4-acetylphenylboronic acid (2.017 g, 12.30 mmol) in toluene (35.0 mL) and ethanol (35.0 mL) and nitrogen was bubbled through the reaction mixture for 15 min. Then $Pd(PPh_3)_4$ (0.237 g, 0.205 mmol) was added, and the reaction was flushed with nitrogen and heated at 95 °C under nitrogen for 8h and then stirred overnight at rt. The reaction was concentrated to dryness under high vacuum and then partitioned between DCM (~ 200 mL) and water (~150 mL). The organic layer was then washed with brine (~ 100 mL), dried ($MsSO_4$), filtered and concentrated. The residue was triturated with MeOH (~ 120 mL) and the remaining solids were redissolved into DCM and concentrated to dryness (~2.7 g of orange solid). This material was dissolved into hot EtOAc (80 mL) and allowed to cool. The resulting solids were collected by filtration and rinsed with Et_2O to yield 1-(4-(6-acetylnaphthalen-2-yl)phenyl)ethanone (1.84 g). LC-MS retention time 2.443 min; m/z 288.98 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0%

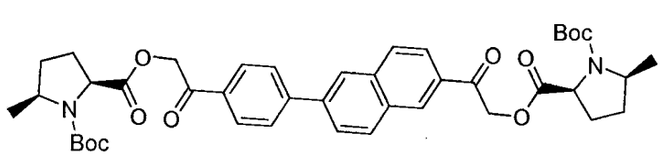
Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.51 (s, 1 H), 8.05 - 8.16 (m, 5 H), 7.98 (d, *J*=8.8 Hz, 1 H), 7.81 - 7.88 (m, 3 H), 2.76 (s, 3 H), 2.68 (s, 3 H).



Intermediate 114b

2-Bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone

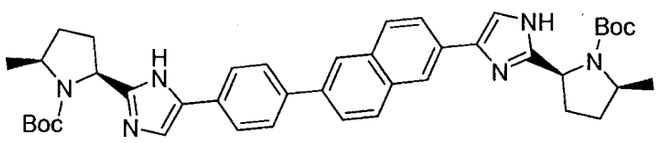
[00524] A solution of bromine (0.669 mL, 13.0 mmol) in DCM (10 mL) was added to a stirred solution of 1-(4-(6-acetylnaphthalen-2-yl)phenyl)ethanone (1.827 g, 6.34 mmol) in DCM (30 mL) and the reaction was stirred at rt for 1d. The reaction mixture was diluted with DCM (~20 mL) and concentrated to dryness to yield 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (2.83 g) which was used without further purification. LC-MS retention time 2.708 min; m/z 446.71 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.57 (s, 1 H), 8.07 - 8.17 (m, 5 H), 8.02 (d, *J*=8.8 Hz, 1 H), 7.88 (d, *J*=8.8 Hz, 3 H), 4.60 (s, 2 H), 4.51 (s, 2 H).



Intermediate 115

(2S,5S)-2-(2-(4-(6-(2-((2S,5S)-1-(*tert*-Butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate

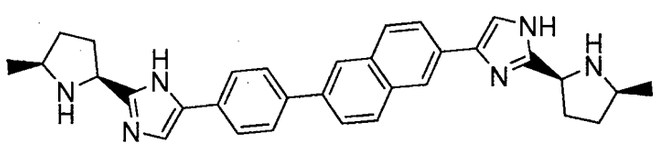
[00525] Hunig's Base (1.662 mL, 9.52 mmol) was added to a stirred slurry of 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (1.42 g, 3.17 mmol) and (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (1.45 g, 6.34 mmol) in acetonitrile (60 mL). The reaction was stirred at rt for 1d (slowly became clear) and the clear orange solution was concentrated and purified on a BIOTAGE® Horizon (160g SiO_2, 30 - 40% EtOAc/hexanes) to yield (2S,5S)-2-(2-(4-(6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (1.81 g) as an off-white solidified foam. LC-MS retention time 3.126 min; m/z 765.87 (M+Na). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.48 (s, 1 H), 8.13 (s, 1 H), 7.99 - 8.11 (m, 5 H), 7.86 (d, *J*=8.3 Hz, 3 H), 5.24 - 5.76 (m, 4 H), 4.41 - 4.59 (m, 2 H), 3.93 - 4.11 (m, 2 H), 2.28 - 2.42 (m, 4 H), 2.11 (br. s., 2 H), 1.77 (br. s., 2 H), 1.49 (br. s., 9 H), 1.48 (br. s., 9 H), 1.35 (br. s., 6 H).



Intermediate 116

tert-Butyl (2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinecarboxylate

[00526] Ammonium acetate (3.76 g, 48.7 mmol) was added to a stirred solution of (2S,5S)-2-(2-(4-(6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (1.81 g, 2.437 mmol) in toluene (40 mL) and the slurry was stirred at rt for 10 min before being heated at 100 °C for 12h. The reaction was cooled to rt, concentrated to dryness and the residue was partitioned between DCM (~150 mL) and 1/2 sat $NaHCO_3$ (aq) (~150 mL). The organic layer was washed with brine (~100 mL), dried ($MgSO_4$), filter and concentrated to a solidified brown foam which was purified by BIOTAGE® Horizon (160 g SiO_2, 1.5-3% MeOH/DCM) to yield *tert*-butyl (2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinecarboxylate (1.46 g) as a yellow-orange solidified foam. LC-MS retention time 2.92 min; m/z 703.32 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



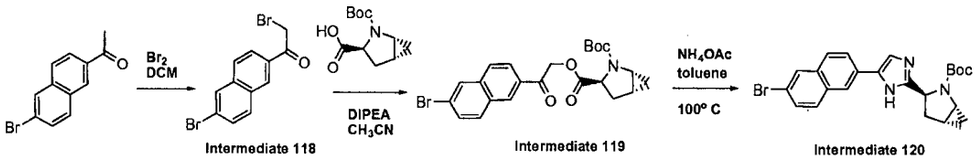
Intermediate 117

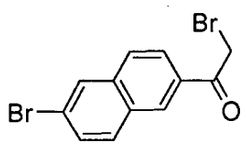
2-((2S,5S)-5-Methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole

[00527] TFA (0.500 mL, 6.49 mmol) was added dropwise to a stirred solution of *tert*-butyl (2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinecarboxylate (228 mg, 0.324 mmol) in DCE (6 mL). During the addition,

precipitate formed which hindered the stirring. DCM (~ 10 mL) was added and the slurry was stirred while the remaining TFA was added. The reaction was stirred at rt for 30 min, additional TFA was added (~0.5 mL) and the reaction was stirred 3h. The reaction was concentrated to yield a TFA salt of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (102 mg, 113 mg, 114 mg) as an orange solid. LC-MS retention time 2.756 min; m/z 503.14 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.32 (s, 1 H), 8.17 (s, 1 H), 8.01 (app t, *J*=8.2 Hz, 2 H), 7.85 - 7.95 (m, 6 H), 7.80 (s, 1 H), 7.73 (s, 1 H), 5.02 (app q, *J*=8.0 Hz, 2 H), 3.92 (dddd, *J*=8.7, 7.0, 6.9, 4.8 Hz, 2 H), 2.52 - 2.67 (m, 4 H), 2.38 - 2.49 (m, 2 H), 1.95 - 2.07 (m, 2 H), 1.55 (app dd, *J*=6.7, 4.4 Hz, 6 H).

Scheme 30



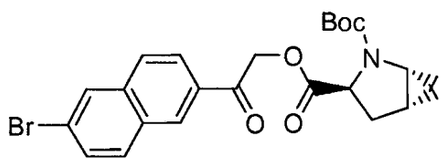


Intermediate 118

2-Bromo-1-(6-bromonaphthalen-2-yl)ethanone

[00528] A solution of bromine (0.682 mL, 13.3 mmol) in DCM (20 mL) was added to a solution of 1-(6-bromonaphthalen-2-yl)ethanone (3.30 g, 13.3 mmol) (>90% purity) in

DCM (60 mL) and the reaction was stirred at rt overnight. The reaction mixture was concentrated to yield 2-bromo-1-(6-bromonaphthalen-2-yl)ethanone (4.35 g) as an off white solid which was used without further purification. LC-MS retention time 2.177 min; m/z 342.92 (MNa+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.49 (s, 1 H), 8.03 - 8.10 (m, 2 H), 7.86 (d, *J*=8.5 Hz, 1 H), 7.85 (d, *J*=8.8 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.0 Hz, 1 H), 4.56 (s, 2 H).

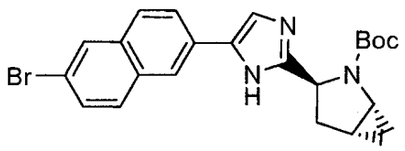


Intermediate 119

(1R,3S,5R)-3-(2-(6-Bromonaphthalen-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

[00529] DIPEA (3.47 mL, 19.88 mmol) was added to a stirred slurry of crude 2-bromo-1-(6-bromonaphthalen-2-yl)ethanone (4.35 g, 13.3 mmol) and (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (3.01 g, 13.25 mmol) in acetonitrile (80 mL) and the reaction was stirred at rt overnight. The reaction was concentrated to dryness and purified by BIOTAGE® Horizon (160g SiO_2, 10-20% EtOAc/hexanes). The fractions containing the desired product were allowed to stand for 3d. Some fractions had crashed large crystals (collected 240 mg, pure desired product by ^{1}H NMR). All fractions containing the desired product were collected and concentrated to a yellow solidified foam which was slurried with Et_2O (~ 40 mL). The white solid that formed was collected by filtration and rinsed with Et_2O to yield (1R,3S,5R)-3-(2-(6-bromonaphthalen-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-

dicarboxylate (3.24 g). LC-MS retention time 2.760 min; m/z 472, 474.02 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 mHz, MeOD) d ppm 8.61 (br s, 1H), 8.17 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.71 (dd, J = 8.6, 1.8 Hz, 1H), 5.75 - 5.66 (m, 1H), 5.61 - 5.46 (m, 1H), 4.34 - 4.26 (m, 1H), 3.46 (br s, 1H), 2.69 - 2.59 (m, 1H), 2.55 - 2.44 (m, 1H), 1.73 (br s, 1H), 1.54 - 1.43 (m, 9H), 0.88 (br s, 1H), 0.59 - 0.53 (m, 1H).



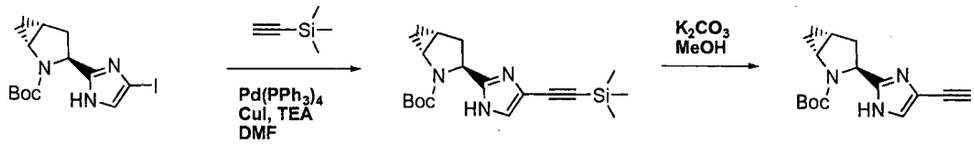
Intermediate 120

(1R,3S,5R)-*tert*-Butyl 3-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

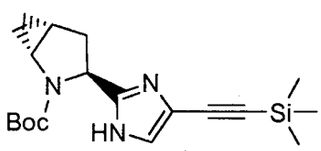
[00530] (1R,3S,5R)-3-(2-(6-Bromonaphthalen-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (3.46 g, 7.28 mmol) and ammonium acetate (11.2 g, 146 mmol) were dissolved into toluene (100 mL) and stirred. Then the reaction was placed into an oil bath which had been preheated to 100 °C and stirred at that temperature for 12h. The reaction was allowed to cool to rt, concentrated and partitioned between DCM (~ 200 mL) and 1/2 sat. aq. $NaHCO_3$ (~150 mL). The organic layer was washed with brine (~100 mL), dried ($MgSO_4$), filtered and concentrated to a solidified tan foam. This material was purified on a BIOTAGE® Horizon (160g SiO_2, loaded with DCM, 30-50% EtOAc/hexanes) to yield (1R,3S,5R)-*tert*-butyl 3-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (3.05 g) as a solidified yellow foam. LC-MS retention time 2.238 min; m/z 452.07, 454.02 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a

PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.14 (br. s., 1 H), 7.96 (d, *J*=1.8 Hz, 1 H), 7.79 (d, *J*=9.0 Hz, 1 H), 7.72 (d, *J*=9.8 Hz, 2 H), 7.53 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.38 (s, 1 H), 4.91 (dd, *J*=9.0, 5.3 Hz, 1 H), 3.25 - 3.56 (m, 2 H), 2.40 - 2.51 (m, 1 H), 1.75 - 1.85 (m, 1 H), 1.38 (br. s., 1 H), 0.86 - 0.93 (m, 1 H), 0.47 - 0.55 (m, 1 H).

Scheme 31



Intermediate 65 Intermediate 121 Intermediate 122

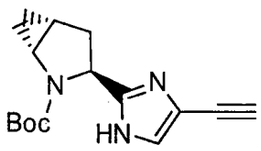


Intermediate 121

(1R,3S,5R)-*tert*-Butyl 3-(4-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00531] Nitrogen was bubbled through a solution of (1R,3S,5R)-*tert*-butyl 3-(5-iodo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.65 g, 4.40 mmol) and Cu(I)I (168 mg, 0.880 mmol) in triethylamine (3.07 mL, 22.0 mmol) and DMF (40 mL) for 20 min. Then, ethynyltrimethylsilane (2.16 g, 22.0 mmol) and $Pd(PPh_3)_4$ (254 mg, 0.220 mmol) were added, the reaction was flushed with nitrogen, sealed and stirred at rt for 24h. The reaction was concentrated to a brown oil, and purified by BIOTAGE® Horizon (160g SiO_2, 20-40% EtOAc/hexanes) to yield (1R,3S,5R)-*tert*-butyl 3-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

(980 mg) as a yellow solid. LC-MS retention time 3.230 min; m/z 346.17 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) d ppm 7.18 (s, 1 H), 4.77 (dd, *J*=9.2, 5.1 Hz, 1 H), 3.20 (br. s., 1 H), 3.14 - 3.39 (m, 1H), 2.33 (dd, *J*=13.2, 9.4 Hz, 1 H), 1.69 - 1.78 (m, 1 H), 1.34 - 1.56 (m, 1 H), 1.49 (s, 9 H), 0.85 (dt, *J*=8.5, 5.7 Hz, 1 H), 0.41 - 0.47 (m, 1 H), 0.22 - 0.24 (m, 9 H).



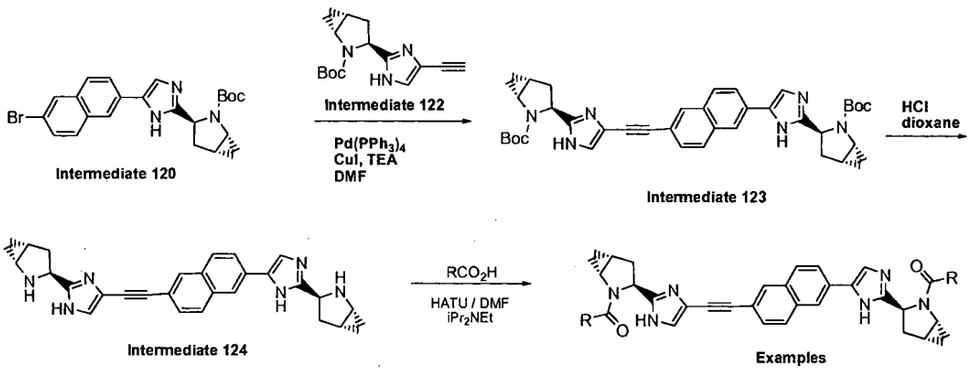
Intermediate 122

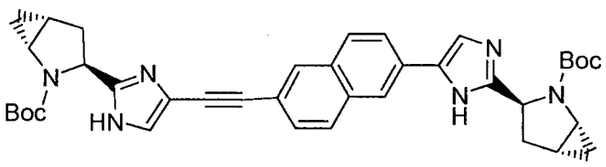
(1R,3S,5R)-*tert*-Butyl 3-(4-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00532] Potassium carbonate (194 mg, 1.40 mmol) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (970 mg, 2.81 mmol) in MeOH (30 mL) and the reaction was stirred under nitrogen and then heated at 50 °C (bath temp) for 4h. The reaction was concentrated to ~5 mL of volume, diluted with DCM (~ 40 mL) and washed with 1/2 sat brine (~20 mL). The organics were dried ($MgSO_4$) filtered and concentrated to a tan solid. This material was purified by BIOTAGE® Horizon (40g SiO_2, loaded with DCM, 35-45% EtOAc/hexanes) to yield (1R,3S,5R)-*tert*-butyl 3-(5-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (747 mg) as a light yellow solid. LC-MS retention time 2.866 min; m/z 272.12 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A /

0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 7.18 (br. s., 1 H), 4.59 (br. s., 1 H), 3.36 - 3.64 (m, 2 H), 2.46 (dd, *J*=13.2, 8.9 Hz, 1 H), 2.18 - 2.31 (m, 1 H), 1.64 - 1.74 (m, 1 H), 1.18 - 1.45 (m, 9 H), 0.83 (dt, *J*=8.5, 5.8 Hz, 1 H), 0.56 (br. s., 1 H).

Scheme 32



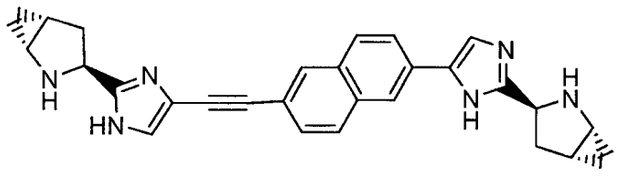


Intermediate 123

tert-Butyl (1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00533] Nitrogen was bubbled through a solution of (1R,3S,5R)-*tert*-butyl 3-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (400 mg, 0.880 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (313 mg, 1.14 mmol) and Cu(I)I (8.4 mg, 0.044 mmol) in triethylamine (0.37 mL, 2.6 mmol) and DMF (8 mL) for 10 min. Then $Pd(PPh_3)4$ (50.9 mg, 0.044 mmol) was added, nitrogen was bubbled through the reaction mixture for 1 min, and then the flask was sealed and heated at 50 °C for 16h. The

reaction was concentrated to under high vacuum) and the residual solids were triturated with EtOAc (~5 mL) and collected by filtration (rinsing with EtOAc and hexanes) to yield *tert*-butyl (1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (595 mg) as a light yellow solid. The material was used without further purification. LC-MS retention time 3.140 min; m/z 647.35 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



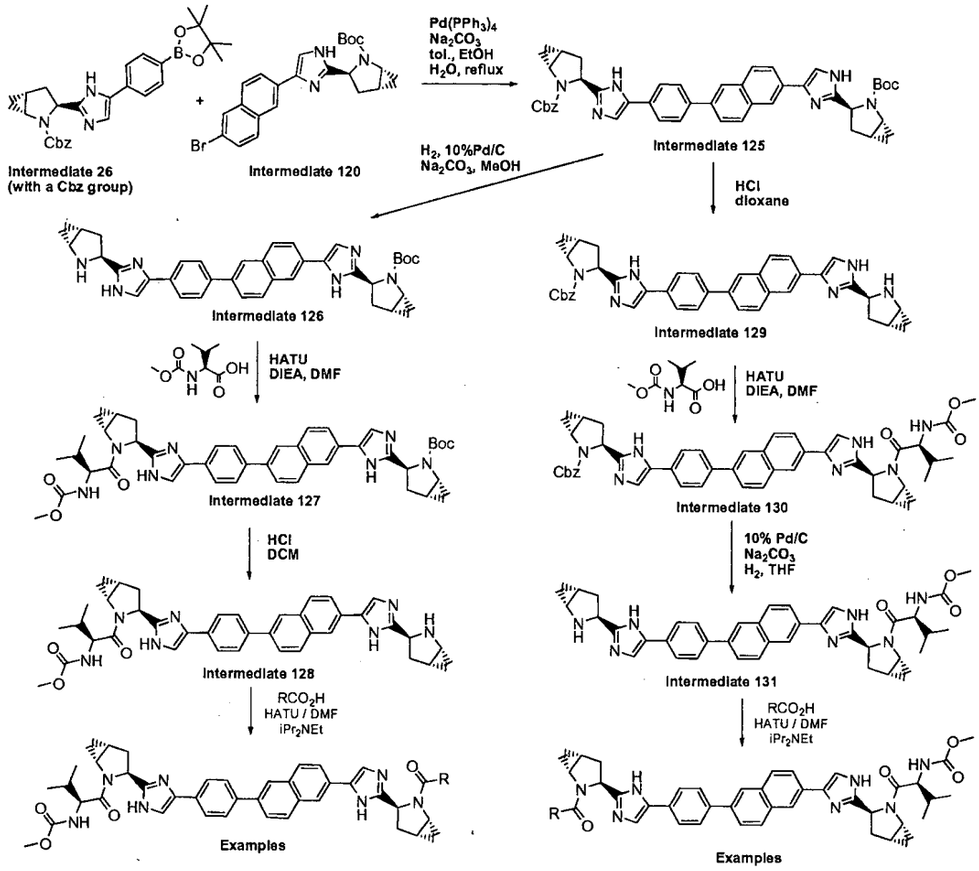
Intermediate 124

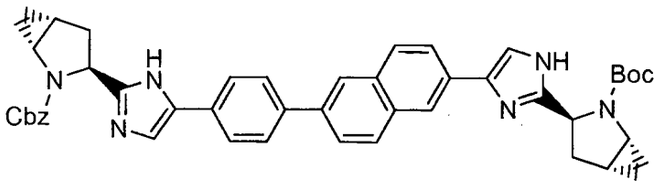
(1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00534] 4M HCl (1.546 mL, 6.18 mmol) in dioxane was added to a solution of *tert*-butyl (1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (200 mg, 0.309 mmol) in dioxane (3 mL) and the reaction was vigorously stirred for 4 h. The reaction slurry was concentrated to yield an HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (177 mg) as a yellow solid. LC-MS retention time 3.403 min; m/z 893.29 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector

at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) d ppm 8.42 (s, 1 H), 8.16 (s, 2 H), 8.05 (d, *J*=8.8 Hz, 1 H), 8.03 (d, *J*=8.8 Hz, 1 H), 7.97 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.74 (s, 1 H), 7.66 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.01 (dd, *J*=10.8, 7.8 Hz, 1 H), 4.78 (dd, *J*=10.8, 8.3 Hz, 1 H), 3.57 - 3.77 (m, 2 H), 3.50 - 3.56 (m, 1 H), 2.61 - 2.92 (m, 4 H), 2.13 - 2.21 (m, 1 H), 2.06 - 2.13 (m, 1 H), 1.25 (ddd, *J*=7.8, 5.0, 2.5 Hz, 1 H), 0.99 - 1.14 (m, 2 H).

Scheme 33



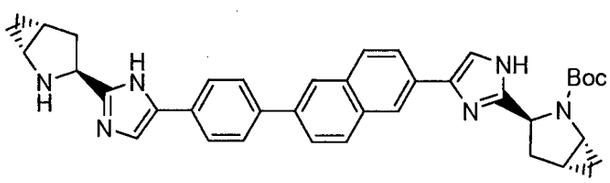


Intermediate 125

(1R,3S,5R)-Benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00535] Nitrogen was bubbled through a biphasic solution of (1R,3S,5R)-benzyl 3-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (prepared in an analogous manner to Intermediate 26) (2.0 g, 4.12 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.872 g, 4.12 mmol) and Na_2CO_3 (2.184 g, 20.60 mmol) in a mixture of EtOH (16.0 mL), toluene (16.0 mL) and water (16.0 mL) for 15 min. Then, $Pd(PPh_3)_4$ (0.143 g, 0.124 mmol) was added, the reaction was flushed with nitrogen, sealed and then heated at 95 °C for 10 h. The crude slurry was diluted with water (~ 20 mL) and extracted with EtOAc (~ 100 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated to a yellow foam. This material was dissolved into a minimal amount of DCM, and purified on a BIOTAGE® Horizon (110g of SiO_2, 70-85% EtOAc/hexanes) to yield (1R,3S,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (2.257 g) as a light yellow solidified foam. LC-MS retention time 4.158 min; m/z 733.17 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.17 (br. s., 1 H), 8.07 (s, 1 H),

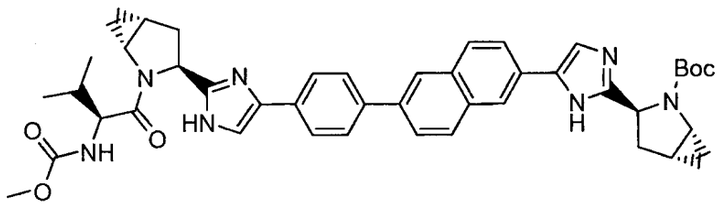
7.86 - 7.94 (m, 2 H), 7.71 - 7.86 (m, 6 H), 7.44 (s, 1 H), 7.32 (s, 1 H), 7.20 (br. s., 5 H), 5.14 (d, *J*=12.3 Hz, 1 H), 4.91 - 5.05 (m, 1 H), 4.63 - 4.77 (m, 1 H), 3.55 - 3.69 (m, 2 H), 3.29 - 3.34 (m, 1 H), 2.46 - 2.59 (m, 2 H), 2.29 - 2.44 (m, 2 H), 1.66 - 1.80 (m, 2 H), 1.30 (br. s., 9 H), 0.80 - 0.93 (m, 2 H), 0.61 (br. s., 2 H).



Intermediate 126

(1R,3S,5R)-*tert*-Butyl 3-(5-(6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

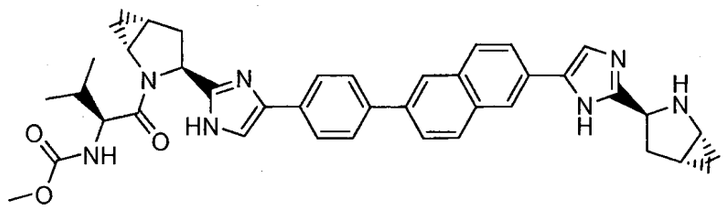
[00536] A reaction mixture of (1R,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (0.305 g, 0.416 mmol) and $NaHCO_2$ (0.070 g, 0.832 mmol) in MeOH (15 mL) was charged with 10% Pd/C (0.022 g, 0.021 mmol). The resulting suspension was vacuum flushed with N_2 (3X) and placed under 1 atm of H_2 (balloon) for 3 h at room temperature. The mixture was then filtered though a pad of diatomaceous earth (CELITE®) and concentrated under vacuum. An off-white solid corresponding to (1R,3S,5R)-*tert*-butyl 3-(5-(6-(4-(2-((1R,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (0.235 g) was recovered and used without further purification. LC/MS $[M+H]^+$= 599; Rt = 1.96 min is product. Column Luna 3u C18 2x50mm; start %B: 0, final %B: 100 Solvent A: 10% Acetonitrile/ 90% H_2O + 1% TFA; Solvent B: 90% Acetonitrile/ 10% H_2O + 1% TFA; flow rate 4 ml/min. Run time: 5 min. Purity = 94 %. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 12.00 (2 H, br. s.), 8.11 - 8.32 (3 H, m), 7.88 - 8.02 (5 H, m), 7.72 - 7.88 (9 H, m), 7.63 (4 H, br. s.), 4.64 (2 H, br. s.), 4.42 (1 H, t, *J*=7.93 Hz), 3.97 - 4.18 (1 H, m), 3.45 (1 H, br. s.), 3.17 (3 H, s), 2.96 (1 H, dd, *J*=13.43, 6.71 Hz), 2.08 - 2.43 (6 H, m), 1.66 (2 H, br. s.), 1.07 - 1.50 (20 H, m), 0.81 - 0.89 (3 H, m), 0.77 (1 H, br. s.), 0.45 - 0.61 (3 H, m), 0.30 (1 H, br. s.).



Intermediate 127

(1R,3S,5R)-*tert*-Butyl 3-(5-(6-(4-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

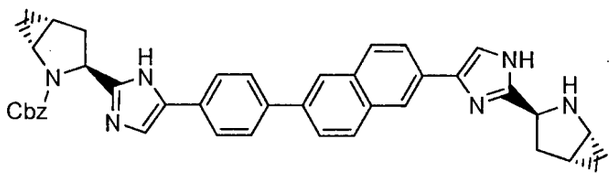
[00537] HATU (0.164 g, 0.432 mmol) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-(6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (0.235 g, 0.392 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.069 g, 0.39 mmol) and DIEA (0.137 mL, 0.785 mmol) in DMF (10 mL) and the resulting yellow solution was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dissolved into methanol, filtered and purified by preparative HPLC (Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Sunfire Prep MS C18 30 x 100mm 5u; Wavelength: 220nM; Flow rate: 30 ml/min; Gradient: 0% B to 100% B over 30 min. with a 2 min hold time) to yield a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-(6-(4-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (0.10 g) as a white solid. LC/MS $[M+H]^+$= 756; Rt = 2.14min is product. Column Luna 3u C18 2x50mm; start %B: 0, final %B: 100 Solvent A: 10% Acetonitrile/ 90% H_2O + 1% TFA; Solvent B: 90% Acetonitrile/ 10% H_2O + 1% TFA; flow rate 4 ml/min. Run time: 5 min. Purity = 96 %. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 14.60 (1 H, br. s.), 8.39 (3 H, d, *J*=4.88 Hz), 8.09 - 8.24 (4 H, m), 7.99 - 8.08 (6 H, m), 7.89 - 7.98 (5 H, m), 7.27 (1 H, d, *J*=8.55 Hz), 4.98 - 5.07 (1 H, m), 4.84 (1 H, br. s.), 4.42 (1 H, t, *J*=7.32 Hz), 3.74 (1 H, br. s.), 3.55 (4 H, s), 2.55 (2 H, d, *J*=9.77 Hz), 2.32 - 2.44 (3 H, m), 2.13 (1 H, dq, *J*=13.43, 6.71 Hz), 1.94 (1 H, dt, *J*=13.28, 6.79 Hz), 1.75 (1 H, dt, *J*=12.89, 6.22 Hz), 1.40 (4 H, d, *J*=10.07 Hz), 1.11 - 1.30 (10 H, m), 0.90 - 1.00 (5 H, m), 0.73 - 0.88 (10 H, m).



Intermediate 128

Methyl (S)-1-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

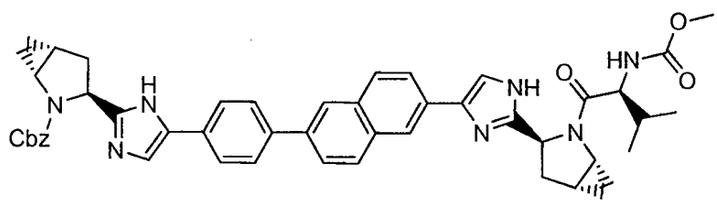
[00538] 4N HCl in dioxane (2 mL, 8.00 mmol) was added to a stirred solution of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-(6-(4-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (0.10 g, 0.12 mmol) in CH_2Cl_2 (20 mL) and the resulting yellow suspension was stirred at rt for 2 h. The reaction was concentrated under vacuum and the resulting residue was triturated with Et_2O to yield an HCl salt of methyl (S)-1-((1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate HCl (47 mg) as a yellow solid. LC/MS $[M+H]^+$=656; Rt =1.73 min is product. Column Luna 3u C18 2x50mm; start %B: 0, final %B: 100 Solvent A: 10% Acetonitrile/ 90% H_2O + 1% TFA; Solvent B: 90% Acetonitrile/ 10% H_2O + 1% TFA; flow rate 4 ml/min. Run time: 5 min. Purity = 95 %. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 14.47 - 15.18 (2 H, m), 9.77 - 10.61 (2 H, m), 8.30 - 8.42 (2 H, m), 8.17 (1 H, s), 7.93 - 8.10 (10 H, m), 7.27 (1 H, d, *J*=8.55 Hz), 5.08 (1 H, t, *J*=7.93 Hz), 4.71 (1 H, t, *J*=8.39 Hz), 4.40 - 4.46 (1 H, m), 3.77 (1 H, br. s.), 3.52 - 3.58 (3 H, m), 3.38 - 3.44 (1 H, m), 2.52 - 2.61 (3 H, m), 2.39 (1 H, dt, *J*=13.58, 6.64 Hz), 2.14 - 2.21 (1 H, m), 1.94 (2 H, dd, *J*=8.24, 4.88 Hz), 1.15 (1 H, d, *J*=5.80 Hz), 0.93 (4 H, d, *J*=6.71 Hz), 0.75 - 0.89 (6 H, m).



Intermediate 129

(1R,3S,5R)-Benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00539] A solution of 4.0 M HCl (1.167 mL, 4.67 mmol) in dioxane was added to a stirred solution of (1R,3S,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (228 mg, 0.311 mmol) in dioxane (3 mL) and the reaction was stirred vigorously at rt for 3h. The reaction was concentrated to yield an HCl salt of (1R,3S,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (233 mg) as a yellow solid. LC-MS retention time 3.988 min; m/z 633.18 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.44 (s, 1 H), 8.28 (s, 1 H), 8.08 - 8.18 (m, 3 H), 7.92 - 8.02 (m, 4 H), 7.84 (br. s., 3 H), 7.31 (br. s., 5 H), 5.21 (d, *J*=12.1, 1 H), 4.95 - 5.05 (m, 2 H), 4.80 - 4.91 (m, 1 H), 3.70 - 3.77 (m, 1 H), 3.59 - 3.67 (m, 1 H), 2.77 - 2.93 (m, 2 H), 2.74 (dd, *J*=13.4, 9.2 Hz, 1 H), 2.46 (dt, *J*=13.5, 6.7 Hz, 1 H), 2.12 - 2.22 (m, 1 H), 1.83 - 1.96 (m, 1 H), 1.27 - 1.35 (m, 1 H), 1.09 (q, *J*=7.9 Hz, 1 H), 0.95 (ddd, *J*=8.7, 5.9, 5.8 Hz, 1 H), 0.75 - 0.83 (m, 1 H).

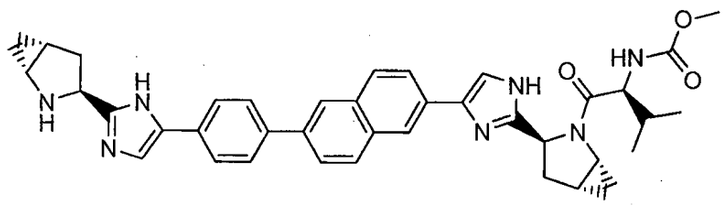


Intermediate 130

(1R,3S,5R)-Benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00540] HATU (203 mg, 0.533 mmol) was added to a stirred solution of (1R,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (225 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (93 mg, 0.53 mmol) in DMF (3 mL) and DIPEA (0.37 mL, 2.1 mmol) and the reaction was stirred at rt for 3 hr. The crude reaction was concentrated under a stream of nitrogen and the residue was dissolved into MeOH and purified by preparative HPLC (MeOH/water with an ammonium acetate buffer) to yield (1R,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (200 mg) as a yellow solid. LC-MS retention time 4.053 min; m/z 790.25 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.28 (s, 2 H), 8.13 (d, *J*=8.8 Hz, 1 H), 8.08 (d, *J*=8.8 Hz, 1 H), 7.94 - 8.02 (m, 4 H), 7.76 - 7.92 (m, 3 H), 7.85 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.29 (br. s., 5 H), 5.21 (d, *J*=12.1 Hz 1 H), 5.16 (dd, *J*=9.2, 6.9 Hz, 1 H), 4.97 (t, *J*=8.2 Hz, 1 H), 4.57 (d, *J*=6.5 Hz, 1 H), 3.78 - 3.87 (m, 1 H), 3.68 (s, 3 H), 3.64 - 3.77 (m, 2 H), 2.66 - 2.77 (m, 2 H), 2.40 - 2.56 (m, 2 H), 2.14 - 2.25 (m, 1 H), 2.05 - 2.14 (m, 1 H), 1.87 (d, *J*=6.5 Hz, 1 H), 1.06 -

1.16 (m, 1 H), 1.02 (d, *J*=6.8 Hz, 3 H), 0.94 (d, *J*=6.8 Hz, 3 H), 0.87 - 0.99 (m, 2 H), 0.74 - 0.82 (m, 1 H).



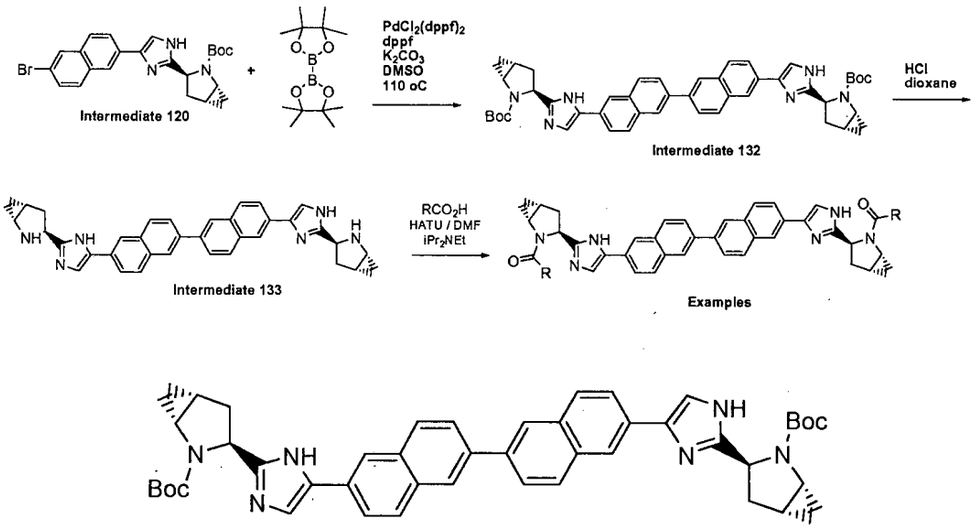
Intermediate 131

Methyl (S)-1-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00541] 10% Palladium on carbon (100 mg, 0.094 mmol) was added to a solution of (1R,5R)-benzyl 3-(5-(4-(6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (190 mg, 0.241 mmol) and Na_2CO_3 (50 mg, 0.472 mmol) in THF (10 mL) and the reaction mixture was vacuum flushed with nitrogen (3X) and then with hydrogen (5X). The reaction mixture was allowed to stir under a balloon of hydrogen for 2h, filtered through diatomaceous earth (CELITE®) and concentrated. The residue was resubmitted to the reaction conditions (50 mg of 10% Pd/C used) overnight at rt before being filtered through diatomaceous earth (CELITE®) and concentrated. The residue was dissolved into DMSO/MeOH, filtered and purified by preparative HPLC (MeOH/H_2O w/ 0.1% TFA) to yield a TFA salt of methyl (2S)-1-((1R,3S,5R)-3-(5-(6-(4-(2-((1R,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (55 mg). LC-MS retention time 2.147 min; m/z 656.21 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium

acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.24 (s, 1 H), 8.12 (d, *J*=8.9 Hz, 1 H), 8.07 (d, *J*=8.9 Hz, 1 H), 7.91 - 8.01 (m, 4 H), 7.83 - 7.90 (m, 3 H), 7.66 (s, 1 H), 5.17 (dd, *J*=9.2, 7.0 Hz, 1 H), 4.67 (dd, *J*=10.7, 7.6 Hz, 1 H), 4.58 (d, *J*=6.7 Hz, 1 H), 3.82 - 3.87 (m, 1 H), 3.69 (s, 3 H), 3.44 - 3.49 (m, 1 H), 2.59 - 2.77 (m, 3 H), 2.48 - 2.56 (m, 1 H), 2.16 - 2.25 (m, 1 H), 2.03 - 2.15 (m, 2 H), 1.21 (ddd, *J*=7.5, 4.9, 2.6 Hz, 1 H), 1.09 - 1.15 (m, 1 H), 1.04 (d, *J*=6.7 Hz, 3 H), 0.98 - 1.03 (m, 1 H), 0.95 (d, *J*=6.7 Hz, 3 H), 0.89 - 0.95 (m, 1 H).

Scheme 34

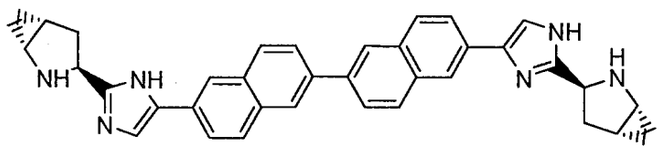


Intermediate 132

(1R,1′R,3S,3′S,5R,5′R)-*tert*-Butyl 3,3′-(4,4′-(2,2′-binaphthyl-6,6′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate)

[00542] Nitrogen was bubbled a solution of (1R,3S,5R)-*tert*-butyl 3-(4-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (250 mg, 0.550 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (69.9 mg, 0.275 mmol), 1,1′-bis-(diphenylphosphino)-ferrocene (15.42 mg, 0.028 mmol) and K_2CO_3 (228 mg, 1.651 mmol) in DMSO (12mL) for 10 min. Then 1,1′-Bis-(diphenylphosphino)-ferrocene) palladium dichloride (22.63 mg, 0.028 mmol) was added to the reaction mixture and the nitrogen bubbling was continued for 10 min before the reaction was sealed and then heated at 110 °C for 20 h. The reaction was partitioned

between water (60 mL) and DCM (60 mL) and the organics were separated, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by BIOTAGE® Horizon (40g SiO_2, 70-100% EtOAc/hexanes) to yield (1R,1'R,3S,3'S,5R,5'R)-*tert*-butyl 3,3'-(4,4'-(2,2'-binaphthyl-6,6'-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate) (67 mg) as a yellow solid. LC-MS retention time 4.348 min; m/z 749.29 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.22 (s, 4 H), 7.91 - 8.02 (m, 6 H), 7.87 (d, *J*=8.5 Hz, 2 H), 7.48 (br. s., 2 H), 4.68 - 4.77 (m, 2 H), 3.61 (br. s., 2 H), 2.56 (dd, *J*=13.1, 8.8 Hz, 2 H), 2.33 - 2.43 (m, 2 H), 1.70 - 1.79 (m, 2 H), 1.31 (br. s., 18 H), 0.87 (dt, *J*=8.5, 5.8 Hz, 2 H), 0.63 (br. s., 2 H).



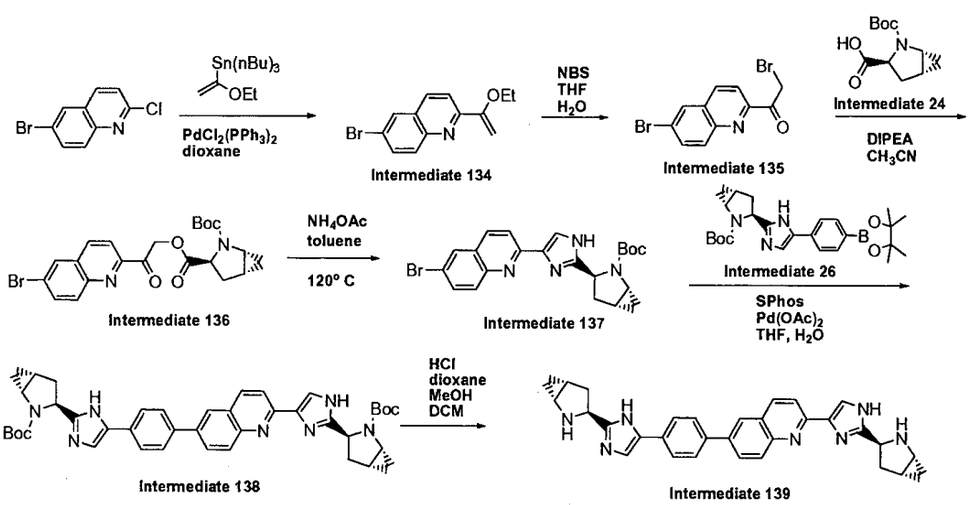
Intermediate 133

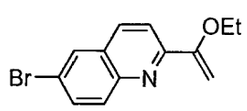
6,6'-Bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)-2,2'-binaphthyl

[00543] 4.0M HCl (1.0 mL, 4.00 mmol) in dioxane was added to a stirred solution of (1R,1'R,3S,3'S,5R,5'R)-*tert*-butyl 3,3'-(4,4'-(2,2'-binaphthyl-6,6'-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate) (62mg, 0.083 mmol) in dioxane (2 mL) and the reaction slurry was stirred vigorously for 3h. The slurry was diluted with MeOH and concentrated to dryness to yield an HCl salt of 6,6'-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)-2,2'-binaphthyl (56 mg) as a light yellow solid. LC-MS retention time 3.971 min; m/z 547.25 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of

220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.44 (s, 2 H), 8.38 (s, 2 H), 8.12 - 8.19 (m, 6 H), 8.09 (dd, 2 H), 7.97 (dd, *J*=8.5, 1.5 Hz, 2 H), 4.97 (dd, *J*=10.5, 8.1 Hz, 2 H), 3.62 - 3.66 (m, 2 H), 2.79 - 2.89 (m, 4 H), 2.15 - 2.22 (m, 2 H), 1.29 - 1.34 (m, 2 H), 1.11 (q, *J*=7.9 Hz, 2 H).

Scheme 35



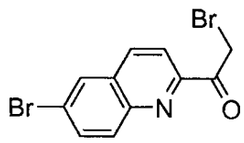


Intermediate 134

6-Bromo-2-(1-ethoxyvinyl)quinoline

[00544] Dichlorobis(triphenylphosphine)-palladium(II) (0.289 g, 0.412 mmol) was added to a solution of 6-bromo-2-chloroquinoline (1.0 g, 4.1 mmol) and tributyl(1-ethoxyvinyl)stannane (1.79 g, 4.95 mmol) in dioxane (8 mL) and the mixture was stirred at 100 °C for 5 h, desired product was identified by LCMS. The crude reaction mixture was concentrated and purified by flash silica gel chromatography (eluted with 1:1

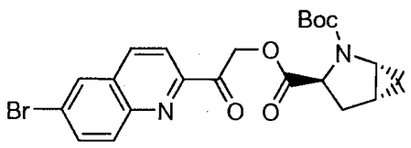
hexanes/DCM) to yield product 6-bromo-2-(1-ethoxyvinyl)quinoline (720 mg) as white solid. LC-MS retention time 4.091 min; m/z 279.84 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 135

2-Bromo-1-(6-bromoquinolin-2-yl)ethanone

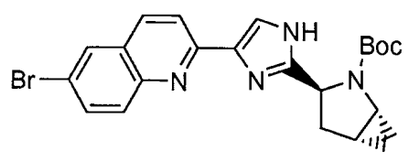
[00545] NBS (407 mg, 2.287 mmol) was added to a solution of 6-bromo-2-(1-ethoxyvinyl)quinoline (530 mg, 1.91 mmol) in THF (10 mL) and water (2.5 mL) and the mixture was stirred at rt for 2 h. The reaction mixture was partitioned between EtOAc and brine and the organic layer was concentrated. The crude material was purified by flash silica gel chromatography (eluted with Et_2O/hexanes, gradient from 0 to 5% Et_2O) to yield 2-bromo-1-(6-bromoquinolin-2-yl)ethanone (380 mg) as white solid. LC-MS retention time 3.988 min; m/z 329.84 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 136

(1R,3S,5R)-3-(2-(6-Bromoquinolin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

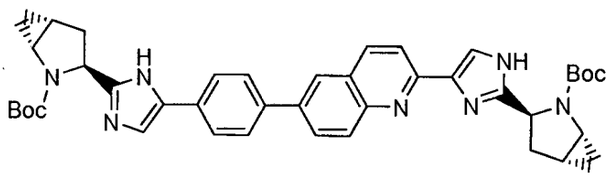
[00546] DIPEA (0.21 mL, 1.2 mmol) was added to a solution of 2-bromo-1-(6-bromoquinolin-2-yl)ethanone (268 mg, 0.815 mmol)) and (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (204 mg, 0.896 mmol) in acetonitrile (8 mL) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash silica gel chromatography (used DCM as loading solvent, eluted with Et_2O/hexanes, gradient from 10% to 30% Et_2O) to yield (1R,3S,5R)-3-(2-(6-bromoquinolin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (332 mg) as white solid. LC-MS retention time 4.283 min; m/z 476.88 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 137

tert-Butyl (1R,3S,5R)-3-(4-(6-bromo-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00547] Ammonium acetate (990 mg, 12.8 mmol) was added to a solution of (1R,3S,5R)-3-(2-(6-bromoquinolin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (407 mg, 0.856 mmol) in toluene (10 mL) and the mixture was stirred at 120 °C for 3 h. The reaction mixture was diluted with sat. aq $NaHCO_3$ (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash silica gel chromatography (eluted with 1 : 1 EtOAc/hexanes) to yield *tert*-butyl (1R,3S,5R)-3-(4-(6-bromo-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (272 mg) as light yellow solid. LC-MS retention time 3.306 min; m/z 456.99 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.08 (d, *J*=8.5 Hz, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.78 (dd, *J*=8.9, 2.2 Hz, 1 H), 7.73 - 8.14 (m, 3 H), 4.86 - 4.98 (m, 1 H), 3.70 - 3.82 (m, 0.5 H), 3.26 - 3.39 (m, 1 H), 2.46 (dd, *J*=13.3, 9.3 Hz, 1 H), 1.84 - 1.91 (m, 0.5 H), 1.74 - 1.84 (m, 1 H), 1.52 (s, 9 H), 0.87 - 0.97 (m, 1 H), 0.48 - 0.61 (m, 1 H).

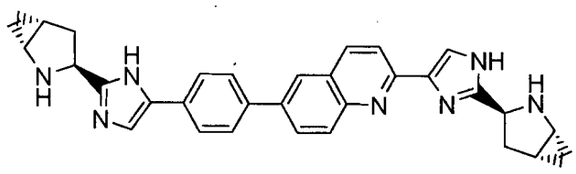


Intermediate 138

tert-Butyl (1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00548] $Pd(OAc)_2$ (7.40 mg, 0.033 mmol) was added to a solution of *tert*-butyl (1R,3S,5R)-3-(4-(6-bromo-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-

carboxylate (150 mg, 0.329 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (149 mg, 0.329 mmol), dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (27.0 mg, 0.066 mmol) and K_2CO_3 (137 mg, 0.988 mmol) in THF (2 mL) and water (0.50 mL) and the reaction mixture was stirred at 110 °C for 2 h. The reaction mixture was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 10mM NH_4OAc buffer) to yield *tert*-butyl (1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (140 mg) as bright yellow solid. LC-MS retention time 3.150 min; m/z 700.36 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



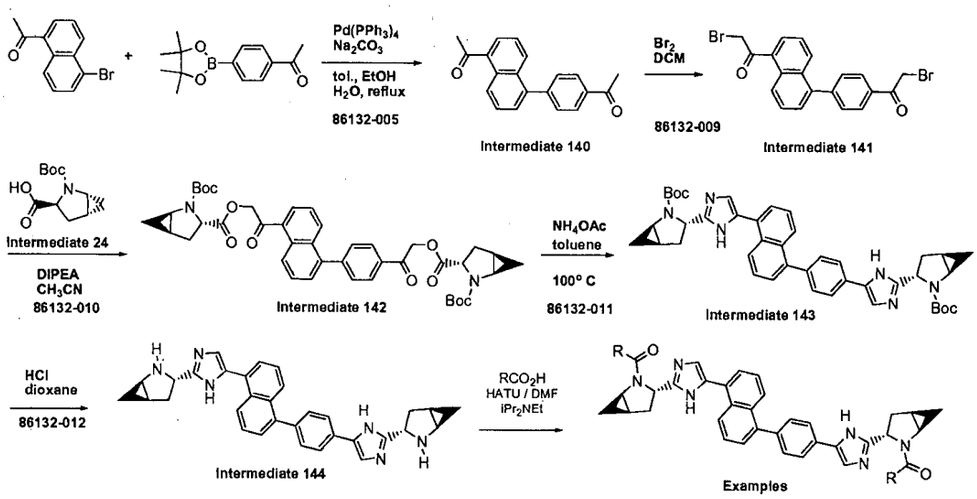
Intermediate 139

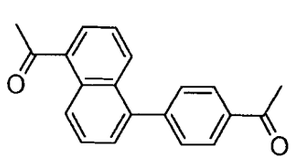
2-(2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)quinoline

[00549] A solution of 4M HCl (1 mL, 4.00 mmol) in dioxane was added to a suspension of *tert*-butyl (1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (130 mg, 0.186 mmol) in dioxane (3 mL), MeOH (0.5 mL) and DCM (3 mL) and the mixture was stirred at rt for 2h. The reaction was concentrated to yield an HCl salt of 2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-

imidazol-4-yl)-6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)quinoline (140 mg) as yellow solid. LC-MS retention time 2.063 min; m/z 500.37 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (d, *J*=9.0 Hz, 1 H), 8.66 (s, 1 H), 8.56 - 8.62 (m, 2 H), 8.47 - 8.53 (m, 2 H), 8.07 (s, 1 H), 8.02 - 8.06 (m, 4 H), 4.97 (dd, *J*=10.8, 8.0 Hz, 1 H), 3.65 - 3.71 (m, 1 H), 3.55 - 3.65 (m, 2 H), 2.73 - 2.86 (m, 3 H), 2.61 - 2.72 (m, 1 H), 2.07 - 2.20 (m, 2 H), 1.25 - 1.35 (m, 2 H), 1.07 (t, 2 H).

Scheme 36

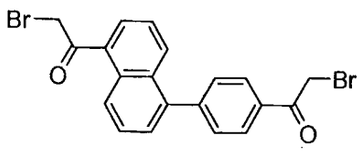




Intermediate 140

1-(4-(5-Acetylnaphthalen-1-yl)phenyl)ethanone

[00550] A solution of sodium carbonate (2.55 g, 24.09 mmol) in water (20 mL) was added to a solution of 1-(5-bromonaphthalen-1-yl)ethanone (1.2 g, 4.8 mmol) and 4-acetylphenylboronic acid (1.03 g, 6.26 mmol) in toluene (20 mL) and ethanol (20 mL) and then heterogeneous solution was vigorously stirred with bubbling nitrogen for 15 min. Then $Pd(PPh_3)_4$ (0.111 g, 0.096 mmol) was added and the reaction vessel was sealed and heated at reflux for 6h. The reaction was cooled and concentrated to dryness. The crude residue was taken into EtOAc (~ 150 mL) and water (~ 100 mL). The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated to an orange solid. The orange solid was purified on a BIOTAGE® Horizon (40 g SiO_2, DCM) to yield 1-(4-(5-acetylnaphthalen-1-yl)phenyl)ethanone (1.31 g) as an off-white solid. LC-MS retention time 3.736 min; m/z 289.19 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, chloroform-d) δ ppm 8.75 (d, *J*=8.8 Hz, 1 H), 8.11 (d, *J*=8.5 Hz, 2 H), 7.99 (d, *J*=8.5 Hz, 1 H), 7.94 (dd, *J*=7.2, 1.1 Hz, 1 H), 7.67 (dd, *J*=8.5, 7.0 Hz, 1 H), 7.58 (d, *J*=8.3 Hz, 2 H), 7.45 - 7.51 (m, 2 H), 2.79 (s, 3 H), 2.70 (s, 3 H).

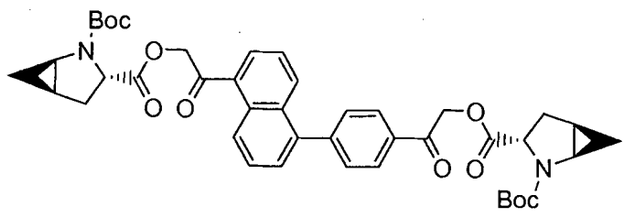


Intermediate 141

2-Bromo-1-(4-(5-(2-bromoacetyl)naphthalen-1-yl)phenyl)ethanone

[00551] A solution of bromine (0.47 mL, 9.1 mmol) in DCM (10 mL) was added to a solution of 1-(4-(5-acetylnaphthalen-1-yl)phenyl)ethanone (1.285 g, 4.46 mmol) in DCM (20 mL) and the reaction was stirred at rt for 1d. The reaction was concentrated to a viscous light orange oil (~1.92 g). By ^1H NMR the major product appears to be the

desired product with peaks corresponding to the two mono brominated regioisomers (~10%). The material was used without purification. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.64 (d, *J*=8.5 Hz, 1 H), 8.13 - 8.17 (m, 2 H), 8.05 (d, *J*=8.5 Hz, 1 H), 7.94 (dd, *J*=7.2, 1.1 Hz, 1 H), 7.71 (dd, *J*=8.8, 7.0 Hz, 1 H), 7.60 - 7.64 (m, 2 H), 7.48 - 7.55 (m, 2 H), 4.60 (s, 2 H), 4.53 (s, 2 H).

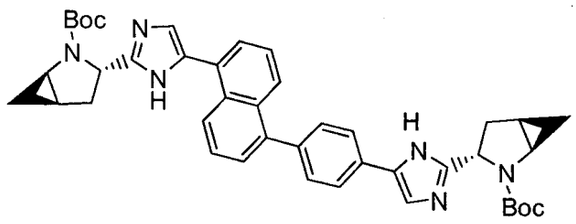


Intermediate 142

(1R,3S,5R)-3-(2-(4-(5-(2-((1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carbonyloxy)acetyl)naphthalen-1-yl)phenyl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

[00552] DIPEA (2.337 mL, 13.38 mmol) was added to a solution of crude 2-bromo-1-(4-(5-(2-bromoacetyl)naphthalen-1-yl)phenyl)ethanone (1.99 g, 4.46 mmol) and (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (2.03 g, 8.92 mmol) in acetonitrile (50mL) and the clear yellow solution was stirred at rt overnight. The reaction was concentrated to a yellow solidified foam which was purified on a BIOTAGE® Horizon (SiO_2, EtOAc/hexanes) to yield (1R,3S,5R)-3-(2-(4-(5-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carbonyloxy)acetyl)naphthalen-1-yl)phenyl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (2.95 g) as a white fluffy solid. LC-MS retention time 4.363 min; m/z 737.38 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in

electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.57 (d, *J*=8.8 Hz, 1 H), 8.14 (d, *J*=8.0 Hz, 2 H), 7.99 - 8.06 (m, 2 H), 7.68 (dd, *J*=8.8, 7.0 Hz, 1 H), 7.64 (d, *J*=8.3 Hz, 2 H), 7.52 - 7.60 (m, 2 H), 5.60 - 5.70 (m, 1 H), 5.32 - 5.56 (m, 3 H), 4.24 - 4.34 (m, 2 H), 3.38 - 3.49 (m, 2 H), 2.59 - 2.69 (m, 1 H), 2.38 - 2.55 (m, 3 H), 1.61 - 1.77 (m, 2 H), 1.47 (br. s., 18 H), 0.81 - 0.94 (m, 2 H), 0.50 - 0.58 (m, 2 H).

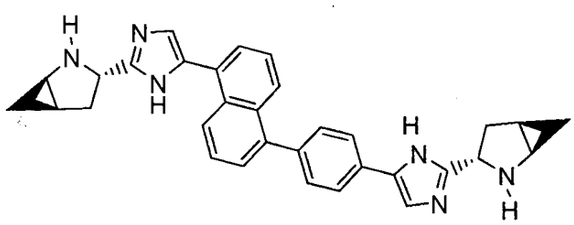


Intermediate 143

(1R,3S,5R)-*tert*-Butyl 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00553] A solution of (1R,3S,5R)-3-(2-(4-(5-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carbonyloxy)acetyl)naphthalen-1-yl)phenyl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (2.01 g, 2.72 mmol) and ammonium acetate (4.19 g, 54.4 mmol) in toluene (40 mL) was stirred and heated at 100 °C overnight. The reaction was concentrated to dryness and the brown solids were partitioned between DCM (150 mL) and 1/2 sat. aq. $NaHCO_3$ (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated. The crude material was not easily purified by flash column chromatography so all fractions containing the desired product or starting material were collected, concentrated and resubmitted to the reaction conditions (now 110 °C overnight). The reaction was concentrated and the brown solids were partitioned between DCM (150 mL) and 1/2 sat $NaHCO_3$ (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated. Approximately ~ 30-35% of the material was purified by preparative HPLC (dissolved into MeOH, filtered, 80-100 % MeOH/water, ammonium acetate buffer) to yield (1R,3S,5R)-*tert*-butyl 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (148 mg) as a yellow solid. The remaining material was purified by preparative HPLC

(dissolved into MeOH, filtered, 60-100 % MeOH/water, TFA buffer) to yield a TFA salt (1R,3S,5R)-*tert*-butyl 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (299 mg). LC-MS retention time 3.100 min; m/z 699.56 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.29 (d, *J*=8.5 Hz, 1 H), 7.90 (d, *J*=8.5 Hz, 1 H), 7.83 (d, *J*=8.3 Hz, 2 H), 7.59 (dd, *J*=7.0, 1.0 Hz, 1 H), 7.53 (dd, *J*=8.5, 7.0 Hz, 1 H), 7.43 - 7.50 (m, 4 H), 7.42 (s, 1 H), 7.23 (s, 1 H), 4.66 - 4.80 (m, 2 H), 3.60 (br. s., 2 H), 2.56 (dt, *J*=13.1, 8.9 Hz, 2 H), 2.32 - 2.46 (m, 2 H), 1.70 - 1.78 (m, 2 H), 1.38 (br. s., 18 H), 0.82 - 0.90 (m, 2 H), 0.63 (br. s., 2 H).



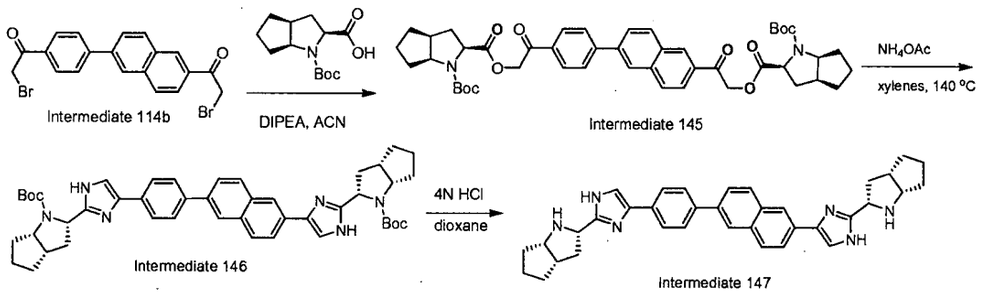
Intermediate 144

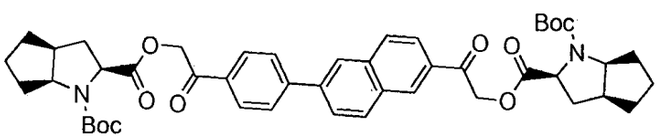
(1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-Azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00554] 4M HCl (0.757 mL, 3.03 mmol) in dioxane was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (141 mg, 0.202 mmol) in dioxane (3.0 mL) and the reaction was stirred at rt for 6h. The solids were washed down the sides of the vial with MeOH and the reaction was concentrated under a stream nitrogen to yield an

HCl salt of (1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (119 mg) as a yellow solid. LC-MS retention time 2.333 min; m/z 499.57 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.15 (d, *J*=8.3 Hz, 1 H), 8.03 - 8.08 (m, 2 H), 8.01 (d, *J*=8.0 Hz, 2 H), 7.95 (s, 1 H), 7.77 (d, *J*=6.5 Hz, 1 H), 7.68 - 7.74 (m, 1 H), 7.65 (d, *J*=8.0 Hz, 2 H), 7.57 - 7.64 (m, 2 H), 5.03 (t, *J*=9.4 Hz, 1 H), 4.97 (dd, *J*=10.8, 8.0 Hz, 1 H), 3.57 - 3.66 (m, 2 H), 2.76 - 2.89 (m, 4 H), 2.11 - 2.21 (m, 2 H), 1.27 - 1.34 (m, *J*=7.7, 5.1, 5.1, 2.6 Hz, 2 H), 1.05 - 1.14 (m, 2 H).

Scheme 37

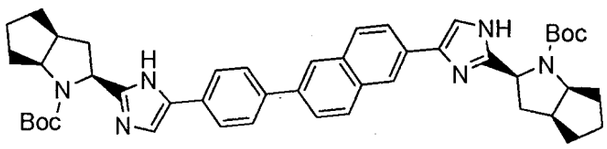




Intermediate 145

(2S,3aS,6aS)-2-(2-(4-(6-(2-((2S,3aS,6aS)-1-(*tert*-Butoxycarbonyl)-octahydrocyclopenta[b]pyrrole-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl)1-*tert*-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate

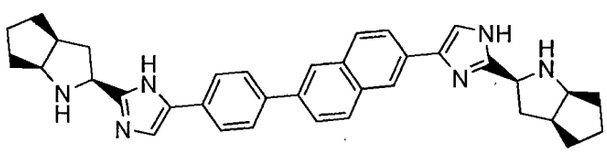
[00555] Neat DIPEA (0.068 mL, 0.388 mmol) was added to a stirred suspension of 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (79 mg, 0.176 mmol) and (2S,3aS,6aS)-1-(*tert*-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (90 mg, 0.353 mmol) in an. acetonitrile (1.5 mL) and chloroform (1.5 mL) and the mixture was stirred at r.t. overnight. Reaction mixture was evaporated to dryness and then purified by silica gel FCC (3% MeOH in DCM) to afford the Intermediate 145 as a tan solid. LC-MS retention time: 2.480 min; m/z 793.7 $(M-H)^-$.



Intermediate 146

(2S,3aS,6aS)-*tert*-Butyl 2-(4-(4-(6-(2-((2S,3aS,6aS)-1-(*tert*-butoxycarbonyl)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

[00556] A stirred suspension of (2S,3aS,6aS)-2-(2-(4-(6-(2-((2S,3aS,6aS)-1-(*tert*-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 1-*tert*-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate (140 mg, 0.176 mmol) and ammonium acetate (272 mg, 3.52 mmol) in xylene (4 mL) was heated at 140 °C for 2 h. Reaction mixture was cooled to r.t. and diluted with EtOAc (20 ml) and washed with satd. $NaHCO_3$, water, brine and dried (Na_2SO_4) to afford a brown solid which was purified by silica gel FCC (3-5% MeOH in DCM) to afford the Intermediate 146. LC-MS retention time: 2.577 min; m/z 755.7 $(M+H)^+$.

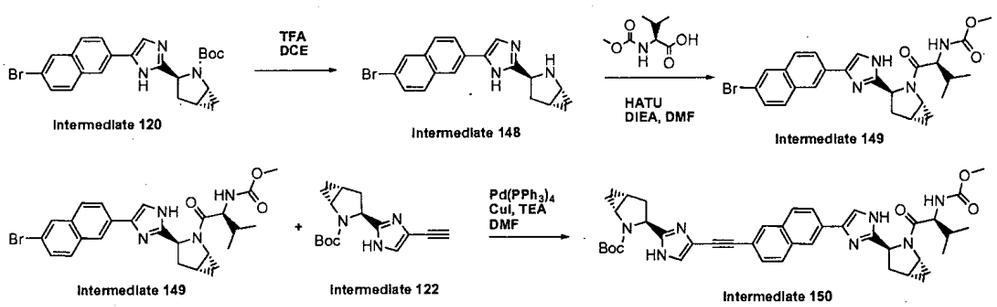


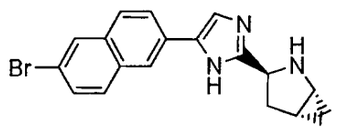
Intermediate 147

(2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-Octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)octahydrocyclopenta[b]pyrrole

[00557] 4N HCl in dioxane (20 equiv) was added to a solution of Intermediate 146 in an. DCM and the mixture was stirred at rt for 2-3 h. Anhydrous toluene was added to the resultant yellow suspension and then evaporated to dryness to afford the Intermediate 147 as a beige solid and isolated as 4HCl salt: LC-MS retention time: 2.343 min; m/z 555 $(M+H)^+$.

Scheme 38



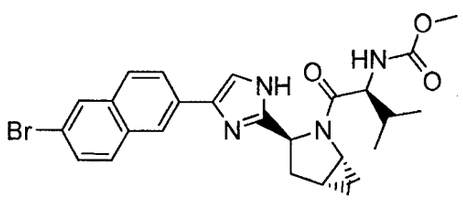


Intermediate 148

(1R,3S,5R)-3-(4-(6-Bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00558] TFA (1.028 mL, 13.34 mmol) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(4-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 120) (606 mg, 1.334 mmol) in DCE (20 mL) and reaction was stirred at rt for 2h. Then additional TFA (1 mL) was added and the reaction was stirred at rt for 4h. The reaction was concentrated to dryness and the crude brown oil was dissolved into diethyl ether and concentrated under vacuum (2X) to yield a TFA salt of (1R,3S,5R)-3-(4-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (786 mg) as a yellow solid. The material was used without further purification. LC-MS retention time 2.558 min; m/z 352.03, 354.05 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100%

Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 10.55 (br. s., 1 H), 8.02 (s, 1 H), 7.93 (d, *J*=1.5 Hz, 1 H), 7.72 (d, *J*=8.5 Hz, 1 H), 7.65 (d, *J*=8.8 Hz. 1 H), 7.59 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.52 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.44 (s, 1 H), 5.10 (dd, *J*=11.8, 7.3 Hz, 1 H), 3.49 - 3.54 (m, 1 H), 2.94 (td, *J*=12.7, 4.6 Hz, 1 H), 2.68 (dd, *J*=13.2, 7.2 Hz, 1 H), 2.06 - 2.14 (m, 1 H), 1.20 - 1.26 (m, 1 H), 1.00 - 1.09 (m, 1 H).

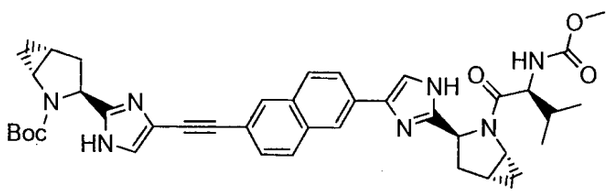


Intermediate 149

Methyl (S)-1-((1R,3S,5R)-3-(4-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00559] HATU (411 mg, 1.082 mmol) was added to a solution of a TFA salt of (1R,3S,5R)-3-(4-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (525 mg, 0.902 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (190 mg, 1.08 mmol) in DMF (10 mL) and DIPEA (0.79 mL, 4.5 mmol) and the reaction was stirred at rt for 4h. The reaction was diluted with EtOAc (~80 mL) and washed with sat. aq. $NaHCO_3$, water (30 mL) and brine (30 mL). The organics were then dried ($MgSO_4$), filtered and concentrated to a brown oil (625 mg). This material was purified on a BIOTAGE® Horizon (40 g SiO_2, 40-80% EtOAc/hexanes) to yield methyl (S)-1-((1R,3S,5R)-3-(4-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (412 mg) as a yellow glass. LC-MS retention time 1.843 min; m/z 511.24, 513.12 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1.0 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



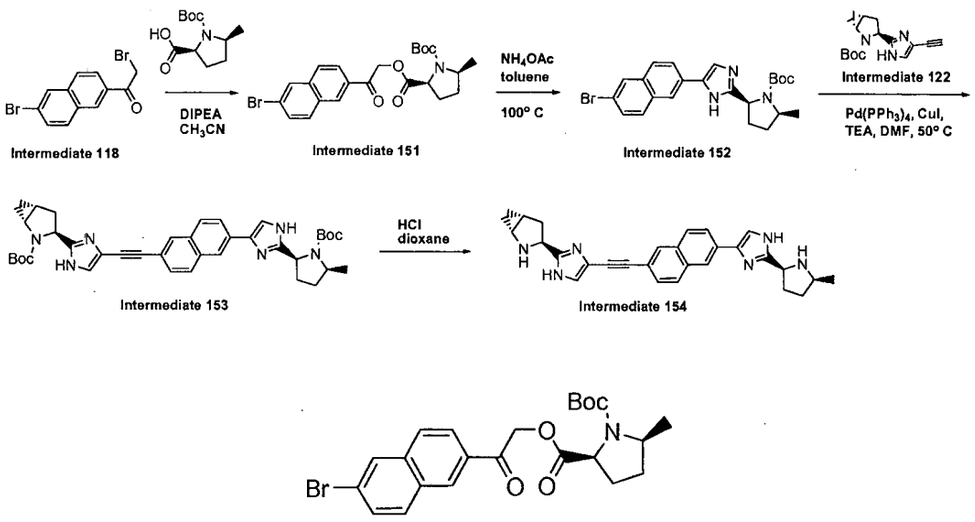
Intermediate 150

(1R,3S,5R)-*tert*-Butyl 3-(4-((6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00560] Nitrogen was bubbled through a mixture of (1R,3S,5R)-*tert*-butyl 3-(5-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 122) (118 mg, 0.432 mmol), methyl (S)-1-((1R,3S,5R)-3-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (170 mg, 0.332 mmol) and CuI (3.17 mg, 0.017 mmol) in DMF (4 mL) and TEA (0.14 mL, 0.10 mmol) for 15 min. Then $Pd(PPh_3)_4$(19.2 mg, 0.017 mmol) was added and the reaction vessel was sealed and heated at 60 °C overnight. The reaction was cooled and then additional CuI (5 mg) and TEA (100 μL) were added to the reaction and nitrogen was bubbled through the reaction for 15 min. Then additional $Pd(PPh_3)_4$ (12 mg) was added and the reaction was sealed and stirred at 70 °C for 24 h. The reaction was concentrated under high vacuum and the residue was partitioned between DCM (25 mL) and water (25 mL). The aqueous was extracted with DCM (2 X 10 mL) and the combined organics were washed with brine (~20 mL), dried ($MgSO_4$), filtered and concentrated to a viscous dark oil. The material was dissolved into MeOH, filtered and purified by preparative HPLC (MeOH/water, ammonium acetate buffer) to yield (1R,3S,5R)-*tert*-butyl 3-(4-((6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (187.4 mg) as a yellow solid. The material was used without further purification. LC-MS retention time

1.720 min; m/z 704.59 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1.0 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 39

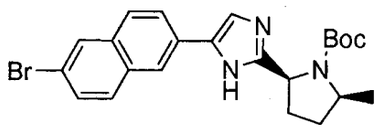


Intermediate 151

(2S,5S)-2-(2-(6-Bromonaphthalen-2-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate

[00561] DIPEA (0.823 mL, 4.71 mmol) was added to a stirred slurry of 2-bromo-1-(6-bromonaphthalen-2-yl)ethanone (Intermediate 118) (1.03 g, 3.14 mmol) and (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (0.720 g, 3.14 mmol) in acetonitrile (50 mL) and the reaction was stirred at rt overnight. The reaction was concentrated to dryness and purified by BIOTAGE® Horizon (40 g SiO_2, 10-20% EtOAc/hexanes) to yield (2S,5S)-2-(2-(6-bromonaphthalen-2-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (1.09 g) as a yellow solidified foam. LC-MS retention time 4.413 min; m/z 476, 478.20 (1:1) (MH+). LC data was recorded on a

Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.57 (br. s., 1 H), 8.14 (d, *J*=1.5 Hz, 1 H), 8.01 (d, *J*=8.5 Hz, 1 H), 7.96 (d, *J*=8.8 Hz, 1 H), 7.91 (d, *J*=8.8 Hz, 1 H), 7.68 (dd, *J*=8.8, 1.8 Hz, 1 H), 5.62 - 5.70 (m, 1 H), 5.47 - 5.60 (m, 1 H), 4.46 (t, *J*=7.3 Hz, 1 H), 3.92 - 4.06 (m, 1 H), 2.26 - 2.37 (m, 2 H), 2.05 - 2.19 (m, 1 H), 1.67 - 1.82 (m, 1 H), 1.46 (d, *J*=6.8 Hz, 9 H), 1.30 (d, *J*=6.5 Hz, 3 H).

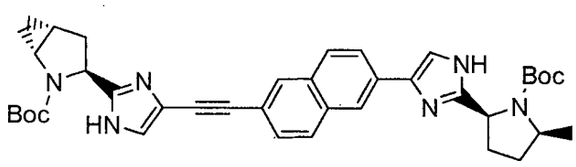


Intermediate 152

(2S,5S)-*tert*-Butyl 2-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate

[00562] Ammonium acetate (3.79 g, 49.1 mmol) was added to a solution of (2S,5S)-2-(2-(6-bromonaphthalen-2-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (1.17 g, 2.47 mmol) in toluene (30 mL) and the reaction was placed into an oil bath which had been preheated to 100 °C and stirred at that temperature overnight. The reaction was allowed to cool to rt, concentrated and partitioned between DCM (100 mL) and 1/2 sat. aq. $NaHCO_3$ (75 mL). The organics layer was washed with brine (~50 mL), dried ($MgSO_4$), filtered and concentrated to a solidified tan foam. This material was purified on a BIOTAGE® Horizon (160 g SiO_2, loaded with DCM, 20-35% EtOAc/hexanes) to yield (2S,5S)-*tert*-butyl 2-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (893 mg) as a solidified tan foam. LC-MS retention time 3.410 min; m/z 456, 458.22 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of

220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.19 (br. s., 1 H), 8.01 (s, 1 H), 7.83 - 7.93 (m, 1 H), 7.76 - 7.83 (m, 2 H), 7.55 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.47 (br. s., 1 H), 4.94 (br. s., 1 H), 3.99 - 4.09 (m, 1 H), 2.22 - 2.36 (m, 2 H), 2.09 - 2.21 (m, 1 H), 1.72 (br. s., 1 H), 1.42 (d, *J*=6.0 Hz, 3 H), 1.34 (br. s., 9 H).

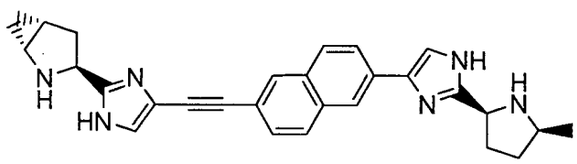


Intermediate 153

(1R,3S,5R)-*tert*-Butyl 3-(4-((6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00563] Nitrogen was bubbled through a solution of (2S,5S)-*tert*-butyl 2-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (127 mg, 0.277 mmol), (1R,3S,5R)-*tert*-butyl 3-(5-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (91 mg, 0.33 mmol) and CuI (2.6 mg, 0.014 mmol) in DMF (3 mL) and TEA (0.12 mL, 0.83 mmol) for 15 min. Then $Pd(PPh_3)_4$(16 mg, 0.014 mmol) was added and the reaction vessel was flushed with nitrogen, sealed and heated at 50 °C overnight. The reaction was cooled to rt, nitrogen was bubbled through the reaction mixture for 20 min., and then additional CuI (~4 mg) and $Pd(PPh_3)_4$ (15 mg) were added. The reaction was flushed with nitrogen for 5 min., sealed and heated at 60 °C for 1d. The reaction was cooled to rt, diluted with methanol, filtered and purified by preparative HPLC (MeOH/water with TFA buffer) to yield a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-((6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (56.7 mg) as a yellow solid. LC-MS retention time 3.161 min; m/z 649.62

(MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.31 (s, 1 H), 8.21 (s, 1 H), 8.07 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.04 (m, 2 H), 7.91 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.77 - 7.87 (m, 1 H), 7.69 (dd, *J*=8.7, 1.4 Hz, 1 H), 5.13 (t, *J*=7.5 Hz, 1 H), 4.12 (br. s., 1 H), 3.61 (br. s., 1 H), 2.66 (br. s., 1 H), 2.45 - 2.54 (m, 1 H), 2.33 - 2.42 (m, 1 H), 2.22 - 2.32 (m, 2 H), 1.75 - 1.86 (m, 2 H), 1.25 - 1.59 (m, 21 H), 1.06 (none, 1 H), 0.90 (dt, *J*=8.5, 5.8 Hz, 1 H), 0.71 (br. s., 1 H).



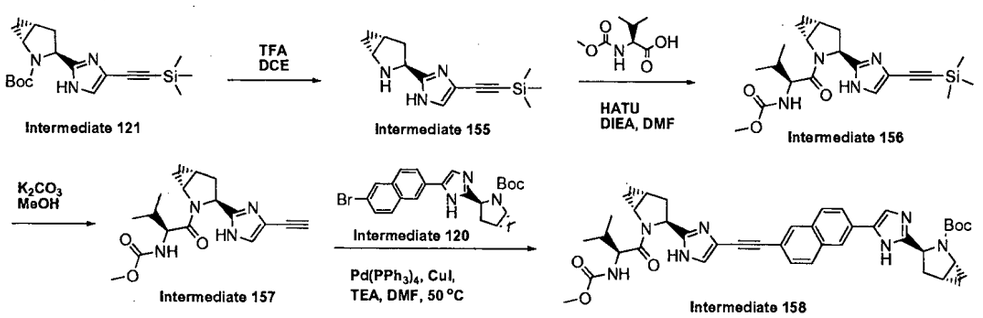
Intermediate 154

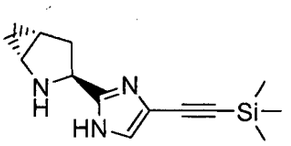
(1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-Methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00564] 4M HCl (0.611 mL, 2.445 mmol) in dioxane was added to a mixture of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-((6-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (53.6 mg, 0.061 mmol) in dioxane (1.5 mL) and the reaction was vigorously stirred for 2h. The reaction was concentrated under a steam of nitrogen overnight to yield an HCl salt of (1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (37 mg) which was used without further purification. LC-MS retention time 2.302 min; m/z 449.40 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The

elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 40



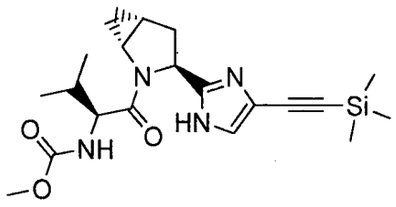


Intermediate 155

(1R,3S,5R)-3-(4-((Trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00565] TFA (500 µl, 6.49 mmol) was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (299 mg, 0.865 mmol) in DCE (5mL) and the reaction was stirred at rt for 30 min. The reaction was concentrated to dryness and then resubmitted to the reaction conditions for 5 h. The reaction was concentrated to yield a TFA salt of (1R,3S,5R)-3-(4-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane as a viscous brown oil which was used without further purification. LC-MS retention time 2.755 min; m/z 246.25 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1

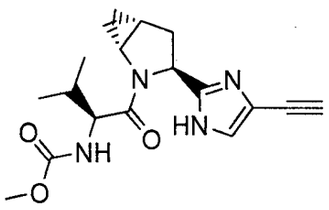
min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 156

Methyl (S)-3-methyl-1-oxo-1-((1R,3S,5R)-3-(4-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)butan-2-ylcarbamate

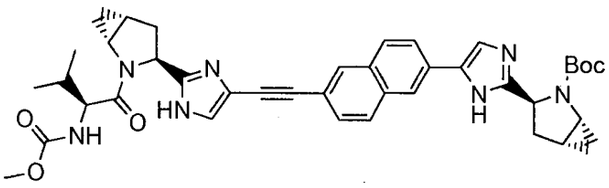
[00566] HATU (428 mg, 1.125 mmol) was added to a stirred solution of (1R,3S,5R)-3-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (212 mg, 0.865 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (197 mg, 1.125 mmol) in DMF (3 mL) and DIPEA (1.2 mL, 6.9 mmol) and the reaction was stirred at rt overnight. The reaction was concentrated to dryness and then purified with a BIOTAGE® Horizon (25g SiO_2, 40-60% EtOAc/hexanes) to yield methyl (S)-3-methyl-1-oxo-1-((1R,3S,5R)-3-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)butan-2-ylcarbamate (203 mg) as a yellow glass. LC-MS retention time 3.095 min; m/z 403.29 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 7.17 (br. s., 1 H), 5.04 - 5.11 (m, 1 H), 4.54 (d, *J*=6.8 Hz, 1 H), 3.65 (s, 3 H), 3.54 - 3.61 (m, 1 H), 2.82 (s, 1 H), 2.39 - 2.50 (m, 1 H), 2.27 - 2.36 (m, 1 H), 2.04 - 2.15 (m, 1 H), 1.94 - 2.04 (m, 1 H), 1.11 (dt, *J*=8.7, 5.6 Hz, 1 H), 0.95 (d, *J*=6.8 Hz, 3 H), 0.90 (d, *J*=6.8 Hz, 3 H), 0.73 - 0.79 (m, 1 H), 0.21 (s, 9 H).



Intermediate 157

Methyl (S)-1-((1R,3S,5R)-3-(4-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

[00567] Potassium carbonate (34.3 mg, 0.248 mmol) was added to a solution of methyl (S)-3-methyl-1-oxo-1-((1R,3S,5R)-3-(5-((trimethylsilyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)butan-2-ylcarbamate (200 mg, 0.497 mmol) in methanol (5 mL) and the reaction was flushed with nitrogen, sealed and then heated at 50 °C for 4h. and then stirred at rt overnight. The reaction was concentrated to dryness and then purified on a BIOTAGE® Horizon (12g SiO_2, 70-90% EtOAc/hexanes) to yield methyl (S)-1-((1R,3S,5R)-3-(5-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (151 mg) as a yellow glass. LC-MS retention time 1.788 min; m/z 331.32 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

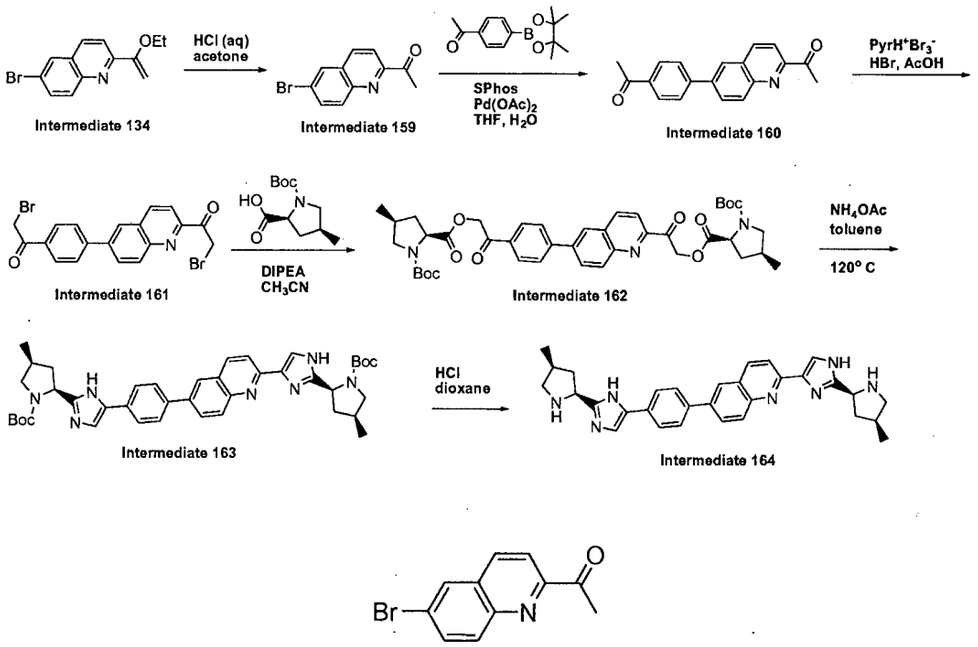


Intermediate 158

(1R,3S,5R)-*tert*-Butyl 3-(5-(6-((2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00568] A mixture of (1R,3S,5R)-*tert*-butyl 3-(5-(6-bromonaphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (208 mg, 0.457 mmol), methyl (S)-1-((1R,3S,5R)-3-(5-ethynyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (151 mg, 0.457 mmol) and CuI (8.70 mg, 0.046 mmol) in DMF (4 mL) and TEA (0.19 mL, 1.4 mmol) was vacuum flushed with nitrogen (6X) over 10 minutes. Then $Pd(PPh_3)_4$ (53 mg, 0.046 mmol) was added and the reaction mixture was vacuum flushed with nitrogen (3X), sealed and heated at 60 °C for 20h. The reaction was concentrated under a steam of nitrogen overnight and then purified preparative HPLC (40-80% MeOH/water with a TFA buffer) to yield a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-(6-((2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (270 mg) as a yellow solid. LC-MS retention time 2.995 min; m/z 704.70 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.18 (s, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.03 (m, 2 H), 7.89 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.69 - 7.85 (m, 1 H), 7.67 (dd, *J*=8.7, 1.4 Hz, 1 H), 5.11 (br. s., 1 H), 4.84 - 4.91 (m, 2 H), 4.55 (d, *J*=5.8 Hz, 1 H), 3.70 - 3.77 (m, 1 H), 3.67 (s, 3 H), 2.72 (dd, *J*=13.6, 9.0 Hz, 1 H), 2.55 - 2.63 (m, 1 H), 2.39 - 2.50 (m, 2 H), 2.11 - 2.20 (m, 1 H), 2.02 - 2.11 (m, 1 H), 1.81 - 1.89 (m, 1 H), 1.45 (br. s., 9 H), 1.07 - 1.14 (m, 1 H), 1.00 (d, *J*=6.8 Hz, 3 H), 0.93 (d, *J*=6.8 Hz, 3 H), 0.84 - 0.93 (m, 2 H), 0.74 (br. s., 1 H).

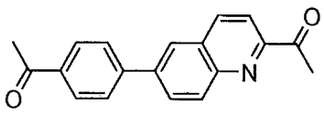
Scheme 41



Intermediate 159

1-(6-Bromoquinolin-2-yl)ethanone

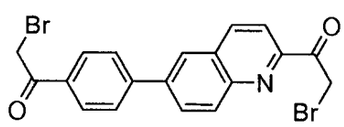
[00569] 3M HCl (aq.) (10 mL, 30.0 mmol) was added to a suspension of 6-bromo-2-(1-ethoxyvinyl)quinoline (780 mg, 2.80 mmol) in acetone (20 mL) and the reaction mixture was stirred at rt for 5 h. The reaction mixture was concentrated, dissolved into THF (20 mL) and treated with 3N HCl (aq.) (5 mL) was clear reaction solution was stirred at 60 °C for 5 h. The reaction was, cooled, neutralized with aq. NaOH and $NaHCO_3$ and extracted with EtOAc. The organic layer was dried, and concentrated to yield crude 1-(6-bromoquinolin-2-yl)ethanone (710 mg) as white solid. LC-MS retention time 3.703 min; m/z 250, 251.99 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 160

1-(6-(4-Acetylphenyl)quinolin-2-yl)ethanone

[00570] $Pd(OAc)_2$ (62.9 mg, 0.280 mmol) was added to a solution of 4-acetylphenylboronic acid (689 mg, 4.20 mmol), 1-(6-bromoquinolin-2-yl)ethanone (700 mg, 2.8 mmol), dicyclohexyl(2',6'- dimethoxybiphenyl-2-yl)phosphine (230 mg, 0.560 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in dioxane (10 mL) and water (2.500 mL) and the reaction mixture was refluxed at 110 °C for 5 h. The reaction mixture was cooled to rt and partitioned between sat.aq NH_4Cl and EtOAc. The organic layer was washed with $NaHCO_3$ and brine and then dried ($MgSO_4$), filtered, concentrated and purified by flash silica gel chromatography (loading solvent: DCM, eluted with 0 ~ 20 % EtOAc/ hexanes) to yield 1-(6-(4-acetylphenyl)quinolin-2-yl)ethanone (781 mg) as white solid. LC-MS retention time 3.776 min; m/z 290.29 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, chloroform-d) δ ppm 8.35 (d, *J*=8.3 Hz, 1 H), 8.34 (d, *J*=8.3 Hz, 1 H), 8.19 (d, *J*=8.5 Hz, 1 H), 8.12 (d, *J*=8.3 Hz, 1 H), 8.08 - 8.16 (m, 3 H), 7.85 (d, *J*=8.3 Hz, 1 H), 7.82 - 7.89 (m, 1 H), 2.91 (s, 3 H), 2.69 (s, 3 H).

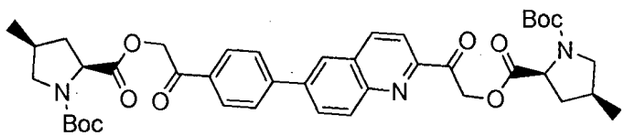


Intermediate 161

2-Bromo-1-(6-(4-(2-bromoacetyl)phenyl)quinolin-2-yl)ethanone

[00571] Pyridinium tribromide (221 mg, 0.691 mmol) was added to a suspension of 1-(6-(4-acetylphenyl)quinolin-2-yl)ethanone (100 mg, 0.346 mmol) and HBr (0.061 mL,

0.35 mmol) in acetic acid (3 mL) the reaction mixture was stirred at 70 °C) for 6 h. The reaction was concentrated under vacuum and the residue was partitioned between aq $NaHCO_3$ (15 mL) and EtOAc (30 mL +10 mL + 10 mL). The organic layers were combined, washed with brine, dried, filtered and concentrated to yield crude 2-bromo-1-(6-(4-(2-bromoacetyl)phenyl)quinolin-2-yl)ethanone (120 mg) as white solid. LC-MS retention time 4.138 min; m/z 448.01 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

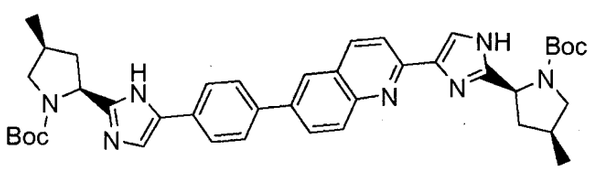


Intermediate 162

(2S,4S)-2-(2-(6-(4-(2-((2S,4S)-1-(*tert*-Butoxycarbonyl)-4-methylpyrrolidine-2-carbonyloxy)acetyl)phenyl)quinolin-2-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate

[00572] DIPEA (0.094 mL, 0.537 mmol) was added to a solution of 2-bromo-1-(6-(4-(2-bromoacetyl)phenyl)quinolin-2-yl)ethanone (60 mg, 0.134 mmol) and (2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (64.6 mg, 0.282 mmol) in acetonitrile (2 mL) and the mixture was stirred at rt for 16 h. The reaction mixture was partitioned between EtOAc (20 mL + 20 mL) / aq $NaHCO_3$ (5 mL). The combined organic layers were washed with aq $NaHCO_3$, brine, dried, filtered and concentrated to yield crude (2S,4S)-2-(2-(6-(4-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carbonyloxy)acetyl)phenyl)quinolin-2-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate (100 mg) as orange solid. This material was used without further purification. LC-MS retention time 4.558 min; m/z 742.36 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a

PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

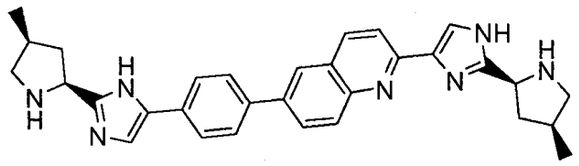


Intermediate 163

(2S,4S)-*tert*-Butyl 2-(5-(4-(2-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)quinolin-6-yl)phenyl)-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

[00573] Ammonium acetate (207 mg, 2.69 mmol) was added to a solution of (2S,4S)-2-(2-(6-(4-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carbonyloxy)acetyl)phenyl)quinolin-2-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate (100 mg, 0.134 mmol) in toluene (3 mL) and the reaction mixture was stirred at 120 °C (microwave reactor) for 3 h. The reaction was partitioned between EtOAc (20 mL + 10 mL + 10 mL) and aq $NaHCO_3$ (10 mL) and the combined organic layers were dried, filtered and concentrated. This crude product was purified by preparative HPLC (H_2O-CH_3CN with 10mM NH_4OAc buffer) to yield product (2S,4S)-*tert*-butyl 2-(5-(6-(4-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinolin-2-yl)-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (16.6 mg) as a yellow solid. LC-MS retention time 3.270 min; m/z 704.72 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5

min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

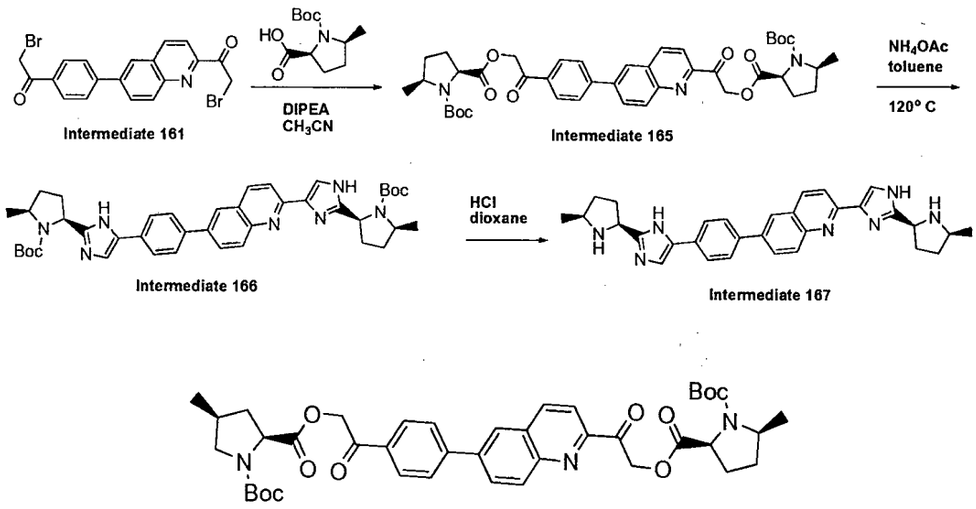


Intermediate 164

2-(2-((2S,4S)-4-Methylpyrrolidin-2-yl)-1H-imidazol-4-yl)-6-(4-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline

[00574] 4M HCl (0.2 mL, 0.800 mmol) in dioxane was added to a solution of (2S,4S)-*tert*-butyl 2-(5-(6-(4-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinolin-2-yl)-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (16.6 mg, 0.024 mmol) in dioxane (1 mL) and the reaction mixture was stirred at rt for 3d. The reaction mixture was concentrated to yield a crude HCl salt of 2-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)-6-(4-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline (19.1 mg) as yellow solid. LC-MS retention time 2.765 min; m/z 504.47 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 42

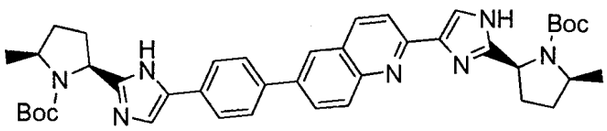


Intermediate 165

(2S,5S)-2-(2-(6-(4-(2-((2S,4S)-1-(*tert*-Butoxycarbonyl)-4-methylpyrrolidine-2-carbonyloxy)acetyl)phenyl)quinolin-2-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate

[00575] DIPEA (0.059 mL, 0.335 mmol) was added to a solution of 2-bromo-1-(6-(4-(2-bromoacetyl)phenyl)quinolin-2-yl)ethanone (50 mg, 0.11 mmol) and (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (54 mg, 0.24 mmol) in acetonitrile (2 mL) and the reaction mixture was stirred at rt for 16 h. The reaction was partitioned between EtOAc (20 +20 mL) / aq $NaHCO_3$ (5 mL). The combined organic layers were washed with sat. aq $NaHCO_3$, brine, dried, filtered and concentrated to yield crude (2S,5S)-2-(2-(6-(4-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)phenyl)quinolin-2-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (69 mg) as orange solid. This crude was used without further purification. LC-MS retention time 4.483 min; m/z 744.61 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10%

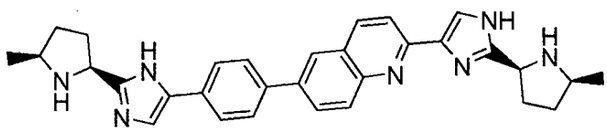
H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 166

(2S,5S)-*tert*-Butyl 2-(5-(4-(2-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)quinolin-6-yl)phenyl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate

[00576] Ammonium acetate (107 mg, 1.39 mmol) was added to a suspension of (2S,5S)-2-(2-(6-(4-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)phenyl)quinolin-2-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (69 mg, 0.093 mmol) in toluene (Volume: 2 mL) and the reaction mixture was stirred at 120 °C (microwave reactor) for 3 h. The reaction was partitioned between EtOAc (10 mL + 5 mL + 5 mL) and aq NaHCO3 (5 mL). The combined organic layers were dried, filtered and concentrated and the crude product was purified by preparative HPLC (H_2O-CH_3CN with 10mM NH_4OAc buffer) to yield product (2S,5S)-*tert*-butyl 2-(4-(6-(4-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)quinolin-2-yl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (13.4 mg) as a yellow solid. LC-MS retention time 4.350min; m/z 702.29 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.37 (d, *J*=8.8 Hz, 1 H), 8.16 (s, 1 H), 8.07 - 8.10 (m, 2 H), 8.03 (d, *J*=8.8 Hz, 1 H), 7.79 - 7.88 (m, 5 H), 7.40 (s, 1 H), 4.90 - 5.07 (m, 2 H), 3.99 - 4.13 (m, 2 H), 2.10 - 2.39 (m, 6 H), 1.68 - 1.82 (m, 2 H), 1.43 (d, *J*=6.0 Hz, 6 H), 1.24 - 1.59 (m, 22 H).

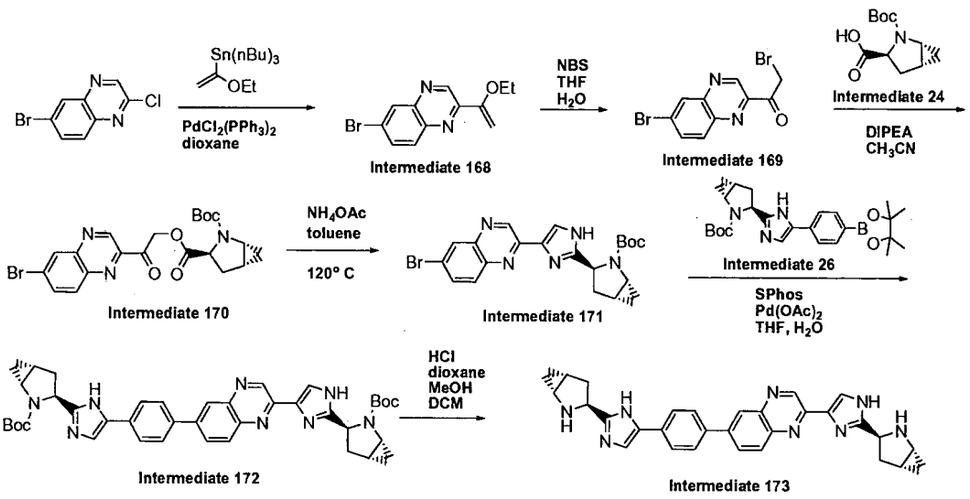


Intermediate 167

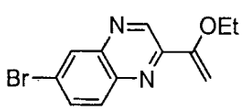
2-(2-((2S,5S)-5-Methylpyrrolidin-2-yl)-1H-imidazol-4-yl)-6-(4-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline

[00577] 4M HCl (0.2 mL, 0.8 mmol) in dioxane was added to a solution of (2S,5S)-*tert*-butyl 2-(5-(6-(4-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinolin-2-yl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (12.7 mg, 0.018 mmol) in dioxane (1 mL) and the mixture was stirred at rt for 3d. The reaction mixture was concentrated to yield a crude HCl salt of 2-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)-6-(4-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline (18.1 mg) as yellow solid. LC-MS retention time 2.597 min; m/z 504.46 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (d, *J*=9.0 Hz, 1 H), 8.66 (s, 1 H), 8.54 - 8.61 (m, 2 H), 8.51 (d, *J*=9.0 Hz, 1 H), 8.50 (d, *J*=8.8 Hz, 1 H), 8.00 - 8.08 (m, 4 H), 7.99 (s, 1 H), 5.14 (t, *J*=8.5 Hz, 1 H), 5.07 (t, *J*=8.0 Hz, 1 H), 3.90 - 4.04 (m, 2 H), 2.52 - 2.75 (m, 4 H), 2.39 - 2.53 (m, 2 H), 1.98 - 2.14 (m, 2 H), 1.59 (dd, *J*=9.7, 6.7 Hz, 6 H).

Scheme 43



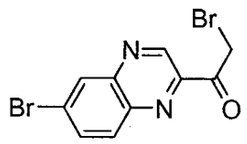
[00578] Intermediate 173 was prepared in an analogous manner to Intermediate 139 in Scheme 35 by utilizing 6-bromo-2-chloroquinoxaline as the starting material rather than 6-bromo-2-chloroquinoline. Analytical data shown below.



Intermediate 168

6-Bromo-2-(1-ethoxyvinyl)quinoxaline

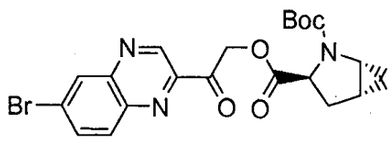
[00579] The reaction yielded the desired product (380 mg) as a white solid. LC-MS retention time 4.178 min; m/z 278.9, 280.98 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 169

2-Bromo-1-(6-bromoquinoxalin-2-yl)ethanone

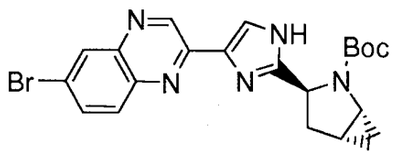
[00580] The reaction yielded the desired product (390 mg) as a white solid. LC-MS retention time 3.743 min; m/z 331.12 (1:2:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 170

(1R,3S,5R)-3-(2-(6-Bromoquinoxalin-2-yl)-2-oxoethyl) 2-*tert*-butyl 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

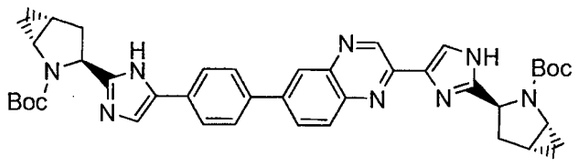
[00581] The reaction yielded the desired product (270 mg) as a pink/orange solid. LC-MS retention time 4.115 min; m/z 473, 475.81 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 171

tert-Butyl (1R,3S,5R)-3-(4-(6-bromo-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00582] The reaction yielded the desired product (125 mg) as a red/orange solid. LC-MS retention time 3.958 min; m/z 453.90, 455.87 (1:1) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.40 (br. s., 1 H), 8.22 (d, *J*=2.0 Hz, 1 H), 7.96 (d, *J*=8.8 Hz, 1 H), 7.93 - 7.99 (m, 1 H), 7.90 (dd, *J*=8.8, 2.0 Hz, 1 H), 4.71 - 4.81 (m, 1 H), 3.59 (br. s., 1 H), 2.49 - 2.63 (m, 1 H), 2.31 - 2.45 (m, 1 H), 1.68 - 1.82 (m, 1 H), 1.16 - 1.53 (m, 5 H), 0.81 - 0.94 (m, 1 H), 0.64 (br. s., 1 H).

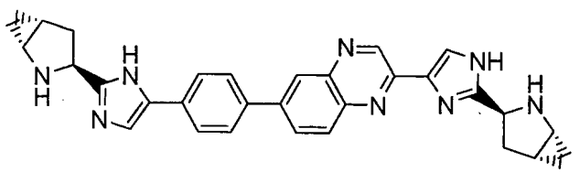


Intermediate 172

tert-Butyl (1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00583] The reaction yielded the desired product (64.4 mg) as a bright yellow solid. LC-MS retention time 3.696 min; m/z 699.3 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u

C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.45 (s, 1 H), 8.31 (s, 1 H), 8.19 (d, *J*=8.3 Hz, 1 H), 8.07 (d, *J*=8.8 Hz, 1 H), 7.97 (s, 1 H), 7.81 - 7.95 (m, 4 H), 7.60 (s, 1 H), 4.57 - 4.80 (m, 2 H), 3.23 - 3.60 (m, 2 H), 2.23 - 2.48 (m, 4 H), 1.61 - 1.75 (m, 2 H), 1.28 (br. s., 18 H), 0.73 - 0.87 (m, 2 H), 0.59 (br. s., 2 H).

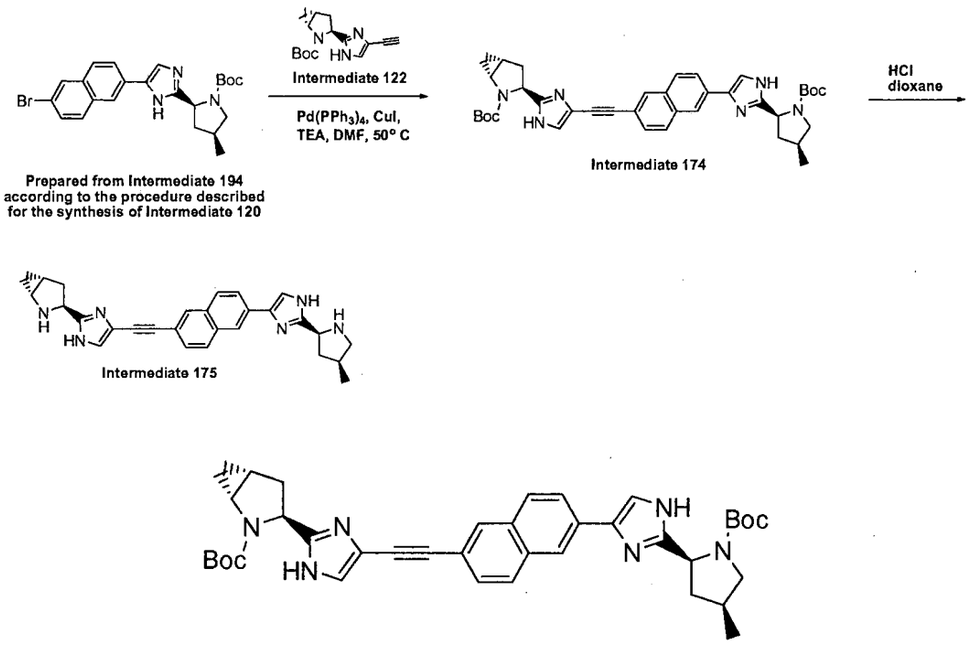


Intermediate 173

Methyl ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00584] The reaction yielded an HCl salt of the desired product (80 mg) as a yellow solid. LC-MS retention time 2.915 min; m/z 501.42 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.54 (s, 1 H), 8.40 - 8.43 (m, 1 H), 8.34 (s, 1 H), 8.23 - 8.30 (m, 2 H), 8.13 (s, 1 H), 8.00 - 8.08 (m, 4 H), 4.88 - 5.08 (m, 2 H), 3.53 - 3.77 (m, 2 H), 2.64 - 2.90 (m, 4 H), 2.08 - 2.22 (m, 2 H), 1.23 - 1.36 (m, 2 H), 1.02 - 1.14 (m, 2 H).

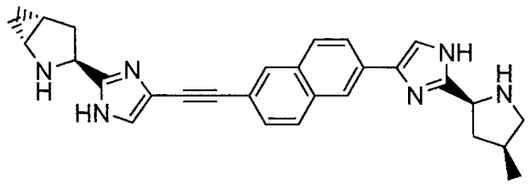
Scheme 44



Intermediate 174

(1R,3S,5R)-*tert*-Butyl 3-(4-((6-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00585] Compound was prepared in an analogous manner to Intermediate 153 with the appropriate starting materials to yield a TFA salt of the title compound (121 mg) as a yellow glass. LC-MS retention time 4.100 min; m/z 647.37 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

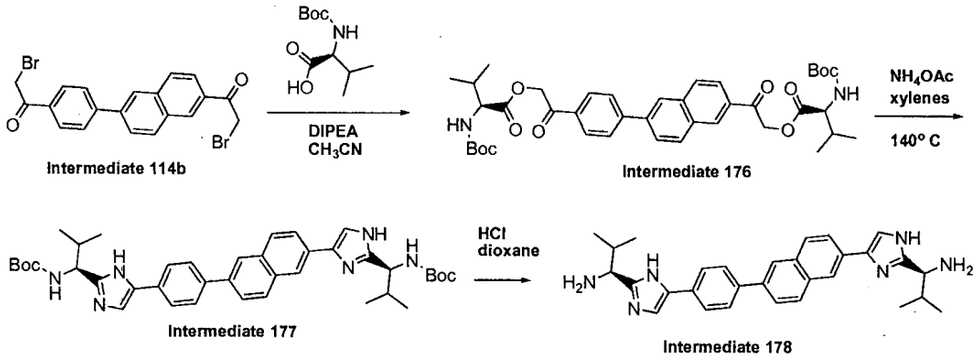


Intermediate 175

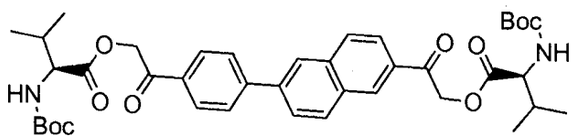
(1R,3S,5R)-3-(4-((6-(2-((2S,4S)-4-Methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00586] 2M HCl (0.33 mL, 0.66 mmol) in dioxane was added to a solution of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-((6-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (115 mg, 0.131 mmol) in dioxane (2 mL) and the reaction was stirred vigorously overnight. The reaction was concentrated to yield an HCl salt of (1R,3S,5R)-3-(4-((6-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (87 mg) which was used without further purification. LC-MS retention time 2.793 min; m/z 449.41 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 45



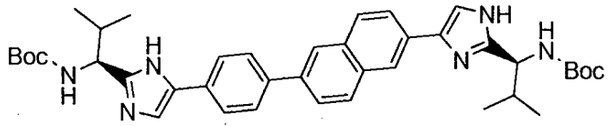
[00587] Intermediate 178 was prepared in an analogous manner to the preparation of Intermediate 117 in Scheme 29 utilizing (S)-2-(*tert*-butoxycarbonylamino)-3-methylbutanoic acid as a starting material rather than (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid. Analytical data for the intermediates shown below.



Intermediate 176

(S)-2-(4-(6-(2-((S)-2-(*tert*-Butoxycarbonylamino)-3-methylbutanoyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl 2-(*tert*-butoxycarbonylamino)-3-methylbutanoate

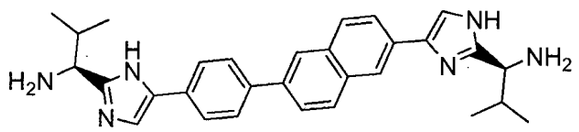
[00588] The reaction yielded the desired product (700 mg) as a tan solid. LC-MS retention time 2.243 min; m/z 717.5 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1.0 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Intermediate 177

tert-Butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-methylpropyl)carbamate

[00589] The reaction yielded the desired product (453 mg) as a yellow solid. LC-MS retention time 2.407 min; m/z 677.6 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1.0 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



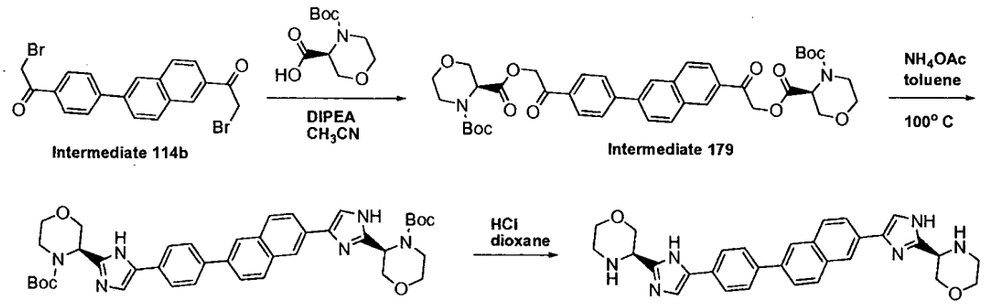
Intermediate 178

(S)-1-(5-(4-(6-(2-((S)-1-Amino-2-methylpropyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-methylpropan-1-amine

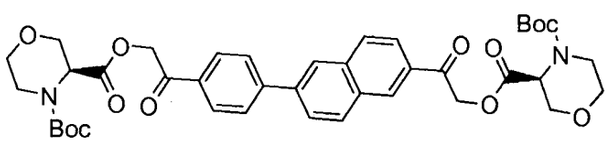
[00590] The reaction yielded an HCl salt of the desired product (390 mg) as a yellow solid. LC-MS retention time 2.080 min; m/z 477.4 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1.0 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM

ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 46



[00591] Intermediate 181 was prepared in an analogous manner to the preparation of Intermediate 117 in Scheme 29 utilizing (S)-4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid as a starting material rather than (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid. Analytical data for the intermediates shown below.

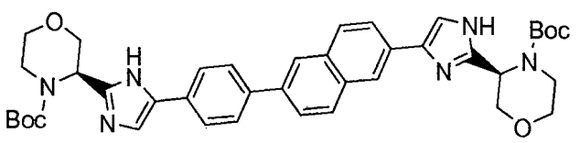


Intermediate 179

(S)-3-(2-(4-(6-(2-((S)-4-(*tert*-Butoxycarbonyl)morpholine-3-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 4-*tert*-butyl morpholine-3,4-dicarboxylate

[00592] The reaction yielded an HCl salt of the desired product (1.60 g) as an off-white solid foam. LC-MS retention time 4.413 min; m/z 770.29 (MNa+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a

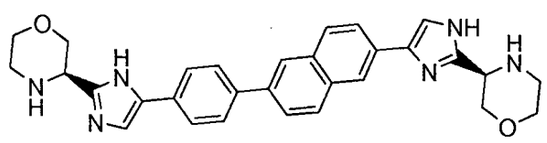
MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.47 (s, 1 H), 8.13 (s, 1 H), 7.98 - 8.11 (m, 5 H), 7.86 (d, *J*=8.3 Hz, 3 H), 5.39 - 5.70 (m, 4 H), 4.66 - 4.83 (m, 2 H), 4.46 - 4.63 (m, 2 H), 3.91 - 4.03 (m, 2 H), 3.68 - 3.85 (m, 4 H), 3.49 - 3.59 (m, 3 H), 3.27 - 3.40 (m, 1 H), 1.51 (s, 18 H).



Intermediate 180

(R)-*tert*-Butyl 3-(5-(4-(6-(2-((R)-4-(*tert*-butoxycarbonyl)morpholin-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)morpholine-4-carboxylate

[00593] The reaction yielded the desired product (1.12 g) as an orange solid. LC-MS retention time 3.608 min; m/z 707.94 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.22 (br. s., 1 H), 8.09 (s, 1 H), 7.90 - 7.97 (m, 2 H), 7.75 - 7.89 (m, 6 H), 7.49 (br. s., 1 H), 7.41 (br. s., 1 H), 5.17 - 5.24 (m, 2 H), 4.42 (t, *J*=11.2 Hz, 2 H), 3.82 - 3.95 (m, 6 H), 3.59 (tt, *J*=11.6, 3.0 Hz, 2 H), 3.39 - 3.51 (m, 2 H), 1.50 (d, *J*=2.8 Hz, 18 H).

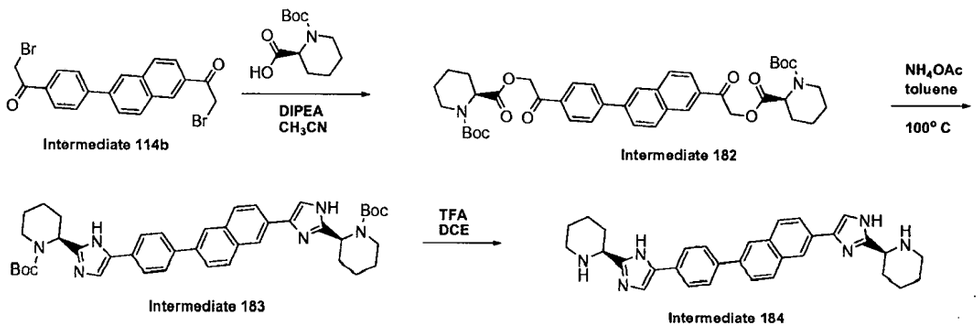


Intermediate 181

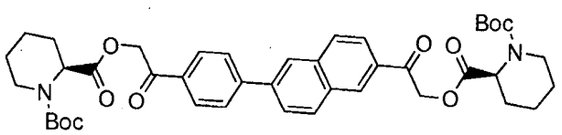
(R)-3-(5-(4-(6-(2-((R)-Morpholin-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)morpholine

[00594] The reaction yielded an HCl salt of the desired product (312 mg) as a yellow solid. LC-MS retention time 2.988 min; m/z 507.72 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 47



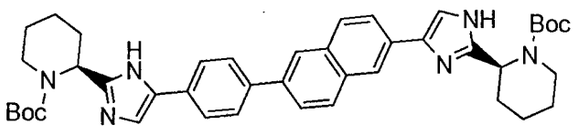
[00595] Intermediate 184 was prepared in an analogous manner to the preparation of Intermediate 117 in Scheme 29 utilizing (S)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid as a starting material rather than (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid. Analytical data for the intermediates shown below.



Intermediate 182

(S)-2-(2-(4-(6-(2-((S)-1-(*tert*-Butoxycarbonyl)piperidine-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 1-*tert*-butyl piperidine-1,2-dicarboxylate

[00596] The reaction yielded the desired product (1.67 g) as a solidified light yellow foam. LC-MS retention time 4.850 min; m/z 766.37 (MNa+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.47 (s, 1 H), 8.13 (s, 1 H), 7.99 - 8.10 (m, 5 H), 7.83 - 7.89 (m, 3 H), 5.32 - 5.67 (m, 4 H), 4.92 - 5.13 (m, 2 H), 3.93 - 4.11 (m, 2 H), 3.00 - 3.28 (m, 2 H), 2.40 (br. s., 2 H), 1.68 - 1.84 (m, 6 H), 1.49 (s, 18 H), 1.39 - 1.67 (m, 4 H)

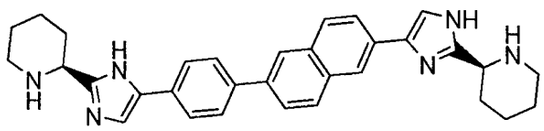


Intermediate 183

(S)-*tert*-Butyl 2-(5-(4-(6-(2-((S)-1-(*tert*-butoxycarbonyl)piperidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)piperidine-1-carboxylate

[00597] The reaction yielded the desired product (1.18 g) as a bright yellow solid. LC-MS retention time 3.778 min; m/z 703.97 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.22 (br. s., 1 H), 8.09 (s, 1 H), 7.93 (t, *J*=7.7 Hz, 2 H), 7.73 - 7.88 (m, 6 H), 7.46 (br. s., 1 H), 7.38 (br. s., 1 H), 5.47 (br.

s., 2 H), 4.03 - 4.15 (m, 2 H), 2.99 - 3.12 (m, 2 H), 2.46 (br. s., 2 H), 1.80 - 1.94 (m, 2 H), 1.50 (d, *J*=2.3 Hz, 18 H), 1.44 - 1.76 (m, 8 H).

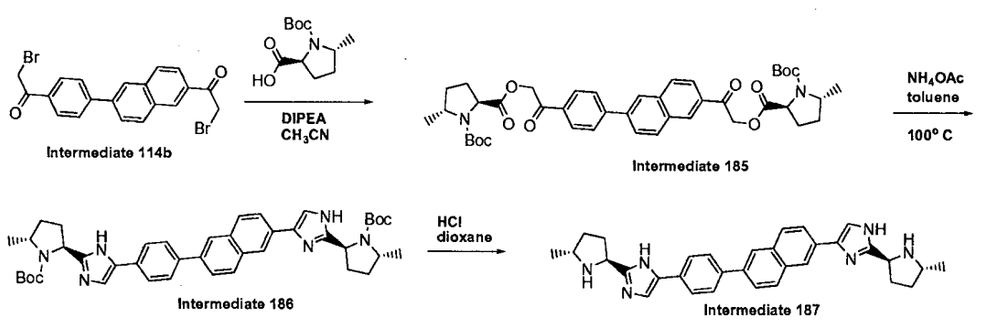


Intermediate 184

(S)-2-(5-(4-(6-(2-((S)-Piperidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)piperidine

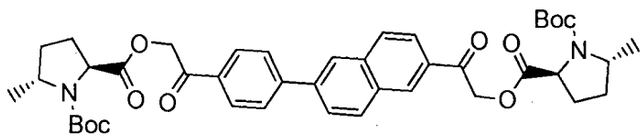
[00598] The reaction yielded an HCl salt of the desired product (280 mg) as a yellow solid. LC-MS retention time 3.015 min; m/z 503.69 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.06 (br. s., 2 H), 9.85 (br. s., 2 H), 8.48 (s, 1 H), 8.36 (s, 1 H), 8.09 - 8.19 (m, 3 H), 7.96 - 8.09 (m, 7 H), 4.70 (br. s., 2 H), 3.42 - 3.53 (m, 2 H), 3.14 (br. s., 2 H), 2.10 - 2.37 (m, 4 H), 1.60 - 2.00 (m, 8 H).

Scheme 48



[00599] Intermediate 187 was prepared in an analogous manner to the preparation of Intermediate 117 in Scheme 29 utilizing (2S,5R)-1-(*tert*-butoxycarbonyl)-5-

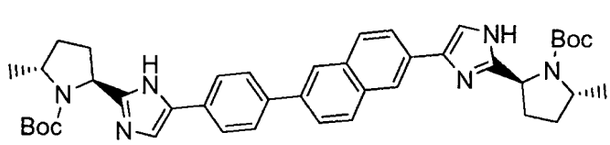
methylpyrrolidine-2-carboxylic acid (prepared according to JOC 1995, p. 5011) as a starting material rather than (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid. Analytical data for the intermediates shown below.



Intermediate 185

(2S,5R)-2-(2-(4-(6-(2-((2S,5R)-1-(*tert*-Butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)naphthalen-2-yl)phenyl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate

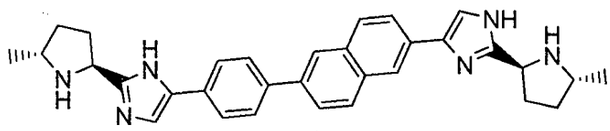
[00600] The reaction yielded the desired product (979 mg). LC-MS retention time 4.796 min; m/z 766.19 (MNa+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, chloroform-d) δ ppm 8.47 (br. s., 1 H), 8.13 (d, *J*=2.5 Hz, 1 H), 7.99 - 8.11 (m, 5 H), 7.86 (dd, *J*=7.8, 2.3 Hz, 3 H), 5.21 - 5.77 (m, 4 H), 4.51 - 4.58 (m, 1 H), 4.47 (dd, *J*=7.8, 4.5 Hz, 1 H), 4.17 - 4.26 (m, 1 H), 4.07 - 4.14 (m, 1 H), 2.23 - 2.48 (m, 6 H), 1.60 - 1.68 (m, 2 H), 1.44 - 1.52 (m, 18 H), 1.25 (d, *J*=6.3 Hz, 3 H), 1.21 (d, *J*=6.3 Hz, 3 H).



Intermediate 186

(2S,5R)-*tert*-Butyl 2-(5-(4-(6-(2-((2S,5R)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate

[00601] The reaction yielded the desired product (561 mg) as an orange solid foam. LC-MS retention time 3.673 min; m/z 703.95 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



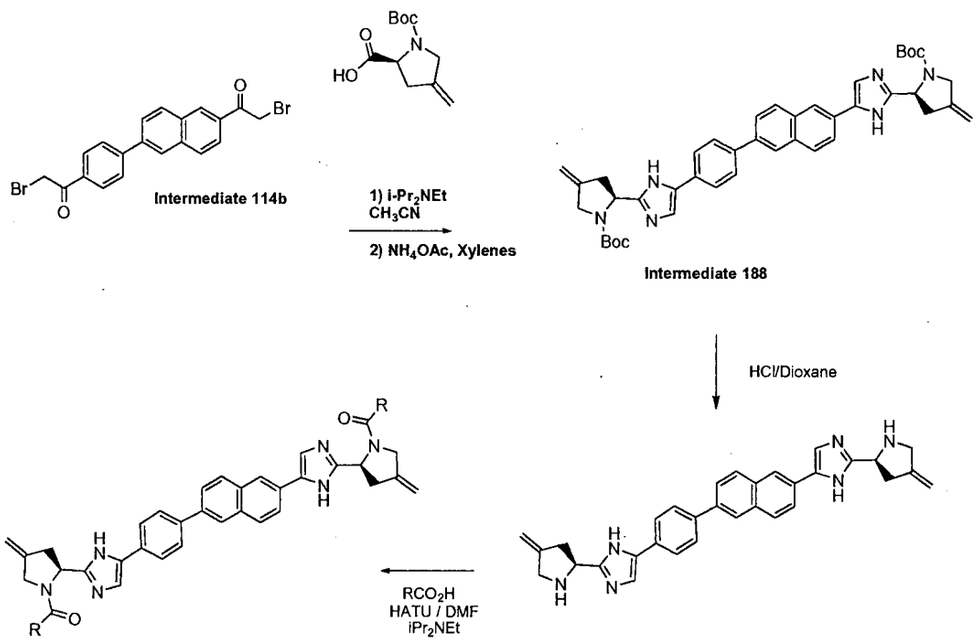
Intermediate 187

2-((2S,5R)-5-Methylpyrrolidin-2-yl)-5-(4-(6-(2-((2S,5R)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazole

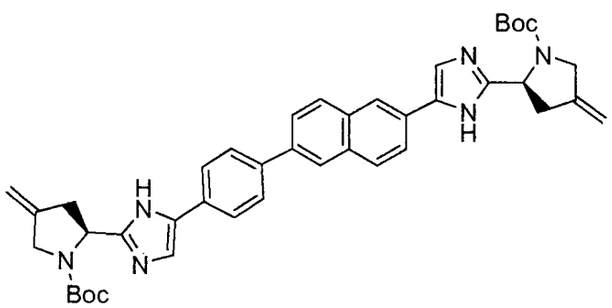
[00602] The reaction yielded an HCl salt of the desired product (157 mg) as a light orange solid. LC-MS retention time 2.975 min; m/z 503.71 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.84 - 10.25 (m, 4 H), 8.54 (s, 1 H), 8.36 (s, 1 H), 7.95 - 8.22 (m, 10 H), 5.15 (br.

s., 2 H), 4.00 (br. s., 2 H), 2.53 - 2.63 (m, 4 H), 2.30 - 2.41 (m, 2 H), 1.67 - 1.82 (m, 2 H), 1.43 (d, *J*=4.3 Hz, 6 H).

Scheme 49



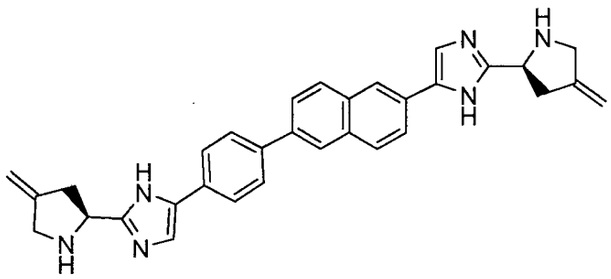
[00603] Intermediate 189 was prepared as shown in Scheme 49 utilizing (S)-1-(*tert*-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid as starting material. Analytical data for the intermediates shown below.



Intermediate 188

tert-Butyl (2S)-2-(4-(4-(6-(2-((2S)-1-(*tert*-butoxycarbonyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinecarboxylate

[00604] Hunig's base (0.43 mL, 2.47 mmol) was added to a stirred solution of (S)-1-(*tert*-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid (509 mg, 2.241 mmol) and 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (500 mg, 1.121 mmol) in MeCN (25 mL). The mixture was stirred for 18h at RT. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with water, saturated sodium bicarbonate solution, and brine. After being concentrated, the residue was taken up in xylene (25 mL) and ammonium acetate (1.3 g, 16.85 mmol) was added. The pressure vessel was sealed and heated at 140 °C for 2.5h. The reaction mixture was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 80g Thompson silica gel cartridge (eluted with 15% B to 100% B over 1 L where Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl (2S)-2-(4-(4-(6-(2-((2S)-1-(*tert*-butoxycarbonyl)-4-methylene-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-4-methylene-1-pyrrolidinecarboxylate (380 mg, 45 % yield). LC-MS retention time 3.32 min; Calcd. for $C_{42}H_{47}N_6O_4$: 699.36 m/z Found 699.41 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.21 (s, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.97 (s, 1H), 7.87-7.83 (m, 6H), 7.54 (s, 1H), 7.46 (s, 1H), 5.14 (s, 2H), 5.19 (s, 2H), 4.30 (br s, 2H), 4.15 (br s, 2H), 3.22-3.16 (m, 2H), 2.81 - 2.76 (m, 2H), 1.51/1.31 (s, 18H).

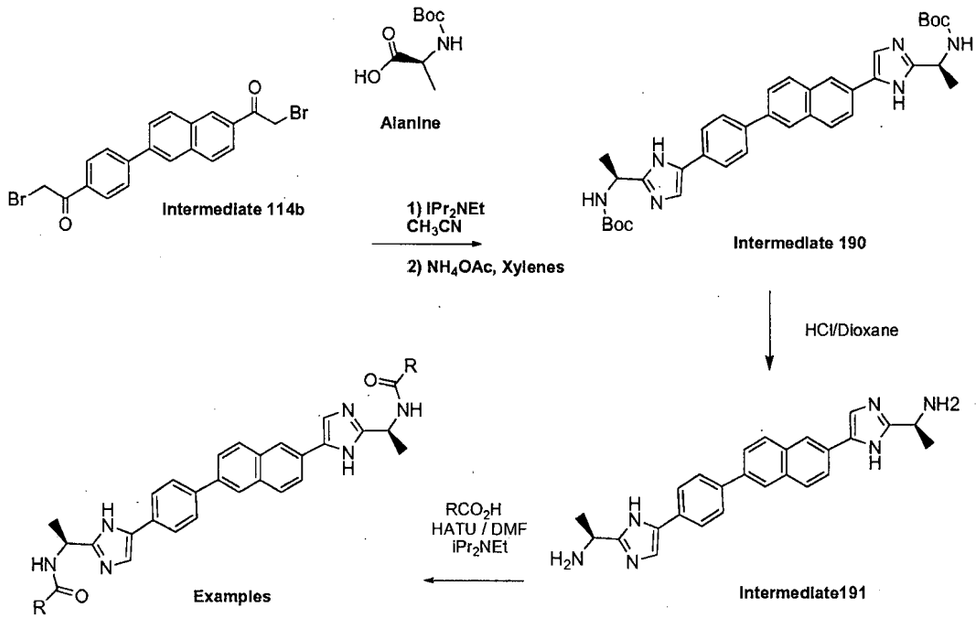


Intermediate 189

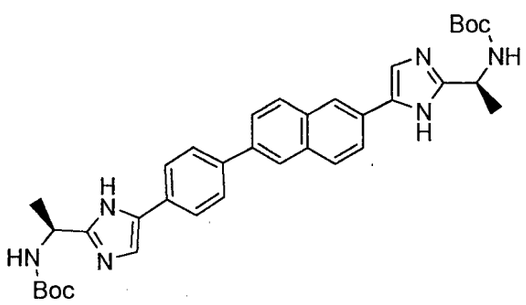
2-((S)-4-Methylenepyrrolidin-2-yl)-4-(4-(6-(2-((S)-4-methylenepyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazole

[00605] A solution of 4N HCl in dioxane (10 mL) was added to *tert*-butyl (2S)-2-(4-(4-(6-(2-((2S)-1-(*tert*-butoxycarbonyl)-4-methylene-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-4-methylene-1-pyrrolidinecarboxylate (380 mg. 0.544 mmol) in MeOH (10 mL) and stirred at ambient conditions for 4 hours, concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 350 mg). LC-MS retention time 2.68 min; Calcd. for $C_{32}H_{31}N_6$: 499.26 m/z Found 499.21 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 50



[00606] Intermediate 191 was prepared as shown in Scheme 50 utilizing (S)-2-(*tert*-butoxycarbonylamino)propanoic acid as starting material. Analytical data for the intermediates shown below.

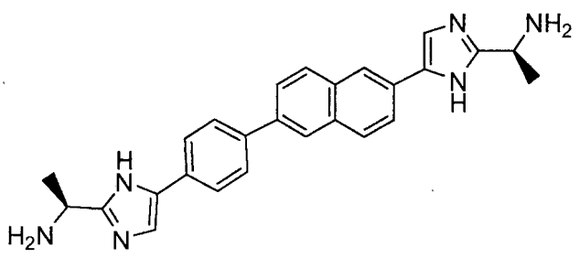


Intermediate 190

tert-Butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)carbamate

[00607] Hunig's base (0.39 mL, 2.24 mmol) was added to a stirred solution of (S)-2-(*tert*-butoxycarbonylamino)propanoic acid (424 mg, 2.24 mmol) and 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (500 mg, 1.121 mmol) in MeCN (50 mL). The mixture was stirred for 18h at RT. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with water, saturated sodium

bicarbonate solution, and brine. After being concentrated, the residue was taken up in xylene (25 mL) and ammonium acetate (1.5 g, 20.18 mmol) was added. The pressure vessel was sealed and heated at 140 °C for 3.5h. The reaction mixture was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 90g Thompson silica gel cartridge (eluted with 15% B to 100% B over 1 L where Solvent B = ethyl acetate and Solvent A = hexanes) to provide *tert*-Butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)ethyl)carbamate (368 mg, 47 % yield). NOTE: Sample was only partially soluble in methylene chloride. LC-MS retention time 3.24 min; Calcd. for $C_{36}H_{43}N_6O_4$: 623.33 m/z Found 623.37 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.11 (s, 1H), 7.95 (t, *J* = 8.24 Hz, 2H), 7.86-7.79 (m, 6H), 7.46 (s, 1H), 7.37 (s, 1H), 4.93-4.89 (m, 2H), 1.57-1.48 (m, 24H).



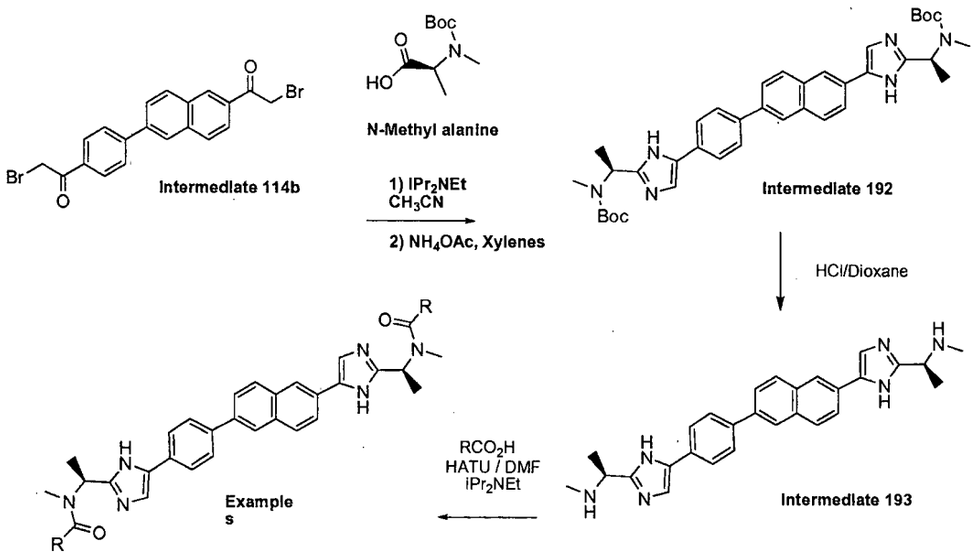
Intermediate191

(S)-1-(4-(4-(6-(2-((S)-1-Aminoethyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)ethanamine

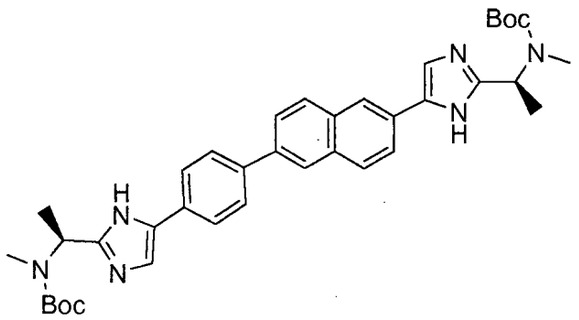
[00608] A solution of 4N HCl in dioxane (10 mL) was added to *tert*-butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-imidazol-4-yl)-2-

naphthyl)phenyl)-1*H*-imidazol-2-yl)ethyl)carbamate (368 mg. 0.59 mmol) in MeOH (10 mL) and stirred at ambient conditions for 5 hours, concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 334 mg). LC-MS retention time 1.33 min; Calcd. for $C_{26}H_{27}N_6$: 423.23 m/z Found 423.17 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min and an analysis time of 3 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 51



[00609] Intermediate 193 was prepared as shown in Scheme 51 utilizing (S)-2-(*tert*-butoxycarbonyl(methyl)amino)propanoic acid as starting material. Analytical data for the intermediates shown below.

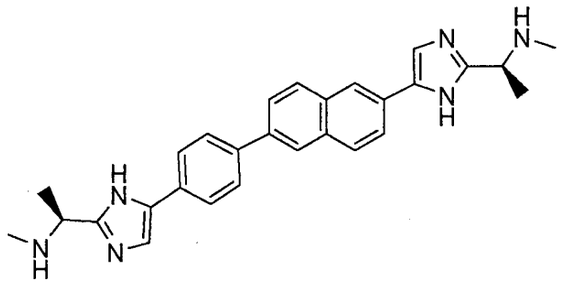


Intermediate 192

tert-Butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)methylcarbamate

[00610] Hunig's base (0.78 mL, 4.48 mmol) was added to a stirred solution of (S)-2-(*tert*-butoxycarbonyl(methyl)amino)propanoic acid (456 mg, 2.241 mmol) and 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (500 mg, 1.121 mmol) in MeCN (50 mL). The mixture was stirred for 18h at RT. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with water, saturated sodium bicarbonate solution, and brine. After being concentrated, the residue was taken up in xylene (25 mL) and ammonium acetate (859 mg, 11.15 mmol) was added. The pressure vessel was sealed and heated at 140 °C for 3h. The reaction mixture was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 90g Thompson silica gel cartridge (eluted with 15% B to 100% B over 1 L where Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)ethyl)methylcarbamate (460 mg, 58% yield). LC-MS retention time 3.28 min; Calcd. for $C_{38}H_{47}N_6O_4$: 651.37 m/z Found 651.34 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H

NMR (500 MHz, MeOD) δ ppm 8.24-8.12 (m, 2H), 7.98-7.82 (m, 8H), 7.52-7.42 (m, 2H), 5.47 (br s, 2H), 2.77 (s, 3H), 2.76 (s, 3H),1.64 (m, 6H), 1.52 (s, 18H).

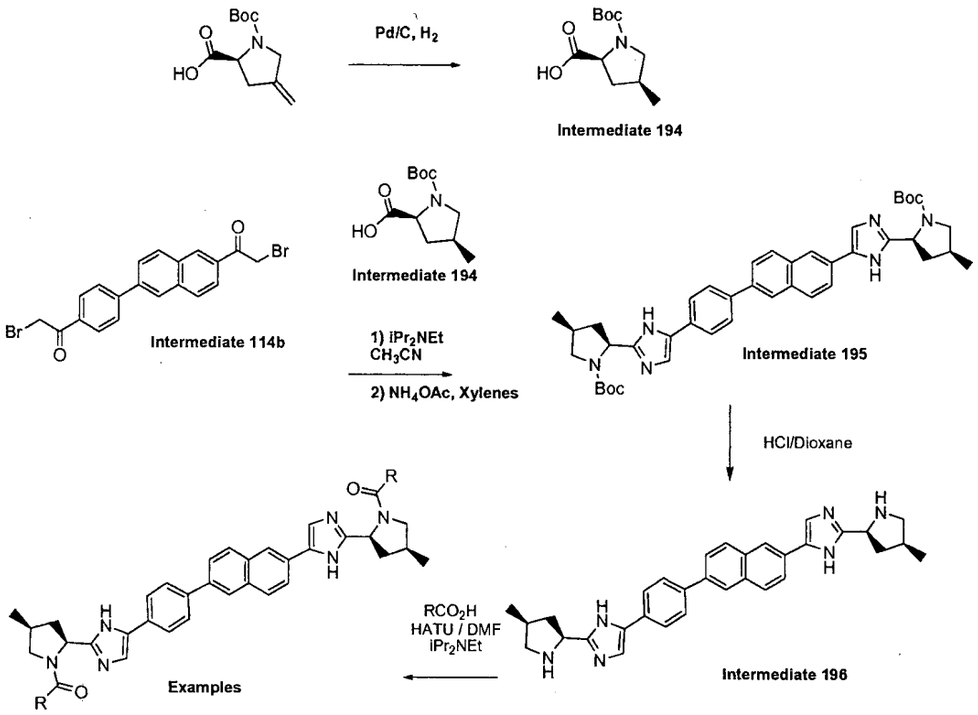


Intermediate 193

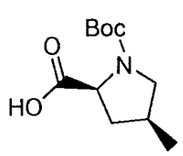
(S)-N-Methyl-1-(4-(4-(6-(2-((S)-1-(methylamino)ethyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)ethanamine

[00611] A solution of 4N HCl in dioxane (10 mL) was added to *tert*-butyl ((1S)-1-(4-(4-(6-(2-((1S)-1-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)ethyl)methylcarbamate (434 mg. 0.667 mmol) in MeOH (10 mL) and stirred at ambient conditions for 3 hours, concentrated and dried under vacuum. Tetra HCl salt (assume theoretical: 396 mg). LC-MS retention time 1.44 min; Calcd. for $C_{28}H_{31}N_6$: 451.26 m/z Found 451.17 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min and an analysis time of 3 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 52



[00612] Intermediate 196 was prepared as shown in Scheme 52 utilizing (2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid as starting material. Analytical data for the intermediates shown below.

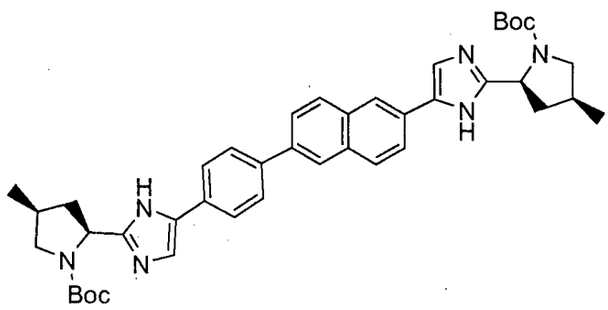


Intermediate 194

(2S,4S)-1-(*tert*-Butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid

[00613] A solution of (S)-1-(*tert*-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid (4 g, 17.60 mmol) in 2-propanol (10 mL) was added to a nitrogen purged suspension of 10% palladium on carbon (936 mg) in 2-propanol (240 mL) and the flask was charged with hydrogen gas (1 atm). After being stirred 18, the catalyst was removed by filtration over CELITE® and the filtrate concentrated. LC analysis showed the sample contained ~14% of the trans isomer, and recrystallization from toluene enriched the cis isomer to 96% (16:1). LC-MS retention time 3.26 min; Calcd. for $C_{11}H_{20}N_6O_4$: 230.14

m/z Found 252.14 $[M+Na]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® 2x5mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 10% methanol / 90% water / 0.1% TFA and Solvent B was 90% methanol/ 10% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 4.21 - 4.17 (m, 1H), 3.76 - 3.67 (m, 1H), 2.96 - 2.92 (m, 1H), 2.49 - 2.46 (m, 1H), 2.30 - 2.29 (m, 1H), 1.59 - 1.51 (m, 1H), 1.47 / 1.43 (m, 9H), 1.10 -1.06 (m, 3H).

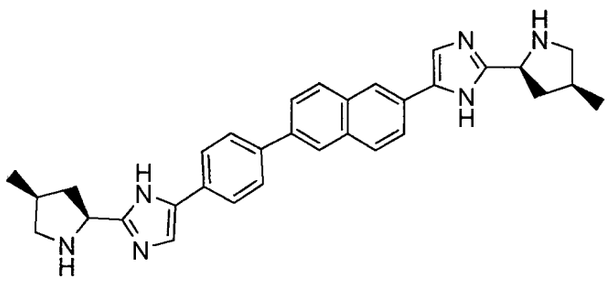


Intermediate 195

tert-Butyl (2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinecarboxylate

[00614] Hunig's base (0.381 mL, 2.181 mmol) was added to a stirred solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (500 mg, 2.18 mmol) and 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (486 mg, 1.09 mmol) in acetonitrile (11 mL). The heterogeneous mixture was stirred for 18h at RT and additional Hunig's base (1 equiv) was added and the mixture was stirred for 24h. The solvent was removed *in vacuo* and the residue was taken up in methylene chloride and washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Wash was repeated 2x. The crude product, isolated as a tan foam, was taken up in xylene (15 mL) and ammonia acetate (1.261 g, 16.36 mmol) was added. The pressure vessel was sealed and placed into a preheated oil bath (140 °C) and stirred for 2h. The reaction

mixture was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 80g Thompson silica gel cartridge (eluted with 25% B to 100% B over 1.5 L and hold 0.5 L B. Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl (2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methyl-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-4-methyl-1-pyrrolidinecarboxylate (214.2 mg 27.9 %) as a yellow foam. LC-MS retention time 3.32 min; Calcd. for $C_{42}H_{51}N_6O_4$: 703.40 m/z Found 703.28 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.12 (s, 1H), 7.96-7.94 (m, 2H), 7.87-7.82 (m, 6H), 7.50 (s, 1H), 7.42 (s, 1H), 4.87 (br. s, 2H), 3.81 (br. s, 2H), 3.24-3.18 (m, 2H), 2.53-2.50 (m, 2H), 2.36 (br s, 2H), 1.82-1.74 (m, 2H), 1.46/1.23 (s, 18H), 1.17-1.16 (m, 6H).



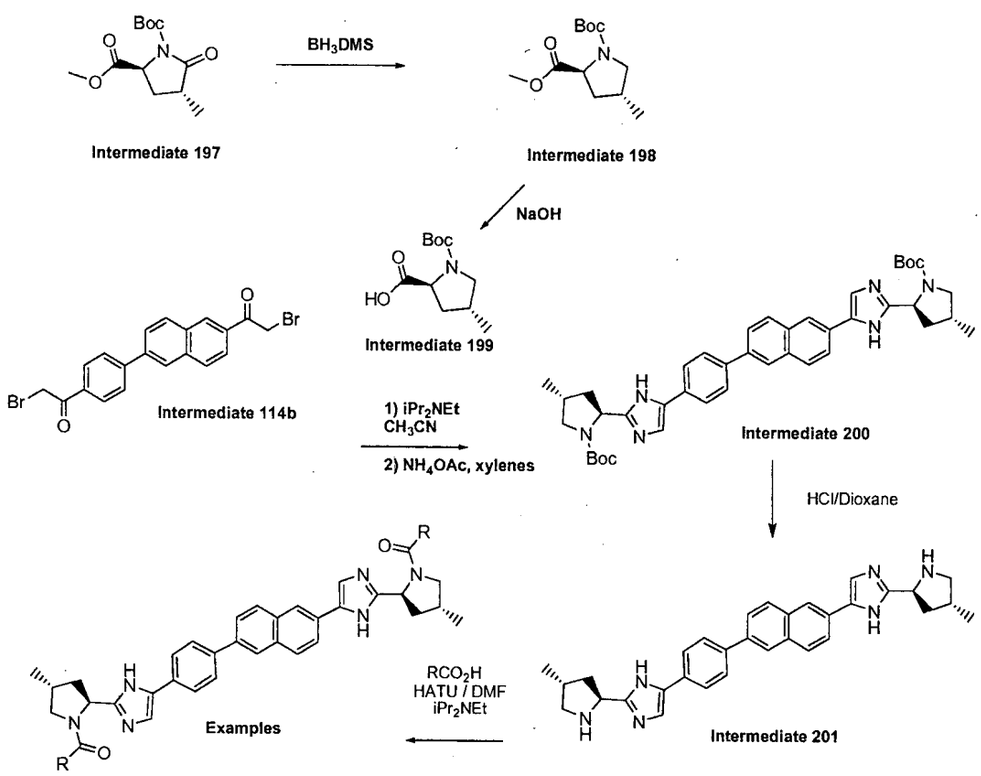
Intermediate196

2-((2S,4S)-4-Methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole

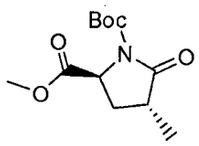
[00615] A solution of 4N HCl in dioxane (15 mL) was added to *tert*-butyl (2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methyl-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-4-methyl-1-pyrrolidinecarboxylate (200 mg. 0.285 mmol) in MeOH (5 mL) and stirred at ambient conditions for 2 hours,

concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 185 mg). LC-MS retention time 2.64 min; Calcd. for $C_{32}H_{35}N_6$: 503.29 m/z Found 503.20 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 53

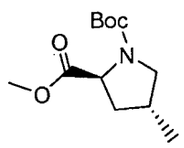


[00616] Intermediate 201 was prepared as shown in Scheme 53 utilizing (2S,4R)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid as starting material. Analytical data for the intermediates shown below.



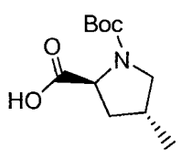
Intermediate 197

[00617] The trans isomer was isolated from a mixture of cis, trans, and the dimethyl analog which could be obtained from methyl iodide alkylation of (S)-1-*tert*-butyl 2-methyl-5-oxopyrrolidine-1,2-dicarboxylate according to the procedure described in Tetrahedron Letters, 2003, 3203-3205. ^{1}H NMR (500 MHz, MeOD) δ ppm 4.66-4.64 (m, 1H), 3.80 (s, 3H), 2.34-2.29 (m, 1H), 2.04-1.99 (m, 1H), 1.49 (s, 9H), 1.21-1.19 (m, 3H).



Intermediate 198

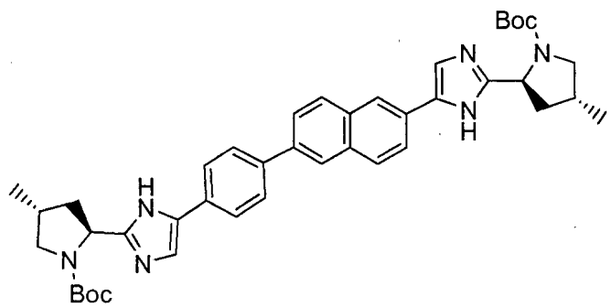
[00618] Borane-methyl sulfide complex (17.67 mL, 35.3 mmol) was added to a solution of Intermediate 197 (6.06 g, 23.55 mmol) in THF (180 mL), and the reaction mixture was heated at 40 °C for 16 hr. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and water (250 mL each). The aqueous layer was extracted with EtOAc (2 X 60 mL), and the combined organic phase was dried with Na_2SO_4, and concentrated *in vacuo*. The resultant colorless oil was purified with a flash chromatography (10-65% EtOAc/Hexane) to afford Intermediate 198 as a colorless oil (3.65 g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4,36-4.33 (dd, J=2.4, 10, 0.4H), 4.26-4.23 (dd, J=3, 8.9, 0.6 H), 3.73-3.63 ('s' overlapped with 'm', 4H), 2.97-2.85 (m, 1H), 2.37 (m, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 1.44-1.39 (two 's', 9H), 1.03-1.00 (two 's', 3H).



Intermediate 199

(2S,4R)-1-(*tert*-Butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid

[00619] To a solution of ester Intermediate 198 (3.63 g, 14.92 mmol) in ethanol (36 mL) was added solution of LiOH (0.393 g, 10.42 mmol) in water (18.00 mL), and the reaction mixture was stirred at room temperature for 22 hr. The organic solvent was evaporated *in vacuo* and the residue was diluted with water (30 mL) and washed with ethylacetate (50 mL). It was chilled in ice-water bath, and acidified to a pH range of ~2 with 1N HCl. It was then extracted with EtOAc (50 mL, 2x). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford Intermediate 199 as a colorless oil, which became a white solid upon extended exposure to high vacuum (3.3g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.37-4.27 (overlapped 'm' 1H), 3.72-3.50 (m, 1H), 3.01-2.83 (overlapped 'm', 1H), 2.50-2.11 (m, 2H), 1.89-1.57 (m, 1H), 1.47-1.39 (two 's', 9H), 1.04-1.03 (two 's', 3H).

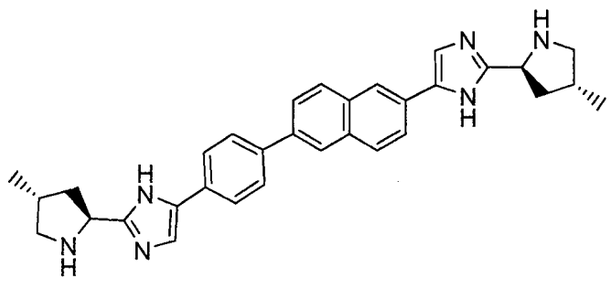


Intermediate 200

tert-Butyl (2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-(*tert*-butoxycarbonyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinecarboxylate

[00620] Hunig's base (0.381 mL, 2.181 mmol) was added to a stirred solution of (2S,4R)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (500 mg, 2.18 mmol) and 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (486 mg, 1.09 mmol) in acetonitrile (11 mL). The heterogeneous mixture was stirred for 18h at RT and additional Hunig's base (1eqv) was added and the mixture was stirred for 24h. The solvent was removed *in vacuo* and the residue was taken up in methylene chloride and washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Wash was repeated 2x. The crude product, isolated as a tan foam, was taken up in xylene (15 mL) and ammonia acetate (1.261 g, 16.36 mmol) was added. The pressure vessel was

sealed and placed into a preheated oil bath (140 °C) and stirred for 2h. The reaction mixture was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 80g Thompson silica gel cartridge (eluted with 25% B to 100% B over 1.5 L and hold 0.5 L B. Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl (2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-(*tert*-butoxycarbonyl)-4-methyl-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-4-methyl-1-pyrrolidinecarboxylate (214.2 mg 27.9 %) as a yellow foam. LC-MS retention time 3.32 min; Calcd. for $C_{42}H_{51}N_6O_4$: 703.40 m/z Found 703.28 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.12 (s, 1H), 7.96-7.94 (m, 2H), 7.87-7.82 (m, 6H), 7.50 (s, 1H), 7.42 (s, 1H), 4.87 (br. s, 2H), 3.81 (br. s, 2H), 3.24-3.18 (m, 2H), 2.53-2.50 (m, 2H), 2.36 (br s, 2H), 1.82-1.74 (m, 2H), 1.46/1.23 (s, 18H), 1.17-1.16 (m, 6H).



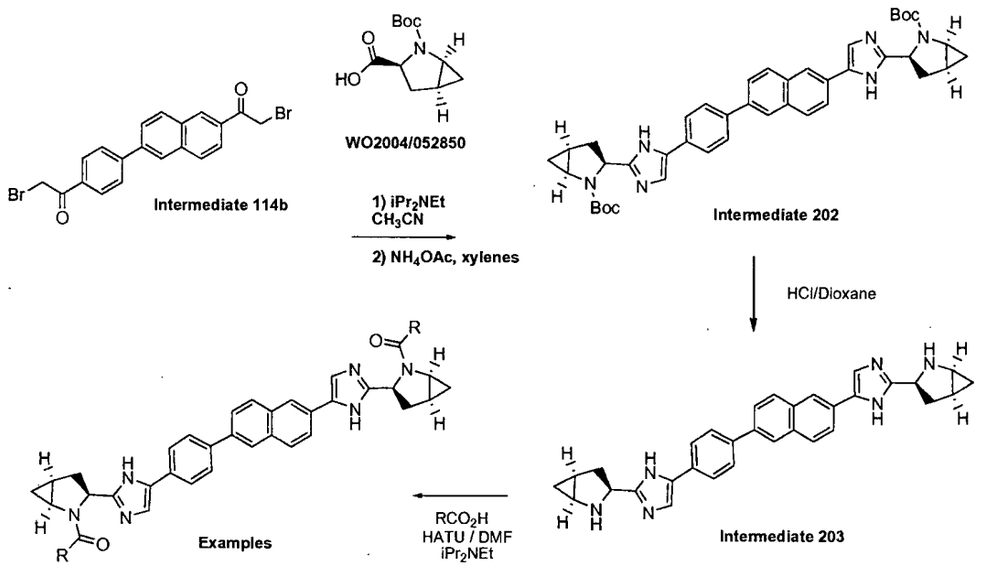
Intermediate 201

2-((2S,4R)-4-Methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4R)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole

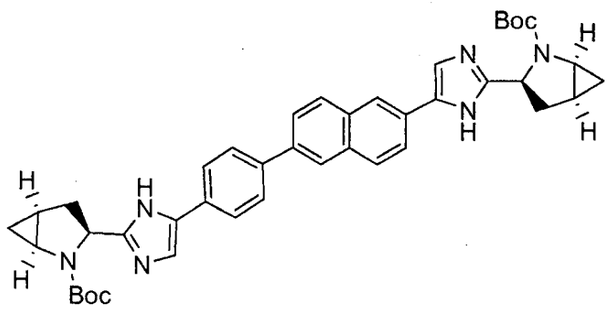
[00621] A solution of 4N HCl in dioxane (15 mL) was added to *tert*-butyl (2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-(*tert*-butoxycarbonyl)-4-methyl-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-4-methyl-1-pyrrolidinecarboxylate (200 mg.

0.285 mmol) in MeOH (5 mL) and stirred at ambient conditions for 2 hours, concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 185 mg). LC-MS retention time 2.64 min; Calcd. for $C_{32}H_{35}N_6$: 503.29 m/z Found 503.20 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 54



[00622] Intermediate 203 was prepared as shown in Scheme 54 utilizing as starting material (1S,3S,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (which could be prepared according to WO 2004/052850). Analytical data for the intermediates shown below.

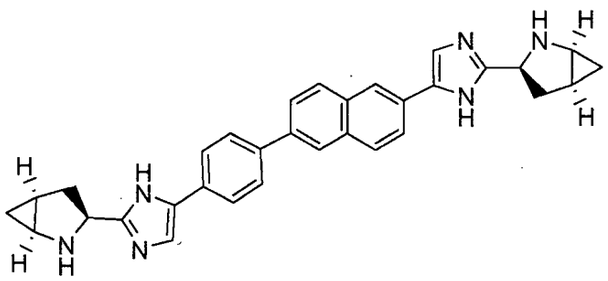


Intermediate 202

tert-Butyl (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00623] Hunig's base (0.384 mL, 2.2 mmol) was added to a stirred solution of 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (0.491 g, 1.100 mmol) and (1S,3S,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (500 mg, 1.1 mmol) in acetonitrile (11 mL). The heterogeneous mixture was stirred for 20h at RT the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Wash was repeated 2x. The crude product was taken up in xylene (11 mL) and ammonia acetate (1.27 g, 16.5 mmol) was added. The pressure vessel was sealed and placed into a preheated oil bath (140 °C) and stirred for 2h. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 80g Thompson silica gel cartridge (eluted with 25% B to 100% B over 1.5 L and hold 0.5 L B. Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (418.9 mg, 43%) as a light yellow solid. LC-MS retention time 3.46 min; Calcd. for $C_{42}H_{47}N_6O_4$: 699.37 m/z Found 699.33 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.11 (s, 1H), 7.96-7.93 (m, 2H), 7.85-7.80 (m, 6H), 7.45 (br. s, 1H), 7.37 (br. s, 1H), 5.36 (br. s, 2H), 3.72 (br. s, 1H), 3.64 (br. s, 1H), 2.82 (br. s, 1H), 2.72 (br s, 1H), 2.43 (br. s, 1H), 2.15 (br. s, 1H), 1.70 (br. s, 2H), 1.55/1.33 (s, 18H), 1.10 (br. s, 1H), 0.94 (br. s, 1H), 0.88 (br. s, 1H), 0.81 (br. s, 1H).

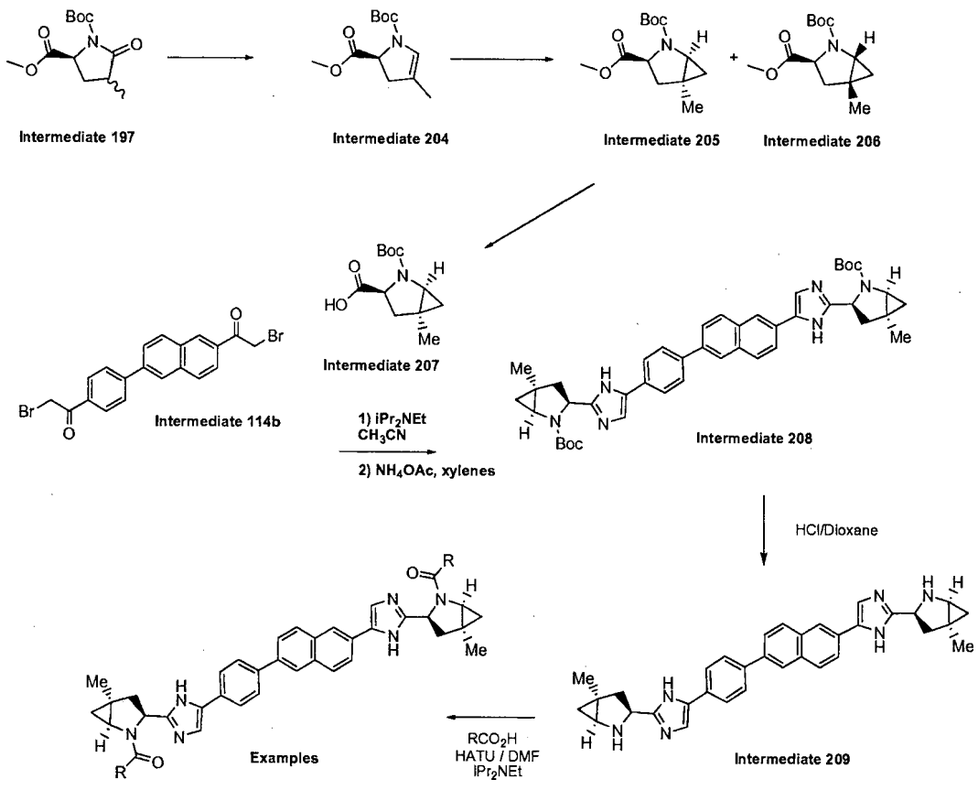


Intermediate 203

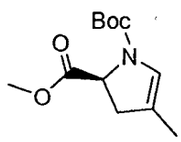
(1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-Azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00624] A solution of 4N HCl in dioxane (10 mL) was added to *tert*-butyl (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1*H*-imidazol-4-yl)-2-naphthyl)phenyl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (375 mg. 0.537 mmol) in MeOH (3 mL) and stirred at ambient conditions for 2 hours, concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 346 mg). LC-MS retention time 2.75 min; Calcd. for $C_{32}H_{31}N_6$: 499.26 m/z Found 499.22 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 55



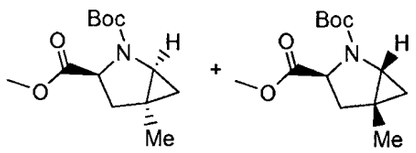
[00625] Intermediate 209 was prepared as shown in Scheme 55 utilizing as starting material (1S,3S,5S)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (which could be prepared according to WO 2004/052850). Analytical data for the intermediates shown below.



Intermediate 204

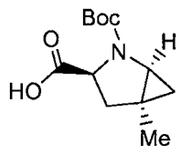
[00626] To a solution of the diastereomeric mixture (at the carbon carrying the methyl group) of Intermediate 197 (4.75g, 18.46 mmol) was added superhydride (19.20 mL, 19.20 mmol) dropwise at -50 °C in a dry ice/acetone bath over 10 min. Hunig's base (13.58 mL, 78 mmol) was added, stirred for 10 min, DMAP (0.122 g, 0.997 mmol) was added as a solid, stirred for 15 min, and trifluoroacetic anhydride (2.98 mL, 21.08 mmol)

was added dropwise over 15 mins. The dry ice/acetone bath was removed and the reaction mixture was stirred for 4 h while being allowed to warm to room temperature. The reaction mixture was washed with water (50 mL), sat. NaCl (30 mL), and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (8-60% EtOAc/Hexane) to afford ester Intermediate 204 as a yellow oil (2.85 g). ^{1}H NMR ($CDCl_3$, 400 MHz): 6.36 (s, 0.5H), 6.25 (s, 0.5H), 4.70-4.57 (m, 1H), 3.78 (s, 3H), 2.96 (m, 1H), 2.54 (m, 1H), 1.70 (s, 3H), 1.50 (s, 4.5H), 1.44 (s, 4.5H).



Intermediate 205 and Intermediate 206

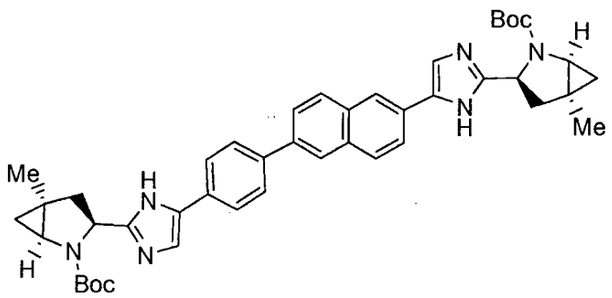
[00627] Diethylzinc (1.1 M in toluene, 59.1 mL, 65.0 mmol) was added dropwise over 20 min to a cooled (-23 °C) toluene (60 mL) solution of Intermediate 203 (5.23 g, 21.68 mmol), and stirred for 10 min. Chloroiodomethane (9.44 mL, 130 mmol) was added dropwise over 10 min, and the reaction mixture was stirred at -21 °C for 16 hr. Sat. $NaHCO_3$ (60 mL) was added to the reaction mixture, the cooling bath was removed, and the mixture was stirred for 10 min. It was then filtered, and the filter cake was washed with toluene (50 mL). The filterate was partitioned, and the organic layer was dried with Na2SO4, and concentrated *in vacuo*. The resulting crude material was purified with flash chromatography (2-10% EtOAc/Hexane) to afford Intermediate 205 (first elute; colorless oil; 2.88 g) and Intermediate 206 (second elute; colorless oil; 1.01g). Relative stereochemical assignment was made based on NOE studies. Intermediate 205: ^{1}H NMR ($CDCl_3$, 400 MHz): 4.65-4.52 (m, 1H), 3.72 (s, 3H), 3.28-3.17 (m, 1H), 2.44-2.32 (m, 1H), 2.16-2.10 (m, 1H), 1.51-1.42 (two s, 9H), 1.24 (s, 3H), 1.07 (m, 1H), 0.69-0.60 (m, 1H).



Intermediate 207

(1S,3S,5S)-2-(*tert*-Butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid

[00628] To a solution of Intermediate 205 (2.88 g, 11.28 mmol) in ethanol (20 mL) was added a solution of LiOH (0.324 g, 13.54 mmol) in water (10.00 mL), and the mixture was stirred at room temperature for 6 hr. Most of the volatile component was removed *in vacuo*, and the residue was partitioned between water (20 mL) and ether (20 mL). The aqueous layer was chilled in an ice-water bath, acidified with a 1N HCl to a pH region of 2, and extracted with EtOAc (30 mL, 4x). The combined organic phase was dried with Na2SO4, evaporated *in vacuo* to give Intermediate 207 as a sticky solid (2.55g). ^{1}H NMR ($CDCl_3$, 400 MHz): 4.64 (m, 1H), 3.25 (appt s, 1H), 2.70-2.40 (m, 1H), 2.14 (m, 1H), 1.54-1.44 (m, 9H), 1.27 (s, 3H), 1.10-0.80 (m, 1H), 0.67 (m, 1H).

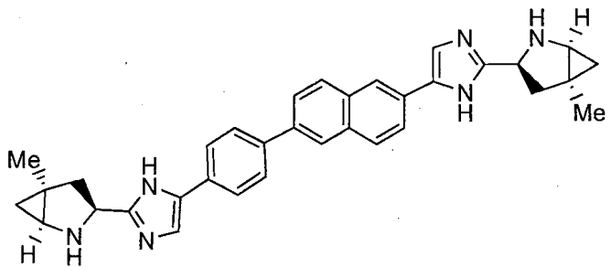


Intermediate 208

tert-Butyl (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00629] Hunig's base (0.475 mL, 2.72 mmol) was added to a stirred solution of 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (0.607 g, 1.36 mmol) and (1S,3S,5S)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (729.0 mg, 2.72 mmol) in dry acetonitrile (12 mL). The heterogeneous mixture was stirred for 20h at RT the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Wash was repeated 2x. The crude product was taken up in xylene (12 mL) and ammonia acetate (1.57 g, 20.39 mmol) was added. The pressure vessel was sealed and placed into a preheated oil bath (140 °C) and stirred for 2h. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed

with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 80g Thompson silica gel cartridge (eluted with 25% B to 100% B over 1.5 L and hold 0.5 L B. Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (279 mg, 27%) as a light yellow solid. LC-MS retention time 3.56 min; Calcd. for $C_{44}H_{51}N_6O_4$: 727.40 m/z Found 727.41 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.11 (s, 1H), 7.96-7.93 (m, 2H), 7.83-7.80 (m, 6H), 7.43 (br. s, 1H), 7.35 (br. s, 1H), 5.35 (br. s, 2H), 3.42 (br. s, 1H), 3.36 (br. s, 1H), 2.61 (br. s, 1H), 2.53 (br.s, 2H), 2.72 (br s, 1H), 1.55/1.33 (s, 25H), 1.06 (br. s, 1H), 0.85 (br. s, 1H), 0.72 (br. s, 1H).



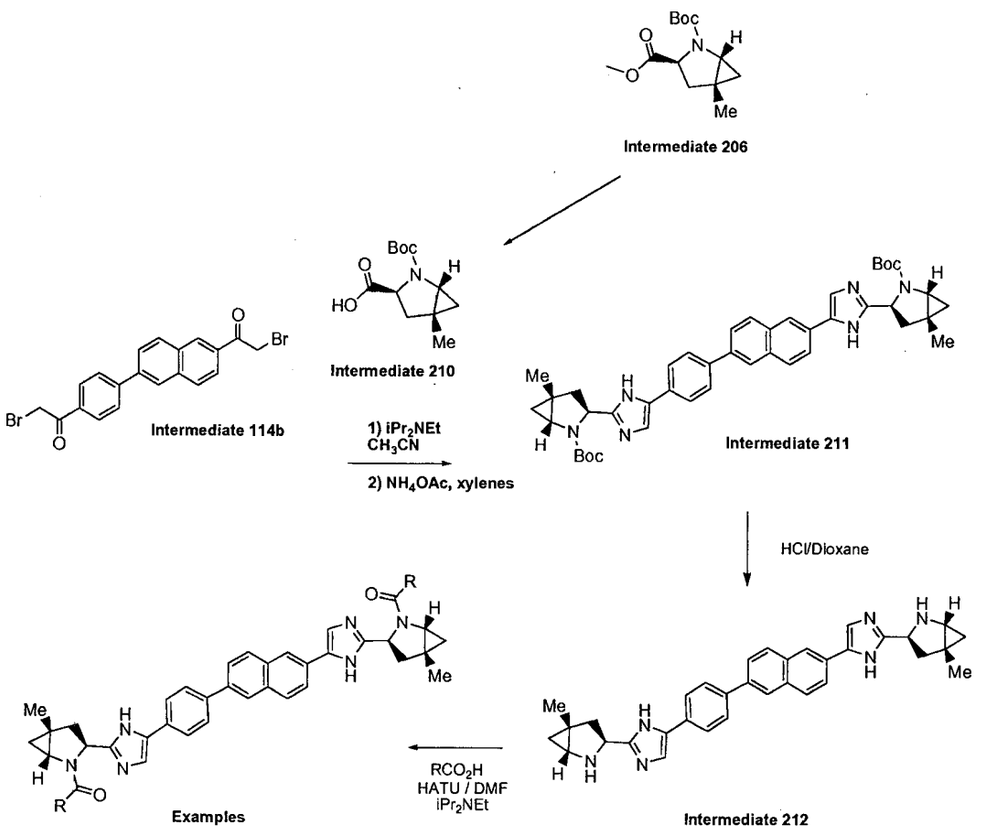
Intermediate 209

(1S,3S,5S)-5-Methyl-3-(4-(4-(6-(2-((1S,3S,5S)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00630] A solution of 4N HCl in dioxane (15 mL) was added to *tert*-butyl (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-

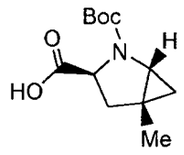
azabicyclo[3.1.0]hexane-2-carboxylate (250 mg. 0.344 mmol) in MeOH (5 mL) and stirred at ambient conditions for 2 hours, concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 231 mg). LC-MS retention time 3.09 min; Calcd. for $C_{34}H_{35}N_6$: 527.29 m/z Found 527.35 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

Scheme 56



[00631] Intermediate 212 was prepared as shown in Scheme 56 utilizing as starting material (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-

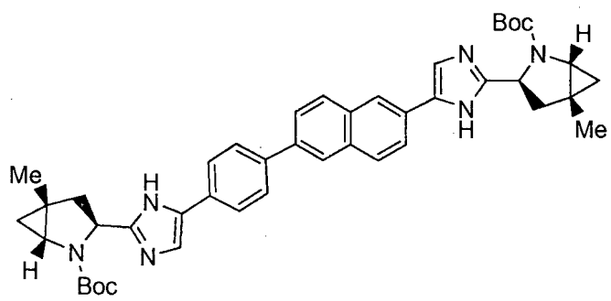
carboxylic acid (which could be prepared according to WO 2004/052850). Analytical data for the intermediates shown below.



Intermediate 210

(1R,3S,5R)-2-(*tert*-Butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid

[00632] Intermediate 210 was prepared from Intermediate 206 as described above for Intermediate 207. ^{1}H NMR ($CDCl_3$, 400 MHz): 4.13 (app br s, 1H), 3.06 (app br s, 1H), 2.55/2.41 (overlapping app br s, 2H), 1.51 (s, 9H), 1.27 (s, 3H), 0.76 (app t, J = 5.6, 1H), 0.60 (app br s, 1H).

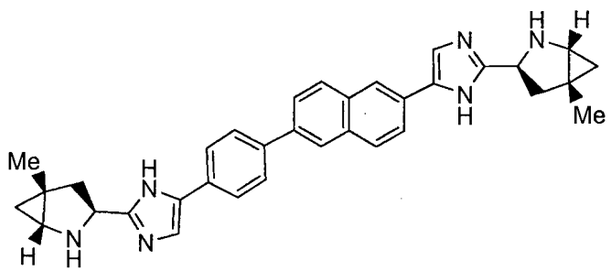


Intermediate 211

tert-Butyl (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate

[00633] Hunig's base (0.29 mL, 1.66 mmol) was added to a stirred solution of 2-bromo-1-(4-(6-(2-bromoacetyl)naphthalen-2-yl)phenyl)ethanone (0.37 g, 0.83 mmol) and (1R,3R,5S)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (0.40 g, 1.66 mmol) in dry acetonitrile (9 mL). The heterogeneous mixture was stirred for 20h at RT the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Wash was repeated 2x. The crude product was taken up in xylene

(9 mL) and ammonia acetate (1.3 g, 16.6 mmol) was added. The pressure vessel was sealed and placed into a preheated oil bath (140 °C) and stirred for 2h. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. After being concentrated, the crude product was charged (methylene chloride) to a 90g Thompson silica gel cartridge (eluted with 25% B to 100% B over 1.5 L and hold 0.5 L B. Solvent B = ethyl acetate and Solvent A = hexanes) to yield *tert*-butyl (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (80 mg, 10%). LC-MS retention time 3.37 min; Calcd. for $C_{44}H_{51}N_6O_4$: 727.40 m/z Found 727.38 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.19 (s, 1H), 8.08 (s, 1H), 7.92-7.91 (m, 2H), 7.85-7.77 (m, 6H), 7.47 (s, 1H), 7.38 (s, 1H), 4.67 (br. s, 2H), 3.93-3.90 (m, 2H), 2.63-2.57 (m, 2H), 2.20-2.14 (m, 2H), 1.31-1.23 (m, 24H), 0.92 (app. d, J=6.7 Hz, 1H), 0.82 (br. s, 1H), 0.77-0.75 (m, 2H).

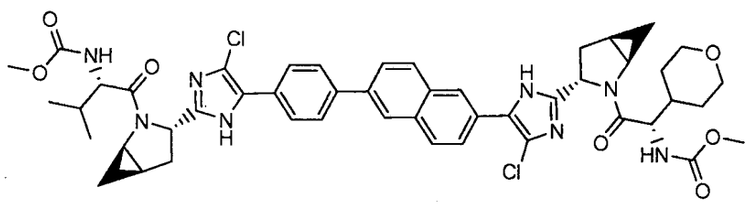


Intermediate 212

(1R,3S,5R)-5-Methyl-3-(4-(4-(6-(2-((1R,3S,5R)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00634] A solution of 4N HCl in dioxane (5 mL) was added to *tert*-butyl (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0] hexane-2-carboxylate (48 mg. 0.066 mmol) in MeOH (1 mL) and stirred at ambient conditions for 2 hours, concentrated, and dried under vacuum. Tetra HCl salt (assume theoretical: 44 mg). LC-MS retention time 2.82 min; Calcd. for $C_{34}H_{35}N_6$: 527.29 m/z Found 527.26 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% methanol / 95% water / 0.1% TFA and Solvent B was 95% methanol/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

EXAMPLES

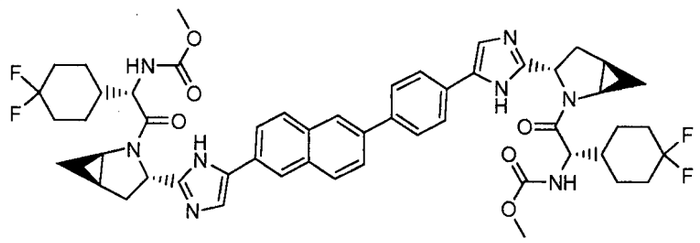


Example 64

Methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00635] N-Chlorosuccinimide (10.4 mg, 0.078 mmol) was added to a stirred solution of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (Example 61) (60 mg, 0.071 mmol) in DMF (1.5 mL) and the reaction vessel was sealed and heated at 50 °C for 16 h. The

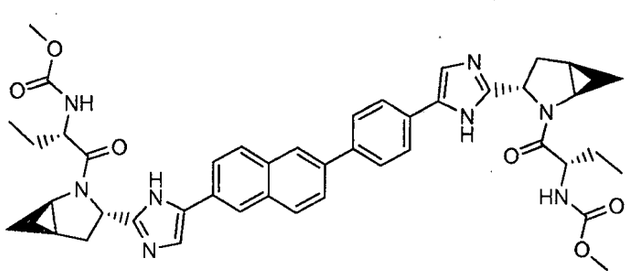
reaction was cooled, partially concentrated and then diluted with MeOH. The solution was filtered and purified by preparative HPLC (MeOH/H_2O, w 0.1% TFA) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (21.4 mg) as a yellow solid. LC-MS retention time 2.798 min; m/z 462.34 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.18 (s, 2 H), 8.03 (d, *J*=8.8 Hz, 1 H), 7.99 (d, *J*=8.8 Hz, 1 H), 7.80 - 7.92 (m, 6 H), 5.06 (ddd, *J*=9.0, 5.8, 3.5 Hz, 2 H), 4.63 (d, *J*=7.5 Hz, 1 H), 4.57 (d, *J*=6.5 Hz, 1 H), 3.92 - 3.98 (m, 2 H), 3.71 - 3.81 (m, 2 H), 3.67 (s, 6 H), 3.35 - 3.44 (m, 2 H), 2.42 - 2.57 (m, 4 H), 1.99 - 2.24 (m, 4 H), 1.40 - 1.66 (m, 4 H), 1.06 - 1.14 (m, 2 H), 1.03 (d, *J*=6.8 Hz, 3 H), 0.95 (d, *J*=6.8 Hz, 3 H), 0.82 (d, *J*=2.8 Hz, 2 H).



Example 65

Methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate

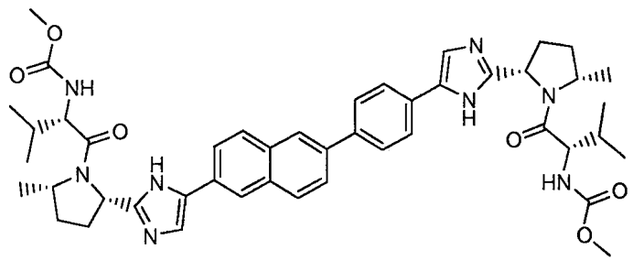
[00636] HATU (67.3 mg, 0.177 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 69) (38.0 mg, 0.059 mmol) and (S)-2-(4,4-difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid (44.5 mg, 0.177 mmol) in DMF (0.7 mL) and DIPEA (0.103 mL, 0.590 mmol). The reaction was diluted with MeOH, filtered, purified by preparative HPLC (water/MeOH w/ 0.1% TFA) and repurified by preparative HPLC (water/MeOH w/ 10 mM ammonium acetate) to yield methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate (22.1 mg) as a light yellow solid. LC-MS retention time 2.713 min; m/z 483.13 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.16 (s, 1 H), 8.11 (s, 1 H), 7.94 (d, *J*=8.5 Hz, 2 H), 7.77 - 7.85 (m, 5 H), 7.47 (s, 1 H), 7.39 (s, 1 H), 7.08 (d, *J*=8.5 Hz, 1 H), 5.15 (ddd, *J*=8.2, 6.3, 6.1 Hz, 2 H), 4.68 (br. s., 2 H), 3.69 - 3.76 (m, 2 H), 3.68 (s, 6 H), 2.41 - 2.57 (m, 4 H), 1.65 - 2.12 (m, 16 H), 1.33 - 1.59 (m, 4 H), 1.06 - 1.17 (m, 2 H), 0.78 (br. s., 2 H).



Example 66

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)butanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)propyl)carbamate

[00637] HATU (89 mg, 0.24 mmol) was added to a stirred solution of a TFA salt of (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 69) (80 mg, 0.084 mmol) and (S)-2-(methoxycarbonylamino)butanoic acid (37.8 mg, 0.235 mmol) in DMF (0.8 mL) and DIPEA (0.15 mL, 0.84 mmol). The reaction was diluted with MeOH, filtered and purified by preparative HPLC (water/MeOH w/ 0.1% TFA) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)butanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)propyl)carbamate (70.1 mg) as a light yellow solid. LC-MS retention time 1.688 min; m/z 785.55 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.26 (s, 1 H), 8.12 (d, *J*=8.8 Hz, 1 H), 8.07 (d, *J*=8.5 Hz, 1 H), 7.93 - 8.00 (m, 4 H), 7.82 - 7.90 (m, 4 H), 5.12 - 5.21 (m, 2 H), 4.58 - 4.65 (m, 2 H), 3.74 - 3.81 (m, 2 H), 3.67 (s, 6 H), 2.70 (ddd, *J*=13.7, 9.0, 4.9 Hz, 2 H), 2.49 (dq, *J*=14.2, 7.1 Hz, 2 H), 2.09 (br. s., 2 H), 1.86 - 1.99 (m, 2 H), 1.64 - 1.77 (m, 2 H), 1.09 - 1.17 (m, 2 H), 1.02 (t, *J*=7.4 Hz, 6 H), 0.92 (br. s., 2 H).

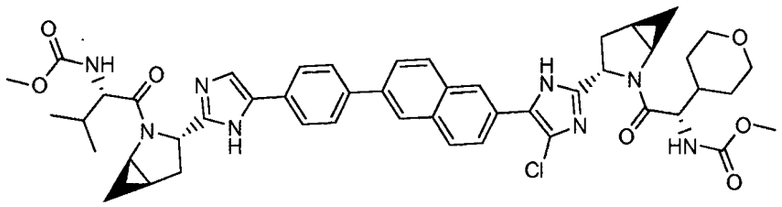


Example 67

Methyl ((1S)-1-(((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00638] HATU (101 mg, 0.266 mmol) was added to a stirred solution of a TFA salt of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 117) (102 mg, 0.106 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (46.6 mg, 0.266 mmol) in DMF (1.0 mL) and DIPEA (0.189 mL, 1.1 mmol) and the reaction was stirred at rt for 2h. The reaction mixture was diluted with MeOH and purified by preparative HPLC ($MeOH/H_2O$ w/ 0.1% TFA) and then repurified by preparative HPLC (acetonitrile/water with 0.1% TFA) to yield a TFA salt of methyl ((1S)-1-(((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (63.8 mg) as a light yellow solid. LC-MS retention time 1.900 min; m/z 817.59 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR presents as a ~4:1 mixture of regioisomers. ^1H NMR (for major regioisomer) (400 MHz, MeOD) δ ppm 8.31 (s, 1 H), 8.27 (s, 1 H), 8.13 (d, *J*=8.5 Hz, 1 H), 8.09 (d, *J*=8.5 Hz, 1 H), 7.94 - 8.02 (m, 5 H), 7.84 - 7.92 (m, 3 H), 5.15 - 5.24 (m, 2 H), 4.13 (dd, *J*=8.7, 1.4 Hz, 2 H), 3.74 (d, *J*=2.8 Hz, 2 H), 3.67 (s, 6 H), 2.50 - 2.60 (m, 2 H), 2.26 -

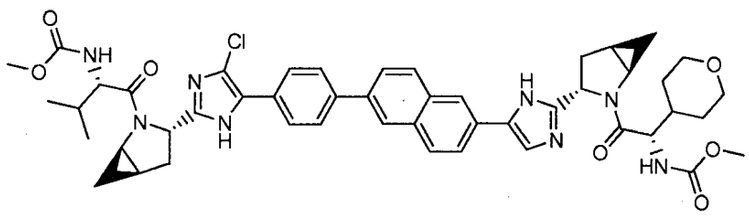
2.45 (m, 4 H), 1.95 - 2.10 (m, 4 H), 1.57 (dd, *J*=6.5, 3.0 Hz, 6 H), 1.32 (t, *J*=6.4 Hz, 2 H), 0.99 (d, *J*=6.8 Hz, 6 H), 0.89 (d, *J*=6.8 Hz, 6 H).



Example 68

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

and

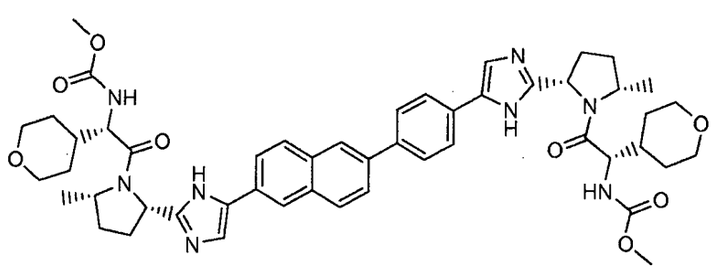


Example 69

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00639] A mixture of two chloroimidazole regioisomers as TFA salts (Examples 68 and 69) (21.4 mg) was isolated from the same reaction that prepared a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (Example 64). The two regioisomeric compounds were separated in multiple injections using SCF chromatography (2-ethylpyridine SCF column (4.6 x 250mm, 5μm) and 80% CO_2 - 20% EtOH/0.1%DEA). The absolute regiochemistry of the separated materials was determined by HMBC

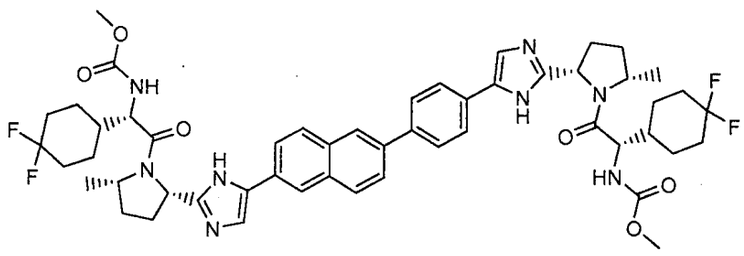
correlation. The reaction yielded methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (7.4 mg) and methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (4.5 mg), each as an off-white solid. For Example 68: LC-MS retention time 2.683 min; m/z 889.17 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. For Example 69: LC-MS retention time 2.695 min; m/z 889.22 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 70

Methyl ((1S)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

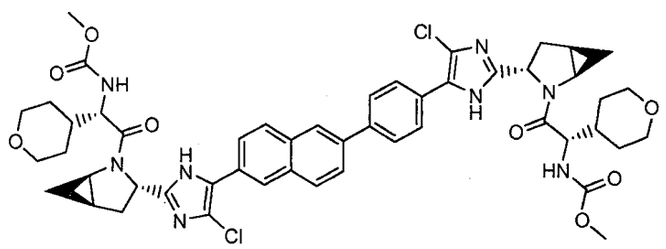
[00640] HATU (73.3 mg, 0.193 mmol) was added to a stirred solution of a TFA salt of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 117) (73.9 mg, 0.077 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (41.9 mg, 0.193 mmol) in DMF (1.0 mL) and DIPEA (0.14 mL, 0.77 mmol) and the reaction was stirred at rt for 30 min. The reaction mixture was diluted with MeOH, filtered and purified by preparative HPLC (MeOH/H_2O w/ 0.1% TFA) to yield a TFA salt of methyl ((1S)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (51.2 mg) as a yellow solid. LC-MS retention time 1.897 min; m/z 901.39 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 71

Methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate

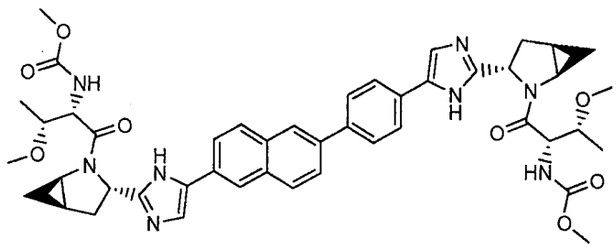
[00641] HATU (70.8 mg, 0.186 mmol) was added to a stirred solution of a TFA salt of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 117) (71.4 mg, 0.074 mmol) and (S)-2-(4,4-difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid (46.8 mg, 0.186 mmol) in DMF (1.0 mL) and DIPEA (0.13 mL, 0.75 mmol) and the reaction was stirred at rt for 1.5h. The reaction was diluted with MeOH, filtered and purified in by preparative HPLC (MeOH/H_2O w/ 0.1% TFA) to yield the desired product a TFA salt of methyl ((1S)-1-(4,4-difluorocyclohexyl)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-(4,4-difluorocyclohexyl)-2-((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate (43.3 mg) as a light yellow solid. LC-MS retention time 2.828 min; m/z 485.22 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 72

Methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(4-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00642] N-Chlorosuccinimide (7.1 mg, 0.053 mmol) was added to a stirred solution of methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (Example 34) (22.7 mg, 0.025 mmol) in DMF (0.5 mL) and the reaction vessel was sealed and the reaction was heated at 50 °C for 12h. The reaction was cooled to rt, additional N-chlorosuccinimide (~3mg) was added and the reaction vessel was sealed and stirred at 50 °C for 2h. The reaction was cooled to rt, diluted with MeOH, filtered and purified by preparative HPLC (Methanol/Water w/ 0.1%TFA) to yield methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(4-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (12 mg) as a yellow solid. LC-MS retention time 2.708 min; m/z 483.25 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.18 (s, 2 H), 8.04 (d, *J*=8.8 Hz, 1 H), 7.99 (d, *J*=8.8 Hz, 1 H), 7.80 - 7.92 (m, 6 H), 5.02 - 5.09 (m, 2 H), 4.63 (d, *J*=6.0 Hz, 2 H), 3.91 - 3.99 (m, 4 H), 3.73 - 3.80 (m, 2 H), 3.67 (s, 6 H), 3.34 - 3.45 (m, 4 H), 2.43 - 2.54 (m, 4 H), 1.98 - 2.13 (m, 4 H), 1.38 - 1.67 (m, 8 H), 1.06 - 1.15 (m, 2 H), 0.81 (br. s., 2 H).

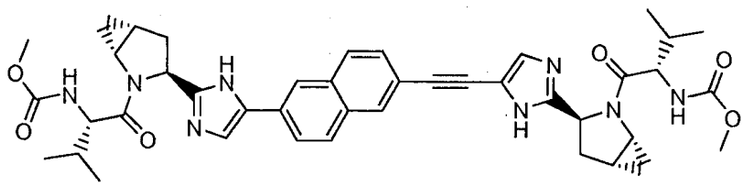


Example 73

Methyl ((1S,2R)-2-methoxy-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)propyl)carbamate

[00643] HATU (65.7 mg, 0.173 mmol) was added to a stirred solution of a TFA salt of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 133) (66 mg, 0.069 mmol) and (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (33.0 mg, 0.173 mmol) in DMF (0.8 mL) and DIPEA (0.121 mL, 0.691 mmol) and the reaction was stirred at rt overnight. The reaction was diluted with MeOH, filtered and purified preparative HPLC (Methanol/water w/ 10 nM ammonium acetate) to yield a TFA salt of methyl ((1S,2R)-2-methoxy-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)propyl)carbamate (51.9 mg, 0.048 mmol, 98 % yield) as an off-white solid. LC-MS retention time 2.383 min; m/z 845.42 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (MeOD, 400 MHz) δ 8.29 (br s, 1H), 8.26 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.00 - 7.93 (m, 4H), 7.91 - 7.82 (m, 4H), 5.18 (td, J = 9.0, 7.0 Hz, 2H), 4.78 (dd, J = 3.9, 1.7 Hz, 2H), 3.92 - 3.79 (m, 4H), 3.68 (s, 6H), 3.35

(s, 3H), 3.35 (m, 3H), 2.76 - 2.65 (m, 2H), 2.59 - 2.47 (m, 2H), 2.15 - 2.05 (m, 2H), 1.19 (d, J = 6.3 Hz, 6H), 1.16 - 1.07 (m, 2H), 0.94 - 0.84 (m, 2H).

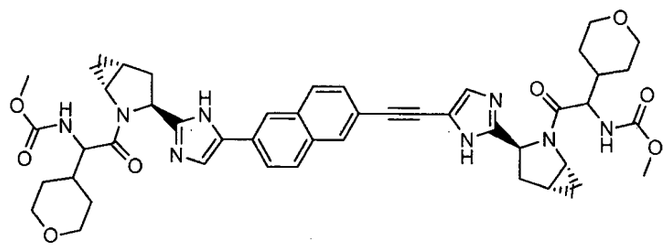


Example 74

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00644] HATU (193 mg, 0.506 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 124) (100 mg, 0.169 mmol) and (R)-2-(methoxycarbonylamino)-3-methylbutanoic acid (89 mg, 0.51 mmol) in DMF (1.5 mL) and DIPEA (0.24 mL, 1.4 mmol) and the clear orange solution was stirred at rt for 3h. The reaction was diluted with methanol, filtered and purified by preparative HPLC (MeOH/water with an ammonium acetate buffer) to yield methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (71 mg) as a light yellow solid. LC-MS retention time 3.706 min; m/z 761.22 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.15 (s, 1 H), 7.96 (s, 1 H), 7.80 -

7.88 (m, 3 H), 7.51 (dd, J=8.4, 1.6 Hz, 1 H), 7.46 (s, 1 H), 7.27 (s, 1 H), 5.18 (dd, J=9.0, 4.8 Hz, 1 H), 5.13 (dd, J=8.8, 4.3 Hz, 1 H), 4.59 (dd, J=11.8, 6.8 Hz, 2 H), 3.68 - 3.72 (m, 1 H), 3.67 (s, 3 H), 3.67 (s, 3 H), 3.59 - 3.64 (m, 1 H), 2.31 - 2.60 (m, 4 H), 2.08 - 2.22 (m, 2 H), 1.99 - 2.08 (m, 2 H), 1.13 (ddd, J=8.6, 5.8, 5.5 Hz, 2 H), 1.00 (dd, J=12.9, 6.9 Hz, 6 H), 0.93 (dd, J=6.7, 2.9 Hz, 6 H), 0.79 (br. s., 2 H).



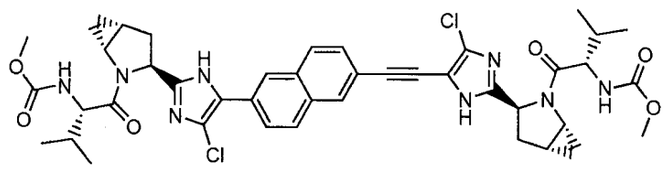
Example 75

(mixture of diastereomers)

Methyl (2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00645] HATU (110 mg, 0.289 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 124) (57 mg, 0.096 mmol) and racemic 2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (62.7 mg, 0.289 mmol) in DMF (1.0 mL) and DIPEA (0.134 mL, 0.770 mmol) and the clear orange solution was stirred at rt for 3h. The reaction was diluted with methanol, filtered and purified by preparative HPLC (MeOH/water with an ammonium acetate buffer) to yield methyl (2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (37.3 mg) as a yellow solid and as a mixture of diastereomers. LC-MS retention time 1.522 min; m/z 845.36 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1

mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Mixture of diastereomers. ^1H NMR (400 MHz, MeOD) δ ppm 8.15 (d, *J*=12.8 Hz, 1 H), 7.96 (s, 1 H), 7.80 - 7.90 (m, 3 H), 7.51 (dd, *J*=8.5, 1.5 Hz, 1 H), 7.46 (d, *J*=5.5 Hz, 1 H), 7.27 (d, *J*=5.3 Hz, 1 H), 5.08 - 5.24 (m, 2 H), 4.61 - 4.69 (m, 1 H), 4.57 (dd, *J*=8.3, 4.5 Hz, 1 H), 3.85 - 4.03 (m, 5 H), 3.63 - 3.79 (m, 8 H), 3.34 - 3.49 (m, 5 H), 2.30 - 2.63 (m, 4 H), 1.99 - 2.16 (m, 3 H), 1.70 - 1.80 (m, 1 H), 1.35 - 1.66 (m, 6 H), 1.16 - 1.26 (m, 1 H), 1.07 - 1.16 (m, 1 H), 0.70 - 0.83 (m, 2 H).

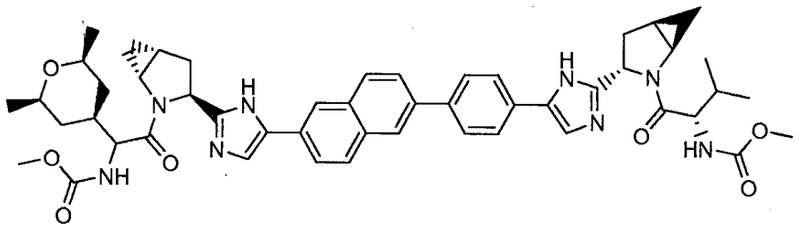


Example 76

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-((4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00646] N-Chlorosuccinimide (13.3 mg, 0.100 mmol) was added to a stirred solution of ((1S)-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (38 mg, 0.050 mmol) in DMF (1 mL) and then the reaction vessel was flushed with nitrogen, sealed and heated at 50 °C for 16h. The reaction was cooled to rt and additional N-chlorosuccinimide (7.4 mg) was added. The reaction was reheated at 50 °C for 3h, cooled to rt, diluted with MeOH (~ 0.5 mL), filtered and purified by preparative HPLC (MeOH/water, TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-((4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)ethynyl)-2-naphthyl)-

1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (5.0 mg) as a yellow solid. LC-MS retention time 4.153 min; m/z 831.02 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.19 (s, 1 H), 8.07 (s, 1 H), 7.87 - 7.99 (m, 3 H), 7.58 (dd, *J*=8.5, 1.3 Hz, 1 H), 5.07 (t, *J*=7.2 Hz, 1 H), 4.98 - 5.03 (m, 1 H), 4.54 - 4.59 (m, 2 H), 3.67 (s, 6 H), 3.62 - 3.75 (m, 2 H), 2.45 - 2.50 (m, 2 H), 2.41 (dd, *J*=7.3, 3.5 Hz, 2 H), 2.09 - 2.21 (m, 2 H), 1.96 - 2.08 (m, 2 H), 1.08 - 1.16 (m, 2 H), 1.02 (t, *J*=6.1 Hz, 6 H), 0.92 - 0.97 (m, 6 H), 0.75 - 0.85 (m, 2 H).

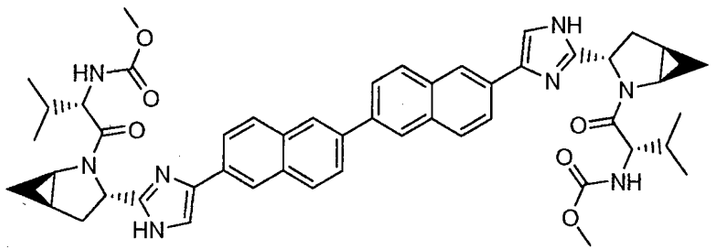


Example 77

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00647] HATU (25.4 mg, 0.067 mmol) was added to a stirred solution of an HCl salt of methyl (S)-1-((1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (Intermediate 128) (42 mg, 0.061 mmol), 2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid (Cap-179 stereoisomer 2) (14.9 mg, 0.061 mmol) and DIEA (0.053 mL, 0.30 mmol)

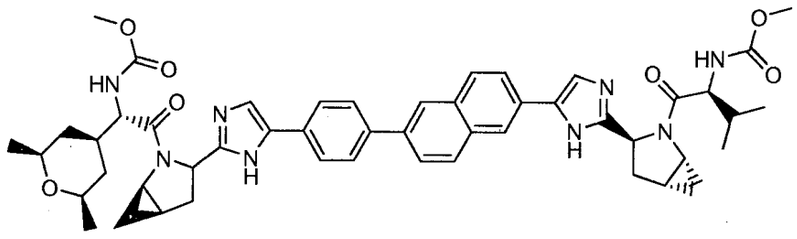
in DMF (2 mL) and the resulting yellowish solution was stirred at rt for 2 h. The reaction was concentrated under reduced pressure and the residue was redissolved into methanol and purified by preparative HPLC. (Solvent A: 05% MeCN / 95% water / 10 mM NH_4Ac; Solvent B: 95% MeCN / 5% water / 10 mM NH_4Ac; Column: Sunfire Prep MS C18 30 X 100mm S10; Wavelength: 220nM; Flow rate: 40 ml/min; Gradient: 0% B to 80% B over 30 min with a 5 min. hold time) to yield methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (26 mg) as a white solid. LC/MS $[M+H]^+$=883; Rt = 2.99min is product. Column Luna 3u C18 2x50mm; start %B: 0, final %B: 100 Solvent A: 5% ACN/ 95% H_2O + 10 mM Ammonium Acetate; Solvent B: 95% ACN/ 5% H_2O + 10 mM Ammonium Acetate; flow rate 4 ml/min. Run time: 5 min. Purity = 97 %. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 11.85 (1 H, br. s.), 11.73 (1 H, br. s.), 8.14 - 8.27 (2 H, m), 7.90 - 7.98 (3 H, m), 7.82 - 7.89 (3 H, m), 7.79 (2 H, d, *J*=8.24 Hz), 7.64 (1 H, s), 7.57 (1 H, s), 7.19 (2 H, t, *J*=9.31 Hz), 5.03 - 5.13 (2 H, m), 4.51 (1 H, t, *J*=7.93 Hz), 4.44 (1 H, t, *J*=7.78 Hz), 3.65 (1 H, br. s.), 3.51 - 3.60 (7 H, m), 3.29 - 3.42 (7 H, m), 2.35 - 2.47 (2 H, m), 2.20 - 2.33 (2 H, m), 2.01 - 2.11 (2 H, m), 1.83 - 1.92 (3 H, m), 1.63 (1 H, d, *J*=12.21 Hz), 1.57 (1 H, d, *J*=11.60 Hz), 0.96 - 1.09 (12 H, m), 0.89 (4 H, d, *J*=6.71 Hz), 0.72 (2 H, br. s.).



Example 78

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6'-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2,2'-binaphthalen-6-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00648] HATU (91 mg, 0.240 mmol) was added to a stirred solution of 6,6′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)-2,2′-binaphthyl (Intermediate 133) (43.9 mg, 0.080 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (42.0 mg, 0.240 mmol) in DMF (1 mL) and DIPEA (0.14 mL, 0.80 mmol) and the clear brown solution was stirred for 2h. The reaction mixture was diluted with MeOH and purified by preparative HPLC (MeOH/water with 0.1% TFA) purified by to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6′-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2,2′-binaphthalen-6-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (28.9 mg) as a yellow solid. LC-MS retention time 1.788 min; m/z 863.46 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.37 (s, 2 H), 8.29 (d, *J*=1.0 Hz, 2 H), 8.15 (d, *J*=8.8 Hz, 2 H), 8.06 - 8.13 (m, 4 H), 7.97 (s, 2 H), 7.86 (dd, *J*=8.7, 1.6 Hz, 2 H), 5.17 (dd, *J*=9.3, 7.0 Hz, 2 H), 4.57 (d, *J*=6.8 Hz, 2 H), 3.80 - 3.86 (m, 2 H), 3.68 (s, 6 H), 2.71 (dd, *J*=13.7, 9.4 Hz, 2 H), 2.46 - 2.56 (m, 2 H), 2.15 - 2.25 (m, 2 H), 2.09 (d, *J*=8.0 Hz, 2 H), 1.08 - 1.16 (m, 2 H), 1.03 (d, *J*=6.8 Hz, 6 H), 0.92 - 0.96 (m, 6 H), 0.88 - 0.96 (m, 2 H).

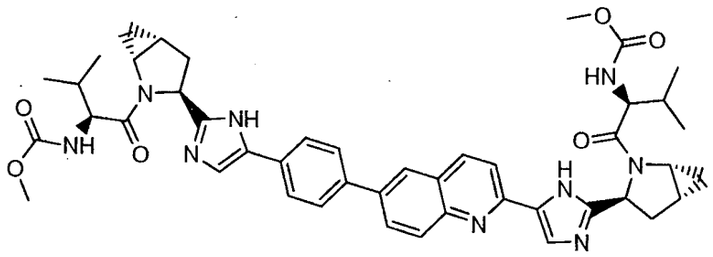


Example 79

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,5R)-2-((2S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((methoxycarbonyl)amino)acetyl)-2-

azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

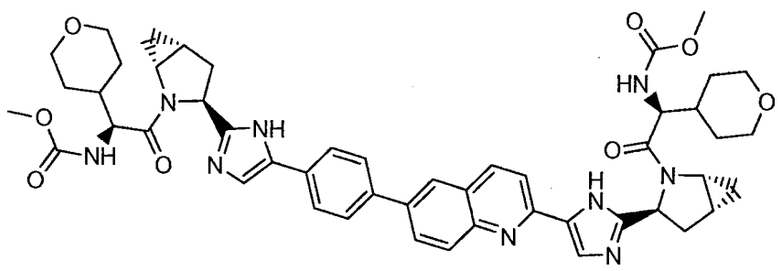
[00649] HATU (35.4 mg, 0.093 mmol) was added to a stirred solution of a TFA salt of methyl (2S)-1-((1R,3S,5R)-3-(5-(6-(4-(2-((1R,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (47 mg, 0.072 mmol) and (S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid (23 mg, 0.093 mmol) in DMF (1mL) and DIPEA (0.050 mL, 0.29 mmol) and the reaction was stirred for 3h. The reaction mixture was diluted with MeOH and purified by preparative HPLC (MeOH/water with 0.1% TFA) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,5R)-2-((2S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (31.3 mg) as a yellow solid. LC-MS retention time 1.670 min; m/z 883.43 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.28 (d, *J*=1.0 Hz, 1 H), 8.26 (s, 1 H), 8.12 (d, *J*=8.8 Hz, 1 H), 8.07 (d, *J*=8.5 Hz, 1 H), 7.93 - 7.99 (m, 4 H), 7.82 - 7.92 (m, 4 H), 5.15 (td, *J*=9.6, 6.9 Hz, 2 H), 4.58 (t, *J*=7.4 Hz, 2 H), 3.79 - 3.86 (m, 2 H), 3.68 (s, 6 H), 3.43 - 3.53 (m, 2 H), 2.65 - 2.75 (m, 2 H), 2.50 (ddd, *J*=13.6, 6.7, 6.5 Hz, 2 H), 2.04 - 2.24 (m, 4 H), 1.54 - 1.62 (m, 1 H), 1.45 - 1.53 (m, 1 H), 0.84 - 1.21 (m, 18 H).



Example 80

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

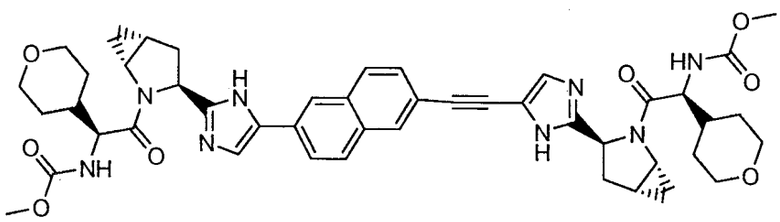
[00650] HATU (64.1 mg, 0.169 mmol) was added to a solution of an HCl salt of 2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)quinoline (Intermediate 139) (50 mg, 0.073 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (29.5 mg, 0.169 mmol) in DMF (1 mL) and DIPEA (0.115 mL, 0.660 mmol) and the reaction mixture was stirred at rt for 16h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (55.3 mg) as a yellow solid. LC-MS retention time 2.883 min; m/z 814.65 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 81

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00651] HATU (64.1 mg, 0.169 mmol) was added to a solution of an HCl salt of 2-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-6-(4-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)quinoline (Intermediate 139) (50 mg, 0.073 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (36.6 mg, 0.169 mmol) in DMF (1 mL) and DIPEA (0.12 mL, 0.66 mmol) and the reaction mixture was stirred at rt for 2 h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (64.8 mg) as a yellow solid. LC-MS retention time 2.553 min; m/z 898.70 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

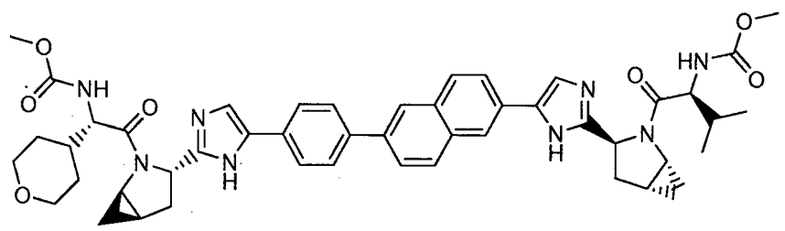


Example 82

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00652] HATU (102 mg, 0.269 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (60 mg, 0.134 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (58.4 mg, 0.269 mmol) in DMF (1.2 mL) and DIPEA (0.19 mL, 1.1 mmol) and the reaction was stirred at rt for 2h. The reaction was diluted with methanol and purified by preparative HPLC (MeOH/water, with an ammonium acetate buffer) to yield methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (48.9 mg) as a light yellow solid. LC-MS retention time 2.572 min; m/z 845.65 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.14 (s, 1 H), 7.96 (s, 1 H), 7.80 - 7.87 (m, 3 H), 7.51 (dd, *J*=8.5, 1.5 Hz, 1 H), 7.45 (s, 1 H), 7.27 (s, 1 H), 5.16 (dd, *J*=8.8, 5.0 Hz, 1 H), 5.11 (dd, *J*=8.8, 4.5 Hz, 1 H), 4.66 (d, *J*=7.5 Hz, 1 H), 4.63 (d, *J*=7.8 Hz, 1 H), 3.90 - 3.98 (m,

4 H), 3.67 (s, 6 H), 3.63 - 3.76 (m, 2 H), 3.33 - 3.44 (m, 4 H), 2.32 - 2.56 (m, 4 H), 1.98 - 2.10 (m, 4 H), 1.35 - 1.67 (m, 8 H), 1.08 - 1.16 (m, 2 H), 0.78 (br. s., 2 H).

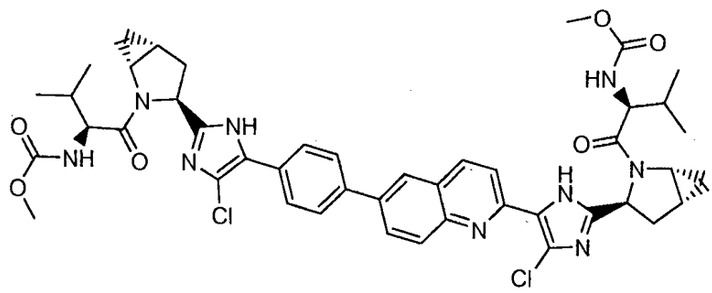


Example 83

Methyl ((1S)-2-((1R,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00653] HATU (27.8 mg, 0.073 mmol) was added to a solution of methyl (2S)-1-((1R,3S,5R)-3-(5-(6-(4-(2-((1R,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)phenyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (Intermediate 131) (40 mg, 0.061 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (15.90 mg, 0.073 mmol) were dissolved into DMF (0.5 mL) and DIPEA (0.053 mL, 0.31 mmol) and the reaction was stirred at rt for 2h. The reaction was diluted with methanol and purified by preparative HPLC (MeOH/water with an ammonium acetate buffer) to yield methyl ((1S)-2-((1R,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (3.5 mg) as a light yellow solid. LC-MS retention time 2.785 min; m/z 855.74 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid.

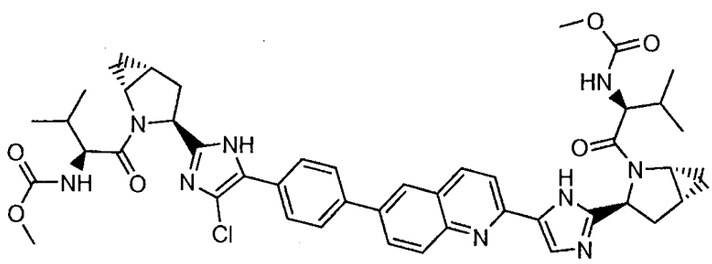
MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.17 (s, 1 H), 8.10 (s, 1 H), 7.93 (dd, *J*=8.5, 3.0 Hz, 2 H), 7.77 - 7.86 (m, 6 H), 7.44 (s, 1 H), 7.35 (s, 1 H), 5.20 (dd, *J*=8.9, 4.6 Hz, 1 H), 5.15 (dd, *J*=8.8, 5.0 Hz, 1 H), 4.66 (d, *J*=7.8 Hz, 1 H), 4.61 (d, *J*=6.8 Hz, 1 H), 3.90 - 3.99 (m, 2 H), 3.68 (s, 6 H), 3.64 - 3.76 (m, 3 H), 3.34 - 3.43 (m, 3 H), 2.39 - 2.61 (m, 4 H), 2.12 - 2.23 (m, 1 H), 1.99 - 2.10 (m, 2 H), 1.52 - 1.67 (m, 2 H), 1.41 - 1.51 (m, 1 H), 1.08 - 1.18 (m, 2 H), 1.02 (d, *J*=6.8 Hz, 3 H), 0.94 (d, *J*=6.8 Hz, 3 H), 0.76 - 0.84 (m, 2 H).



Example 84

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

and

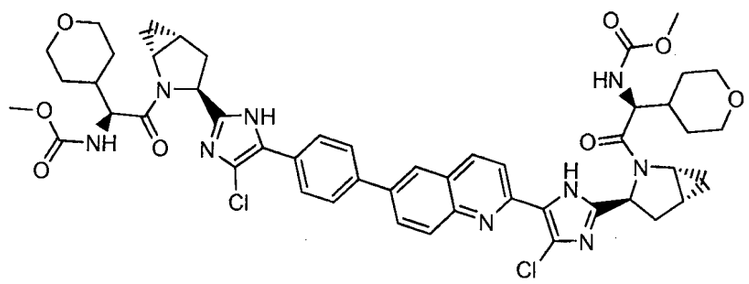


Example 85

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00654] N-Chlorosuccinimide (6.01 mg, 0.045 mmol) was added to a stirred solution of a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (Example 80) (26 mg, 0.022 mmol) in DMF (0.5 mL) and the reaction mixture was stirred at 50 °C for 16 h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield two products: 1) A TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (12.4 mg) as yellow solid. LC-MS retention time 3.871 min; m/z 882.55 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.53 (d, *J*=8.8 Hz, 1 H), 8.26 (d, *J*=8.8 Hz, 1 H), 8.23 (s, 1 H), 8.17 (s, 2 H), 7.82 - 7.93 (m, 4 H), 5.16 (dd, *J*=8.8, 5.3 Hz, 1 H), 5.06 (t, *J*=7.2 Hz, 1 H), 4.53 - 4.63 (m, 2 H), 3.68 - 3.76 (m, 2 H), 3.67 (s, 6 H), 2.44 - 2.60 (m, 4 H), 2.11 - 2.24 (m, 2 H), 1.97 - 2.09 (m, 2 H), 1.09 - 1.18 (m, 2 H), 1.03 (dd, *J*=6.8, 3.3 Hz, 6 H), 0.95 (dd, *J*=6.8, 2.4 Hz, 6 H), 0.75 - 0.87 (m, 2 H). 2) A TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (4.8 mg) as yellow solid. LC-MS retention time 2.98 min; m/z 848.60 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0%

Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 8.64 (d, *J*=8.8 Hz, 1 H), 8.34 (s, 1 H), 8.32 (s, 1 H), 8.25 - 8.29 (m, 2 H), 8.09 (d, *J*=8.8 Hz, 1 H), 7.86 - 7.96 (m, 4 H), 5.18 - 5.25 (m, 1 H), 5.03 - 5.09 (m, 1 H), 4.53 - 4.62 (m, 2 H), 3.64 - 3.83 (m, 2 H), 3.64 - 3.69 (m, 6 H), 2.42 - 2.70 (m, 4 H), 1.97 - 2.24 (m, 4 H), 1.08 - 1.17 (m, 2 H), 1.02 (dd, *J*=6.8, 2.4 Hz, 6 H), 0.94 (t, *J*=6.8 Hz, 6 H), 0.76 - 0.91 (m, 2 H).

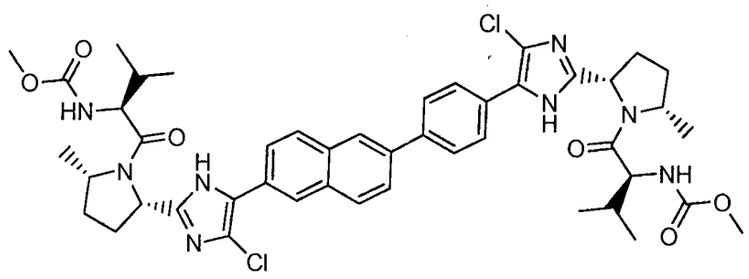


Example 86

Methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00655] N-Chlorosuccinimide (6.68 mg, 0.050 mmol) was added to a solution of a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (Example 81) (31 mg, 0.025 mmol) in DMF (0.5 mL) and the reaction mixture was stirred at 50 °C for 16 h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-(4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-

yl)ethyl)carbamate (12.1 mg) as yellow solid. LC-MS retention time 3.511 min; m/z 484.17 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.60 (d, *J*=8.8 Hz, 1 H), 8.27 - 8.33 (m, 2 H), 8.21 (s, 2 H), 7.89 - 7.95 (m, 2 H), 7.83 - 7.88 (m, 2 H), 5.15 (dd, *J*=8.7, 5.6 Hz, 1 H), 5.05 (dd, *J*=8.3, 6.3 Hz, 1 H), 4.64 (dd, *J*=11.3, 7.8 Hz, 2 H), 3.87 - 4.00 (m, 4 H), 3.73 - 3.81 (m, 2 H), 3.68 (s, 6 H), 3.33 - 3.48 (m, 4 H), 2.41 - 2.61 (m, 4 H), 1.95 - 2.16 (m, 4 H), 1.39 - 1.70 (m, 8 H), 1.06 - 1.18 (m, 2 H), 0.81 (m, 2 H).

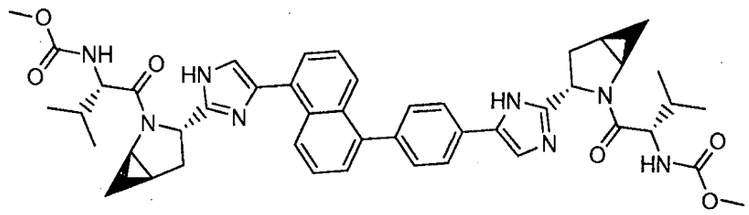


Example 87

Methyl ((1S)-1-(((2S,5S)-2-(4-chloro-5-(4-(6-(4-chloro-2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00656] N-Chlorosuccinimide (18.88 mg, 0.141 mmol) was to a stirred solution of a TFA salt of methyl ((1S)-1-(((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (105 mg, 0.129 mmol) in DMF (3.0 mL) and then and the reaction was flushed with nitrogen, sealed and heated at 50 °C overnight. By LCMS a

1.3:1.6:1 of starting material : mono-Cl (presumably both regioisomers : dichloro). The reaction was concentrated, dissolved into MeOH, filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield recovered starting material (36.2 mg), a mixture of the two mono-chloroimidazole regioisomers (56.6 mg) (Example 94 and Example 95) and a TFA salt of methyl ((1S)-1-(((2S,5S)-2-(4-chloro-5-(4-(6-(4-chloro-2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (20.4 mg) as a yellow solid. LC-MS retention time 2.482 min; m/z 885.84 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

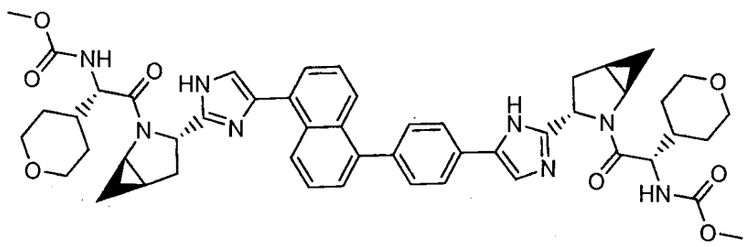


Example 88

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

[00657] HATU (62.8 mg, 0.165 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 144) (42.6 mg, 0.066 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (28.9 mg, 0.165 mmol) in DMF (0.8 mL) and DIPEA (0.092 mL, 0.53 mmol) and the

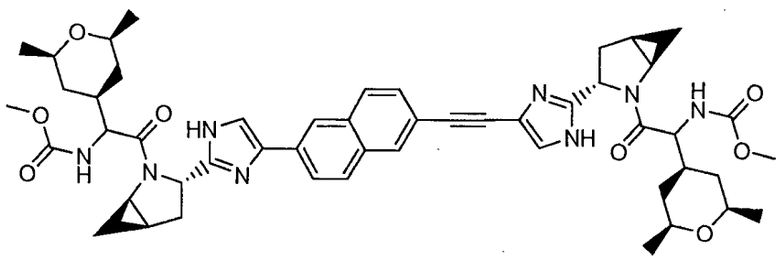
reaction was stirred at rt for 2h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (MeOH/water with TFA buffer) to yield the a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-1-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (53.7 mg) as an off-white solid. LC-MS retention time 2.821 min; m/z 813.88 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (500 MHz, MeOD) δ ppm 8.06 (d, *J*=8.5 Hz, 1 H), 7.98 (d, *J*=8.5 Hz, 1 H), 7.95 (s, 1 H), 7.91 (d, *J*=8.5 Hz, 2 H), 7.78 (s, 1 H), 7.65 - 7.73 (m, 4 H), 7.59 - 7.64 (m, 2 H), 5.18 (ddd, *J*=12.5, 9.2, 7.0 Hz, 2 H), 4.59 (dd, *J*=6.4, 3.4 Hz, 2 H), 3.80 - 3.87 (m, 2 H), 3.69 (s, 6 H), 2.73 (dt, *J*=13.4, 9.2 Hz, 2 H), 2.48 - 2.59 (m, 2 H), 2.18 - 2.28 (m, 2 H), 2.10 (br. s., 2 H), 1.08 - 1.15 (m, 2 H), 1.06 (d, *J*=7.0 Hz, 3 H), 1.04 (d, *J*=7.0 Hz, 3 H), 0.99 (d, *J*=6.7 Hz, 3 H), 0.95 (d, *J*=6.7 Hz, 3 H), 0.89 - 0.94 (m, 2 H).



Example 89

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-1-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

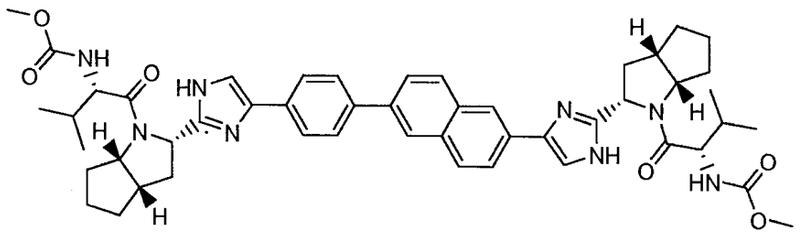
[00658] HATU (62.8 mg, 0.165 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)naphthalen-1-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 144) (42.6 mg, 0.066 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (35.9 mg, 0.165 mmol) in DMF (0.8 mL) and DIPEA (0.092 mL, 0.53 mmol) and the reaction was stirred at rt for 4h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (MeOH/water with ammonium acetate buffer) to yield methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-1-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (42.6 mg, 0.066 mmol) as an off-white solid. LC-MS retention time 1.965 min; m/z 897.59 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.23 (d, *J*=8.2 Hz, 1 H), 7.91 (d, *J*=8.5 Hz, 1 H), 7.82 (d, *J*=8.2 Hz, 2 H), 7.52 - 7.59 (m, 2 H), 7.44 - 7.51 (m, 4 H), 7.41 (s, 1 H), 7.21 (s, 1 H), 5.23 (dd, *J*=8.9, 4.6 Hz, 1 H), 5.18 (dd, *J*=8.9, 4.9 Hz, 1 H), 4.68 (dd, *J*=7.5, 2.6 Hz, 2 H), 3.89 - 4.01 (m, 4 H), 3.70 - 3.77 (m, 2 H), 3.69 (s, 6 H), 3.35 - 3.45 (m, 4 H), 2.43 - 2.63 (m, 4 H), 2.00 - 2.14 (m, 4 H), 1.52 - 1.71 (m, 6 H), 1.41 - 1.52 (m, 2 H), 1.10 - 1.18 (m, 2 H), 0.79 - 0.86 (m, 2 H).



Example 90

Methyl ((1S)-1-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((1R,3S,5R)-3-(4-((6-(2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate

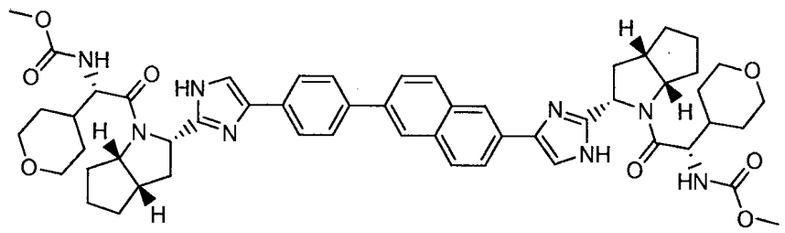
[00659] An HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 124) (50 mg, 0.073 mmol), 2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid (Cap-179 stereoisomer 2) (36.9 mg, 0.151 mmol), HATU (58.6 mg, 0.154 mmol) and DIEA (0.077 mL, 0.441 mmol) were combined in DMF (3 mL) and the resulting yellow solution was stirred at rt for 15h. The volatiles were removed under reduced pressure and the residue was redissolved in methanol and purified by preparative HPLC (Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Sunfire Prep MS C18 30 x 100mm 5u; Wavelength: 220nM; Flow rate: 40 ml/min; Gradient: 10% B to 80% B over 30 min. with a 5 min hold time) to yield a TFA salt of methyl ((1S)-1-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((1R,3S,5R)-3-(4-((6-(2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl)carbamate (43 mg) as a white solid. LC/MS $[M+H]^+$= 902; Rt = 1.93 min is product. Column PHENOMENEX® 10u C18 3.0x50mm; start %B: 0, final %B: 100 Solvent A: 10% MeOH/ 90% H_2O + 1% TFA; Solvent B: 90% MeOH/ 10% H_2O + 1% TFA; flow rate 4 mL/min. Run time: 5 min. Purity = 98 %. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.38 (1 H, br. s.), 8.14 - 8.22 (1 H, m), 8.09 (1 H, d, *J*=8.85 Hz), 7.93 - 8.00 (2 H, m), 7.62 (1 H, d, *J*=8.85 Hz), 7.25 (2 H, t, *J*=7.48 Hz), 5.02 (2 H, t, *J*=6.87 Hz), 4.51 (1 H, dd, *J*=7.78, 6.56 Hz), 4.45 (1 H, t, *J*=7.93 Hz), 3.82 (1 H, br. s.), 3.67 (1 H, d, *J*=13.73 Hz), 3.54 (6 H, s), 3.31 - 3.42 (3 H, m), 2.33 (2 H, br. s.), 1.85 - 1.97 (2 H, m), 1.43 - 1.52 (1 H, m), 1.22 - 1.31 (1 H, m), 1.03 - 1.12 (10 H, m), 0.89 - 1.01 (9 H, m), 0.82 (1 H, br. s.), 0.75 (1 H, br. s.).



Example 91

Methyl ((1S)-1-(((2S,3aS,6aS)-2-(4-(6-(4-(2-((2S,3aS,6aS)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)hexahydrocyclopenta[b]pyrrol-1(2H)-yl)carbonyl)-2-methylpropyl)carbamate

[00660] HATU (60.9 mg, 0.160 mmol) was added to a stirred solution of an HCl salt of (2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)octahydrocyclopenta[b]pyrrole (51 mg, 0.073 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (Intermediate 147) (28.1 mg, 0.160 mmol) and DIPEA (0.076 mL, 0.44 mmol) in DCM (1.5 mL) and the reaction mixture was stirred at rt for 2h. The crude reaction mixture was concentrated to dryness and purified by preparative HPLC (TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((2S,3aS,6aS)-2-(4-(6-(4-(2-((2S,3aS,6aS)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)hexahydrocyclopenta[b]pyrrol-1(2H)-yl)carbonyl)-2-methylpropyl)carbamate (23.7 mg) as a white solid. LC-MS retention time 2.462 min; m/z 867.8 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

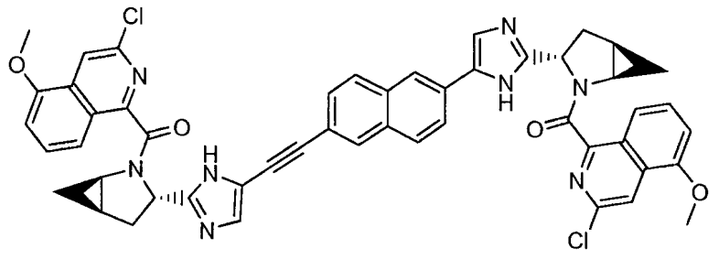


Example 92

Methyl ((1S)-2-((2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)hexahydrocyclopenta[b]pyrrol-2(2H)-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)hexahydrocyclopenta[b]pyrrol-1(2H)-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00661] HATU (62.1 mg, 0.163 mmol) was added to a stirred solution of an HCl salt of (2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)octahydrocyclopenta[b]pyrrole (51 mg, 0.073 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (Intermediate 147) (52 mg, 0.074 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (35.5 mg, 0.163 mmol) and DIPEA (0.078 mL, 0.45 mmol) in DCM (1.5 mL) and the mixture was stirred at rt for 2 h. The crude reaction mixture was concentrated to dryness and purified by preparative HPLC 9TFA buffer) to yield a TFA salt of methyl ((1S)-2-((2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)hexahydrocyclopenta[b]pyrrol-2(2H)-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)hexahydrocyclopenta[b]pyrrol-1(2H)-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (25.8 mg) as a white solid. LC-MS retention time 2.350 min; m/z 477.5 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM

ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

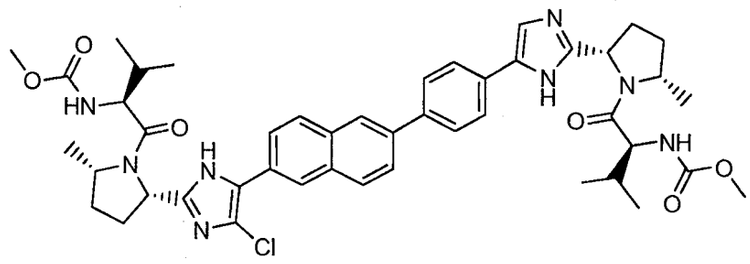


Example 93

3-Chloro-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-5-methoxyisoquinoline

[00662] HATU (48.1 mg, 0.127 mmol) was added to a solution of an HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 124) (30 mg, 0.051 mmol) and 3-chloro-5-methoxyisoquinoline-1-carboxylic acid (30.1 mg, 0.127 mmol) in DMF (0.8 mL) and DIPEA (0.071 mL, 0.45 mmol) and stirred at rt overnight. The reaction was diluted with MeOH, filtered, and purified by preparative HPLC (MeOH/water with an NH_4OAc buffer) and repurified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of 3-chloro-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((3-chloro-5-methoxy-1-isoquinolinyl)carbonyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-5-methoxyisoquinoline (40.9 mg) as a yellow solid. LC-MS retention time 3.621 min; m/z 887.34 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1%

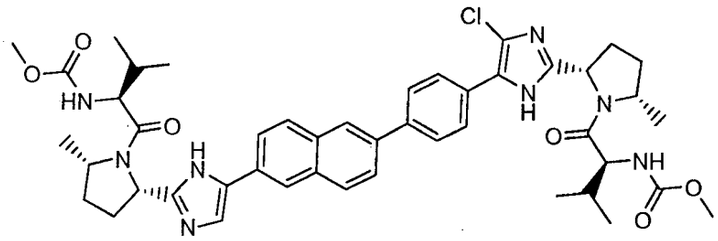
trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 94

Methyl ((1S)-1-(((2S,5S)-2-(4-(4-(6-(4-chloro-2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

and

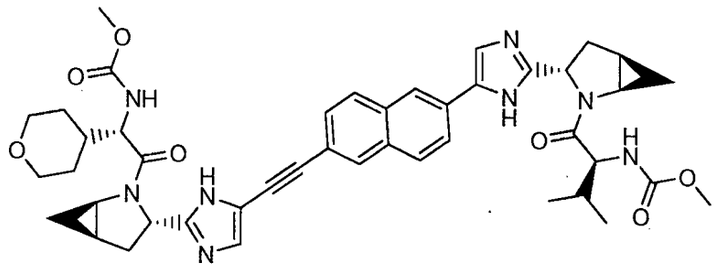


Example 95

Methyl ((1S)-1-(((2S,5S)-2-(4-chloro-5-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00663] These two compounds were prepared in the reaction that prepared methyl ((1S)-1-(((2S,5S)-2-(4-chloro-5-(4-(6-(4-chloro-2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (Example 87) and they were isolated as a mixture of mono-chloroimidazole regioisomers. The two regioisomers were separated by SCFC on a CHIRALCEL® OJ-H column (30 x 250mm, 5μm) using Solvents: 75% CO_2 - 25%

EtOH/0.1%DEA. The absolute regiochemistry of the two mono-chloroimidazole regioisomers was not determined so each was arbitrarily assigned. Example 94: Methyl ((1S)-1-(((2S,5S)-2-(4-(4-(6-(4-chloro-2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (18.6 mg) was isolated as a yellow solid. LC-MS retention time 3.756 min; m/z 851.62 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Example 95: Methyl ((1S)-1-(((2S,5S)-2-(4-chloro-5-(4-(6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (24.1 mg) was isolated as a yellow solid. LC-MS retention time 3.770 min; m/z 851.64 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

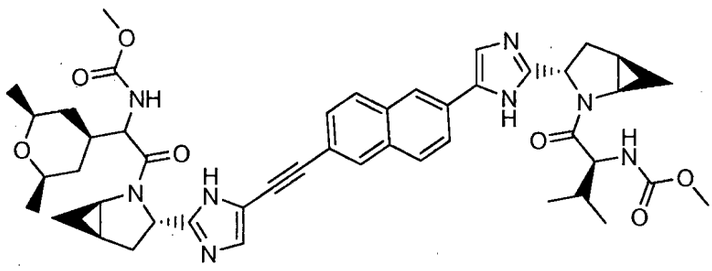


Example 96

Methyl ((1S)-2-((1R,3S,5R)-3-(4-((6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00664] 4M HCl (0.370 mL, 1.48 mmol) in dioxane was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-((6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 150) (69 mg, 0.074 mmol) in dioxane (2 mL) and slurry was stirred for 1.5 h. The reaction mixture was then concentrated under a stream of nitrogen and the intermediate product was treated with (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (20.9 mg, 0.096 mmol), DMF (1.5 mL), DIPEA (0.078 mL, 0.44 mmol) and finally HATU (36.6 mg, 0.096 mmol). The reaction mixture was stirred at rt overnight, diluted with MeOH, filtered and purified by preparative HPLC (MeOH/water with 0.1%TFA) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-((6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (35.3 mg) as a yellow solid. LC-MS retention time 2.726 min; m/z 803.74 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid.

MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.27 (s, 1 H), 8.18 (s, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.02 (m, 2 H), 7.88 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.74 (s, 1 H), 7.67 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.15 (dd, *J*=9.3, 7.0 Hz, 1 H), 5.09 (dd, *J*=9.0, 6.3 Hz, 1 H), 4.59 (d, *J*=7.8 Hz, 1 H), 4.56 (d, *J*=6.5 Hz, 1 H), 3.91 - 4.00 (m, 2 H), 3.74 - 3.84 (m, 2 H), 3.67 (s, 6 H), 3.34 - 3.45 (m, 2 H), 2.70 (dd, *J*=13.6, 9.5 Hz, 1 H), 2.61 (dd, *J*=13.8, 8.8 Hz, 1 H), 2.40 - 2.54 (m, 2 H), 2.14 - 2.23 (m, 1 H), 2.01 - 2.13 (m, 3 H), 1.56 - 1.64 (m, 1 H), 1.38 - 1.55 (m, 3 H), 1.05 - 1.14 (m, 2 H), 1.01 (d, *J*=6.8 Hz, 3 H), 0.92 (d, *J*=6.8 Hz, 3 H), 0.82 - 0.92 (m, 2 H).

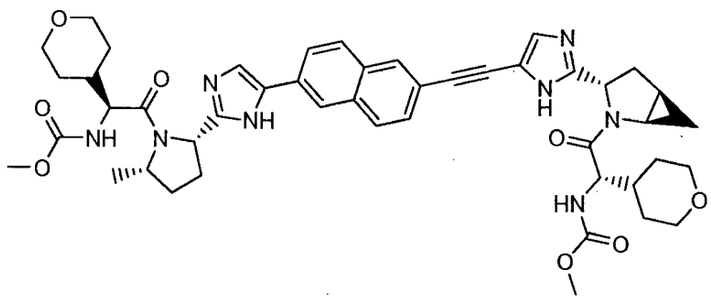


Example 97

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00665] 4M HCl (0.34 mL, 1.3 mmol) in dioxane was added to a solution of (1R,3S,5R)-*tert*-butyl 3-(5-((6-(2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 150) (62.7 mg, 0.067 mmol) in dioxane (2 mL) the slurry was stirred for 1.5 h. The reaction was then concentrated under a stream of nitrogen to dryness and then treated with 2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid (Cap-179 stereoisomer 2) (21.45 mg, 0.087 mmol), DMF (1.5 mL), DIPEA (0.071 mL, 0.40 mmol) and finally HATU (33.3 mg, 0.087 mmol). The reaction mixture was stirred at rt overnight diluted with MeOH, filtered and purified by preparative HPLC (MeOH/water with 0.1%TFA) to yield a TFA salt of

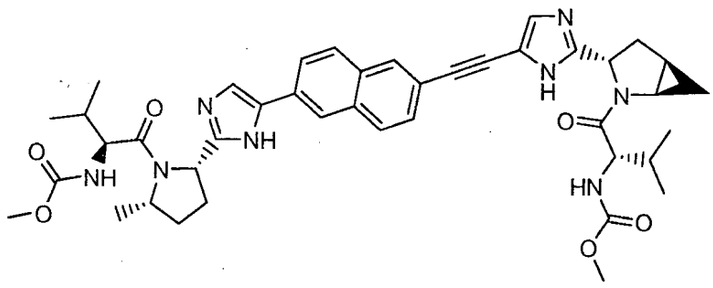
methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (28 mg) as a yellow solid. LC-MS retention time 2.898 min; m/z 831.80 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.27 (s, 1 H), 8.17 (s, 1 H), 8.05 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.02 (m, 2 H), 7.88 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.74 (s, 1 H), 7.66 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.15 (dd, *J*=9.2, 6.9 Hz, 1 H), 5.10 (dd, *J*=9.0, 6.3 Hz, 1 H), 4.56 (t, *J*=6.0 Hz, 2 H), 3.73 - 3.85 (m, 2 H), 3.67 (s, 6 H), 3.43 - 3.54 (m, 2 H), 2.70 (dd, *J*=13.7, 9.4 Hz, 1 H), 2.61 (dd, *J*=13.6, 9.0 Hz, 1 H), 2.40 - 2.54 (m, 2 H), 2.01 - 2.23 (m, 4 H), 1.55 - 1.64 (m, 1 H), 1.46 (d, *J*=12.0 Hz, 1 H), 1.17 (dd, *J*=6.0, 4.3 Hz, 6 H), 1.04 - 1.13 (m, 3 H), 1.01 (d, *J*=6.8 Hz, 3 H), 0.96 - 1.03 (m, 1 H), 0.92 (d, *J*=6.8 Hz, 3 H), 0.88 - 0.93 (m, 1 H), 0.82 - 0.87 (m, 1 H).



Example 98

Methyl ((1S)-2-((2S,5S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00666] HATU (43.2 mg, 0.114 mmol) was added an HCl salt of (1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 154) (27 mg, 0.045 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (24.7 mg, 0.114 mmol) in DMF (1 mL) and DIPEA (0.056 mL, 0.32 mmol) and the reaction mixture was stirred at rt for 2h. The reaction was concentrated under a stream of nitrogen, dissolved into MeOH, filtered and purified by preparative HPLC (MeOH/water with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-2-((2S,5S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (31.4 mg) as a yellow solid. LC-MS retention time 2.658 min; m/z 847.80 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. The ^1H NMR presents as a ~1:3.5 mixture of rotamers. The ^1H NMR for the major rotamer is: ^1H NMR (400 MHz, MeOD) δ ppm 8.29 (s, 1 H), 8.18 (s, 1 H), 8.06 (d, *J*=8.5 Hz, 1 H), 8.01 (d, *J*=8.8 Hz, 1 H), 7.99 (s, 1 H), 7.89 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.74 (s, 1 H), 7.67 (dd, *J*=8.4, 1.4 Hz, 1 H), 5.19 (dd, *J*=10.5, 7.0 Hz, 1 H), 5.09 (dd, *J*=8.9, 6.4 Hz, 1 H), 4.59 (d, *J*=7.5 Hz, 1 H), 4.22 (d, *J*=9.3 Hz, 1 H), 3.86 - 4.00 (m, 4 H), 3.72 - 3.82 (m, 2 H), 3.67 (s, 6 H), 3.23 - 3.45 (m, 4 H), 2.50 - 2.70 (m, 2 H), 2.24 - 2.50 (m, 3 H), 1.90 - 2.13 (m, 4 H), 1.70 - 1.85 (m, 1 H), 1.57 (d, *J*=6.5 Hz, 3 H), 1.30 - 1.64 (m, 6 H), 1.23 (d, *J*=11.5 Hz, 1 H), 1.04 - 1.12 (m, 1 H), 0.85 (br. s., 1 H).

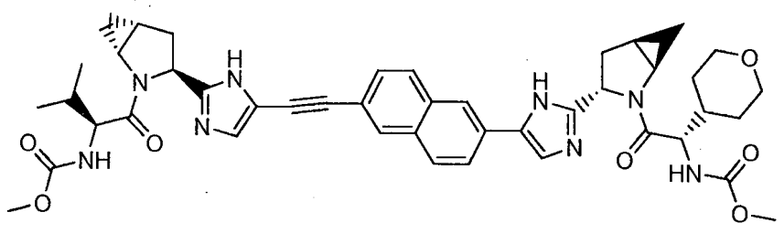


Example 99

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

[00667] HATU (43.2 mg, 0.114 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 154) (10.1 mg, 0.017 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (7.44 mg, 0.042 mmol) in DMF (0.5 mL) and DIPEA (0.021 mL, 0.119 mmol) and the reaction mixture was stirred at rt for 2h. The reaction was concentrated, dissolved into MeOH, filtered and purified by preparative HPLC (MeOH/water with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-((6-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (9.3 mg) as a yellow solid. LC-MS retention time 2.930 min; m/z 763.75 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR presents as a ~1:3 mixture of rotamers, the data for the major rotamer is: ^1H NMR (400 MHz, MeOD) δ ppm 8.30 (s, 1 H), 8.19 (s, 1 H), 8.07 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.03 (m, 2 H), 7.90 (dd, *J*=8.5, 1.5 Hz, 1 H), 7.77 (s, 1 H), 7.65 - 7.71 (m, 1 H), 5.19

(dd, *J*=10.2, 6.9 Hz, 1 H), 5.10 (dd, *J*=9.2, 6.4 Hz, 1 H), 4.55 (d, *J*=6.5 Hz, 1 H), 4.13 (d, *J*=8.8 Hz, 1 H), 3.67 (s, 6 H), 3.65 - 3.79 (m, 2 H), 1.95 - 2.68 (m, 8 H), 1.57 (d, *J*=6.5 Hz, 3 H), 1.31 (d, *J*=6.3 Hz, 1 H), 1.01 (d, *J*=7.0 Hz, 3 H), 0.98 (d, *J*=7.0 Hz, 3 H), 0.93 (d, *J*=6.8 Hz, 3 H), 0.88 (d, *J*=6.8 Hz, 3 H), 0.84 - 1.14 (m, 2 H).

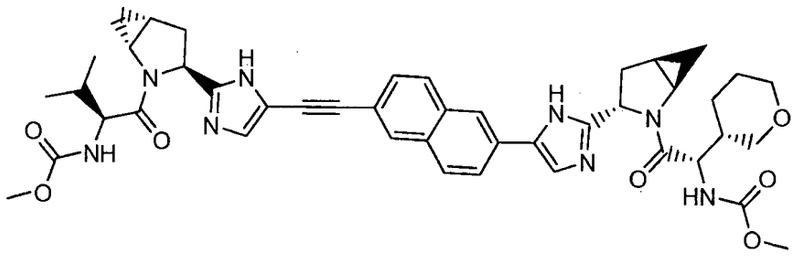


Example 100

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00668] 4M HCl (0.32 mL, 1.3 mmol) in dioxane was added to mixture of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-(6-((2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 158) (60 mg, 0.064 mmol) in dioxane (0.5 mL) and the reaction was stirred vigorously for 4 h. The reaction was concentrated to dryness. Then (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (18.2 mg, 0.084 mmol), DMF (0.5 mL), DIPEA (0.067 mL, 0.39 mmol) and finally HATU (31.8 mg) were added to the crude material and the reaction was stirred at rt for 1h. The reaction was partially concentrated with a stream on nitrogen, diluted with MeOH, filtered and purified preparative HPLC (MeOH/water with a TFA buffer) and then repurified preparative HPLC (MeOH/water with an ammonium acetate buffer). The material was purified a third time by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (27.7 mg) as a white solid. LC-MS retention time 3.291 min; m/z

803.67 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.27 (s, 1 H), 8.19 (s, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.03 (m, 2 H), 7.88 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.78 (s, 1 H), 7.68 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.15 (dd, *J*=9.0, 7.0 Hz, 1 H), 5.09 (dd, *J*=9.3, 6.5 Hz, 1 H), 4.80 (d, 2 H), 4.54 (d, *J*=6.5 Hz, 1 H), 3.87 - 3.93 (m, 1 H), 3.70 - 3.79 (m, 3 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.54 - 3.63 (m, 1 H), 3.34 - 3.40 (m, 1 H), 2.59 - 2.74 (m, 2 H), 2.40 - 2.55 (m, 2 H), 2.00 - 2.22 (m, 4 H), 1.71 - 1.81 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.05 - 1.14 (m, 2 H), 1.01 (d, *J*=6.8 Hz, 3 H), 0.93 (d, *J*=6.8 Hz, 3 H), 0.88 (br. s., 2 H).

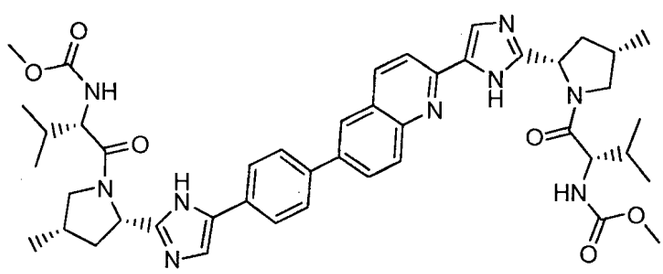


Example 101

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-((3S)-tetrahydro-2H-pyran-3-yl)ethyl)carbamate

[00669] 4M HCl (0.3 mL, 1.3 mmol) in dioxane was added to mixture of a TFA salt of (1R,3S,5R)-*tert*-butyl 3-(5-(6-((2-((1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 158) (60 mg, 0.064 mmol) in dioxane (0.5 mL) and the reaction was stirred vigorously for 4h. The reaction was concentrated to dryness. Then (S)-2-(methoxycarbonylamino)-2-((S)-

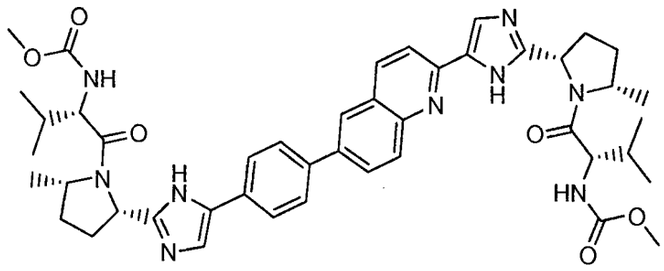
tetrahydro-2H-pyran-3-yl)acetic acid (Cap-177a) (18.2 mg, 0.084 mmol), DMF (0.5 mL), DIPEA (0.067 mL, 0.39 mmol) and finally HATU (32 mg, 0.084 mmol) was added to the crude material and the reaction was stirred at rt for 1h. The reaction was partially concentrated, diluted with MeOH, filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) and repurified in one injection by Prep HPLC (MeOH/water with an ammonium acetate buffer) to yield methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-((3S)-tetrahydro-2H-pyran-3-yl)ethyl)carbamate (30.5 mg) as a white solid. LC-MS retention time 3.376 min; m/z 803.66 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.14 (s, 1 H), 7.94 (s, 1 H), 7.78 - 7.86 (m, 3 H), 7.49 (dd, *J*=8.5, 1.5 Hz, 1 H), 7.45 (s, 1 H), 7.26 (s, 1 H), 5.15 (ddd, *J*=12.9, 8.7, 4.5 Hz, 2 H), 4.57 (d, *J*=6.8 Hz, 1 H), 3.70 - 3.86 (m, 3 H), 3.67 (br. s., 3 H), 3.66 (br. s., 3 H), 3.58 - 3.64 (m, 1 H), 3.53 (t, *J*=8.3 Hz, 1 H), 3.45 (dd, *J*=11.4, 8.2 Hz, 1 H), 2.31 - 2.57 (m, 4 H), 1.93 - 2.17 (m, 5 H), 1.67 - 1.84 (m, 2 H), 1.50 - 1.63 (m, 2 H), 1.08 - 1.17 (m, 2 H), 0.98 (d, *J*=6.8 Hz, 3 H), 0.92 (d, *J*=6.8 Hz, 3 H), 0.78 (br. s., 2 H).



Example 102

Methyl ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00670] HATU (20.99 mg, 0.055 mmol) was added to a solution of an HCl salt of 2-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)-6-(4-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline (Intermediate 164) (16.5 mg, 0.024 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (9.7 mg, 0.055 mmol) in DMF (0.5 mL) and DIPEA (0.038 mL, 0.22 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (8.3 mg, 6.94 μmol, 28.9 % yield) as a yellow solid. LC-MS retention time 3.555 min; m/z 818.78 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.60 (d, *J*=8.5 Hz, 1 H), 8.34 (d, *J*=1.8 Hz, 1 H), 8.32 (s, 1 H), 8.26 - 8.31 (m, 1 H), 8.21 - 8.26 (m, 1 H), 8.06 (d, *J*=8.5 Hz, 1 H), 7.97 - 8.03 (m, 1 H), 8.00 (d, *J*=8.5 Hz, 1 H), 7.93 (s, 1 H), 7.87 - 7.92 (m, 2 H), 5.19 - 5.36 (m, 2 H), 4.29 - 4.41 (m, 2 H), 4.24 (t, *J*=6.9 Hz, 2 H), 3.67 (s, 6 H), 3.44 (q, *J*=11.0 Hz, 2 H), 2.62 - 2.74 (m, 2 H), 2.46 - 2.61 (m, 2 H), 1.97 - 2.12 (m, 2 H), 1.82 - 1.97 (m, 2 H), 1.26 (dd, *J*=6.3, 3.3 Hz, 6 H), 0.91 - 0.96 (m, 6 H), 0.89 (dd, *J*=6.7, 5.1 Hz, 6 H).

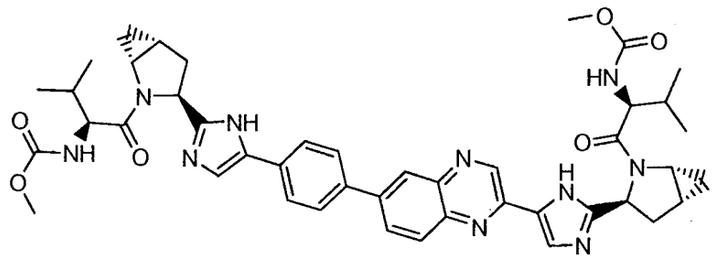


Example 103

Methyl ((1S)-1-(((2S,5S)-2-(4-(6-(4-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00671] HATU (15.74 mg, 0.041 mmol) was added to a solution of a crude HCl salt of 2-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)-6-(4-(2-((2S,5S)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline (Intermediate 167) (12.35 mg, 0.018 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (7.25 mg, 0.041 mmol) in DMF (0.5 mL) and DIPEA (0.028 mL, 0.16 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((2S,5S)-2-(4-(6-(4-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (3.9 mg) as a yellow solid. LC-MS retention time 3.616 min; m/z 818.73 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.68 (d, *J*=8.8 Hz, 1 H), 8.39 (d, *J*=1.3 Hz, 1 H), 8.30 - 8.35 (m, 2 H), 8.26 - 8.31 (m, 1 H), 8.16 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.06 (m, 3 H), 7.89 - 7.94 (m, 2 H), 5.14 - 5.31 (m, 2 H), 4.14 (dd, *J*=8.8, 5.0 Hz, 2 H), 3.68 (s, 6 H), 2.47 - 2.59 (m, 2 H), 2.23 - 2.43 (m, 4 H),

1.95 - 2.10 (m, 4 H), 1.56 (dd, *J*=6.7, 3.6 Hz, 6 H), 1.01 - 1.07 (m, 2 H), 0.99 (dd, *J*=6.7, 3.4 Hz, 6 H), 0.89 (dd, *J*=6.8, 1.8 Hz, 6 H).

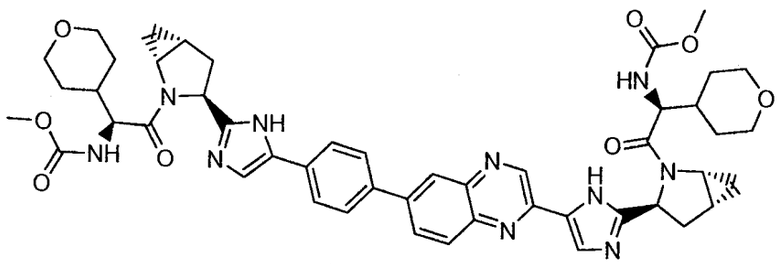


Example 104

Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00672] HATU (50.7 mg, 0.133 mmol) was added to a solution of an HCl salt of methyl ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (Intermediate 173) (41.7 mg, 0.058 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (23.4 mg, 0.133 mmol) in DMF (1 mL) and DIPEA (0.09 mL, 0.5 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (22.3 mg) as a yellow solid. LC-MS retention time 3.451 min; m/z 815.72 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1%

trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (400 MHz, MeOD) δ ppm 9.41 (s, 1 H), 8.43 (d, *J*=8.5 Hz, 1 H), 8.41 - 8.47 (m, 1 H), 8.28 (d, *J*=1.3 Hz, 2 H), 8.03 (d, *J*=8.5 Hz, 1 H), 8.00 - 8.07 (m, 1 H), 7.87 - 7.95 (m, 3 H), 5.10 - 5.26 (m, 2 H), 4.57 (t, *J*=6.7 Hz, 2 H), 3.76 - 3.89 (m, 2 H), 3.68 (s, 6 H), 2.70 (dd, *J*=13.7, 9.2 Hz, 2 H), 2.44 - 2.56 (m, 2 H), 2.14 - 2.26 (m, 2 H), 2.04 - 2.14 (m, 2 H), 1.07 - 1.16 (m, 2 H), 1.02 (dd, *J*=6.8, 2.0 Hz, 6 H), 0.93 (dd, *J*=6.8, 2.0 Hz, 6 H), 0.83 - 0.99 (m, 2 H).

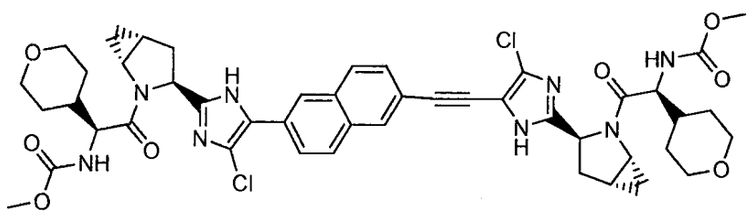


Example 105

Methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00673] HATU (12.24 mg, 0.032 mmol) was added to a solution of an HCl salt of methyl ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (Intermediate 173) (10.1 mg, 0.014 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (7.0 mg, 0.032 mmol) in DMF (0.5 mL) and DIPEA (0.022 mL, 0.13 mmol) and the reaction mixture was stirred at rt for 2h. The reaction was diluted with MeOH, filtered and purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)-2-quinoxalinyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (7.3

mg) as a yellow solid. LC-MS retention time 3.251 min; m/z 899.79 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.41 (s, 1 H), 8.41 - 8.47 (m, 2 H), 8.27 - 8.31 (m, 2 H), 8.03 (d, *J*=8.5 Hz, 1 H), 8.01 - 8.06 (m, 1 H), 7.87 - 7.95 (m, 3 H), 5.09 - 5.26 (m, 2 H), 4.61 (t, *J*=7.2 Hz, 2 H), 3.90 - 4.01 (m, 4 H), 3.80 - 3.90 (m, 2 H), 3.68 (s, 6 H), 3.34 - 3.47 (m, 4 H), 2.70 (dd, *J*=13.6, 9.3 Hz, 2 H), 2.45 - 2.57 (m, 2 H), 1.99 - 2.19 (m, 4 H), 1.36 - 1.68 (m, 8 H), 1.02 - 1.16 (m, 2 H), 0.79 - 0.96 (m, 2 H).

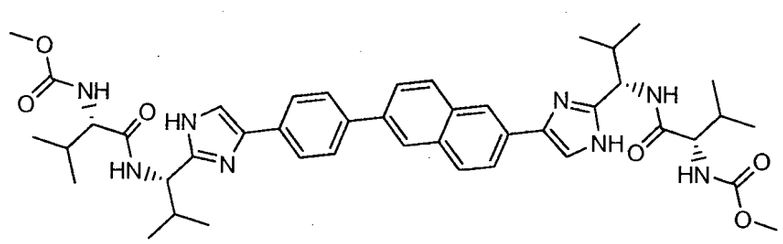


Example 106

Methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-((4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00674] N-Chlorosuccinimide (6.97 mg, 0.052 mmol) was added to a stirred solution of methyl ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (Example 82) (21.0 mg, 0.025 mmol) in DMF and then the reaction vessel was flushed with a stream of nitrogen, sealed and heated at 50 °C for 3h. Additional N-chlorosuccinimide (5.0 mg) was added and the

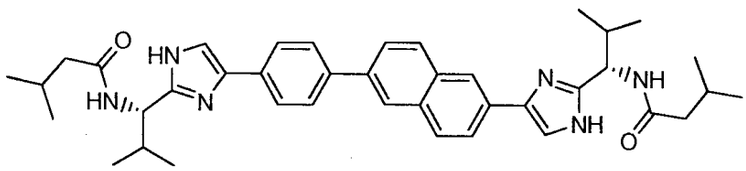
reaction vessel was flushed with nitrogen, sealed and heated at 50 °C for 3h, then the reaction was cooled and concentrated under a stream on nitrogen. The remnants were dissolved into MeOH, filtered, and purified by preparative HPLC (MeOH/water with TFA buffer) to yield a TFA salt of methyl ((1S)-2-((1R,3S,5R)-3-(4-chloro-5-(6-((4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (8.1 mg) as a yellow solid. LC-MS retention time 4.276 min; m/z 457.47 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.18 (s, 1 H), 8.07 (s, 1 H), 7.98 (d, *J*=8.8 Hz, 1 H), 7.93 (d, *J*=8.5 Hz, 1 H), 7.88 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.59 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.05 (dd, *J*=8.5, 6.3 Hz, 1 H), 4.99 (t, *J*=6.9 Hz, 1 H), 4.62 (d, *J*=7.5 Hz, 2 H), 3.91 - 3.98 (m, 4 H), 3.74 - 3.81 (m, 1 H), 3.68 - 3.72 (m, 1 H), 3.67 (s, 6 H), 3.34 - 3.45 (m, 4 H), 2.45 - 2.56 (m, 2 H), 2.39 - 2.44 (m, 2 H), 1.96 - 2.11 (m, 4 H), 1.37 - 1.66 (m, 8 H), 1.05 - 1.14 (m, 2 H), 0.74 - 0.84 (m, 2 H).



Example 107

Methyl ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-methylpropyl)carbamoyl)-2-methylpropyl)carbamate

[00675] HATU (77 mg, 0.20 mmol) was added to a stirred solution of an HCl salt of (S)-1-(5-(4-(6-(2-((S)-1-amino-2-methylpropyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-methylpropan-1-amine (Intermediate 178) (57.4 mg, 0.092 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (35.4 mg, 0.202 mmol) and DIPEA (0.096 mL, 0.55 mmol) in DCM (1.5 mL) and the reaction mixture was stirred at rt for 2 h. The crude reaction mixture was concentrated to dryness and purified by preparative HPLC (TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-methylpropyl)carbamoyl)-2-methylpropyl)carbamate (60.4 mg) as a white solid. LC-MS retention time 2.253 min; m/z 759.6 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

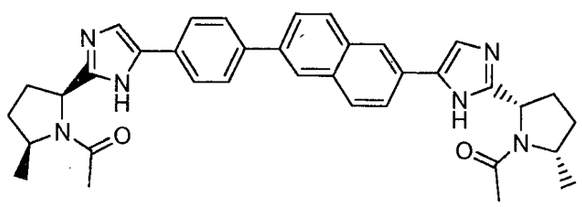


Example 108

3-Methyl-N-((1S)-2-methyl-1-(4-(4-(6-(2-((1S)-2-methyl-1-((3-methylbutanoyl)amino)propyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)propyl)butanamide

[00676] HATU (119 mg, 0.313 mmol) was added to a stirred solution of an HCl salt of (S)-1-(5-(4-(6-(2-((S)-1-amino-2-methylpropyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)-2-methylpropan-1-amine (Intermediate 178) (89 mg, 0.142 mmol), 3-methylbutanoic acid (32 mg, 0.31 mmol) and DIPEA (0.149 mL, 0.855 mmol)

in DCM (2 mL) and the reaction mixture was stirred at rt for 2 h. The crude reaction mixture was concentrated to dryness and purified twice by preparative HPLC (TFA buffer) to yield a TFA salt of 3-methyl-N-((1S)-2-methyl-1-(4-(4-(6-(2-((1S)-2-methyl-1-((3-methylbutanoyl)amino)propyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)propyl)butanamide (54.6 mg) as a beige solid. LC-MS retention time 2.375 min; m/z 645.6 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 5% acetonitrile / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% acetonitrile / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

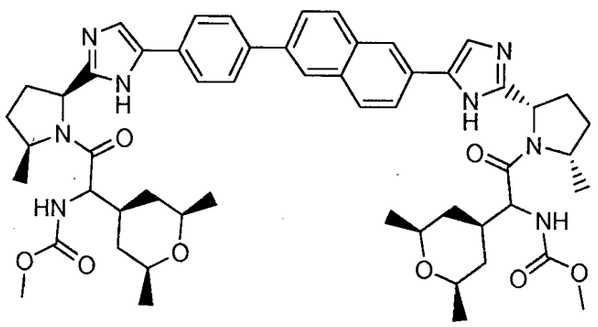


Example 109

2-((2S,5S)-1-Acetyl-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole

[00677] HATU (63.2 mg, 0.166 mmol) was added to a solution of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 117) (contaminated with ammonium acetate) (38 mg, 0.076 mmol) and (S)-2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid (40.8 mg, 0.166 mmol) in DMF (1.0 mL) and DIPEA (0.053 mL, 0.30 mmol) and the reaction was at rt overnight. The reaction mixture was diluted with MeOH, filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of 2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (20 mg) as a yellow solid. LC-MS retention time 3.123 min; m/z 587.62 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped

with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.30 (s, 1 H), 8.27 (s, 1 H), 8.13 (d, *J*=8.8 Hz, 1 H), 8.09 (d, *J*=8.8 Hz, 1 H), 7.93 - 8.01 (m, 4 H), 7.84 - 7.91 (m, 4 H), 5.25 (q, *J*=8.4 Hz, 2 H), 4.31 - 4.40 (m, 2 H), 2.53 - 2.66 (m, 2 H), 2.28 - 2.40 (m, 4 H), 2.25 (s, 3 H), 2.25 (s, 3 H), 1.88 - 1.97 (m, 2 H), 1.47 (dd, *J*=6.5, 3.5 Hz, 6 H), 1.14 - 1.19 (m, 1 H).

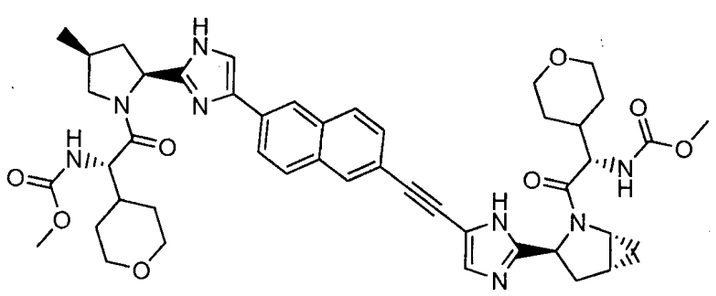


Example 110

Methyl (1-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate

[00678] HATU (61.9 mg, 0.163 mmol) was added to a solution of an HCl salt of 2-((2S,5S)-5-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,5S)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 117) (48 mg, 0.074 mmol) and 2-((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)-2-(methoxycarbonylamino)acetic acid (Cap-179 stereoisomer 2) (39.9 mg, 0.163 mmol) in DMF (0.8 mL) and DIPEA (0.09 mL, 0.52 mmol) and the reaction was stirred rt for 2h. The reaction was diluted with MeOH, filtered and purified in two injections by prep HPLC (MeOH/water with TFA buffer) to yield a TFA salt of methyl (1-((2R,4r,6S)-2,6-

dimethyltetrahydro-2H-pyran-4-yl)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate (55.5 mg) as a light yellow solid. LC-MS retention time 3.506 min; m/z 479.54 (1/2 MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. The ^1H NMR presented as a complex mixture of rotamers.

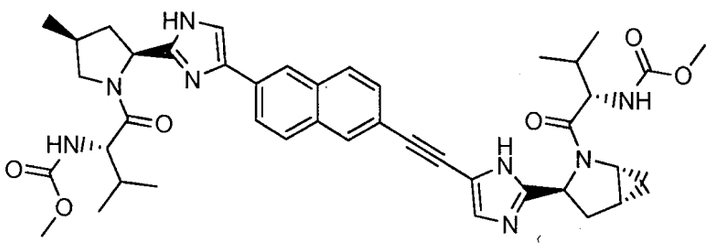


Example 111

Methyl ((1S)-2-((2S,4S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00679] HATU (23.99 mg, 0.063 mmol) was added to a solution of an HCl salt of (1R,3S,5R)-3-(4-((6-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 175) (15 mg, 0.025 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (13.70 mg, 0.063 mmol) in DMF (0.4 mL) and DIPEA (0.03 mL, 0.2 mmol) and the reaction was stirred at rt for 1.5h. The reaction was diluted with MeOH, filtered and purified in two injections by preparative HPLC (MeOH/water with TFA buffer) to a TFA

salt of methyl ((1S)-2-((2S,4S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (12.0 mg) as a yellow solid. LC-MS retention time 3.040 min; m/z 847.76 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.18 (s, 1 H), 8.05 (d, *J*=8.8 Hz, 1 H), 7.97 - 8.02 (m, 2 H), 7.88 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.76 (s, 1 H), 7.67 (dd, *J*=8.4, 1.4 Hz, 1 H), 5.23 (dd, *J*=10.9, 6.9 Hz, 1 H), 5.09 (dd, *J*=9.0, 6.5 Hz, 1 H), 4.59 (d, *J*=7.8 Hz, 1 H), 4.34 - 4.41 (m, 1 H), 4.28 (d, *J*=8.0 Hz, 1 H), 3.86 - 4.00 (m, 4 H), 3.75 - 3.81 (m, 1 H), 3.67 (s, 3 H), 3.67 (s, 3 H), 3.32 - 3.50 (m, 5 H), 2.39 - 2.74 (m, 4 H), 1.87 - 2.13 (m, 4 H), 1.27 - 1.65 (m, 8 H), 1.25 (d, *J*=6.3 Hz, 3 H), 1.04 - 1.14 (m, 1 H), 0.86 (br. s., 1 H).

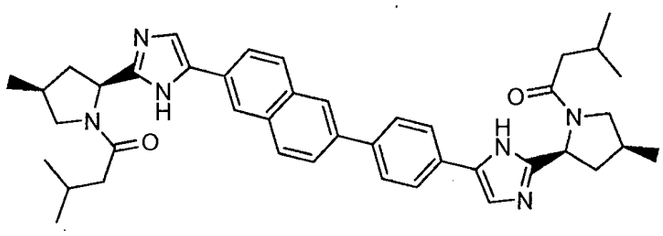


Example 112

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

[00680] HATU (60.8 mg, 0.160 mmol) was added to a solution of an HCl salt of (1R,3S,5R)-3-(4-((6-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)ethynyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 175) (38 mg,

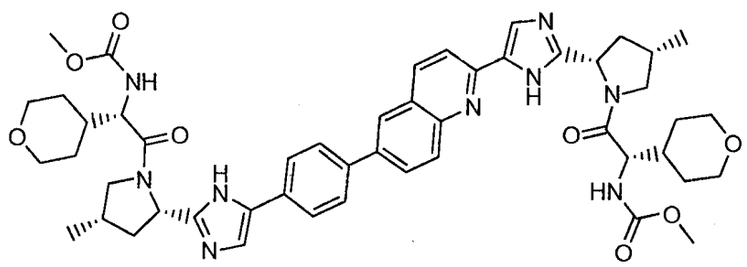
0.064 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (28.0 mg, 0.160 mmol) in DMF (0.7 mL) and DIPEA (0.08 mL, 0.4 mmol) and stirred at rt for 1.5h. The reaction was diluted with MeOH, filtered and purified twice by preparative HPLC (MeOH/water with TFA buffer) to yield a TFA salt methyl ((1S)-1-(((2S,4S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (19.1 mg) as an off-white solid. LC-MS retention 3.288 time min; m/z 763.74 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.18 (s, 1 H), 8.05 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.03 (m, 2 H), 7.88 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.76 (s, 1 H), 7.67 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.24 (dd, *J*=10.9, 7.2 Hz, 1 H), 5.10 (dd, *J*=9.0, 6.5 Hz, 1 H), 4.55 (d, *J*=6.5 Hz, 1 H), 4.30 - 4.37 (m, 1 H), 4.23 (d, *J*=7.3 Hz, 1 H), 3.72 - 3.79 (m, 1 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.43 (t, *J*=10.4 Hz, 1 H), 2.49 - 2.74 (m, 3 H), 2.44 (ddd, *J*=13.6, 6.7, 6.4 Hz, 1 H), 2.11 - 2.22 (m, 1 H), 1.98 - 2.11 (m, 2 H), 1.89 (q, *J*=12.0 Hz, 1 H), 1.25 (d, *J*=6.3 Hz, 3 H), 1.06 - 1.15 (m, 1 H), 1.00 (d, *J*=6.8 Hz, 3 H), 0.95 - 0.98 (m, 1 H), 0.94 (d, *J*=4.0 Hz, 3 H), 0.92 (d, *J*=3.8 Hz, 3 H), 0.88 (d, *J*=6.8 Hz, 3 H).



Example 113

2-((2S,4S)-4-Methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole

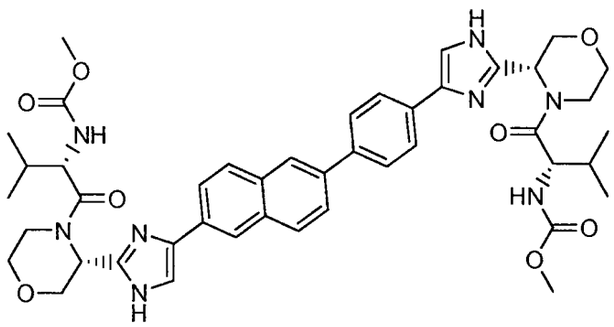
[00681] HATU (76 mg, 0.200 mmol) was added to a solution of an HCl salt of 2-((2S,4S)-4-methylpyrrolidin-2-yl)-5-(4-(6-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)naphthalen-2-yl)phenyl)-1H-imidazole (Intermediate 196) (64.8 mg, 0.1 mmol), 3-methylbutanoic acid (22.5 mg, 0.220 mmol) and DIPEA (0.122 mL, 0.700 mmol) in DCM (2 mL) and the mixture was stirred rt overnight. The reaction mixture was evaporated to dryness and then purified by preparative HPLC to afford a TFA salt of 2-((2S,4S)-4-methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (61.7 mg) as an off-white solid. LC-MS retention time 1.853 min; m/z 671.64 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 114

Methyl ((1S)-2-((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00682] HATU (12.75 mg, 0.034 mmol) was added to a solution of 2-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)-6-(4-(2-((2S,4S)-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)quinoline (Intermediate 164) (10 mg, 0.015 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (7.28 mg, 0.034 mmol) in DMF (0.5 mL) and DIPEA (0.023 mL, 0.13 mmol) and the mixture was stirred at rt for 16 h. The reaction was concentrated and the residue was purified by preparative HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of methyl ((1S)-2-((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-quinolinyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (8.6 mg) as a yellow solid. LC-MS retention time 3.243 min; m/z 902.90 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.61 (d, *J*=8.8 Hz, 1 H), 8.35 (d, *J*=1.8 Hz, 1 H), 8.22 - 8.33 (m, 3 H), 8.07 (d, *J*=8.8 Hz, 1 H), 8.00 (d, *J*=8.5 Hz, 1 H), 7.97 - 8.04 (m, 1 H), 7.89 (d, *J*=8.5 Hz, 1 H), 7.85 - 7.95 (m, 2 H), 5.17 - 5.33 (m, 2 H), 4.32 - 4.45 (m, 2 H), 4.28 (dd, *J*=8.2, 5.4 Hz, 2 H), 3.83 - 3.98 (m, 4 H), 3.67 (s, 6 H), 3.22 - 3.54 (m, 6 H), 2.63 - 2.75 (m, 2 H), 2.46 - 2.61 (m, 2 H), 1.83 - 2.04 (m, 4 H), 1.52 - 1.64 (m, 2 H), 1.30 - 1.53 (m, 6 H), 1.26 (dd, *J*=6.3, 4.0 Hz, 6 H).

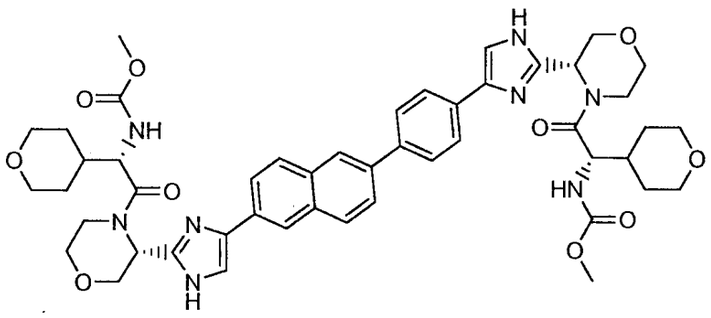


Example 115

Methyl ((1S)-1-(((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-3-morpholinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-morpholinyl)carbonyl)-2-methylpropyl)carbamate

[00683] HATU (96 mg, 0.252 mmol) was added to a solution of an HCl salt of (R)-3-(5-(4-(6-(2-((R)-morpholin-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)morpholine (Intermediate 181) (71.6 mg, 0.110 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (44.2 mg, 0.252 mmol) in DMF (1.0 mL) and DIPEA (0.13 mL, 0.77 mmol) and the reaction mixture was flushed with nitrogen, sealed and stirred at rt for 3h. The reaction was concentrated under a stream of nitrogen overnight, diluted with MeOH (~ 5 mL), filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-3-morpholinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-morpholinyl)carbonyl)-2-methylpropyl)carbamate (75.5 mg) as a off-white solid LC-MS retention time 3.351 min; m/z 822.07 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR presents as a mixture of rotamers. ^1H NMR (400 MHz, MeOD) δ ppm 8.47 (s, 0.5 H), 8.33 (s, 0.5 H), 8.27 (s, 1 H), 7.85 - 8.17 (m, 10 H), 5.95 (d, *J*=4.5 Hz, 2 H), 4.71

(dd, *J*=12.5, 7.8 Hz, 1 H), 4.35 - 4.58 (m, 4 H), 3.94 - 4.20 (m, 5 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.53 - 3.78 (m, 3 H), 2.76 - 2.91 (m, 1 H), 2.12 (br. s., 2 H), 1.05 - 1.19 (m, 6 H), 0.81 - 1.00 (m, 6 H).

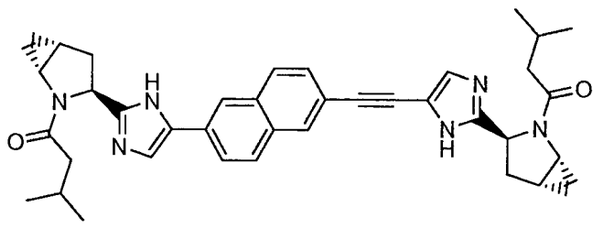


Example 116

Methyl ((1S)-2-((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-3-morpholinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-morpholinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00684] HATU (88 mg, 0.231 mmol) was added to a solution of an HCl salt of (R)-3-(5-(4-(6-(2-((R)-morpholin-3-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)morpholine (Intermediate 181) (65.5mg, 0.100 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (50.2 mg, 0.231 mmol) in DMF (1.0 mL) and DIPEA (0.12 mL, 0.70 mmol) and the reaction mixture was flushed with nitrogen, sealed and stirred at rt for 3h. The reaction was concentrated under a stream of nitrogen overnight, diluted with MeOH (~ 5 mL), filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-2-((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-3-morpholinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-morpholinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (75 mg) as an off-white solid. LC-MS retention time 3.120 min; m/z 906.15 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

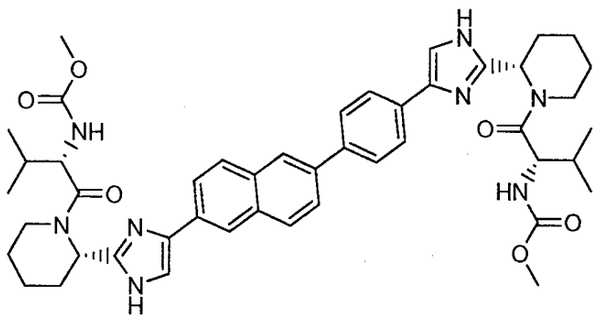
B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.



Example 117

(1R,3S,5R)-2-(3-Methylbutanoyl)-3-(4-(6-((2-((1R,3S,5R)-2-(3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane

[00685] HATU (74.8 mg, 0.197 mmol) was added to a stirred solution of an HCl salt of (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)ethynyl)naphthalen-2-yl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 124) (64.7 mg, 0.098 mmol), 3-methylbutanoic acid (22.09 mg, 0.216 mmol) and DIPEA (0.103 mL, 0.590 mmol) in DCM (1.5 mL) and the reaction mixture was stirred at rt for 2-3 h. The reaction was concentrated to dryness and purified by preparative HPLC (TFA buffer) to yield a TFA salt of (1R,3S,5R)-2-(3-methylbutanoyl)-3-(4-(6-((2-((1R,3S,5R)-2-(3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)ethynyl)-2-naphthyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (51.5 mg) as a beige solidified foam. LC-MS retention time 1.775 min; m/z 615.41 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode.

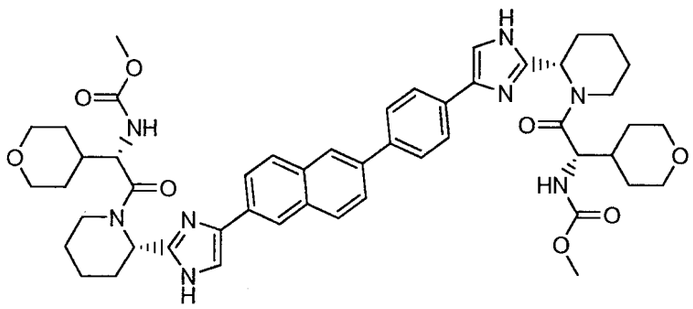


Example 118

Methyl ((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-piperidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-piperidinyl)carbonyl)-2-methylpropyl)carbamate

[00686] HATU (93 mg, 0.245 mmol) was added to a solution of an HCl salt of (S)-2-(5-(4-(6-(2-((S)-piperidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)piperidine (Intermediate 184) (69.0 mg, 0.106 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (42.9 mg, 0.245 mmol) in DMF (1.0 mL) and DIPEA (0.13 mL, 0.75 mmol) and the reaction was flushed with nitrogen, sealed and stirred at rt for 1h. The reaction was concentrated under a stream of nitrogen overnight, diluted with MeOH (~ 5 mL), filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-piperidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-piperidinyl)carbonyl)-2-methylpropyl)carbamate (88.9 mg) as a light yellow solid. LC-MS retention time 3.530 min; m/z 818.08 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR presents as a mixture of rotamers. ^1H NMR (400 MHz, MeOD) δ ppm 8.46 (s,

0.65 H), 8.33 (br. s., 0.35 H), 8.27 (s, 1 H), 7.84 - 8.15 (m, 10 H), 6.05 (br. s., 1.3 H), 5.80 - 5.90 (m, 0.7 H), 4.67 - 4.78 (m,1.3 H), 4.42 - 4.50 (m, 2 H), 3.99 - 4.10 (m, 0.7 H), 3.78 (br. s., 3.5 H), 3.69 (br. s., 2.5 H), 3.40 - 3.52 (m, 0.7 H), 2.61 - 2.73 (m, 1.3 H), 2.46 - 2.59 (m, 1.3 H), 2.37 (br. s., 0.7 H), 2.03 - 2.24 (m, 4 H), 1.91 - 2.02 (m, 1.3 H), 1.63 - 1.88 (m, 5.4 H), 1.45 - 1.62 (m, 1.4.H), 1.11 (t, *J*=6.8 Hz, 7.3 H), 0.93 - 1.03 (m, 4.7H).

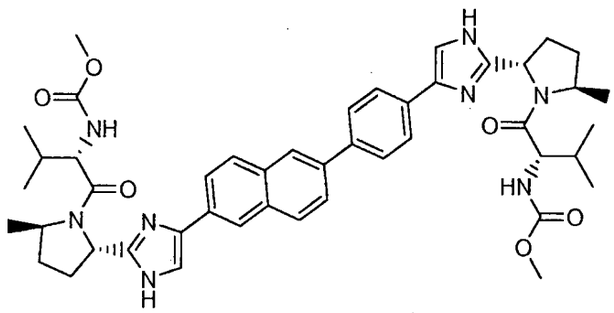


Example 119

Methyl ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-piperidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-piperidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00687] HATU (84 mg, 0.222 mmol) was added to a solution of an HCl salt of (S)-2-(5-(4-(6-(2-((S)-piperidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)piperidine (Intermediate 184) (62.5 mg, 0.096 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (48.2 mg, 0.222 mmol) in DMF (1.0 mL) and DIPEA (0.12 mL, 0.68 mmol) and the reaction was flushed with nitrogen, sealed and stirred at rt for 1h. The reaction was concentrated under a stream of nitrogen overnight, diluted with MeOH (~ 5 mL), filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-piperidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-1-piperidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (71.2 mg) as a light yellow solid. LC-MS retention time 3.348 min; m/z 902.10 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8

mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR presents as a mixture of rotamers. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.45 (s, 0.6 H), 8.32 (br. s., 0.4 H), 8.27 (s, 1 H), 8.02 - 8.15 (m, 4.4 H), 7.85 - 8.02 (m, 5.6 H), 6.08 (br. s., 1.2 H), 5.90 (br. s., 0.8 H), 4.70 (br. s., 1.2 H), 4.45 - 4.59 (m, 2 H), 3.90 - 4.10 (m, 4 .8 H), 3.77 (s, 3.6 H), 3.69 (br. s., 2.4 H), 3.36 - 3.50 (m, 5 H), 2.35 - 2.73 (m, 3 H), 1.36 - 2.22 (m, 20 H).

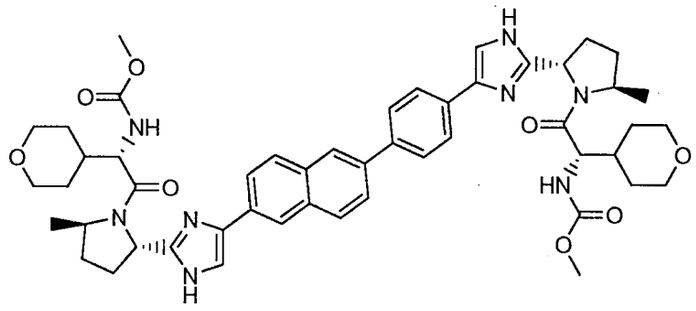


Example 120

Methyl ((1S)-1-(((2S,5R)-2-(4-(4-(6-(2-((2S,5R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00688] HATU (62.0 mg, 0.163 mmol) was added to a solution of an HCl salt of 2-((2S,5R)-5-methylpyrrolidin-2-yl)-5-(4-(6-(2-((2S,5R)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazole (Intermediate 187) (46 mg, 0.071 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (28.6 mg, 0.163 mmol) DMF (0.7 mL) and DIPEA (0.09 mL, 0.5 mmol) and the reaction vessel was flushed with nitrogen, sealed and stirred at rt for 1h. The reaction was concentrated under a stream of nitrogen overnight, diluted with MeOH (~ 3 mL), filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-1-(((2S,5R)-2-(4-(4-(6-(2-((2S,5R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (53.3 mg) as a light yellow

solid. LC-MS retention time 3.255 min; m/z 818.08 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR presents as a complex mixture of rotamers. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.31 (s, 0.5 H), 8.26 - 8.30 (m, 1.5 H), 8.13 (d, *J*=8.8 Hz, 1 H), 8.08 (d, *J*=8.5 Hz, 1 H), 7.93 - 8.00 (m, 4 H), 7.83 - 7.93 (m, 4 H), 5.67 (t, *J*=7.8 Hz, 0.7 H), 5.38 - 5.45 (m, 1.3 H), 4.44 - 4.68 (m, 3.3 H), 3.92 (dd, *J*=8.2, 4.4 Hz, 0.7 H), 3.66 (s, 3.5 H), 3.41 (s, 1 H), 3.35 (s, 1.5 H), 2.53 - 2.92 (m, 3.3 H), 1.96 - 2.30 (m, 6 H), 1.78 - 1.87 (m, 0.7 H), 1.43 - 1.53 (m, 3.5 H), 1.33 (dd, *J*=6.3, 2.5 Hz, 2.5 H), 0.98 - 1.06 (m, 6 H), 0.96 (d, *J*=6.8 Hz, 2.4 H), 0.84 (d, *J*=6.8 Hz, 3.6 H).

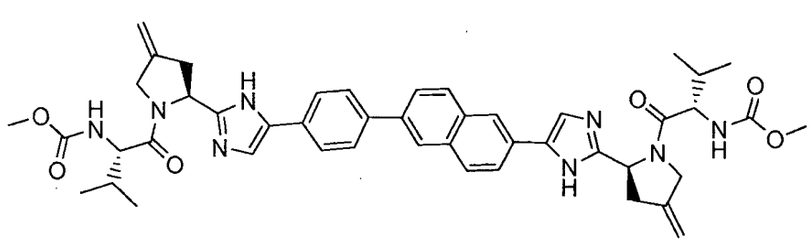


Example 121

Methyl ((1S)-2-((2S,5R)-2-(4-(4-(6-(2-((2S,5R)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00689] HATU (55.8 mg, 0.147 mmol) was added to a solution of vial an HCl salt of 2-((2S,5R)-5-methylpyrrolidin-2-yl)-5-(4-(6-(2-((2S,5R)-5-methylpyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazole (Intermediate 187) (41.4 mg, 0.064 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (31.9

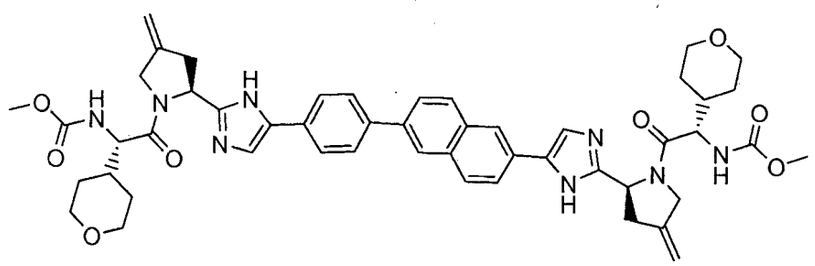
mg, 0.147 mmol) in DMF (0.7 mL) and DIPEA (0.08 mL, 0.4 mmol) and the reaction vessel was flushed with nitrogen, sealed and stirred at rt for 1h. The reaction was concentrated under a stream of nitrogen overnight, diluted with MeOH (~ 3 mL), filtered and purified by preparative HPLC (MeOH/water with a TFA buffer) to yield a TFA salt of methyl ((1S)-2-((2S,5R)-2-(4-(4-(6-(2-((2S,5R)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (27.6 mg) as a light yellow solid LC-MS retention time 3.135 min; m/z 902.15 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 3u C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where Solvent A was 10% MeOH / 90% H_2O / 0.1% trifluoroacetic acid and Solvent B was 10% H_2O / 90% MeOH / 0.1% trifluoroacetic acid. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. Mixture of rotamers by ^{1}H NMR. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.31 (s, 0.5 H), 8.25 - 8.29 (m, 1.5 H), 8.13 (d, *J*=8.8 Hz, 1 H), 8.08 (dd, *J*=8.8, 2.5 Hz, 1 H), 7.93 - 8.00 (m, 4 H), 7.82 - 7.92 (m, 4 H), 5.71 (t, *J*=7.9 Hz, 0.8 H), 5.37 - 5.45 (m, 1.2 H), 4.47 - 4.69 (m, 3 H), 3.89 - 4.07 (m, 5 H), 3.67 (s, 3 H), 3.24 - 3.43 (m, 7 H), 2.57 - 2.92 (m, 3 H), 1.96 - 2.29 (m, 6 H), 1.79 - 1.87 (m, 1 H), 1.35 - 1.67 (m, 11 H), 1.33 (dd, *J*=6.5, 2.5 Hz, 3 H).



Example 122

Methyl ((1S)-1-(((2S)-2-(4-(6-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

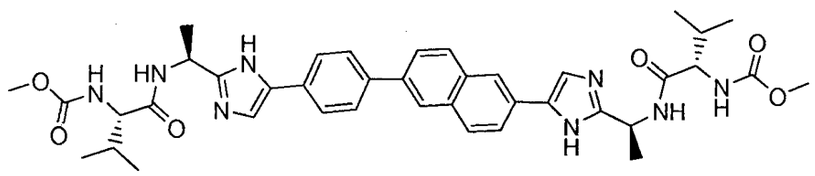
[00690] HATU (102 mg, 0.269 mmol) was added to a stirred solution of the tetra HCl salt of 2-((S)-4-methylenepyrrolidin-2-yl)-4-(4-(6-(2-((S)-4-methylenepyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazole (Intermediate 189) (86 mg, 0.148 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (47.1 mg, 0.269 mmol), and Hunig's base (0.234 mL, 1.34 mmol) in DMF (6 mL). The reaction was stirred 4h at room temperature and purified by preparative HPLC (MeOH/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((2S)-2-(4-(6-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (65 mg, 46%). LC-MS retention time 3.22 min; Calcd. for $C_{46}H_{53}N_8O_6$: 813.40 Found m/z 813.7 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeCN/ 95% water / 10mM NH4OAc and Solvent B was 95%MeCN/ 5% water / 10mM NH_4OAc. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 8.0-7.85 (m, 8H), 5.50-5.45 (m, 2H), 5.32 (s, 2H), 5.28 (s, 2H), 4.72 (d, *J*=11.6 Hz, 2H), 4.60 (dd, *J*=11.3, 3.4 Hz, 2H), 4.21 (dd, *J*=7.6, 2.8 Hz, 2H), 3.68 (s, 6H), 2.98 - 2.92 (m, 2H), 2.10 - 2.06 (m, 2H), 1.06-1.02 (m, 2H), 0.97 -0.94 (m, 12H).



Example 123

Methyl ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

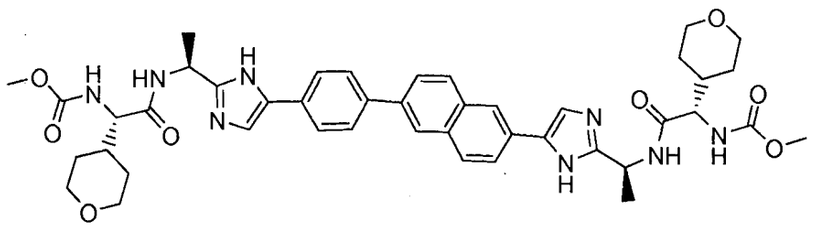
[00691] HATU (102 mg, 0.269 mmol) was added to a stirred solution of the tetra HCl salt of 2-((S)-4-methylenepyrrolidin-2-yl)-4-(4-(6-(2-((S)-4-methylenepyrrolidin-2-yl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazole (Intermediate 189) (86 mg, 0.148 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (58.4 mg, 0.269 mmol), and Hunig's base (0.234 mL, 1.34 mmol) in DMF (6 mL). The reaction was stirred 5h at room temperature and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate. LC-MS retention time 2.81 min; Calcd. for $C_{50}H_{57}N_8O_8$: 897.43 Found m/z 897.41 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water/0.1% TFA and Solvent B was 95%MeOH/5% water/0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (s, 2H), 8.4 (d, *J*=8.8 Hz, 1H), 8.09 (d, *J*=9.0 Hz, 1H), 8.01-7.85 (m, 8H), 5.50-5.44 (m, 2H), 5.32 (s, 2H), 5.28 (s, 2H), 4.75 (d, *J*=14.6 Hz, 2H), 4.63 (dd, *J*=13.3, 4.5 Hz, 2H), 4.27 (dd, *J*=8.3, 3.5 Hz, 2H), 3.99-3.91 (m, 4H) 3.69 (s, 6H), 3.41-3.37 (m 4H), 3.0 -2.94 (m, 2H), 2.02 - 1.98 (m, 2H), 1.68-1.65 (m, 2H), 1.59-1.32 (m, 8H).



Example 124

Methyl ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)carbamoyl)-2-methylpropyl)carbamate

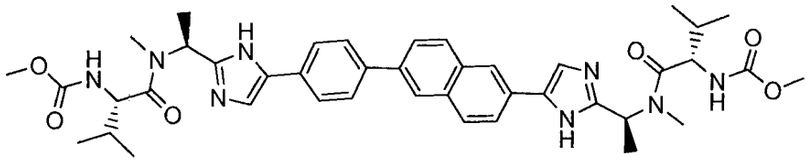
[00692] HATU (149 mg, 0.393 mmol) was added to a stirred solution of the tetra HCl salt of (S)-1-(4-(4-(6-(2-((S)-1-aminoethyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)ethanamine (Intermediate 191) (111 mg, 0.148 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (47.1 mg, 0.196 mmol), and Hunig's base (0.343 mL, 1.96 mmol) in DMF (8 mL). The reaction was stirred 4h at room temperature and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt methyl ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)carbamoyl)-2-methylpropyl)carbamate (91 mg, 47%). LC-MS retention time 2.96 min; Calcd. for $C_{40}H_{49}N_8O_6$: 737.38 Found m/z 737.45 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.35 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 7.99-7.88 (m, 8H), 5.30-5.27 (m, 2H), 3.99-3.97 (m, 2H), 3.70 (s, 6H), 2.14 (br. s, 2H), 1.78-1.75 (m, 6H), 0.99 -0.95 (m, 12H).



Example 125

Methyl ((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

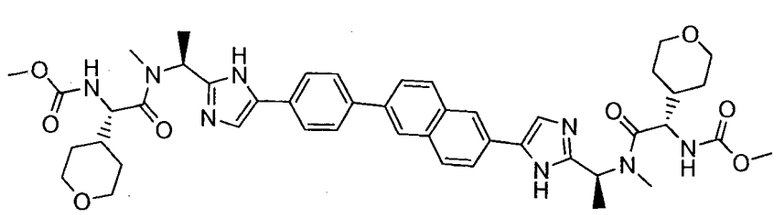
[00693] HATU (149 mg, 0.393 mmol) was added to a stirred solution of the tetra HCl salt of (S)-1-(4-(4-(6-(2-((S)-1-Aminoethyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)ethanamine (Intermediate 191) (83 mg, 0.196 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (85 mg, 0.393 mmol), and Hunig's base (0.343 mL, 1.96 mmol) in DMF (8 mL). The reaction was stirred 5h at room temperature and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)amino)ethyl) -1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (89 mg, 42%). LC-MS retention time 2.64 min; Calcd. for $C_{44}H_{53}N_8O_8$: 821.40 Found m/z 821.80 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% AcCN/ 95% water/10mM NH4OAc and Solvent B was 95%AcCN/5% water/10mM NH4OAc. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.34 (s, 1H), 8.2 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 7.99-7.87 (m, 8H), 5.29-5.26 (m, 2H), 4.02-4.00 (m, 2H), 3.98-3.93 (m, 4H) 3.71 (s, 6H), 3.41-3.37 (m 4H), 2.02 (br. s, 2H), 1.79-1.76 (m, 6H), 1.62 (d, *J*=13.0 Hz, 2H), 1.49-1.39 (m, 6H).



Example 126

Methyl ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)(methyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)(methyl)carbamoyl)-2-methylpropyl)carbamate

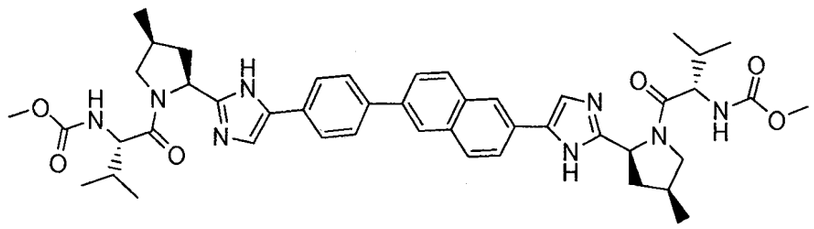
[00694] HATU (84 mg, 0.222 mmol) was added to a stirred solution of the tetra HCl salt of (S)-N-Methyl-1-(4-(4-(6-(2-((S)-1-(methylamino)ethyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)ethanamine (Intermediate 193) (66 mg, 0.111 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (38.9 mg, 0.222 mmol), and Hunig's base (0.194 mL, 1.11 mmol) in DMF (5 mL). The reaction was stirred 5h at room temperature and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)(methyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)(methyl)carbamoyl)-2-methylpropyl)carbamate. LC-MS retention time 1.78 min; Calcd. for $C_{42}H_{53}N_8O_6$: 765.41 Found m/z 765.41 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min and an analysis time of 3 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt; rotamers, 500 MHz, MeOD) δ ppm 8.44/8.34 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.10-7.88 (m, 9H), 6.17-6.14/5.33-5.30 (m, 2H), 4.64-4.6/4.41-4.39 (m, 2H), 3.84/3.66 (s, 3H), 3.83/3.59 (s, 3H), 3.37 (s, 6H), 2.10-2.05 (m, 2H), 1.90-1.87/1.85-1.82 (m, 6H), 1.15 - 0.90 (m, 12H).



Example 127

Methyl ((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)(methyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)(methyl)amino)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

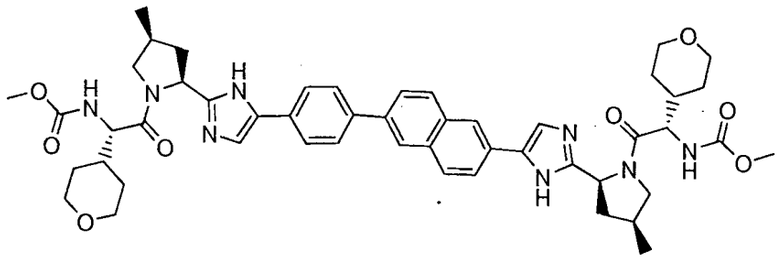
[00695] HATU (84 mg, 0.222 mmol) was added to a stirred solution of the tetra HCl salt of (S)-N-Methyl-1-(4-(4-(6-(2-((S)-1-(methylamino)ethyl)-1H-imidazol-4-yl)naphthalen-2-yl)phenyl)-1H-imidazol-2-yl)ethanamine (Intermediate 193) (66 mg, 0.111 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (48 mg, 0.222 mmol), and Hunig's base (0.194 mL, 1.11 mmol) in DMF (5 mL). The reaction was stirred 5h at room temperature and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of Methyl methyl ((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)(methyl)amino)ethyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)ethyl)(methyl)amino)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate. LC-MS retention time 1.58 min; Calcd. for $C_{46}H_{57}N_8O_8$: 849.43 Found m/z 849.46 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x30mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 1 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 2 min, a hold time of 1 min and an analysis time of 3 min where Solvent A was 5% MeOH/ 95% water/0.1% TFA and Solvent B was 95%MeOH/5% water/0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, rotamers 500 MHz, MeOD) δ ppm 8.45/8.34 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 8.06-7.88 (m, 8H), 6.21-6.18/5.38-5.34 (m, 2H), 4.73-4.70/4.47-4.45 (m, 2H), 4.02-3.94 (m, 4H) 3.84/3.63 (s, 3H), 3.83/3.60 (s, 3H), 3.46-3.38 (m 4H), 3.37/3.35 (s, 6H), 2.02 (br. s, 2H), 1.91-1.88/1.84-1.81 (m, 6H), 1.68 (d, *J*=13.0 Hz, 2H), 1.53-1.42 (m, 6H).



Example128

Methyl ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00696] HATU (32 mg, 0.085 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (25 mg, 0.039 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (14.9 mg, 0.085 mmol), and Hunig's base (0.054 mL, 0.308 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (24.5 mg, 57.8%). LC-MS retention time 3.05 min; Calcd. for $C_{46}H_{57}N_8O_6$: 817.44 Found m/z 817.36 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.99-7.85 (m, 8H), 5.27-5.22 (m, 2H), 4.37-4.33 (m, 2H), 4.25-4.23 (m, 2H), 3.68 (s, 6H), 3.47-3.41 (m, 2H), 2.72-2.68 (m 2H), 2.55 (br. s, 2H), 2.07-2.03 (m, 2H), 1.92-1.87 (m, 2H), 1.27-1.26 (m, 6H), 0.95-0.9 (m, 12H).

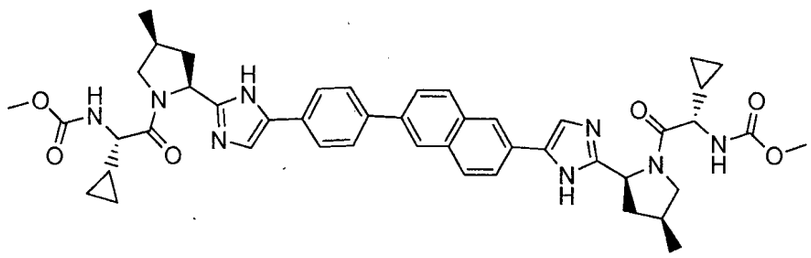


Example 129

Methyl (2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00697] HATU (64.5 mg, 0.170 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (50 mg, 0.077 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (36.8 mg, 0.170 mmol), and Hunig's base (0.11 mL, 0.617 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl (2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate. LC-MS retention time 2.84 min; Calcd. for $C_{50}H_{61}N_8O_8$: 901.46 Found m/z 901.42 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water/0.1% TFA and Solvent B was 95%MeOH/5% water/0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^1H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.6 Hz,

1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.85 (m, 8H), 5.25-5.21 (m, 2H), 4.42-4.39 (m, 2H), 4.30-4.27 (m, 2H), 3.96-3.92 (m, 4H), 3.68 (s, 6H), 3.49-3.35 (m 6H), 2.71-2.38 (m, 2H), 2.58-2.54 (m, 2H), 1.97 - 1.89 (m, 4H), 1.60 (d, *J*=13.0 Hz, 2H), 1.48-1.26 (m, 12H).

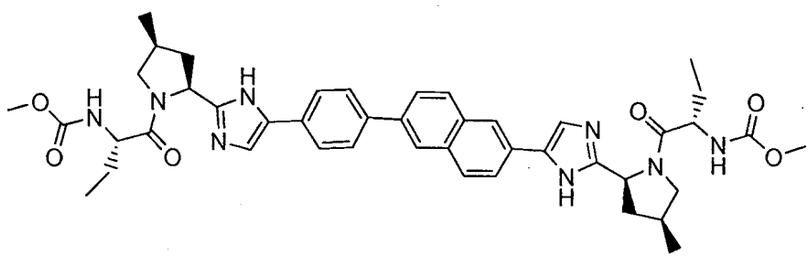


Example 130

Methyl (1-cyclopropyl-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(cyclopropyl((methoxycarbonyl)amino)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate

[00698] HATU (39 mg, 0.102 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (30 mg, 0.085 mmol), (S)-2-cyclopropyl-2-(methoxycarbonylamino)acetic acid (17.62 mg, 0.102 mmol), and Hunig's base (0.065 mL, 0.37 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl (1-cyclopropyl-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(cyclopropyl((methoxycarbonyl)amino)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate (24.5 mg, 57.8%). LC-MS retention time 3.08 min; Calcd. for $C_{46}H_{53}N_8O_6$: 813.41 Found m/z 813.45 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined

using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.32 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.99-7.87 (m, 8H), 5.29-5.24 (m, 2H), 4.30 (br. s, 2H), 3.82-3.80 (m, 2H), 3.68 (s, 6H), 3.43-3.37 (m, 2H), 2.72-2.68 (m 2H), 2.55 (br. s, 2H), 1.91-1.86 (m, 2H), 1.25-1.24 (m, 6H), 1.11 (br. s, 2H), 0.60-0.58 (m, 4H), 0.53-0.51 (m, 2H), 0.04-0.38 (m, 2H).

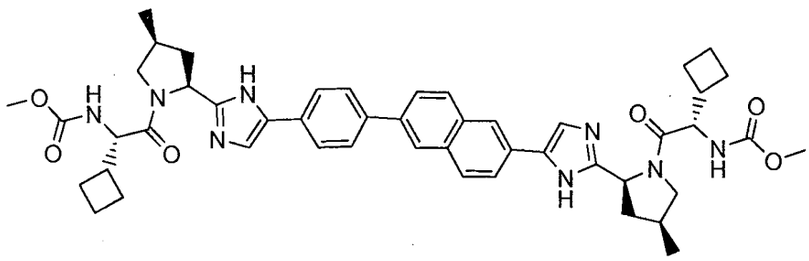


Example 131

Methyl ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)butanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)propyl)carbamate

[00699] HATU (45 mg, 0.119 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (35 mg, 0.054 mmol), (S)-2-(methoxycarbonylamino)butanoic acid (19.14 mg, 0.119 mmol), and Hunig's base (0.075 mL, 0.432 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)butanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl) propyl)carbamate (36.4 mg, 61.7%). LC-MS retention time 2.91 min; Calcd. for $C_{44}H_{53}N_8O_6$: 789.41 Found m/z 789.41 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and

Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.86 (m, 8H), 5.27-5.22 (m, 2H), 4.37 (br. s, 2H), 4.24-4.23 (m, 2H), 3.67 (s, 6H), 3.44-3.39 (m, 2H), 2.72-2.68 (m 2H), 2.58 (br. s, 2H), 1.88-1.84 (m, 2H), 1.47-1.25 (m, 6H), 0.98-0.92 (m, 10H).

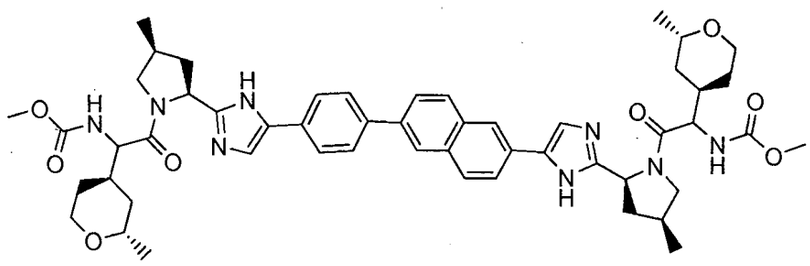


Example 132

Methyl ((1S)-1-cyclobutyl-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-cyclobutyl-2-((methoxycarbonyl)amino)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate

[00700] HATU (45 mg, 0.119 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (35 mg, 0.054 mmol), (S)-2-cyclobutyl-2-(methoxycarbonylamino)acetic acid (22.23 mg, 0.119 mmol) (prepared in a similar manner as Cap-51 using commercially available (S)-2-(*tert*-butoxycarbonylamino)-2-cyclobutylacetic acid as a starting material) and Hunig's base (0.075 mL, 0.432 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-cyclobutyl-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-cyclobutyl-2-((methoxycarbonyl)amino)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate (25.6 mg, 43.6%). LC-MS retention time 3.13 min; Calcd. for $C_{48}H_{57}N_8O_6$: 841.44 Found m/z 841.48 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm

column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.86 (m, 8H), 5.26-5.21 (m, 2H), 4.41-4.37 (m, 4H), 3.68 (s, 6H), 3.48-3.43 (m, 2H), 2.71-2.66 (m 4H), 2.56 (br. s, 2H), 1.96-1.87 (m, 14H), 1.27-1.26 (m, 6H).

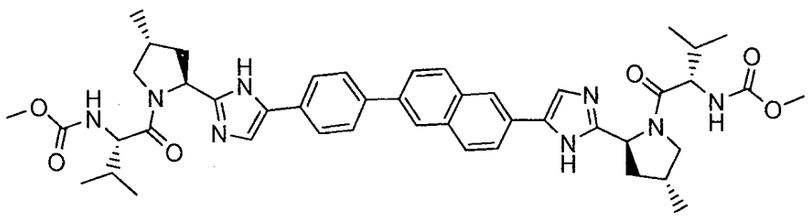


Example 133

Methyl ((1S)-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-1-((2S,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2-oxoethyl)carbamate

[00701] HATU (32 mg, 0.085 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (25 mg, 0.039 mmol), 2-(methoxycarbonylamino)-2-((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)acetic acid (Cap-178, stereoisomer 1) (19.61 mg, 0.085 mmol) and Hunig's base (0.054 mL, 0.308 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-1-

((2S,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2-oxoethyl)carbamate (21.3 mg, 45.2%). LC-MS retention time 2.94 min; Calcd. for $C_{52}H_{64}N_8O_8$: 929.49 Found m/z 929.64 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water/0.1% TFA and Solvent B was 95%MeOH/5% water/0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.32 (s, 1H), 8.28 (s, 1H), 8.15 - 8.12 (m, 1H), 8.09-8.06 (m, 1H), 8.02-7.94 (m, 5H), 7.90-7.86 (m, 3H), 5.28-5.23 (m, 2H), 4.50-4.48 (m, 2H), 4.44 (br. s, 2H), 3.95-3.91 (m, 2H), 3.71-3.68 (s, 10H), 3.46-3.41 (m, 2H), 2.72-2.67 (m, 2H), 2.55-2.52 (m, 2H), 2.19 (br. s, 2H), 1.97 - 1.92 (m, 2H), 1.60 (br. s, 2H), 1.48-1.46 (m, 2H), 1.39 (br. s, 2H), 1.30-1.26 (m, 8H), 1.14-1.10 (m, 6H).

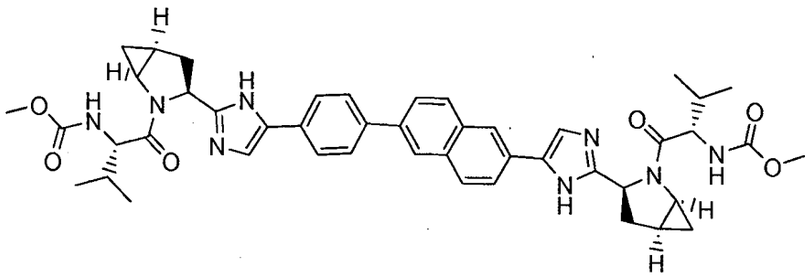


Example 134

Methyl ((1S)-1-(((2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00702] HATU (65 mg, 0.171 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4R)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4R)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 201) (50 mg, 0.077 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (30 mg, 0.170 mmol), and Hunig's base (0.108 mL, 0.308 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to

afford a bis TFA salt of methyl ((1S)-1-(((2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (60.7 mg, 71%). LC-MS retention time 3.12 min; Calcd. for $C_{46}H_{57}N_8O_6$: 817.44 Found m/z 817.46 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.86 (m, 8H), 5.43-5.38 (m, 2H), 4.26-4.24 (m, 2H), 4.09-4.05 (m, 2H), 3.69 (s, 6H), 3.64 (br. s, 2H), 2.76-2.73 (m 2H), 235-2.32 (m, 2H), 2.25-2.22 (m, 2H), 2.11-2.09 (m, 2H), 1.22-1.20 (m, 6H), 0.98-0.93 (m, 12H).

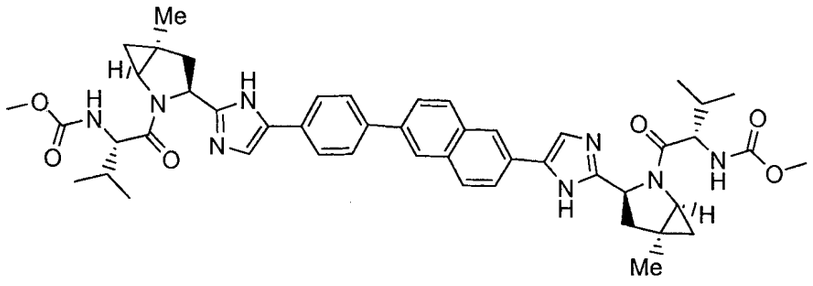


Example 135

Methyl ((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

[00703] HATU (65 mg, 0.171 mmol) was added to a stirred solution of the tetra HCl salt of (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (Intermediate 203) (50 mg, 0.078 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (30 mg,

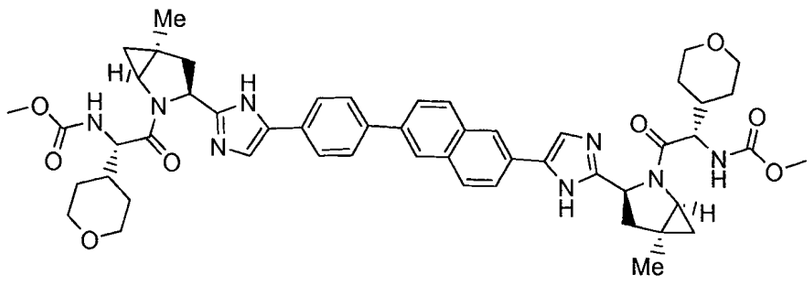
0.111 mmol), and Hunig's base (0.108 mL, 0.621 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (54 mg, 63%). LC-MS retention time 3.15 min; Calcd. for $C_{46}H_{53}N_8O_6$: 813.41 Found m/z 813.45 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.26 (s, 1H), 8.12 (d, *J*=8.6 Hz, 1H), 8.07 (d, *J*=8.6 Hz, 1H), 7.98-7.86 (m, 8H), 5.80-5.74 (m, 2H), 4.36-4.34 (m, 2H), 4.02-3.99 (m, 2H), 3.73 (s, 6H), 2.99-2.95 (m, 2H), 2.28-2.25 (m 2H), 2.16 (br. s, 2H), 2.04 (br.s, 2H), 1.24-1.20 (m, 2H), 1.08 (br. s, 2H), 1.02-1.00 (m, 12H).



Example 136

Methyl ((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

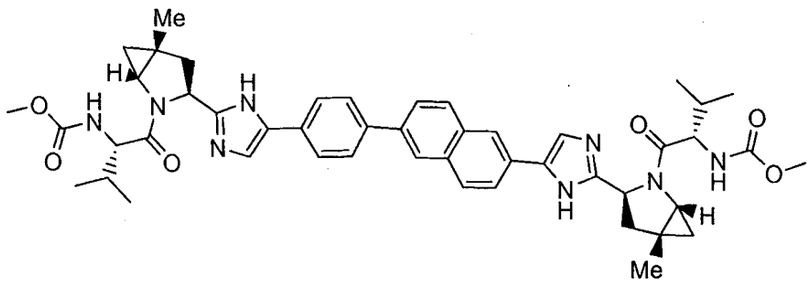
[00704] HATU (62 mg, 0.164 mmol) was added to a stirred solution of the tetra HCl salt of (1S,3S,5S)-5-methyl-3-(4-(4-(6-(2-((1S,3S,5S)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo [3.1.0]hexane (Intermediate 209) (50 mg, 0.074 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (28.7 mg, 0.164 mmol), and Hunig's base (0.104 mL, 0.595 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of Methyl ((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (45 mg, 54%). LC-MS retention time 3.15 min; Calcd. for $C_{48}H_{57}N_8O_6$: 841.44 Found m/z 841.50 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.25 (s, 1H), 8.11 (d, *J*=8.5 Hz, 1H), 8.06 (d, *J*=8.7 Hz, 1H), 7.97-7.85 (m, 8H), 5.82-5.75 (m, 2H), 4.31-4.28 (m, 2H), 3.73-3.71 (m, 8H), 2.75-2.69 (m, 2H), 2.44-2.37 (m 2H), 2.17-2.12 (m, 2H), 1.40 (s, 6H), 1.1-1.11 (m, 4H), 1.01-0.99 (m, 12H).



Example 137

Methyl ((1S)-2-((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00705] HATU (62 mg, 0.164 mmol) was added to a stirred solution of the tetra HCl salt of (1S,3S,5S)-5-methyl-3-(4-(4-(6-(2-((1S,3S,5S)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo [3.1.0]hexane (Intermediate 209) (50 mg, 0.074 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (35.5 mg, 0.164 mmol), and Hunig's base (0.104 mL, 0.595 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-2-((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate (46.3 mg, 51%). LC-MS retention time 3.15 min; Calcd. for $C_{52}H_{61}N_8O_6$: 925.46 Found m/z 463.36 $[M/2+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.31 (s, 1H), 8.25 (s, 1H), 8.10 (d, *J*=8.8 Hz, 1H), 8.06 (d, *J*=8.8 Hz, 1H), 7.97-7.85 (m, 8H), 5.80-5.74 (m, 2H), 4.36-4.35 (m, 2H), 3.99-3.95 (m, 4H), 3.76-3.74 (m, 8H), 3.43-3.35 (m, 4 H), 2.75-2.68 (m, 2H), 2.44-2.37 (m 2H), 2.06-2.04 (m, 2H), 1.74 (app. d, *J*=13 Hz, 2H), 1.52-1.35 (m, 12H), 1.22-1.19 (m, 2H), 1.14-1.12 (m, 2H).

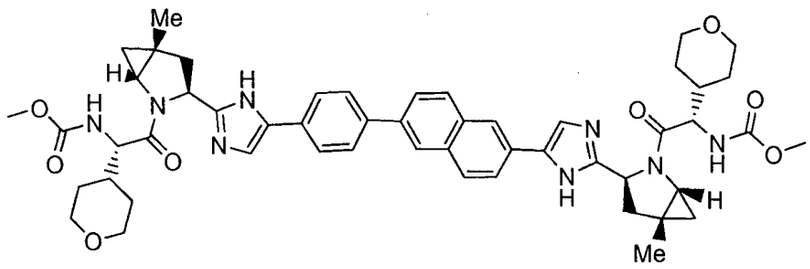


Example 138

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

[00706] HATU (31 mg, 0.082 mmol) was added to a stirred solution of the tetra HCl salt of (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 211) (25 mg, 0.037 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (14 mg, 0.082 mmol), and Hunig's base (0.052 mL, 0.297 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of Methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (17 mg, 41%). LC-MS retention time 3.10 min; Calcd. for $C_{48}H_{57}N_8O_6$: 841.44 Found m/z 841.542 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.27 (s, 1H), 8.26 (s,

1H), 8.12 (d, *J*=8.5 Hz, 1H), 8.07 (d, *J*=8.7 Hz, 1H), 7.98-7.93 (m, 4H), 7.88-7.85 (m, 4H), 5.09-5.04 (m, 2H), 4.55-4.53 (m, 2H), 3.38 (s, 6H), 3.57 (br.s, 2H), 2.81-2.75 (m, 2H), 2.33-2.27 (m 2H), 2.22-2.16 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 1.05-0.93 (m, 16H).

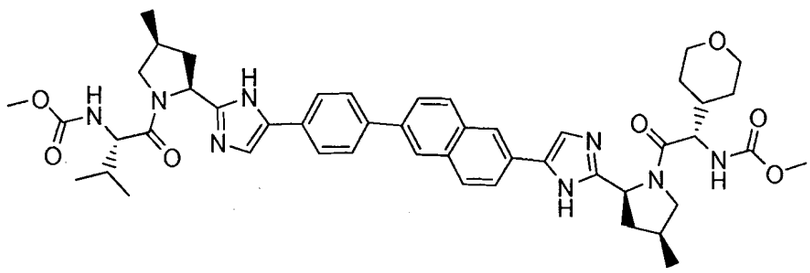


Example 139

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

[00707] HATU (34.8 mg, 0.092 mmol) was added to a stirred solution of the tetra HCl salt of (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (Intermediate 211) (28 mg, 0.042 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (20 mg, 0.092 mmol), and Hunig's base (0.085 mL, 0.333 mmol) in DMF (2 mL). The reaction was stirred 1h at room temperature and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate (13 mg, 25%). LC-MS retention time 2.92 min; Calcd. for $C_{52}H_{61}N_8O_6$: 925.46 Found m/z 92.53 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.28 (s, 2H), 8.14 (d, *J*=8.8 Hz, 1H), 8.07 (d, *J*=8.6 Hz, 1H), 8.00-7.96 (m, 4H), 7.91-7.84 (m, 4H), 5.08-5.02 (m, 2H), 4.59-4.56 (m, 2H), 4.00-3.94 (m, 4H), 3.69 (s, 6H), 3.62 (br. s, 2H), 3.44-3.38 (m, 4H), 2.81-2.78 (m, 2H), 2.31-2.29 (m, 2H), 2.09 (br. s, 2H), 1.60-1.47 (m, 8H), 1.43 (s, 3H), 1.44 (s, 3H), 1.04 (br. s, 2H), 0.98-0.97 (m, 2H).

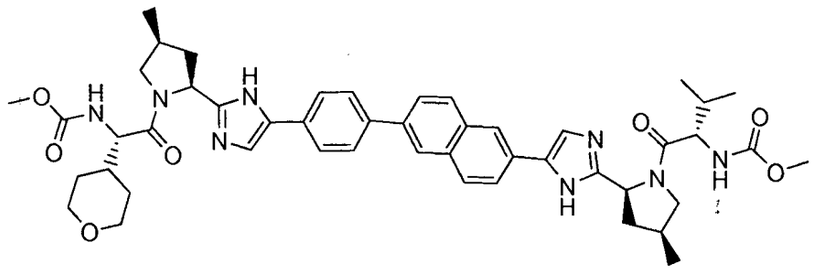


Example 140

Methyl ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00708] HATU (97 mg, 0.254 mmol) was added to a stirred solution of the tetra HCl salt of 2-((2S,4S)-4-methyl-2-pyrrolidinyl)-4-(4-(6-(2-((2S,4S)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazole (Intermediate 196) (150 mg, 0.231 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (50 mg, 0.231 mmol), and Hunig's base (0.162 mL, 0.925 mmol) in DMF (1 mL). The reaction was stirred 1h at room temperature before addition of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (40.5 mg, 0.231 mmol) and add'l Hunig's base (0.162 mL, 0.925 mmol) and HATU (97 mg, 0.254 mmol). The mixture was stirred further at rt for 1h and partially concentrated by purge of nitrogen gas. The residue was taken up in MeOH and purified by preparative HPLC (MeCN/water with 0.1% TFA). A second method of chromatography was applied to separate the isomers: SFC Diol-HL column, 20% methanol with 0.1 % DEA; 4.6 x 250mm, 5μm Mobile Phase: 80% CO_2 - 20% methanol

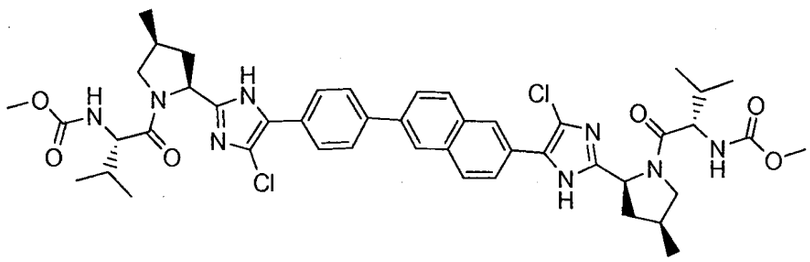
with 0.1% DEA; Temp: 35 °C; Pressure: 150 bar; Flow rate: 2 ml/min; UV monitored at 328 nm. The isolated sample was taken up in methanol (3 mL) and neat TFA (50 mL) was added at rt. The mixture was concentrated down to dryness and placed on high vacuum to afford a bis TFA salt of methyl ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (78.2 mg, 29.5 % yield). LC-MS retention time 2.95 min; Calcd. for $C_{48}H_{59}N_8O_7$: 859.45 Found m/z 859.50 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water/0.1% TFA and Solvent B was 95%MeOH/5% water/0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.01-7.85 (m, 8H), 5.26-5.22 (m, 2H), 4.42-4.36 (m, 2H), 4.30-4.27 (m, 1H), 4.24-4.23 (m, 1H), 3.95-3.91 (m, 2H), 3.68 (s, 6H), 3.47-3.36 (m 2H), 3.08-3.04 (m, 1H), 2.70 (br. s, 2H), 2.55 (br. s, 2H), 2.08-2.03 (m, 1H), 1.97 - 1.87 (m, 3H), 1.59 (d, *J*=13.0 Hz, 1H), 1.48-1.26 (m, 10H) 0.95-0.90 (m, 6H).



Example 141

Methyl ((1S)-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-2-naphthyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate

[00709] The other isomer as reported in Example 140. LC-MS retention time 2.98 min; Calcd. for $C_{48}H_{59}N_8O_7$: 859.45 Found m/z 859.58 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water/0.1% TFA and Solvent B was 95%MeOH/5% water/0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 7.99-7.86 (m, 4H), 7.91-7.85 (m, 4H), 5.26-5.21 (m, 2H), 4.41-4.36 (m, 4H), 4.28(d, *J*=8.24 Hz, 1H), 4.24 (d, *J*=7.32 Hz, 1H), 3.95-3.91 (m, 2H), 3.68 (s, 6H), 3.47-3.36 (m 2H), 2.73-2.66 (m, 2H), 2.59-2.53 (m, 2H), 2.07-2.03 (m, 1H), 1.97 - 1.87 (m, 3H), 1.59 (d, *J*=13.0 Hz, 1H), 1.51-1.25 (m, 11H) 0.95-0.90 (m, 6H).



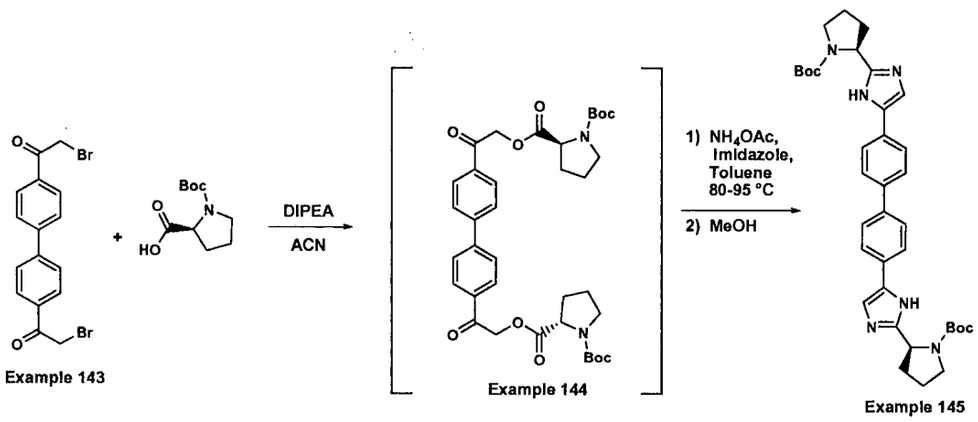
Example 142

Methyl ((1S)-1-(((2S,4S)-2-(4-chloro-5-(6-(4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

[00710] The NCS (17.98 mg, 0.135 mmol) was added to a nitrogen purged solution of Example 128 (55 mg, 0.067 mmol) in DMF (1 mL) and the reaction mixture was stirred for 18 h at 50 °C. The solvent was removed by concentrate, and the crude product was taken up in CH2Cl2 and charged to a 4 g Thompson silica gel cartridge. Gradient elution was performed from 5-100% B over 1 L. A/B (A = CH_2Cl_2; B = 10% MeOH / EtOAc). A sample of the purified product was taken up in MeOH and subject to preparative HPLC

(MeCN/water with 0.1% TFA) to afford a bis TFA salt of methyl ((1S)-1-(((2S,4S)-2-(4-chloro-5-(6-(4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-naphthyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl) carbamate. LC-MS retention time 4.48 min; Calcd. for $C_{46}H_{55}Cl_2N_8O_6$: 885.36 Found m/z 885.34 $[M+H]^+$. LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped a PHENOMENEX® Luna C18 2.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 0.8 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 4 min, a hold time of 1 min and an analysis time of 5 min where Solvent A was 5% MeOH/ 95% water / 0.1% TFA and Solvent B was 95%MeOH/ 5% water / 0.1% TFA. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (TFA salt, 500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.18 (s, 1H), 8.03 (d, *J*=8.6 Hz, 1H), 8.00 (d, *J*=8.6 Hz, 1H), 7.90-7.83 (m, 6H), 5.09-5.04 (m, 2H), 4.30-4.7 (m, 2H), 4.24-4.23 (m, 2H), 3.68 (s, 6H), 3.43-3.99 (m, 2H), 2.58-2.56 (m 2H), 2.43 (br. s, 2H), 2.05-2.04 (m, 2H), 1.93-1.87 (m, 2H), 1.24-1.22 (m, 6H), 0.97-0.91 (m, 12H).

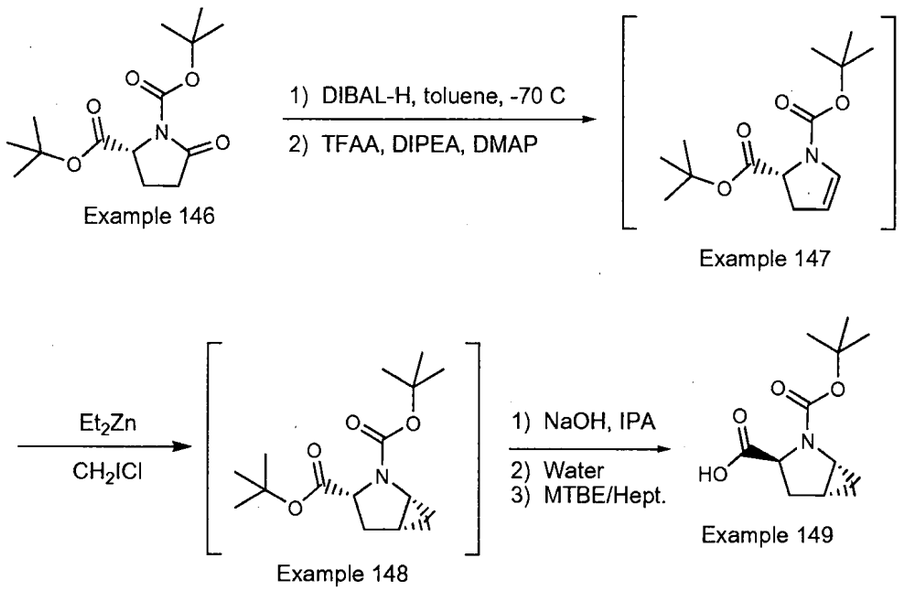
Example 145



[00711] A stirred suspension of Example 143 (10.0g, 25.3 mmol) and Boc-L-Proline (11.4g, 53.0 mmol, 2.1 equiv) in 100 mL of acetonitrile was charged with diisopropylethylamine (6.75 g, 52.3 mmol, 2.07 equiv). The resulting mixture was warmed to 35 °C and allowed to stir for 3 hours. The mixture was cooled to 20 °C and

the organic phase was washed three times with 50 mL of 13 wt% aqueous NaCl. The rich organic stream was solvent exchanged into pure toluene *via* vacuum distillation to provide Example 144 as a solution in ca. 60 mL toluene. A separate 500 mL jacketed reactor was charged with ammonium acetate (38.9 g, 504.9 mmol, 20 equiv), imidazole (6.9 g, 101.0 mmol, 4 equiv) and 50 mL of toluene. The resulting suspension was warmed to an internal temperature of 92-95 °C. The toluene solution of Example 144 was added while maintaining a temperature of 92-95 °C. The resulting mixture was allowed to stir at 92-95 °C for 15 hours. The resulting slurry was cooled to 55-60 °C and methanol (150 mL) was added while maintaining a temperature of 55-60 °C. The slurry was held at this temperature for 3 hours, cooled to 20 °C over a 1 hour and held at 20 °C for an additional 18 hours. The crystals were collected via filtration and washed with methanol. The cake was deliquored for 2 hours and then dried under vacuum at 50-55 °C for 18 hours to yield 12.1 g of Example 145 a light yellow solid (76.1 % yield with an HPLC AP of 97.8).

Example 149



Example 146

Example 147

Example 148

Example 149

[00712] In a 500-mL reactor Example 146 (commercially available, 17.5 g, 1.00 equiv) was dissolved in THF (87.5 mL). The resulting solution was cooled to -75 °C and 1.5M DIBAL-H in toluene (61.3 mL, 1.5 equiv) was charged while maintaining the temperature below -70 °C. The resulting solution was stirred at -70 °C for 1 hour. Trifluoroacetic

acid (2.3 mL, 0.5 equiv) was charged over 10 minutes maintaining the internal temperature below -70 °C. Triethylamine (51.3 mL, 6 equiv) was then charged over 15 minutes maintaining the internal temperature below -70 °C. Trifluoroacetic anhydride (11.2 mL, 1.3 equiv) was charged over 10 minutes maintaining the internal temperature below -70 °C. The reaction was then allowed to warm to room temperature over 90 minutes and quenched *via* inverse addition to a solution of 20 wt % aqueous citric acid monohydrate (96.6 g, 1.5 equiv) while maintaining a temperature below 15 °C. The resulting mixture was stirred at room temperature for 2 hours then the lower aqueous layer was discarded. The product rich organic layer was washed twice with 70 mL saturated aqueous sodium bicarbonate. Solid sodium bicarbonate (1.7 g, 0.1 g/g Example 146) was charged and the solution was solvent exchanged into pure toluene under vacuum to provide Example 147 as a solution in 2 L/kg toluene.

[00713] A solution of Example 147 (16.5g theoretical from Example 146) in 33 mL toluene was polish filtered into a 250 mL reactor. Trifluorotoluene (50 mL) and chloroiodomethane (43.2 g, 4.0 equiv) were then charged and the resulting solution cooled to -20 °C. 1.1M Diethylzinc in toluene (111 mL, 2.0 equiv) was charged while maintaining the internal temperature < -8 °C. The resulting solution was stirred at -15 to -20 °C for 14 hours. The reaction mixture was warmed to 0 °C then quenched via inverse addition to a solution of 20 wt % aqueous citric acid (135.7 g, 2.3 equiv). The reactor was rinsed with toluene (82 mL) and the rinse added to the quench solution. The resulting biphasic mixture was stirred for 20 minutes then the lower aqueous layer was split and discarded. The rich organic was washed twice with 60 mL 13 wt % aqueous NaCl followed by 60 mL saturated $NaHCO_3$. The resulting solution was solvent exchanged into pure IPA under vacuum to provide Example 148 as a solution in 10 L/kg IPA.

[00714] A 250mL reactor was charged with a solution of Example 148 (147 mL, 14.7g theoretical from Example 146) in IPA. The solution was warmed to 35 °C and solid sodium hydroxide (6.2 g, 3.0 equiv) was added. The resulting mixture was stirred at 35 °C overnight. Water (44 mL) was added and the organic solvents removed under vacuum. MTBE (145 ml) was added and the pH adjusted to 3.0 with 6N aqueous HCl. The aqueous layer was split and discarded. The product rich organic was washed with 60 mL water then azeotropically dried under vacuum *via* constant volume addition of

MTBE. The solution was concentrated to 55 mL and stirred at 50 °C for 30 minutes. The solution was cooled to room temperature over 1 hour during which time a slurry formed. Heptane (90 mL) was charged over 90 min and the resulting slurry aged for 1h. The solids were collected on a medium glass frit and washed with 22.5 mL 3:1 heptane:MTBE followed by 22.5 mL heptane. The tan solid was dried in a 50 °C vacuum oven to provide 5.48 g (46%) Example 149 with 94.9 LCAP purity.

[00715] The crude Example 149 was dissolved in 55 mL MTBE at 50 °C. The resulting solution was concentrated to 20 mL and cooled to room temperature over 1 hour. Heptane (33mL) was then added over 90 minutes. The resulting solids were collected on a medium glass frit, washed with heptane (15mL), and dried in a 50 °C vacuum oven to provide 4.45 g (98.8 AP, 98.8% chiral purity, 37% from Example 146) of the desired product as a tan powder.

[00716] It is expected that the above reaction sequence (for the formation of Example 149) would be general enough to tolerate other functionality as well. For example, the *tert*-butoxycarbonyl group on the C2 carbon of Example 147 could potentially be replaced with an amide or another ester. Likewise, the *tert*-butoxycarbonyl protecting group on the nitrogen could be replaced by other protecting groups (such as other carbamates, amides, alkyl, aryl) or could be absent entirely (replaced with a hydrogen).

BIOLOGICAL ACTIVITY

[00717] 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.*, 49(4):1346-1353 (Apr. 2005). Assay methods incorporating luciferase reporters have also been used as described (Apath.com).

[00718] HCV-neo replicon cells and replicon cells containing resistance substitutions in the NS5A region were used to test the currently described family of compounds. The compounds were determined to have differing degrees of reduced inhibitory activity on cells containing mutations vs. the corresponding inhibitory potency against wild-type cells. Thus, the compounds of the present disclosure can be effective in inhibiting the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO

04/014852. It should be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC_{50} (Effective 50% inhibitory concentration) values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment, compounds of the present disclosure are inhibitory versus 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC_{50} values against HCV 1b are as follows: A = 0.4 pM-10 pM; B = 10.1 pM - 1.00 nM; and C = 1.01 nM - 1 μM.

[00719] 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 Number (unless noted otherwise)	EC50 (μM)	Range
Intermediate 52		C
Intermediate 70		C
Intermediate 114		C
1		C
2	2.18E-06	A
3		B
4		C
5		B
6		A
7		B
8		B
9		A
10		A
11	1.82E-05	B
12		C
13		C
14		C

Example Number (unless noted otherwise)	EC50 (μM)	Range
15		B
16		A
17		C
18		A
19		B
20		A
21		A
22		B
23	8.88E-04	B
24		B
25A		C
25B		C
26		B
27	4.77E-06	A
28		B
29		A
30		A
31		B
32		B
33		A
34		A
35		A
36		A
37		A
38	4.21E-05	B
39		B
40		A
41		A
42		B

Example Number (unless noted otherwise)	EC50 (μM)	Range
43		A
44		A
45		B
46	0.17	C
47		A
48		B
49		A
50		B
51		B
52	5.90E-06	A
53	1.81E-03	C
54		A
55		A
56		A
57		A
58	8.49E-04	B
59		A
60		A
61		A
62		A
63		A
64		A
65	9.97E-07	A
66		A
67		A
68		A
69		A
70		A
71	2.11E-06	A

Example Number (unless noted otherwise)	EC50 (μM)	Range
72		A
73		A
74		
75	1.23E-04	C
76		
77		A
78		A
79		A
80	1.08E-06	A
81		A
82	4.22E-05	B
83		A
84		A
85		A
86		A
87		A
88		A
89		A
90		A
91		A
92		A
93	0.04	C
94		A
95		A
96		B
97		A
98		B
99		A
100		A

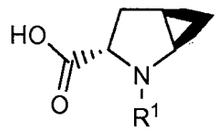
Example Number (unless noted otherwise)	EC50 (μM)	Range
101		A
102		A
103		A
104	2.01E-06	A
105		A
106		A
107		A
108		
109	0.18	C
110		A
111		A
112		A
113		
114		B
115		A
116		B
117		
118	3.74E-05	B
119		A
120		A
121		A
122		A
123		A
124		B
125	1.36E-04	B
126	6.54E-04	B
127		A
128		A
129		B

Example Number (unless noted otherwise)	EC50 (μM)	Range
130		A
131		---
132		A
133		A
134		A
135		B
136		A
137		A
138		A
139		A
140		A
141		A
142		A

[00720] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

1. A process for preparing a compound of formula (X)

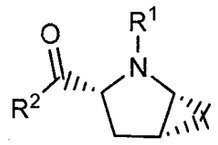


(I);

wherein R^1 is selected from hydrogen and a nitrogen protecting group;

the process comprising:

(a) reacting a compound of formula (II)



(II);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen and a nitrogen protecting group; and

R^2 is selected from amino, alkoxy, and arylalkoxy; and

with a base, and

(b) treating the product of step (a) with water.

2. The process of claim 1 wherein R^1 is hydrogen.

3. The process of claim 1 wherein R^1 is a nitrogen protecting group.

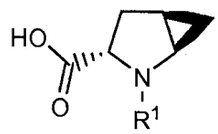
4. The process of claim 3 wherein the nitrogen protecting group is a *tert*-butoxycarbonyl group.

5. The process of claim 1 wherein the base is selected from a metal alkoxide and a metal hydroxide.

6. The process of claim 5 wherein the base is selected from sodium ethoxide, sodium isopropoxide, sodium *tert*-butoxide, sodium hydroxide, lithium hydroxide,

potassium hydroxide, potassium isopropoxide, potassium *tert*-butoxide, lithium *tert*-butoxide, and lithium isopropoxide.

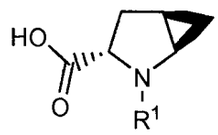
7. The process of claim 1 further comprising treating a product of formula (I)



(I),

wherein R^1 is hydrogen;

with a nitrogen protecting reagent to provide a compound of formula (I)

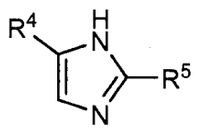


(I),

wherein R^1 is a nitrogen protecting group.

8. The process of claim 7 wherein the nitrogen protecting group is *tert*-butoxycarbonyl.

9. A process for preparing a compound of formula (Z)



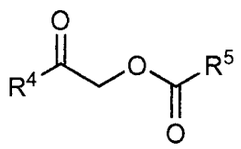
(III),

or a pharmaceutically acceptable salt thereof, wherein:

$R^4$and R^5 are independently selected from hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, and heterocyclylalkyl;

the process comprising:

treating a compound of formula (Q)



(IV),

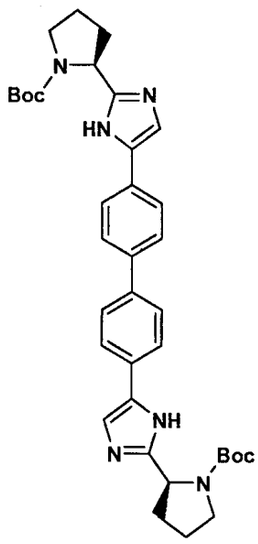
with a base in the presence of ammonium acetate.

10. The process of claim 9 wherein the base is selected from a tertiary amine, an aromatic amine, an aniline, and a substituted imidazole.

11. The process of claim 9 wherein the base is selected from 1,4-dimethylpiperazine, 3-quinuclidinol, 3-methylpyridine, 1-methylimidazole, dimethylbutylamine, N,N-dimethylaniline, dimerpranol, quinoxazoline, creatinine, 2-methylimidazole, 4-methylimidazole, imidazole, morpholine, N-methylmorpholine, 1,8-diazabicycloundec-7-ene, 1,4-diazabicyclo[2.2.2]octane, collidine, 4-chloroimidazole, 2-chloroimidazole, 4-cyanoimidazole, benzimidazole, diisopropylethylamine and 2,6-lutidine.

12. The process of claim 9 wherein the base is imidazole.

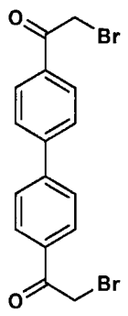
13. A process for the preparation of Example 145



Example 145,

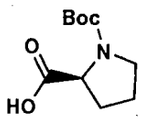
the process comprising:

(a) treating Example 143



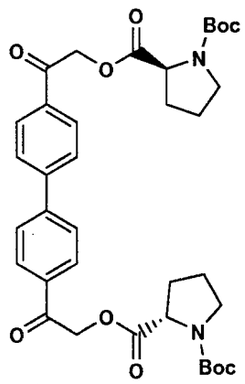
Example 143,

with Example 144



Example 144,

in the presence of a base to produce a compound of formula (V)



(V);

(b) treating the compound of formula (V) with ammonium acetate in the presence of a base; and

(c) treating the product of step (b) with methanol.

14. The process of claim 13 which is a continuous process.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/055045

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/54
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/052850 A2 (SQUIBB BRISTOL MYERS CO [US]; VU TRUC CHI [US]; BRZOZOWSKI DAVID B [US) 24 June 2004 (2004-06-24) cited in the application Scheme VIB on p. 25 compound XVI to XVIII	1-8
X	HANESSIAN S ET AL: "Probing the Importance of Spacial and Conformational Domains in Captopril Analogs for Angiotensin Converting Enzyme Activity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 8, no. 16, 18 August 1998 (1998-08-18), pages 2123-2128, XP004137231, ISSN: 0960-894X, DOI: DOI:10.1016/S0960-894X(98)00377-1 Scheme 2	1-8

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2011	20/04/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/055045

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[X] No protest accompanied the payment of additional search fees.

International Application No. PCT/ US2010/ 055045

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

   Process for preparing compounds of formula (X)

   ---

2. claims: 9-12

   Process for preparing compound (Z)

   ---

3. claims: 13, 14

   Process for preparing example 145

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/055045

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/043107 A1 (PACK SHAWN K [US] ET AL) 12 February 2009 (2009-02-12) for claims 9-12: p. 8 and bases on page 4, paragraph 0080; for claims 13 and 14 examples on pages 7-8 -----	9-14
X	WO 2008/021936 A2 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 21 February 2008 (2008-02-21) for claims 9-12: example 132 step c on page 140-141 and scheme 5 on pages 33-34; -----	9-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/055045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004052850 A2	24-06-2004	AU 2003297647 A1	30-06-2004
		BR 0317139 A	29-11-2005
		CA 2508619 A1	24-06-2004
		CN 1791401 A	21-06-2006
		EP 1581487 A2	05-10-2005
		JP 2006516121 T	22-06-2006
		JP 2011006440 A	13-01-2011
		JP 2011006441 A	13-01-2011
		KR 20050088309 A	05-09-2005
		MX PA05005970 A	18-08-2005
		US 2009018311 A1	15-01-2009
		US 2010274025 A1	28-10-2010
		US 2005090539 A1	28-04-2005
US 2009043107 A1	12-02-2009	AR 067896 A1	28-10-2009
		AU 2008284097 A1	12-02-2009
		CA 2695711 A1	12-02-2009
		CN 101778841 A	14-07-2010
		CO 6251317 A2	21-02-2011
		EA 201000300 A1	30-06-2010
		EP 2178863 A1	28-04-2010
		JP 2010535784 T	25-11-2010
		KR 20100045992 A	04-05-2010
		PE 06112009 A1	16-05-2009
		WO 2009020825 A1	12-02-2009
WO 2008021936 A2	21-02-2008	CN 101534829 A	16-09-2009
		EP 2049114 A2	22-04-2009
		JP 2010500415 T	07-01-2010
		US 2010233120 A1	16-09-2010
		US 2008044380 A1	21-02-2008

TRADUCCION
SOLICITUD
INTERNACIONAL

INHIBIDORES DEL VIRUS DE HEPATITIS C

Descripción de la Invención

La presente descripción se refiere a procesos para fabricar compuestos útiles en el tratamiento de infección por virus de hepatitis C (VHC).

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 virus de la inmunodeficiencia humana tipo 1). Una fracción sustancial de estos individuos infectados por el VHC desarrolla una enfermedad hepática progresiva grave, incluyendo cirrosis y carcinoma hepatocelular.

El actual tratamiento de referencia para el VHC, que usa una combinación de interferón pegilado y ribavirina, presenta una tasa de éxito no óptima para conseguir una respuesta vírica mantenida y provoca numerosos efectos secundarios. Por lo tanto, existe una clara y percibida necesidad desde hace mucho tiempo, de desarrollar terapias eficaces para cubrir esta necesidad médica no satisfecha.

El VHC es un virus de ARN de polaridad positiva. Basándose en una comparación de la secuencia de aminoácidos deducida y la gran similitud en la región 5′ no traducida, el VHC ha sido clasificado como un género diferente de la familia Flaviviridae. Todos los miembros de la familia

Flaviviridae presentan viriones encapsulados que contienen un genoma de ARN de polaridad positiva que codifica todas las proteínas específicas del virus conocidas mediante traducción de un marco de lectura abierto, ininterrumpido y único.

Se encuentra una heterogeneidad considerable en la secuencia de nucleótidos y de aminoácidos codificados en todo el genoma del VHC debido a la alta tasa de errores de la ARN polimerasa dependiente de ARN que carece de capacidad correctora. Se han caracterizado al menos seis genotipos principales, y se han descrito más de 50 subtipos distribuidos por todo el mundo. La significación clínica de la heterogeneidad genética del VHC ha demostrado una propensión a la aparición de mutaciones durante el tratamiento con monoterapia, por lo tanto es deseable el uso de otras opciones de tratamiento. El posible efecto modulador de los genotipos sobre la patogénesis y terapia sigue sin comprenderse.

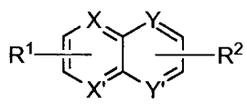
El genoma de ARN cadena simple de VHC tiene una longitud de aproximadamente 9500 nucleótidos y tiene un único marco de lectura abierto (ORF, por sus siglas en inglés) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En las células infectadas, esta poliproteína es escindida en múltiples sitios por proteasas celulares y víricas para producir las proteínas estructurales y no estructurales (NS, por sus siglas en inglés). En el caso

del VHC, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A y NS5B) es llevada a cabo por dos proteasas víricas. Se cree que la primera es una metaloproteasa y escinde la unión entre NS2 y NS3; la segunda es una serina proteasa contenida en la región del extremo N de NS3 (también denominada en el presente documento proteasa NS3) y actúa de mediadora de todas las posteriores escisiones cadena abajo de NS3, tanto en cis, en el sitio de escisión de NS3 y NS4A, como en trans, para el resto de los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A parece desempeñar varias funciones, ya sea actuando de cofactor para la proteasa NS3 como ayudando en la localización en la membrana de NS3 y otros componentes de las replicasas víricas. Para la adecuada actividad de proteasa es necesaria la formación de un complejo NS3-NS4A, lo que supone una eficacia proteolítica mayor de los eventos de escisión. La proteína NS3 también muestra actividades de nucleósido trifosfatasa y ARN helicasa. NS5B (también denominada VHC polimerasa) es una ARN polimerasa dependiente de ARN que está implicada en la replicación de VHC con otras proteínas de VHC, entre otras NS5A, en un complejo de replicasa.

Se desean compuestos útiles para tratar pacientes infectados por VHC que inhiban de forma selectiva la replicación viral del VHC. En particular, son deseables compuestos que sean eficaces para inhibir la función de la

proteína NS5A. La proteína NS5A de VHC se describe, por ejemplo, en las siguientes referencias: S. L. Tan, y col., *Virology*, 284:1-12 (2001); K.-J. Park, y col., *J. Biol. Chem.*, 30711-30718 (2003); T. L. Tellinghuisen, y col., *Nature*, **435**, 374 (2005); R. A. Love, y col., *J. Virol*, **83**, 4395 (2009); N. Appel, y col., *J. Biol. Chem.*, **281**, 9833 (2006); L. Huang, *J. Biol. Chem.*, **280**, 36417 (2005); C. Rice, y col., WO2006093867.

En su primer aspecto, la presente descripción proporciona un compuesto de fórmula (I)



(I),

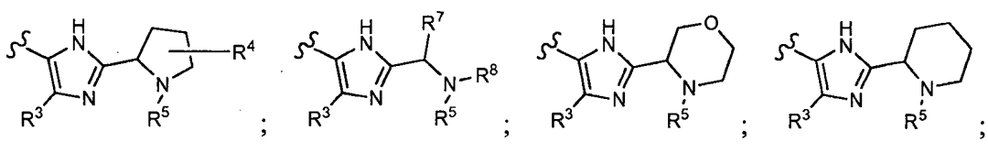
o una sal farmacéuticamente aceptable del mismo; en donde

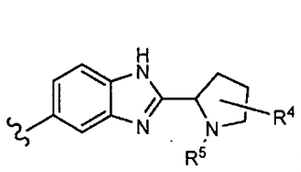
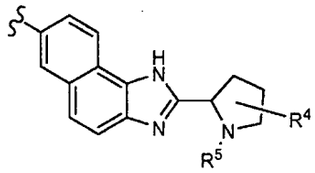
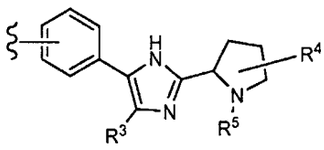
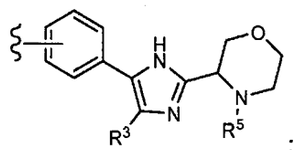
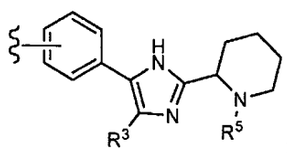
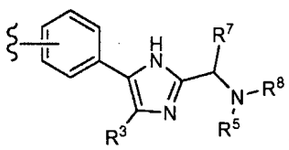
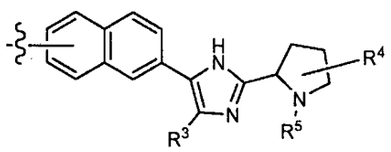
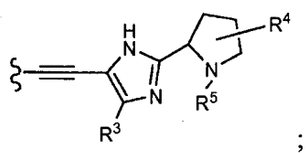
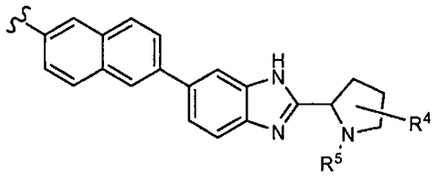
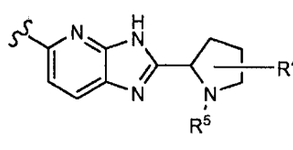
X y X′ se seleccionan independientemente cada uno de CH, CR^1 y N;

Y y Y′ se seleccionan independientemente cada uno de CH, CR^2 y N;

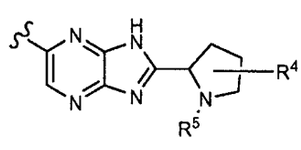
con la condición de que no más de dos de X, X′, Y e Y′ sean N;

R^1 y R^2 se seleccionan independientemente de




;

;

;

;

;

;

;

;

;

;

;

; y

;

cada uno de R^3 se selecciona independientemente de hidrógeno, ciano y halo;

cada uno de R^4 se selecciona independientemente de entre hidrógeno y alquilo, pudiendo formar el alquilo opcionalmente un anillo fusionado de tres a cinco miembros con un átomo de carbono adyacente, en el que este anillo está opcionalmente sustituido con uno o dos grupos metilo; o R^4 y el carbono al que está unido forma un grupo eleleno;

cada R^5 se selecciona independientemente de hidrógeno y $-C(O)R^6$;

cada R^6 se selecciona independientemente de alcoxi, alquilo, arilalcoxi, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo; y

cada uno de R^7 y R^8 se selecciona independientemente de hidrógeno y alquilo.

En una primera modalidad del primer aspecto, la presente descripción proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde:

X y X' se seleccionan independientemente de CH y CR^1; y

Y e Y' se seleccionan independientemente de CH y $CR^{2'}$

En una segunda modalidad del primer aspecto, la presente descripción proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en donde

X y X' se seleccionan independientemente de CH y CR^1; y

Y e Y' son cada uno N.

En una tercera modalidad del primer aspecto, la presente descripción proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en donde

Y y X' son cada uno N;

X se selecciona de CH y CR^1; y

Y' se selecciona de CH y $CR^{2'}$

En una cuarta modalidad del primer aspecto, la presente descripción proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde:

X' es N; y

X se selecciona de CH y CR^1; y

Y e Y' se seleccionan independientemente de CH y CR^2.

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

En una cuarta modalidad del segundo aspecto, la presente descripción proporciona una composición que comprende un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, un portador farmacéuticamente aceptable, y al menos un compuesto adicional que presenta actividad anti-VHC, en donde al menos

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

En una quinta modalidad del segundo aspecto, la presente descripción proporciona una composición que comprende un compuesto de Fórmula (I) o una de sus sales farmacéuticamente aceptables, un portador farmacéuticamente aceptable y al menos un compuesto adicional que tenga actividad contra el VHC, en donde al menos uno de los compuestos adicionales es eficaz para inhibir la función de un objetivo seleccionada de metaloproteasa 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.

En un tercer aspecto la presente descripción proporciona un proceso de tratamiento de 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 tercer aspecto, el proceso comprende además administrar al menos un compuesto adicional que tenga

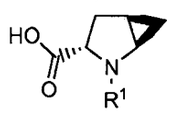
actividad contra el VHC antes, después o simultáneamente al compuesto de la Fórmula (I), o una de sus sales farmacéuticamente aceptables. En una segunda modalidad del tercer aspecto, al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad del tercer aspecto, el interferón se selecciona de interferón alfa-2B, interferón alfa pegilado, interferón de consenso, interferón alfa-2A e interferón tau linfoblastoide.

En una cuarta modalidad del tercer aspecto, la presente descripción proporciona un proceso para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una de sus sales farmacéuticamente aceptables, y al menos un compuesto adicional que tenga actividad anti-VHC antes, después o simultáneamente al compuesto de la Fórmula (I), o una de sus sales farmacéuticamente aceptables, en donde 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 auxiliares de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta modalidad del tercer aspecto, la presente descripción proporciona un proceso para tratar una

infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una de sus sales farmacéuticamente aceptables, y al menos un compuesto adicional que tenga actividad anti-VHC antes, después o simultáneamente al compuesto de la Fórmula (I), o una de sus sales farmacéuticamente aceptables, en donde al menos uno de los compuestos adicionales es eficaz para inhibir la función de un objetivo que se selecciona a partir de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, salida de VHC, proteína NS5A de VHC e IMPDH para el tratamiento de una infección por VHC.

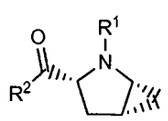
En un cuarto aspecto de la presente descripción se proporciona un proceso para preparar un compuesto de Fórmula (X)



(I);

en donde R^1 se selecciona de hidrógeno y un grupo protector de nitrógeno; que comprende el proceso:

i) hacer reaccionar un compuesto de fórmula (II),



(II);

o una sal farmacéuticamente aceptable del mismo; en

donde

R^1 se selecciona de hidrógeno y un grupo protector de nitrógeno; y

R^2 se selecciona de amino, alcoxi y arilacoxi; y

con una base, y

(b) tratar el producto de la etapa (a) con agua.

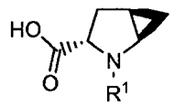
En una primera modalidad del cuarto aspecto, R^1 es hidrógeno.

En una segunda modalidad del cuarto aspecto, R^1 es un grupo protector de nitrógeno. En una tercera modalidad del cuarto aspecto, el grupo protector de nitrógeno es un grupo *terc*-butoxicarbonilo.

En una quinta modalidad del cuarto aspecto, la base se selecciona de un alcóxido metálico y un hidróxido metálico. En una sexta modalidad del cuarto aspecto, la base se selecciona de etóxido de sodio, isopropóxido de sodio, *terc*-butóxido de sodio, hidróxido de sodio, hidróxido de litio, hidróxido de potasio, isopropóxido de potasio, *terc*-butóxido de potasio, *terc*-butóxido de litio e isopropóxido de litio.

En una séptima modalidad del cuarto aspecto, el proceso comprende, además, tratar un producto de

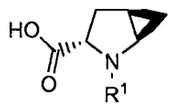
Fórmula (I)



(I),

en donde R^1 es hidrógeno;

con un reactivo protector de nitrógeno, proporcionando un compuesto de Fórmula (I)

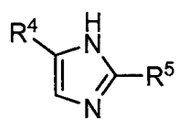


(I),

en donde R^1 es un grupo protector de nitrógeno.

En una octava modalidad del cuarto aspecto, el grupo protector de nitrógeno es *terc*-butoxicarbonilo.

En un quinto aspecto de la presente descripción se proporciona un proceso para preparar un compuesto de fórmula (Z)



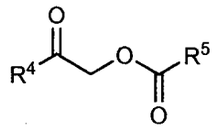
(III),

o una sal farmacéuticamente aceptable del mismo; en donde

R^4 y R^5 se seleccionan independientemente de hidrógeno, alquilo, arilo, arilalquilo, heterociclilo y heterociclilalquilo;

el proceso comprende:

tratar un compuesto de Fórmula (Q)

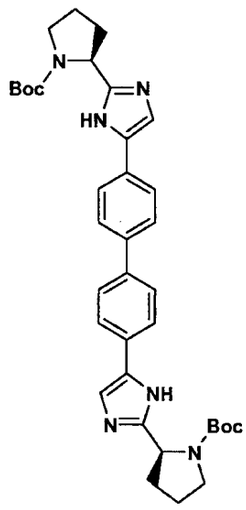


(IV),

con una base en presencia de acetato de amonio.

En una primera modalidad del quinto aspecto, la base se selecciona de una amina terciaria, una amina aromática, una anilina y un imidazol sustituido. En una segunda modalidad del quinto aspecto, la base se selecciona de 1,4-dimetilpiperazina, 3-quinuclidinol, 3-metilpiridina, 1-metilimidazol, dimetilbutilamina, N,N-dimetilanilina, dimerpranol, quinoxazolina, creatinina, 2-metilimidazol, 4-metilimidazol, imidazol, morfolina, N-metilmorfolina, 1,8-diazabicicloundec-7-eno, 1,4-diazabiciclo[2.2.2]octano, colidina, 4-cloroimidazol, 2-cloroimidazol, 4-cianoimidazol, bencimidazol, diisopropiletilamina y 2,6-lutidina. En una tercera modalidad, la base es imidazol.

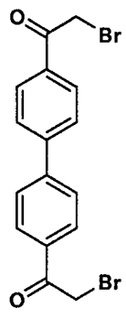
En un sexto aspecto, la presente descripción proporciona un proceso para la preparación del Ejemplo 145



Ejemplo 145,

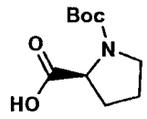
el proceso comprende:

(a) tratar el Ejemplo 143



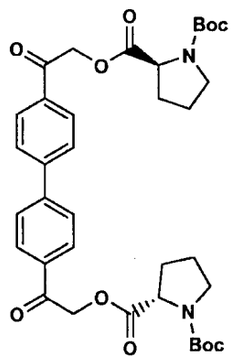
Ejemplo 143,

con el Ejemplo 144



Ejemplo 144

en presencia de una base para producir un compuesto de Fórmula (V)



(V);

(b) tratar un compuesto de Fórmula (V) con acetato de amonio en presencia de una base; y

(c) tratar el producto de la etapa (b) con metanol.

En una primera modalidad del séptimo aspecto, el proceso es un proceso continuo.

Otros aspectos de la presente modalidad pueden incluir combinaciones adecuadas de modalidades reveladas en el presente documento.

Se pueden encontrar aún otros aspectos y modalidades en la descripción proporcionada en el presente documento.

La descripción de la presente modalidad en el presente documento se interpretaría de forma congruente con las leyes y principios de la formación de enlaces químicos. En algunos casos puede ser necesario retirar un átomo de hidrógeno con el fin de acomodar un sustituyente en cualquier localización dada.

Se entenderá que los compuestos comprendidos por la

presente modalidad son aquellos que son adecuadamente estables para usar como un agente farmacéutico.

Se desea que la definición de cualquier sustituyente o variable en una localización particular en una molécula sea independiente de sus definiciones en otro lugar en esa molécula. Por ejemplo, cuando R^1 y R^2 contienen ambos un grupo R^4, los dos grupos R^4 pueden ser iguales o diferentes.

Todas las patentes, solicitudes de patentes y referencias bibliográficas citadas en la memoria descriptiva se incorporan en el presente documento mediante referencia en su totalidad. En el caso de inconsistencias, la presente descripción, incluyendo definiciones, prevalecerá.

Tal como se usa en el presente documento descriptivo, los siguientes términos tienen los significados indicados:

Como se usa en el presente documento, las formas del singular "un", "uno" y "el/la" incluyen referencia al plural a menos que el contexto indique claramente lo contrario.

A no ser que se indique de otro modo, todos los grupos arilo, cicloalquilo y heterociclilo de la presente descripción 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 el presente documento, 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 el presente documento, se refiere a un grupo alquenilo unido a la porción molecular principal mediante un átomo de oxígeno.

El término "alqueniloxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo alqueniloxi unido a la porción molecular principal mediante un grupo carbonilo.

El término "alcoxi", como se usa en el presente documento, se refiere a un grupo alquilo unido a la porción molecular parental a través de un átomo de oxígeno.

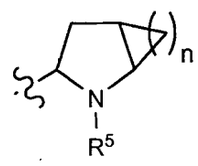
El término "alcoxialquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alcoxi.

El término "alcoxialquilcarbonilo", como se usa en el presente documento, se refiere a un grupo alcoxialquilo unido a la porción molecular parental a través de un grupo carbonilo.

El término "alcoxicarbonilo", como se usa en el presente documento, se refiere a un grupo alcoxi unido a la porción molecular parental a través de un grupo carbonilo.

El término "alquilcarboniloxi", tal como se usa en el presente documento, se refiere a un grupo alquilcarbonilo unido a la porción molecular principal mediante un átomo de oxígeno.

El término "alquilo," tal como se usa en el presente documento, se refiere a un grupo derivado de un hidrocarburo saturado de cadena lineal o ramificada que contiene de uno a seis átomos de carbono. En los compuestos de la presente descripción, cuando R^4 es alquilo, cada alquilo puede formar opcionalmente un anillo de tres miembros condensado con un átomo de carbono adyacente proporcionando la estructura mostrada a continuación:



en donde n se selecciona de 1 y 2,

El término "alquilcarbonilo", como se usa en el presente documento, se refiere a un grupo alquilo unido a la porción molecular parental a través de un grupo carbonilo.

El término "alquilsulfanilo", tal como se usa en el presente documento, se refiere a un grupo alquilo unido a la porción molecular principal mediante un átomo de azufre.

El término "alquilsulfonilo," tal como se usa en el presente documento, se refiere a un grupo alquilo unido a la porción molecular principal mediante un grupo sulfonilo.

El término "amino", tal como se usa en el presente documento, se refiere a $-NR^qR^s$, en donde R^q y R^s se seleccionan independientemente de hidrógeno, alquilo y arilalquilo.

El término "arilo," tal como se usa en el presente documento, 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 descripción pueden estar unidos a la porción 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 descripción están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alquenilo, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, un segundo grupo arilo, arilalcoxi, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo, oxo y $-P(O)OR_2$, donde cada R se selecciona independientemente de hidrógeno y alquilo; y donde la parte

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

El término "arilalcoxi", tal como se usa en el presente documento, se refiere a un grupo arilo unido a la porción molecular parental a través de un grupo alcoxi.

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

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

sustituido, halo, haloalcoxi, haloalquilo, hidroxi, $-NR^xR^y$, y oxo.

El término "arilcarbonilo," tal como se usa en el presente documento, se refiere a un grupo arilo unido a la porción molecular principal mediante un grupo carbonilo.

El término "base", tal como se usa en el presente documento, se refiere a un compuesto que acepta protones.

El término "proceso continuo", tal como se usa en el presente documento, se refiere a un proceso de múltiples etapas en el que no se aíslan los intermediarios formados.

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

El término "cicloalquilo", tal como se usa en el presente documento, se refiere a un sistema anular de hidrocarburo saturado monocíclico o bicíclico que tiene de tres a catorce átomos de carbono y cero heteroátomos. Ejemplos representativos de grupos cicloalquilo incluyen, pero no están limitados a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, biciclo[3.1.1]heptilo y adamantilo. Los grupos cicloalquilo de la presente descripción están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxilo, 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, hidroxilo, nitro y oxo.

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

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

El término "cicloalquilsulfonilo", tal como se usa en el presente documento, se refiere a un grupo cicloalquilo unido a la porción molecular parental a través de un grupo sulfonilo.

El término "etileno", tal como se usa en el presente documento, se refiere a $=CH_2$.

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

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

El término "haloalcoxi", como se usa en el presente documento, se refiere a un grupo haloalquilo unido a la porción molecular parental a través de un átomo de oxígeno.

El término "haloalcoxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo haloalcoxi unido a la porción molecular principal a través de un grupo carbonilo.

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

El término "heterociclilo", tal como se usa en el presente documento, 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 de seis y siete miembros tienen de ninguno a tres dobles enlaces. El término "heterociclilo" también incluye grupos bicíclicos en los que el anillo heterocíclico está condensado con otro grupo heterociclilo monocíclico o un grupo carbocíclico, aromático o no aromático, de tres a siete miembros; grupos bicíclicos en los que el anillo heterociclilo está sustituido con un anillo espirocíclico de tres a siete miembros; así como grupos bicíclicos puenteados tales como 7-azabiciclo[2.2.1]hept-7-ilo, 2-azabiciclo[2.2.2]oct-2-ilo y 2-azabiciclo[2.2.2]oct-3-ilo. Los grupos heterociclilo de la presente descripción pueden estar unidos a la porción

molecular principal a través de cualquier átomo de carbono o átomo de nitrógeno del grupo. Ejemplos de grupos heterociclilo incluyen, pero no están limitados a, benzotienilo, furilo, imidazolilo, indolinilo, indolilo, isoquinolinilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, piperazinilo, piperidinilo, pirazolilo, piridinilo, pirrolidinilo, pirrolopiridinilo, pirrolilo, quinolinilo, tetrahidropiranilo, tiazolilo, tienilo y tiomorfolinilo. Los grupos heterociclilo de la presente descripción están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alquenilo, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, un segundo grupo heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxilo, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo y oxo, en los que la parte alquilo del arilalquilo y el heterociclilalquilo está no sustituida y en los que 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 "heterociclilalcoxi", tal como se usa en el presente documento, se refiere a un grupo heterociclilo unido a la porción molecular principal a través de un grupo alcoxi.

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

El término "heterociclilalquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos heterociclilo. 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 el presente documento, se refiere a un grupo heterociclilalquilo unido a la porción molecular principal a través de un grupo carbonilo.

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

unido a la porción molecular principal a través de un grupo carbonilo.

El término "heterocicliloxi," tal como se usa en el presente documento, se refiere a un grupo heterociclilo unido a la porción molecular principal mediante un átomo de oxígeno.

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

El término "hidroxilo", como se usa en el presente documento, se refiere a -OH.

El término "hidroxialquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos hidroxilo.

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

El término "alcóxico metálico", tal como se usa en el presente documento, se refiere a M-OR, en el que M es un metal seleccionado de sodio, litio y potasio y R es un grupo alquilo.

El término "hidróxido metálico", tal como se usa en el presente documento, se refiere a M-OH, en donde M es un

metal seleccionado de sodio, litio y potasio.

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

El término "grupo protector de nitrógeno", tal como se usa en el presente documento, se refiere a grupos que pretender proteger un grupo amino frente a reacciones no deseadas durante el proceso de síntesis. Grupos protectores de N incluyen, pero no están limitados a, grupos acilo tales como acetilo, benzoilo, 2-bromoacetilo, 4-bromobenzoilo, *terc*-butilacetilo, carboxaldehído, 2-cloroacetilo, 4-clorobenzoilo, α-clorobutirilo, 4-nitrobenzoilo o-nitrofenoxiacetilo, ftalilo, pivaloilo, propionilo, tricloroacetilo y trifluoroacetilo; grupos sulfonilo tales como bencenosulfonilo y p-toluenosulfonilo; grupos formadores de carbamato tales como benciloxicarbonilo, benciloxicarbonilo (Cbz), *terc*-butiloxicarbonilo (Boc), p-clorobenciloxicarbonilo y p-metoxibenciloxicarbonilo.

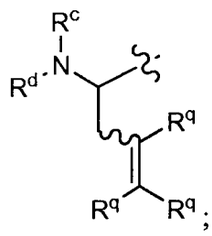
El término "reactivo protector de nitrógeno", tal como se usa en el presente documento, se refiere a un compuestos que en las condiciones de reacción añade un grupo protector de nitrógeno a un átomo de nitrógeno que hay que proteger.

El término "$-NR^cR^d$," tal como se usa en el presente documento, se refiere a dos grupos, R^c y R^d, que están unidos a la porción molecular principal a través de un átomo de

nitrógeno. R^c y R^d se seleccionan independientemente de hidrógeno, alqueniloxicarbonilo, alcoxialquilcarbonilo, alcoxicarbonilo, alquilo, alquilcarbonilo, cicloalquiloxi, alquilsulfonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilalquilcarbonilo, arilcarbonilo, ariloxicarbonilo, arilsulfonilo, cicloalquilo, cicloalquiloxicarbonilo, cicloalquilsulfonilo, formilo, haloalcoxicarbonilo, heterociclilo, heterociclilalcoxicarbonilo, heterociclilalquilo, heterociclilalquilcarbonilo, heterociclilcarbonilo, heterocicliloxicarbonilo, hidroxialquilcarbonilo, (NR^eR^f)alquilo, (NR^eR^f)alquilcarbonilo, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, -C(NCN)OR' y $-C(NCN)NR^xR^y$, donde R' se selecciona de alquilo y fenilo no sustituido y donde la parte alquilo del arilalquilo, el arilalquilcarbonilo, el heterociclilalquilo y el heterociclilalquilcarbonilo están además opcionalmente sustituidos con un grupo $-NR^eR^f$; y donde el arilo, la parte arilo del arilalcoxicarbonilo, el arilalquilo, el arilalquilcarbonilo, el arilcarbonilo, el ariloxicarbonilo y el arilsulfonilo, el heterociclilo y la parte heterociclilo del heterociclilalcoxicarbonilo, el heterociclilalquilo, el heterociclilalquilcarbonilo, el heterociclilcarbonilo y el heterocicliloxicarbonilo están además opcionalmente sustituidas con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo,

haloalcoxi, haloalquilo y nitro.

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



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

El término "(NR^cR^d)alquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^cR^d$. La parte alquilo de (NR^cR^d)alquilo, está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados de alcoxi, alcoxialquilcarbonilo, alcoxicarbonilo, alquilsulfanilo, alquinilo C_2, arilalcoxicarbonilo, carboxi, ciano, cicloalquilo, halo, heterociclilo, heterociclilcarbonilo, hidroxilo y (NR^eR^f)carbonilo; estando, además, el heterociclilo opcionalmente sustituido con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "$-NR^eR^f$," tal como se usa en el presente documento, se refiere a dos grupos, R^e y R^f, que están unidos

a la porción molecular principal a través de un átomo de nitrógeno. R^e y R^f se seleccionan independientemente de hidrógeno, alquilo, arilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, (cicloalquil)alquilo no sustituido, heterociclilo no sustituido, heterociclilalquilo no sustituido, (NR^xR^y)alquilo y (NR^xR^y)carbonilo.

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

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

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

El término "$-NR^xR^y$," tal como se usa en el presente documento, se refiere a dos grupos, R^x y R^y, que están unidos a la porción 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 el presente documento, 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 el presente documento, se refiere a un grupo $-NR^xR^y$ unido a la porción molecular principal a través de un grupo carbonilo.

El término "$-NR^xR^y$," tal como se usa en el presente documento, se refiere a dos grupos, R^x y R^y, que están unidos a la porción molecular principal a través de un átomo de nitrógeno. R^x y R^y se seleccionan independientemente de hidrógeno y alquilo.

El término "$(NR^{x'}R^{y'})$carbonilo," tal como se usa en el presente documento, se refiere a un grupo $-NR^{x'}R^{y'}$ unido a la porción molecular principal a través de un grupo carbonilo.

El término "oxo", como se usa en el presente documento, se refiere a =O.

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

Existen centros asimétricos en los compuestos de la presente descripción. Estos centros se designan con los

símbolos "R" o "S", dependiendo de la configuración de los sustituyentes alrededor del átomo de carbono quiral. Debe entenderse que la descripción engloba todas las formas isoméricas estereoquímicas, o sus mezclas, que poseen la capacidad de inhibir NS5A. Se pueden preparar estereoisómeros individuales de los compuestos sintéticamente a partir de materiales iniciales comercialmente disponibles que contienen centros quirales o por preparación de mezclas de productos enantioméricos seguido de separación como por ejemplo conversión a una mezcla de diastereómeros seguido de separación o recristalización, técnicas cromatográficas o separación directa de enantiómeros en columnas cromatográficas quirales. Los compuestos de partida de estereoquímica particular, bien están comercialmente disponibles o bien se pueden preparar y resolver mediante técnicas conocidas en la técnica.

Ciertos compuestos de la presente discusión pueden existir también en formas conformacionales estables diferentes que pueden ser separables. La asimetría torsional debida a rotación restringida sobre un enlace individual asimétrico, por ejemplo debido a su impedimento estérico o tensión de anillo, puede permitir la separación de conformadores diferentes. La presente revelación incluye cada isómero conformacional de estos compuestos y mezclas de los mismos.

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

La expresión "compuestos de la presente descripción" y expresiones equivalentes, pretenden incluir compuestos de Fórmula (I), y sus enantiómeros, diastereoisómeros y sales farmacéuticamente aceptables. De forma similar, las referencias a los intermediarios se pretende que engloben sus sales cuando el contexto lo permita.

Se pretende que la presente descripción incluya todos los isótopos de los átomos que aparecen en los presentes compuestos. Los isótopos incluyen los átomos que tienen el mismo número atómico pero diferentes números másicos. Como ejemplo general y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen ^{13}C y ^{14}C. Los compuestos marcados con isótopos de la invención generalmente se pueden preparar por técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en el presente documento, usando un reactivo marcado con isótopo apropiado en lugar del reactivo no marcado que se usa en otros casos. Tales compuestos pueden tener una diversidad de usos potenciales, por ejemplo como estándares y reactivos en determinación de actividad biológica. En el caso de los

isótopos estables, dichos compuestos pueden tener el potencial de modificar favorablemente propiedades biológicas, farmacológicas o farmacocinéticas.

Los compuestos de la presente discusión pueden existir como sales farmacéuticamente aceptables. El término "sal farmacéuticamente aceptable", como se usa en el presente documento, representa sales o formas híbridas de los compuestos de la presente descripción que son solubles en agua o solubles en aceite o dispersables, que son, dentro del alcance del juicio médico bien fundamentado, adecuadas para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica, u otro problema o complicación es proporcional con una relación beneficio/riesgo razonable, y son efectivos para su uso deseado. Las sales se pueden preparar durante el aislamiento y purificación finales de los compuestos o por separado haciendo reaccionar un átomo de nitrógeno adecuado con un ácido adecuado. Las sales de adición representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, camforato, camforsulfonato; digluconato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formiato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, 2-naftalenosulfonato,

oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluenosulfonato y undecanoato. Ejemplos de ácidos que se pueden usar para formar sales de adición farmacéuticamente aceptables incluyen ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico y fosfórico, y ácidos orgánicos tales como ácido oxálico, maleico, succínico y cítrico.

Las sales de adición básica se pueden preparar durante el aislamiento y la purificación finales de los compuestos haciendo reaccionar un grupo carboxilo con una base adecuada tal como el hidróxido, carbonato, o bicarbonato de un catión metálico o con amoniaco o una amina 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 básicas incluyen etilenodiamina,

etanolamina, dietanolamina, piperidina y piperazina.

Cuando es posible que, para uso en terapia, se puedan administrar cantidades terapéuticamente eficaces de un compuesto de Fórmula (I), así como sus sales farmacéuticamente aceptables, en forma de compuestos químicos en bruto, es posible presentar el ingrediente activo como una composición farmacéutica. Por consiguiente, la descripción proporciona además composiciones farmacéuticas que incluyen cantidades terapéuticamente eficaces de compuestos de Fórmula (I) o sus sales farmacéuticamente aceptables, y uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. La expresión "cantidad terapéuticamente eficaz," tal como se usa en el presente documento, se refiere a la cantidad total de cada ingrediente activo que es suficiente para mostrar un beneficio significativo al paciente, por ejemplo, una reducción mantenida de la carga vírica. Cuando se aplica a un principio activo individual, administrado solo, el término se refiere a ese ingrediente solo. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los principios activos que provoca el efecto terapéutico, ya se administren combinados, en serie o de forma simultánea. Los compuestos de la Fórmula (I) y sus sales farmacéuticamente aceptables, son tal como se describen anteriormente. El/los *portador(es)*, diluyente(s), o excipiente(s) deben ser aceptables en el sentido de que sean

compatibles con los otros ingredientes de la formulación y no deletéreos para el receptor de los mismos. De conformidad con otro aspecto de la presente descripción se proporciona también un proceso para la preparación de una formulación farmacéutica que incluye mezclar un compuesto de Fórmula (I), o una de sus sales farmacéuticamente aceptables, con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. El término "farmacéuticamente aceptable", tal como se usa en el presente documento, se refiere a los compuestos, materiales, composiciones y/o formas farmacéuticas que son, dentro del alcance del criterio médico habitual, adecuados para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica u otro problema o complicación acorde con una relación beneficio/riesgo razonable, y son eficaces para su uso deseado.

Las formulaciones farmacéuticas pueden presentarse en formas monodosis que contienen una cantidad predeterminada de principio activo por monodosis. En una monoterapia para la prevención y tratamiento de enfermedad mediada por VHC son típicos niveles de dosis que varían de aproximadamente 0,01 a aproximadamente 250 miligramos por kilogramo ("mg/kg") de peso corporal por día, con preferencia de aproximadamente 0,05 a aproximadamente 100 mg/kg de peso corporal por día de los compuestos de la presente descripción. Habitualmente, las

composiciones farmacéuticas de la presente descripción se administrarán desde aproximadamente 1 a aproximadamente 5 veces al día o de forma alternativa, en forma de infusión continua. Dicha administración puede usarse como terapia crónica o aguda. La cantidad de principio activo que puede combinarse con los materiales portador para producir una única forma farmacéutica variará dependiendo de la afección que se esté tratando, de la gravedad de la afección, del tiempo de administración, la vía de administración, la velocidad de excreción del compuesto usado, la duración del tratamiento y la edad, sexo, peso y afección del paciente. Las formulaciones monodosis son las que contienen una dosis o subdosis diaria, tal como se indica anteriormente en el presente documento, o una fracción apropiada de las mismas de un principio activo. Generalmente, el tratamiento se inicia con dosis pequeñas sustancialmente por debajo de la dosis óptima del compuesto. Después, la dosis se aumenta en pequeños incrementos hasta que se alcanza el efecto óptimo en las circunstancias dadas. En general, el compuesto se administra, de la forma más deseable a un nivel de concentración que generalmente conseguirá resultados antiviralmente eficaces sin provocar efectos secundarios dañinos ni perjudiciales.

Cuando las composiciones de esta descripción comprenden una combinación de un compuesto de la presente

descripción y uno o más agentes terapéuticos o profilácticos adicionales, tanto el compuesto como el agente adicional habitualmente están presentes a niveles de dosis de aproximadamente 10 a 150%, y más preferentemente entre aproximadamente 10 y 80% de la dosis que normalmente se administra en una pauta de monoterapia.

Las formulaciones farmacéuticas se pueden adaptar para administración por cualquier vía apropiada, por ejemplo por la vía oral (incluyendo la bucal o la sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual, o transdérmica), vaginal, o parenteral (incluyendo inyecciones o infusiones subcutáneas, intracutáneas, intramusculares, intra-articulares, intrasinoviales, intraesternales, intratecales, intralesionales, intravenosas, o intradérmicas). Tales formulaciones se pueden preparar por cualquier proceso conocido en la técnica de farmacia, por ejemplo por unión en asociación el ingrediente activo con el/los *portador(es)* o excipiente(s). Son preferentes la administración oral o la administración mediante inyección.

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

Por ejemplo, para administración oral en la forma de un comprimido o una cápsula, el componente de fármaco activo se puede combinar con un portador inerte farmacéuticamente aceptable no tóxico, oral tal como etanol, glicerol, agua y similares. Los polvos se prepararon moliendo el compuesto a un tamaño fino adecuado y mezclando con un portador farmacéutico molido de forma similar tal como un carbohidrato comestible, como, por ejemplo, almidón o manitol. También puede estar presente agente aromatizante, conservante, dispersante y colorante.

Las cápsulas se hacen preparando una mezcla en polvo, como se describe anteriormente y cubiertas de gelatina formadas cargadas. Se pueden añadir agentes deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio, o polietilenoglicol sólido a la mezcla en polvo antes de la operación de carga. Un agente disgregante o solubilizante tal como agar-agar, carbonato de calcio, o carbonato de sodio puede también añadirse para incrementar la disponibilidad del medicamento cuando la cápsula es ingerida.

Además, cuando se desee o sea necesario, también pueden incorporarse aglutinantes, lubricantes, agentes disgregantes y agentes colorantes adecuados a la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de

maíz, gomas naturales y sintéticas tales como goma arábiga, gomo de tragacanto o alginato de sodio, carboximetilcelulosa, polietilenoglicol, ceras, y similares. Los lubricantes usados en estas formas de dosificación incluyen oleato de sodio, cloruro de sodio y similares. Los disgregadores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantana, y similares. Los comprimidos se formularon, por ejemplo, preparando un mezcla en polvo, granulando o soldando con fusión incompleta, añadiendo un lubricante y disgregante, y prensando en comprimidos. Se preparó una mezcla en polvo mezclando el compuesto, molido adecuadamente, con un diluyente o base como se describe anteriormente, y opcionalmente, con un ligando tal como carboximetilcelulosa, un alginato, galatina, o polivinilpirrolidina, un retardante de solución tal como parafina, un acelerados de resorción tal como una sal cuaternaria y/o agente de absorción tal como bentonita, caolín o fosfato dicálcico. La mezcla en polvo se puede granular por humectación con un aglutinante tal como jarabe, pasta de almidón, mucílago de goma arábiga, o soluciones de materiales celulósicos o poliméricos y forzándola a pasar a través de un tamiz. Como una alternativa para granular, la mezcla en polvo puede hacerse pasar por la máquina compresora y el resultado son postas formadas imperfectamente rotas en gránulos. Los gránulos se pueden lubricar para evitar que se adhieran al comprimido formando

moldes por medio de la adición de ácido esteárico, una sal de estearato, talco, o aceite mineral. La mezcla lubricada se comprime después en comprimidos. Los compuestos de la presente revelación se pueden combinar también con un portador inerte que fluye libre y se pueden comprimir en comprimidos directamente sin ir a través de las formas de granulación o formación de postas. Se pueden proporcionar un revestimiento protector transparente u opaco constituido por un revestimiento sellante de goma laca, un revestimiento de azúcar o de material polimérico, y un revestimiento pulido de cera. Se pueden añadir tintes a estos recubrimientos para distinguir dosificaciones unitarias diferentes.

Los fluidos orales tales como una solución, jarabes y elixires se pueden preparar en forma de dosificación unitaria tal que una cantidad dada contiene una cantidad predeterminada del compuesto. Los jarabes se pueden preparar disolviendo el compuesto en una solución acuosa adecuadamente aromatizada, mientras que se prepararon elixires por el uso de un portador no tóxico. Se pueden añadir también solubilizadores y emulsionantes tales como alcoholes isoestearílicos etoxilados y éteres de polioxietileno sorbitol, conservantes, aditivo aromático tal como aceite de menta o edulcorantes naturales, o sacarina u otros edulcorantes artificiales y similares.

Donde sea apropiado, se pueden encapsular las

formulaciones de dosificación unitaria para administración. La formulación se pueden preparar también para prolongar o mantener la liberación como por ejemplo revistiendo o incrustando material particulado en polímeros, ceras, o similares.

Los compuestos de la Fórmula (I), y sus sales farmacéuticamente aceptables, también pueden administrarse en forma de sistemas de administración de liposomas, tales como vesículas unilaminares, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas se pueden formas a partir de una diversidad de fosfolípidos, tales como colesterol, estearilamina, o fosfatidilcolinas.

Los compuestos de la Fórmula (I) y sus sales farmacéuticamente aceptables también pueden administrarse usando anticuerpos monoclonales como portadores individuales a los que se acoplan las moléculas de compuesto. Los compuestos pueden estar acoplados también con polímeros solubles como transportadores de fármacos marcables como objetivos. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol, o polietilenóxidopolilisina sustituida con residuos de palitoilo. Además, los compuestos pueden acoplarse a una clase de polímeros biodegradables útiles en lograr liberación controlada de un fármaco, por

ejemplo, ácido poliláctico, caprolactona poliépsilon, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos, y copolímeros de bloque de hidrogeles reticulados o anfipáticos.

Las formulaciones farmacéuticas adaptadas para administración transdérmica pueden presentarse como parches discretos que se desea que permanezcan en contacto íntimo con la epidermis de un receptor durante un periodo de tiempo prolongado. 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.

Para tratamientos del ojo o de otros tejidos externos, por ejemplo boca y piel, las formulaciones se aplican preferentemente como una pomada o crema tópica. Cuando se formula en una pomada, el ingrediente activo se puede usar bien con una base parafínica o bien con una base de pomada mezclable en agua. Alternativamente, el ingrediente activo se puede formular en una crema con una base de aceite-en-agua o con una base de agua-en-aceite.

Las formulaciones farmacéuticas adaptadas para administraciones tópicas para el ojo incluyen gotas oculares

en las que el ingrediente activo se disuelve o suspende en un portador adecuado, especialmente un solvente acuoso.

Las formulaciones farmacéuticas adaptadas para administración tópica en la boca incluyen tabletas, pastillas y enjuagues bucales.

Las formulaciones farmacéuticas adaptadas para administración rectal pueden presentarse como supositorios o como enemas.

Las formulaciones farmacéuticas adaptadas para administración nasal en las que el portador es un sólido incluyen un polvo grueso que tiene un tamaño de 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. Las formulaciones adecuadas en las que el transportador es un líquido, para administración como una pulverización nasal o como gotas nasales, incluyen soluciones acuosas o soluciones aceitosas del ingrediente activo.

Las formulaciones adaptadas para administración por inhalación incluyen espolvoreados o neblinas de partículas finas, que se pueden generar por medio de diversos tipos de aerosoles, nebulizadores, o insufladores presurizados en dosis medidas.

Las formulaciones farmacéuticas adaptadas para

administración vaginal pueden presentarse como pesarios, tampones, cremas, geles, pastas, espumas o formulaciones de pulverización.

Las formulaciones farmacéuticas adaptadas para administración parenteral incluyen soluciones de inyección estériles acuosas y no acuosas que pueden contener anti-oxidantes, tampones, bacteriostáticos y solutos que vuelven a la formulación isotónica con la sangre del receptor deseado; y suspensiones estériles acuosas y no acuosas que pueden incluir agentes en suspensión y agentes espesantes. Las formulaciones pueden presentarse en recipientes de dosis unitaria o de multidosis, por ejemplo ampollas y viales sellados, y pueden almacenarse en una condición secada por congelación (liofilizada) que requiere sólo la adición del transportador líquido estéril, por ejemplo agua para inyecciones, inmediatamente antes de usar. Se pueden preparar soluciones y suspensiones de inyección extemporáneas a partir de polvos estériles, gránulos y comprimidos.

Debería entenderse que además de los ingredientes mencionados en particular anteriormente, las formulaciones pueden incluir otros agentes convencionales en la técnica que se han considerado para el tipo de formulación en cuestión, por ejemplo aquellos adecuados para administración oral pueden incluir agentes saborizantes.

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 descripción también se pueden administrar con una ciclosporina, por ejemplo, ciclosporina A. La ciclosporina A ha demostrado que es 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 a continuación enumera algunos ejemplos ilustrativos de compuestos que se pueden administrar con los compuestos de la presente descripción. Los compuestos de la descripción se pueden administrar con otros compuestos con actividad contra el VHC en terapia de combinación, bien de forma conjunta o por separado o combinando los compuestos para formar una composición.

Tabla 1

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
NIM811 Debio-025		Inhibidores de ciclofilina	Novartis Debiopharm
Zadaxin		Immunomodulador	Sciclone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista de TLR9	Coley
Batabulin (T67)	Anticanceroso	βInhibidor de β- tubulina	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	Antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., Nueva York, NY
Summetrel	Antiviral	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	Inhibidor de VHC	Achillion / Gilead
Compuestos y sales de pirazolopirimidina Del documento WO2005/047288 26 de mayo de 2005	Antiviral	Inhibidores de VHC	Arrow Therapeutics Ltd.
Levovirina	Antiviral	Inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	Inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
XTL-6865 (XTL-002)	Antiviral	Anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	Inhibidor de la serina proteasa NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly y Co. Inc., Indianapolis, IN
HCV-796	Antiviral	Inhibidor de la replicasa NS5B	Wyeth / Viropharma
NM-283	Antiviral	Inhibidor de la replicasa NS5B	Idenix / Novartis
GL-59728	Antiviral	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
GL-60667	Antiviral	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
2'C MeA	Antiviral	Inhibidor de la replicasa NS5B	Gilead
PSI6130	Antiviral	Inhibidor de la replicasa NS5B	Roche
R1626	Antiviral	Inhibidor de la replicasa NS5B	Roche
2'C Metil adenosina	Antiviral	Inhibidor de la replicasa NS5B	Merck
JTK-003	Antiviral	Inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Levovirina	Antiviral	Ribavirina	ICN Pharmaceuticals, Costa Mesa, CA

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
Ribavirina	Antiviral	Ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Viramidina	Antiviral	Profármaco de ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazima	Antiviral	Ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	Inhibidor de serina proteasas	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
SCH 503034	Antiviral	Inhibidor de serina proteasas	Schering Plough
Zadazim	Inmunomodulador	Inmunomodulador	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Inmunomodulador	Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
CELLCEPT®	Inmunosupresor	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	IFN-α2b de albúmina	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferón	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferón	IFN-ω	Intarcia Therapeutics

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
IFN-β y EMZ701	Interferón	IFN-β y EMZ701	Transición Therapeutics Inc., Ontario, Canadá
REBIF®	Interferón	IFN-β1a	Serono, Ginebra, Suiza
Roferon A	Interferón	IFN-α2a	F. Hoffmann-La Roche LTD, Basilea, Suiza
Intrón A	Interferón	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intrón A y Zadaxin	Interferón	IFN-α2b/α1-timosina	RegeneRx Biopharma. Inc., Bethesda, MD / SciClone Pharmaceuticals Inc, San Mateo, CA
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, Reino Unido
Omniferon	Interferón	IFN-α natural	Viragen Inc., Plantation, FL
Pegasys	Interferón	IFN-α2a pegilado	F. Hoffmann-La Roche LTD, Basilea, Suiza
Pegasys y Ceplene	Interferón	IFN-α2a PEGilado / modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
Pegasys y Ribavirina	Interferón	IFN-α2a pegilado/ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza
PEG-Intrón	Interferón	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intrón / ribavirina	Interferón	IFN-α2b PEGilado/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Protección hepática	Antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Protección hepática	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Inhibidor de serina proteasas	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	Inhibidor de la replicasa NS5B	Genelabs
ANA-971	Antiviral	Agonista de TLR-7	Anadys
Boceprevir	Antiviral	Inhibidor de serina proteasas	Schering Plough
TMS-435	Antiviral	Inhibidor de serina proteasas	Tibotec BVBA, Mechelen, Bélgica
BI-201335	Antiviral	Inhibidor de serina proteasas	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
MK-7009	Antiviral	Inhibidor de serina proteasas	Merck
PF-00868554	Antiviral	Inhibidor de replicasas	Pfizer

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
ANA598	Antiviral	Inhibidor no nucleosídico de polimerasa NS5B	Anadys Pharmaceuticals, Inc., San Diego, CA, USA
IDX375	Antiviral	Inhibidor no nucleosídico de replicasa	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	Inhibidor de polimerasa NS5B	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canadá
PSI-7851	Antiviral	Inhibidor nucleosídico de polimerasa	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	Inhibidor de polimerasa NS5B	ViroChem Pharma
VCH-916	Antiviral	Inhibidor de polimerasa NS5B	ViroChem Pharma
GS-9190	Antiviral	Inhibidor de polimerasa NS5B	Gilead
Peg-interferón lamda	Antiviral	Interferón	ZymoGenetics / Bristol-Myers Squibb

Los compuestos de la presente descripción también se pueden usar como reactivos de laboratorio. Los compuestos pueden ser una contribución decisiva para proporcionar herramientas de investigación para diseñar ensayos de replicación del virus, validación de sistemas de ensayo en animales y estudios de biología estructural para potenciar más el conocimiento de los mecanismos de la enfermedad por VHC. Además, los compuestos de la presente descripción son

útiles para establecer o determinar el sitio de unión de otros compuestos antivirales, por ejemplo, por inhibición competitiva.

Los compuestos de esta descripción 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 descripción pretende incluir compuestos que tienen la Fórmula (I) cuando se preparan por procesos de síntesis o por procesos metabólicos que incluyen los que se producen en el cuerpo humano o animal (*en vivo*) o procesos que se producen *in vitro*.

Las abreviaturas usadas en la presente solicitud, incluyendo en particular en los ejemplos ilustrativos siguientes, son bien conocidas por los expertos en la técnica. Algunas de las abreviaturas usadas son las siguientes: Ph para fenilo; DME para 1,2-dimetoxietano; TFA para ácido trifluoroacético; DCM para diclorometano; HATU para hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio; DMF para N,N-dimetilformamida; iPr_2EtN, DIEA o DIPEA para diisopropiletilamina; h, hr o hrs

para horas; MeOD para CD_3OD; MeOH para metanol; min o mins para minutos; EtOH para etanol; Et para etilo; DMSO para dimetilsulfóxido; ta o TA para temperatura ambiente, tr o TR para tiempo de retención; EDCI para clorhidrato de 1-(3-dimetilaminopropilo)-3-etilcarbodiimida; Boc, boc o BOC para *terc*-butoxicarbonilo; EtOAc o EtOAc para acetato de etilo; THF para tetrahidrofurano; TBDPS para t-butildimetilsililo; DMAP para 4-dimetilaminopiridina; TBAF para fluoruro de tetrabutilamonio; OAc para acetato; AcOH para ácido acético; SEMCl para cloruro de 2-(trimetilsilil)etoximetilo; d para días; TEA o Et_3N para trietilamina; ACN o MeCN para acetonitrilo; NCS para N-clorosuccinimida; NBS para N-bromosuccinimida; Et_2O para dietil éter; DCE para 1,2-dicloroetano; d para días; y DEA para dietilamina.

La presente descripción se describirá ahora en relación con determinadas modalidades que no se pretende que limiten su alcance. Por el contrario, la presente descripción abarca todas las alternativas, modificaciones y equivalentes y puede incluirse dentro del alcance de las reivindicaciones. Así, los siguientes ejemplos, que incluyen modalidades específicas, ilustrarán una práctica de la presente descripción, entendiéndose que los ejemplos son para fines de ilustración de determinadas modalidades y se presentan para proporcionar lo que se cree que es la descripción más útil y fácilmente entendible de sus procesos y aspectos

conceptuales.

Los materiales de partida pueden obtenerse de fuentes comerciales o prepararse mediante procesos ya establecidos en la bibliografía conocidos por las personas expertas en la técnica.

Síntesis de Caps comunes

Condiciones de ensayo de los compuestos

La valoración de la pureza y el análisis de masas de baja resolución se llevaron a cabo en un sistema de CL Shimadzu CL acoplado con un sistema de EM Waters MICROMASS® ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. Condiciones adicionales de CL aplicables a la presente sección, a no ser que se indique de otro modo.

Condiciones de EM-W1

Columna = XTERRA® 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 5 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones de EM-W2

Columna = XTERRA® 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Velocidad de flujo = 4 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones de EM-W5

Columna = XTERRA® 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 30

Tiempo de gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 5 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones-D1

Columna = XTERRA® C18 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Velocidad de flujo = 4 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

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

Condiciones-D2

Columna = PHENOMENEX® Luna 4.6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Velocidad de flujo = 4 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones-M3

Columna = XTERRA® C18 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 40

Tiempo de gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 5 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condición I

Columna = PHENOMENEX® Luna 3.0X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 4 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condición II

Columna = PHENOMENEX® Luna 4.6X50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 5 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condición III

Columna = HPLC XTERRA® C18 3.0 x 50mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

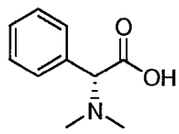
Velocidad de flujo = 4 ml/min

Longitud de onda = 220 nm

solvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

solvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

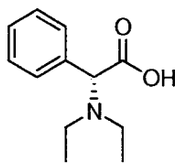
Cap-1



Ácido (R)-2-(dimetilamino)-2-fenilacético

Se añadió una suspensión de Pd al 10%/C (2.0 g) en metanol (10 ml) a una mezcla de (R)-2-fenilglicina (10 g, 66.2 mmol), formaldehído (33 ml de 37% en peso en agua), HCl 1N (30 ml) y metanol (30 ml) y se expuso a H_2 (413.57 kPa) durante 3 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de *Cap*-1 como agujas blancas (4.0 g). Rotación óptica: -117.1° [c = 9.95 mg/ml en H_2O; λ = 589 nm]. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); CL (Cond. I): T_R = 0.25; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; encontrado 180.17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; encontrado 180.1017.

Cap-2

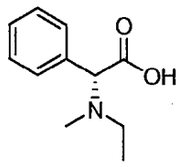


Ácido (R)-2-(dietilamino)-2-fenilacético

Se añadió $NaBH_3CN$ (6.22 g, 94 mmol) en porciones durante unos pocos minutos a una mezcla enfriada (hielo/agua) de (R)-2-fenilglicina (6.02 g, 39.8 mmol) y MeOH (100 ml), y se agitó durante 5 min. Se añadió acetaldehído (10 ml) gota a gota durante 10 minutos y se continuó agitando a la misma temperatura fría durante 45 minutos y a temperatura ambiente durante ~6.5 horas. La mezcla de reacción se volvió a enfriar con baño de hielo-agua, se trató con agua (3 ml) y luego se inactivó con una adición gota a gota de HCl concentrado durante ~ 45 min hasta que el pH de la mezcla fue ~ 1.5 - 2.0. El baño de enfriamiento se retiró y se continuó agitando mientras se añadía HCl concentrado con el fin de mantener el pH de la mezcla aproximadamente a 1,5-2.0. La mezcla de reacción se agitó durante una noche, se filtró para separar la suspensión blanca y el filtrado se concentró a vacío. El material bruto se recristalizó en etanol proporcionando la sal HCl de *Cap*-2 como un sólido blanco brillante en dos tandas (tanda-1: 4.16 g; tanda-2: 2.19 g). RMN de ^1H (DMSO-d_6. δ = 2.5 ppm, 400 MHz): 10.44 (1.00, s ancho, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (m ancho, 2H), 2.98 (m

ancho, 2H), 1.20 (s ancho aparente, 6H). Tanda-1: $[\alpha]^{25}$ -102.21° (c = 0.357, H_2O); canda-2: $[\alpha]^{25}$ -99.7° (c = 0.357, H_2O). CL (Cond. I): T_R = 0.43 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; encontrado 208.26

Cap-3

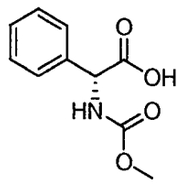


Se añadió secuencialmente acetaldehído (5.0 ml, 89.1 mmol) y una suspensión de Pd al 10%/C (720 mg) en metanol/H_2O (4 ml/1 ml) a una mezcla enfriada (~ 15 °C) de (R)-2-fenilglicina (3.096g, 20.48 mmol), HCl 1N (30 ml) y metanol (40 ml). Se retiró el baño de enfriamiento y la mezcla de reacción se agitó bajo un 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 fue necesario a través de la reacción]. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de ácido (R)-2-(etilamino)-2-fenilacético como un sólido blanco brillante (2.846 g). RMN de ^1H (DMSO-d_6. δ = 2.5 ppm, 400 MHz): δ 14.15 (s ancho, 1H), 9.55 (s ancho, 2H), 7.55-7.48 (m, 5H), 2.88 (m ancho, 1H), 2.73 (m ancho, 1H), 1.20 (t aparente, *J* = 7.2, 3H). CL (Cond. I): T_R = 0.39 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$

$C_{10}H_{14}NO_2$: 180.10; encontrado 180.18.

Se añadió una suspensión de Pd al 10%/C (536 mg) en metanol/H_2O (3 ml/1 ml) a una mezcla de ácido (R)-2-(etilamino)-2-fenilacético/HCl (1.492 g, 6.918 mmol), formaldehído (20 ml de 37% en peso en agua), HCl 1N (20 ml) y metanol (23 ml). La mezcla de reacción se agitó bajo un 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 *Cap*-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). CL (Cond. I): T_R = 0.39 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; encontrado 194.18; EMAR: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; encontrado 194.1181.

Cap-4



Ácido (R)-2-(metoxicarbonilamino)-2-fenilacético

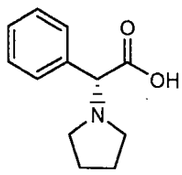
Se añadió $ClCO_2Me$ (3.2 ml, 41.4 mmol) gota a gota a

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 ^1H (DMSO-d_6. δ = 2.5 ppm, 400 MHz): 7.98 (d, J = 8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J = 8. 1H), 3.56 (s, 3H), 1.33 (s, 9H). CL (Cond. I): T_R = 1.53 min; índice de homogeneidad ~90 %; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; encontrado 288.15.

Se añadió TFA (16 ml) gota a gota a una solución enfriada (hielo/agua) en CH_2Cl_2 (160 ml) del producto anterior durante 7 minutos y se retiró el baño de enfriamiento y la mezcla de reacción se agitó durante 20 horas. Puesto que la desprotección todavía no fue completa, se añadió más TFA (1.0 ml) y se continuó agitando durante otras 2 horas más. El componente volátil se eliminó a vacío, y el residuo oleoso resultante se trató con éter dietílico (15 ml) y hexanos (12 ml) proporcionando un precipitado. El precipitado se filtró y

se lavó con éter dietílico/hexanos (relación ~1:3; 30 ml) y se secó a vacío proporcionando *Cap*-4 como un sólido blanco apelusado (5.57 g). Rotación óptica: -176.9° [c = 3.7 mg/ml en H_2O; λ = 589 nm]. RMN de ^1H (DMSO-d_6. δ = 2.5 ppm, 400 MHz): δ 12.84 (s ancho, 1H), 7.96 (d, *J* = 8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, *J* = 8.3, 1H), 3.55 (s, 3H). CL (Cond. I): T_R = 1.01 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; encontrado 210.17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; encontrado 210.0756.

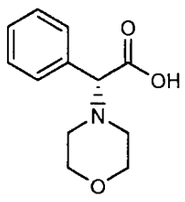
Cap-5



Se calentó a 100°C durante 21 horas una mezcla de (R)-2-fenilglicina (1.0 g, 6.62 mmol), 1,4-dibromobutano (1.57 g, 7.27 mmol) y Na_2CO_3 (2.10 g, 19.8 mmol) en etanol (40 ml). La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró, y el filtrado se concentró a vacío. El residuo se disolvió en etanol y se acidificó con HCl 1N hasta pH 3-4, y el componente volátil se eliminó a vacío. El material bruto resultante se purificó por una HPLC de fase inversa (agua/metanol/TFA) proporcionando la sal TFA de *Cap*-5 como una espuma blanca semiviscosa (1.0 g). RMN de ^1H (DMSO-d_6. δ = 2.5. 500 MHz) δ 10.68 (s ancho, 1H), 7.51 (m, 5H),

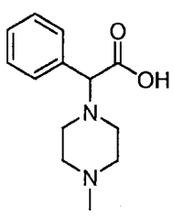
5.23 (s, 1H), 3.34 (s ancho aparente, 2H), 3.05 (s ancho aparente, 2H), 1.95 (s ancho aparente, 4H); T_R = 0.30 min (Cond. I); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; encontrado 206.25.

Cap-6



La sal TFA de *Cap*-6 se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el proceso de preparación de *Cap*-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); T_R = 0.32 min (Cond. I); >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; encontrado 222.20; EMAR: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; encontrado 222.1121.

Cap-7



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

Se añadió gota a gota una solución en CH_2Cl_2 (200 ml) de cloruro de p-toluenosulfonilo (8.65 g, 45.4 mmol) a

una solución (-5 °C) en CH_2Cl_2 (200 ml) de 2-hidroxi-2-fenilacetato de (S)-bencilo (10.0 g, 41.3 mmol), trietilamina (5.75 ml, 41.3 mmol) y 4-dimetilaminopiridina (0.504 g, 4.13 mmol), mientras se mantenía la temperatura de -5 °C a 0 °C. La reacción se agitó a 0 °C durante 9 horas, y luego se almacenó en un congelador (-25 °C) durante 14 horas. Se dejó descongelar hasta temperatura ambiente y se lavó con agua (200 ml), HCl 1N (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 2-fenil-2-(tosiloxi)acetato de bencilo como un aceite viscoso que solidificó en reposo (16.5 g). La integridad quiral del producto no se verificó y dicho producto se usó en la etapa siguiente sin purificación adicional. RMN de ^1H (DMSO-d_6. δ = 2.5, 500 MHz) δ 7.78 (d, J = 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, J = 12.5, 1H), 5.10 (d, J = 12.5, 1H), 2.39 (s, 3H). T_R = 3.00 (Cond. III); índice de homogeneidad >90%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; encontrado 419.04.

Se calentó a 65°C durante 7 horas una solución en THF (75 ml) de 2-fenil-2-(tosiloxi)acetato de bencilo (6.0 g, 15.1 mmol), 1-metilpiperazina (3.36 ml, 30.3 mmol) y N,N-diisopropiletilamina (13.2 ml, 75.8 mmol). Se dejó enfriar la reacción hasta temperatura ambiente y el componente volátil se eliminó a vacío. El residuo se repartió entre acetato de etilo y agua, y la fase orgánica se lavó con agua y salmuera,

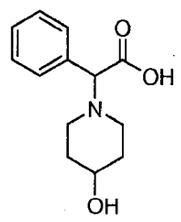
se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó por cromatografía instantánea (gel de sílice, etilo acetato) proporcionando 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo como un aceite viscoso anaranjado-pardo (4.56 g). El análisis HPLC quiral (CHIRALCEL®OD-H) indicó que la muestra es una mezcla de estereoisómeros en una relación 38.2 a 58.7, La separación de los estereoisómeros 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 estereoisómero-1(1.474 g) y el estereoisómero-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). T_R = 2.10 (Cond. III); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; encontrado 325.20,

Se añadió una solución en metanol (10 ml) de cualquiera de los estereoisómeros 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 *Cap*-7, contaminado con ácido fenilacético como una espuma color castaño (867.6 mg; la masa es superior al rendimiento teórico). El producto se usó en la etapa siguiente sin purificación adicional. RMN de ^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), 2.19 (s, 3H); T_R = 0.31 (Cond. II); índice de homogeneidad >90%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; encontrado 235.15; EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; encontrado 235.1440,

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

Cap-8

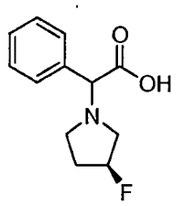


8a: enantiómero-1
8b: enantiómero-2

La separación estereoisomérica del intermediario 2-

(4-hidroxipiperidin-1-il)-2-fenil acetato de bencilo se efectuó usando las siguientes condiciones: se disolvió el compuesto (500 mg) en etanol/heptano (5 ml/45 ml). La solución resultante se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 2 cm ID x 25 cm de longitud, 10 µm) eluyendo con 80:20 de heptano/etanol a 10 ml/min, controlada a 220 nm, proporcionando 186.3 mg de estereoisómero-1 y 209.1 mg de estereoisómero-2 como aceites viscosos amarillo claro. Estos ésteres bencílicos se sometieron a hidrogenación de conformidad con la preparación de *Cap*-7 proporcionando *Cap*-8: RMN de ^{1}H (DMSO-d_6, δ = 2.5, 500 MHz) 7.40 (d, J = 7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). T_R = 0.28 (Cond. II); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; encontrado 236.07; EMAR: Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; encontrado 236.1283.

Cap-9

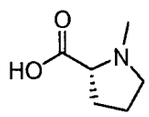


9a: diastereómero-1
9b: diastereómero -2

La separación diastereomérica del intermediario 2-((S)-3-fluoropirrolidin-1-il)-2-fenilacetato de bencilo se efectuó usando las siguientes condiciones: se separó el éster (220 mg) en una columna HPLC quiral (Chiracel OJ-H, 0.46 cm

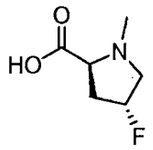
ID x 25 cm L, 5 µm) eluyendo con 95% de CO_2/5% de metanol con 0.1% de TFA, a una presión de $10x10^5$ Pa, 70 ml/min de Velocidad de flujo, y una temperatura de 35 °C. Se concentró el eluato de HPLC para los estereoisómeros respectivos y el residuo se disolvió en CH_2Cl_2 (20 ml) y se lavó con un medio acuoso (10 ml agua + 1 ml de solución saturada de $NaHCO_3$). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 92.5 mg de fracción-1 y 59.6 mg de fracción-2, Estos ésteres bencílicos se sometieron a hidrogenación de conformidad con la preparación de *Cap*-7 para preparar Caps 9a y 9b. *Cap*-9a (diastereómero-1; la muestra es una sal TFA como resultado de la purificación en una HPLC de fase inversa usando H_2O/metanol/TFA como solvente): RMN de ^1H (DMSO-d_6, δ = 2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d de m, J = 53.7, 1H), 5.09 (s ancho, 1H), 3.84-2.82 (m ancho, 4H), 2.31-2.09 (m, 2H). T_R = 0.42 (Cond. I); índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14; *Cap*-9b (diastereómero-2): RMN de ^1H (DMSO-d_6, δ = 2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d de m, J = 55.9. 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). T_R = 0.44 (Cond. I); CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14.

Cap-10



A una solución de D-prolina (2.0 g, 17 mmol) y formaldehído (2.0 ml de 37% en peso en H_2O) en metanol (15 ml) se añadió una suspensión de Pd al 10%/C (500 mg) en metanol (5 ml). La mezcla se agitó bajo un 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 *Cap*-10 como un sólido blanquecino (2.15 g). RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, J = 9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). T_R = 0.28 (Cond. II); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; encontrado 129.96.

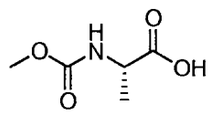
Cap-11



Una mezcla de ácido (2S,4R)-4-fluoropirrolidin-2-carboxílico (0.50 g, 3.8 mmol), formaldehído (0.5 ml de 37% en peso en H_2O), HCl 12 N (0.25 ml) y Pd al 10%/C (50 mg) en metanol (20 ml) se agitó bajo un 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 *Cap*-11 como un sólido blanco (337.7 mg). RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) 5.39 (d m, *J* = 53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, *J* = 31.5, 13.5, 4.5, 1H), 3.33 (dd, *J* = 25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). T_R = 0.28 (Cond. II); índice de homogeneidad >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; encontrado 148.06.

Cap-12 (igual que Cap 52)

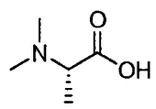


Ácido (S)-2-(metoxicarbonilamino)propanoico

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 combinada se secó (Na_2SO_4), se filtró y se concentró a vacío proporcionando un aceite incoloro (2.58 g). Se purificaron 500 mg de este material por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando 150 mg de *Cap*-12 como un aceite incoloro. RMN de ^1H (DMSO-d_6, δ =

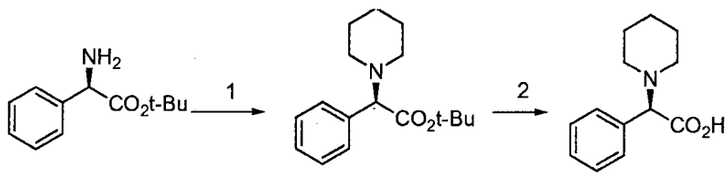
2.5, 500 MHz) 7.44 (d, J = 7.3, 0.8H), 7.10 (s ancho, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

Cap-13



Se agitó una mezcla de L-alanina (2.5 g, 28 mmol), formaldehído (8.4 g, 37% en peso), HCl 1N (30 ml) y Pd al 10%/C (500 mg) en metanol (30 ml) en una atmósfera de hidrógeno (344.64 kPa) durante 5 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío proporcionando la sal HCl de *Cap*-13 como un aceite que solidificó en reposo a vacío (4.4 g; la masa es superior al rendimiento teórico). El producto se usó sin purificación adicional. RMN de ^{1}H (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.1 (s ancho, 1H), 4.06 (q, J = 7.4, 1H), 2.76 (s, 6H), 1.46 (d, J = 7.3, 3H).

Cap-14



Cap-14

Ácido (R)-2-fenil-2-(piperidin-1-il)acético

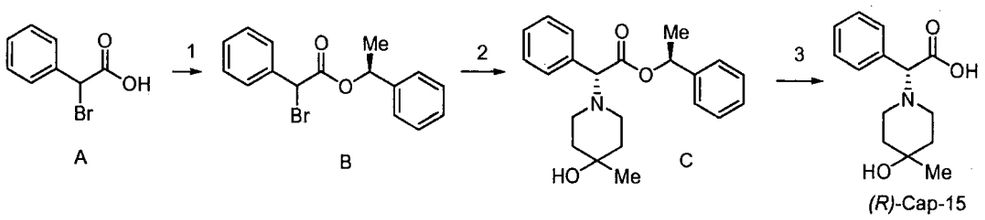
Etapa 1: Una mezcla éster *terc*-butílico de (R)-(-)-D-fenilglicina (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) y ácido acético (0.352 ml,

6.15 mmol) se agitó en metanol a 0 °C. A esta mezcla se añadió dialdehído glutárico (2.23 ml, 12.3 mmol) gota a gota durante 5 minutos. La mezcla de reacción se agitó calentando hasta temperatura ambiente y se continuó agitando a la misma temperatura durante 16 horas. El solvente se eliminó seguidamente y el residuo se repartió con NaOH acuoso al 10% y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta sequedad proporcionando un aceite transparente. Este material se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando el éster intermediario (2.70 g, 56%) como un aceite transparente. RMN de ^1H (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 10.9 Hz, 1H), 2.99 (t, J = 11.2 Hz, 1H), 2.59 (t, J = 11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, J = 1.82 Hz, 3H), 1.40 (s, 9H). CL/EM: Anal. Calculado para $C_{17}H_{25}NO_2$: 275; encontrado: 276 $(M+H)^+$.

Etapa 2: A una solución agitada del éster intermediario (1.12 g, 2.88 mmol) en diclorometano (10 ml) se añadió TFA (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se concentró hasta sequedad dando un aceite amarillo claro. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0.1%). Las fracciones apropiadas se reunieron y se concentraron hasta sequedad a

vacío. El residuo se disolvió entonces en una cantidad mínima de metanol y se aplicó en cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos se aclararon con metanol (40 ml) y luego eluyó el compuesto deseado usando amoníaco 2M en metanol (50 ml). Las fracciones que contenían producto se reunieron y concentraron y el residuo se suspendió en agua. La liofilización de esta solución proporcionó el compuesto del título (0.492 g, 78%) como un sólido amarillo claro. RMN de ^{1}H (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (s ancho, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (s ancho, 2H). CL/EM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

Cap-15



Etapa 1: 2-Bromo-2-fenilacetato de (S)-1-feniletilo: A una mezcla de ácido α-bromofenilacético (10.75 g, 0.050 mol), (S)-(-)-1-feniletanol (7.94 g, 0.065 mol) y DMAP (0.61 g, 5.0 mmol) en diclorometano seco (100 ml) se añadió EDCI sólido (12.46 g, 0.065 mol) todo de una vez. La solución resultante se agitó a temperatura ambiente en Ar durante 18 horas y luego se diluyó con acetato de etilo, se lavó (H_2O x 2, salmuera), se secó (Na_2SO_4), se filtró y se concentró dando un aceite amarillo pálido. La cromatografía

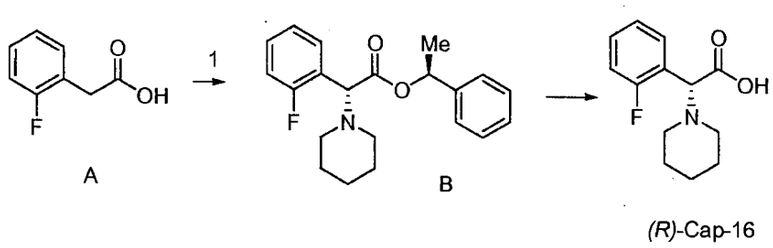
instantánea (SiO_2/ hexano-etilo acetato, 4:1) de este aceite proporcionó el compuesto del título (11.64 g, 73%) como un sólido blanco. RMN de ^1H (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, *J* = 6.6 Hz, 0.5H), 5.94 (q, *J* = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, *J* = 6.6 Hz, 1.5H), 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 título (0.306 g, 60%) como un sólido blanco y luego el correspondiente isómero (S,S)(0.120 g, 23%), también como un sólido blanco. Isómero (S,R): RMN de ^1H (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, *J* =

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

Etapa 3: ácido (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0.185 g, 0.52 mmol) en diclorometano (3 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando el compuesto del título (como sal TFA) como un sólido azulado pálido (0.128 g, 98%). CLEM: Anal. Calculado para $C_{14}H_{19}NO_3$: 249; encontrado: 250 $(M+H)^+$.

Cap-16



(R)-Cap-16

Etapa 1: 2-(2-fluorofenil)acetato de (S)-1-

feniletilo: Una mezcla de ácido 2-fluorofenilacético (5.45 g, 35.4 mmol), (S)-1-feniletanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) y DMAP (0.561 g, 4.60 mmol) en CH_2Cl_2 (100 ml) se agitó a temperatura ambiente durante 12 horas. El solvente 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 combinadas 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 título 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).

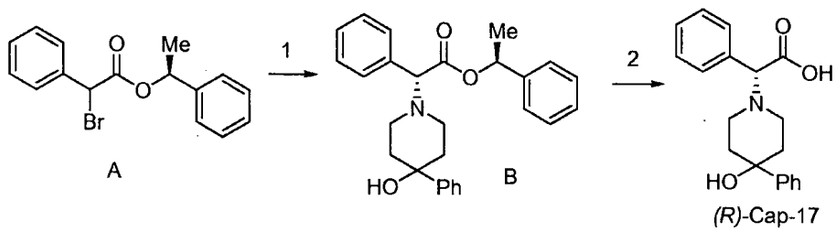
Etapa 2: 2-(2-Fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo): A una solución de 2-(2-fluorofenil)acetato de (S)-1-feniletilo (5.00 g, 19.4 mmol) en THF (1200 ml) a 0°C se añadió DBU (6.19 g, 40.7 mmol) y la solución se dejó calentar hasta temperatura ambiente mientras se agitaba durante 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 combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. Al residuo se añadió piperidina (5.73 ml, 58.1 mmol) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles se concentraron entonces a vacío y el residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-30% de éter dietílico-hexano) proporcionando una mezcla pura de diastereoisómeros (relación 2:1 por RMN de ^1H) como un aceite amarillo (2.07 g, 31%), junto con material de partida sin reaccionar (2.53 g, 51%). Otra cromatografía de la mezcla diastereomérica (BIOTAGE®/ 0-10% éter dietílico-tolueno) proporcionó el compuesto del título como un aceite incoloro (0.737 g, 11%). RMN de ^1H (400 MHz, CD_3OD) δ 7.52 (ddd, J = 9.4, 7.6, 1.8 Hz, 1H), 7.33 - 7.40 (m, 1), 7.23 - 7.23 (m, 4H), 7.02 - 7.23 (m, 4H), 5.86 (q, J = 6.6 Hz, 1H), 4.45 (s, 1H), 2.39 - 2.45 (m, 4H), 1.52 - 1.58 (m, 4H), 1.40 - 1.42 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H). CLEM: Anal. Calculado para $C_{21}H_{24}FNO_2$: 341; encontrado: 342 $(M+H)^+$.

Etapa 3: ácido (R)-2-(2-fluorofenil)-2-(piperidin-1-il)acético: Una mezcla de 2-(2-

fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo) (0.737 g, 2.16 mmol) y $Pd(OH)_2$ al 20%/C (0.070 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (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 título 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). CLEM: Anal. Calculado para $C_{13}H_{16}FNO_2$: 237; encontrado: 238 $(M+H)^+$.

Cap-17

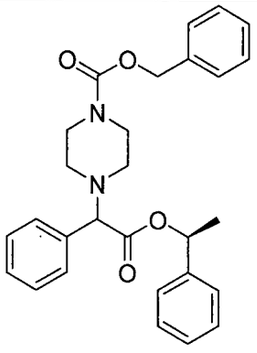


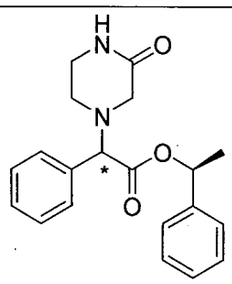
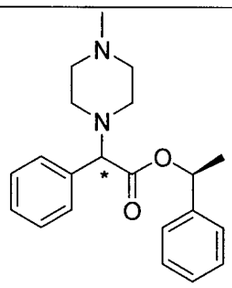
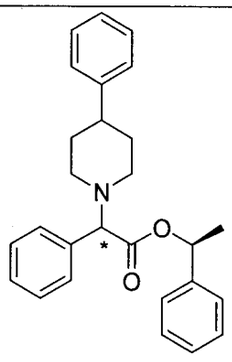
Etapa 1: (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1.50 g, 4.70 mmol) en THF (25 ml) se añadió trietilamina (1.31 ml, 9.42 mmol), seguido por yoduro de tetrabutilamonio (0.347 g, 0.94 mmol). La mezcla de reacción se agitó a temperatura ambiente

durante 5 minutos y luego se añadió una solución de 4-fenil-4-hidroxipiperidina (1.00 g, 5.64 mmol) en THF (5 ml). La mezcla se agitó durante 16 horas y luego se diluyó con acetato de etilo (100 ml), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó en una columna de gel de sílice (acetato de etilo 0-60%-hexano) proporcionando una mezcla aproximadamente 2:1 de diastereoisómeros, como se juzgó por RMN de ^1H. La separación de esos isómeros se llevó a cabo usando cromatografía de fluido supercrítico (CHIRALCEL® OJ-H, 30 x 250mm; 20% etanol en CO_2 a 35 °C), dando primero el isómero (R) del compuesto del título (0.534 g, 27%) como un aceite amarillo y luego el isómero (S) correspondiente (0.271 g, 14%), también como un aceite amarillo. Isómero (S,R): 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). CLEM: 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). CLEM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$.

Los ésteres siguientes se prepararon de una forma similar:

Intermediario-17a		Diastereómero 1: RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 1.36 (d, *J*=6.41 Hz, 3H) 2.23 - 2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, *J*=6.71 Hz, 1H) 7.15 - 7.52 (m, 15H). CLEM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458.22; Encontrado: 459.44 $(M+H)^+$. Diastereómero 2: RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27 - 2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19 - 7.27 (m, 3H) 7.27 - 7.44 (m, 10H). CLEM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458.22; Encontrado: 459.44 $(M+H)^+$.

Intermediario -17b		Diastereómero 1: TR = 11.76 min (Condición II); CLEM: Análisis calculado para: C20H22N2O3 338.16 Encontrado: 339.39 (M+H)+; Diastereómero 2: TR = 10.05 min (Condición II); CLEM: Análisis calculado para: C20H22N2O3 338.16; Encontrado: 339.39 (M+H)+.
Intermediario -17c		Diastereómero 1: T_R = 4.55 min (Condición I); CLEM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338.20 Encontrado: 339.45 $(M+H)^+$; Diastereómero 2: T_R = 6.00 min (Condición I); CLEM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338.20 Encontrado: 339.45 $(M+H)^+$.
Intermediario -17d		Diastereómero 1: T_R = 7.19 min (Condición I); CLEM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399.22 Encontrado: 400.48 $(M+H)^+$; Diastereómero 2: T_R = 9.76 min (Condición I); CLEM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399.22 Encontrado: 400.48 $(M+H)^+$.

Condiciones de SFC quiral para determinar el tiempo de retención:

Condición I

Columna: Columna CHIRALPAK® AD-H, 4.62X50 mm, 5µm

solventes: 90% de CO_2 - metanol al 10% con DEA al 0.1%

Temp: 35 °C

Presión: 15 MPa

Velocidad de flujo: 2.0 ml/min.

UV monitoreado a 220 nm

Inyección: 1.0 mg/3 ml de metanol

Condición II

Columna: Columna CHIRALCEL® OD-H, 4.62X50 mm, 5µm

solventes: 90% de CO_2 - metanol al 10% con DEA al 0.1%

Temp: 35 °C

Presión: 15 MPa

Velocidad de flujo: 2.0 ml/min.

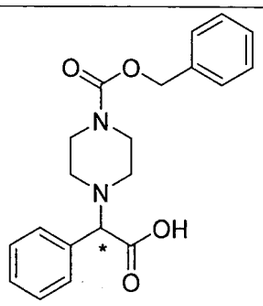
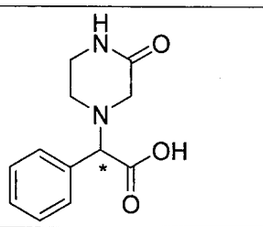
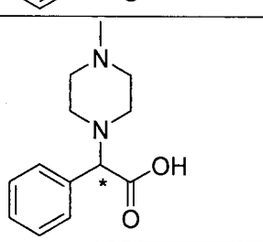
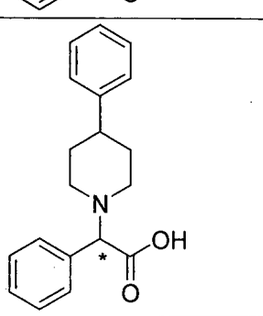
UV monitoreado a 220 nm

Inyección: 1.0 mg/ml de metanol

Cap-17, Etapa 2: ácido (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0.350 g, 0.84 mmol) en diclorometano (5 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando el compuesto del título

(como sal TFA) como un sólido blanco (0.230 g, 88%). CLEM: Anal. Calculado para $C_{19}H_{21}NO_3$: 311.15; encontrado: 312 $(M+H)^+$.

Los siguientes ácidos carboxílicos se prepararon en forma ópticamente pura de una forma similar:

Cap-17a		T_R = 2.21 (Condición II); RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 2.20 - 2.35 (m, 2H) 2.34 - 2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06 - 7.53 (m, 10H). CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_4$ 354.16; Encontrado: 355.38 $(M+H)^+$.
Cap-17b		T_R = 0.27 (Condición III); CLEM: Análisis calculado para: $C_{12}H_{14}N_2O_3$ 234.10; Encontrado: 235.22 $(M+H)^+$.
Cap-17c		T_R = 0.48 (Condición II); CLEM: Análisis calculado para: $C_{13}H_{18}N_2O_2$ 234.14; Encontrado: 235.31 $(M+H)^+$.
Cap-17d		T_R = 2.21 (Condición I); CLEM: Análisis calculado para: $C_{19}H_{21}NO_2$ 295.16; Encontrado: 296.33 $(M+H)^+$.

Condiciones de CLEM para determinar el tiempo de retención

Condición I

Columna: PHENOMENEX® Luna 4.6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Velocidad de flujo = 4 ml/min

Longitud de onda = 220

solvente A = metanol al 10% - H_2O al 90% - TFA al 0.1%

solvente B = metanol al 90% - H_2O al 10% - TFA al 0.1%

Condición II

Columna: Waters-Sunfire 4.6 X 50 mm S5

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Velocidad de flujo = 4 ml/min

Longitud de onda = 220

solvente A = metanol al 10% - H_2O al 90% - TFA al 0.1%

solvente B = metanol al 90% - H_2O al 10% - TFA al 0.1%

Condición III

Columna: PHENOMENEX® 10µ 3.0 X 50 mm

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

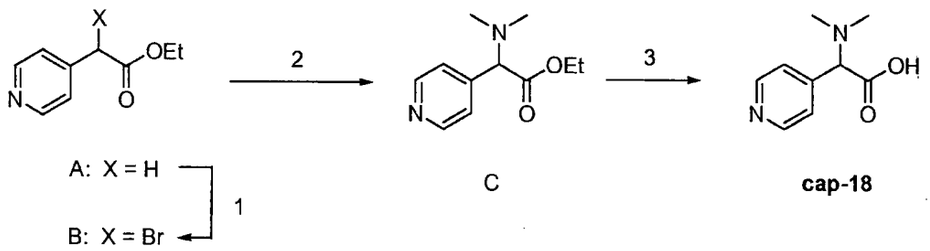
Velocidad de flujo = 4 ml/min

Longitud de onda = 220

solvente A = metanol al 10% - H_2O al 90% - TFA al 0.1%

solvente B = metanol al 90% - H_2O al 10% - TFA al 0.1%

Cap-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 argón se añadió DBU (0.99 ml, 6.66 mmol). La mezcla de reacción se dejó calentar hasta temperatura ambiente durante 30 minutos y luego se enfrió hasta -78 °C. A esta mezcla se añadió CBr_4 (2.21 g, 6.66 mmol) y se continuó agitando a -78 °C durante 2 horas. Seguidamente la mezcla de reacción se inactivó con NH_4Cl acuoso saturado y se separaron las fases. La fase orgánica se lavó (salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío. El aceite amarillo resultante se purificó inmediatamente por cromatografía instantánea (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del título (1.40 g, 95%) como un aceite amarillo algo inestable. RMN de ^1H (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.6, 1.8 Hz, 2H), 7.45

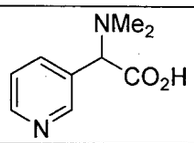
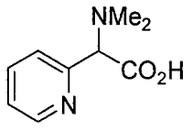
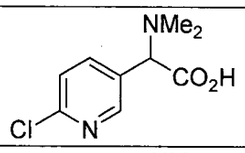
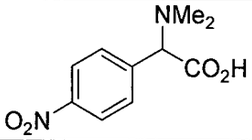
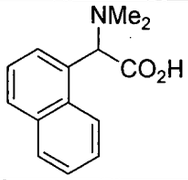
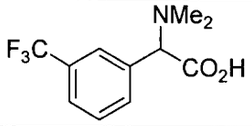
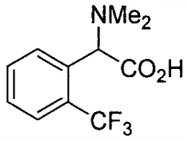
(dd, J = 4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). CLEM: Anal. Calculado para $C_9H_{10}BrNO_2$: 242, 244; encontrado: 243, 245 $(M+H)^+$.

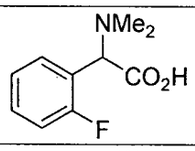
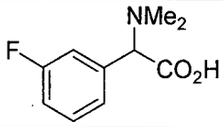
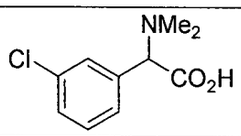
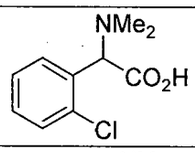
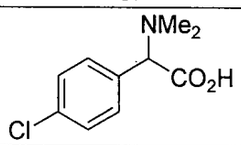
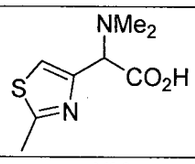
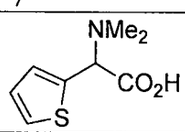
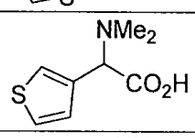
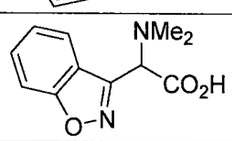
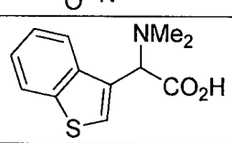
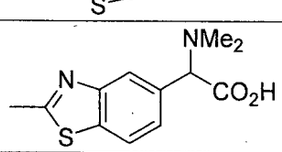
Etapa 2: 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo: A una solución de 2-(4-piridil)-2-bromoacetato de (R,S)-etilo (1.40 g, 8.48 mmol) en DMF (10 ml) a temperatura ambiente se añadió dimetilamina (2M en THF, 8.5 ml, 17.0 mmol). Después de completarse la reacción (que se juzgó por cromatografía en capa fina) los volátiles se eliminaron a vacío y el residuo se purificó por cromatografía instantánea (columna BIOTAGE®, 40+M SiO_2; 50%-100% de acetato de etilo-hexano) proporcionando el compuesto del título (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). CLEM: Anal. Calculado para $C_{11}H_{16}N_2O_2$: 208; encontrado: 209 $(M+H)^+$.

Etapa 3: ácido (R,S)-2-(4-piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.200 g, 0.960 mmol) en una mezcla de THF-metanol-H_2O (1:1:1, 6 ml) se añadió LiOH en polvo (0.120 g, 4.99 mmol) a temperatura ambiente. La solución se agitó durante 3 horas y luego se acidificó hasta pH 6 usando HCl 1N. La fase acuosa se lavó con acetato de etilo y luego se liofilizó dando el diclorhidrato del compuesto del título como un sólido amarillo (que contenía LiCl). El producto se usó como

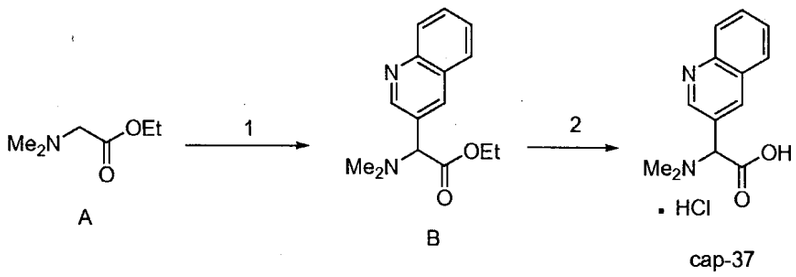
tal en las posteriores etapas. RMN de ^1H (400 MHz, DMSO-d_6) δ 8.49 (d, *J* = 5.7 Hz, 2H), 7.34 (d, *J* = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

Los siguientes ejemplos se prepararon de una forma similar usando el proceso descrito antes;

Cap-19		CLEM: Anal. Calculado para $C_9H_{12}N_2O_2$: 180; encontrado: 181 $(M+H)^+$.
Cap-20		CLEM: sin ionización. RMN de ^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).
Cap-21		CLEM: Anal. Calculado para $C_9H_{11}ClN_2O_2$: 214, 216; encontrado: 215, 217 $(M+H)^+$.
Cap-22		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-23		CLEM: Anal. Calculado para $C_{14}H_{15}NO_2$: 229; encontrado: 230 $(M+H)^+$.
Cap-24		CLEM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-25		CLEM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.

Cap-26		CLEM: Anal. Calculado para C10H12FNO2: 197; encontrado: 198 (M+H)+.
Cap-27		CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-28		CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-29		CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-30		CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-31		CLEM: Anal. Calculado para $C_8H_{12}N_2O_2S$: 200; encontrado: 201 $(M+H)^+$.
Cap-32		CLEM: Anal. Calculado para $C_8H_{11}NO_2S$: 185; encontrado: 186 $(M+H)^+$.
Cap-33		CLEM: Anal. Calculado para $C_8H_{11}NO_2S$: 185; encontrado: 186 $(M+H)^+$.
Cap-34		CLEM: Anal. Calculado para $C_{11}H_{12}N_2O_3$: 220; encontrado: 221 $(M+H)^+$.
Cap-35		CLEM: Anal. Calculado para $C_{12}H_{13}NO_2S$: 235; encontrado: 236 $(M+H)^+$.
Cap-36		CLEM: Anal. Calculado para $C_{12}H_{14}N_2O_2S$: 250; encontrado: 251 $(M+H)^+$.

Cap-37

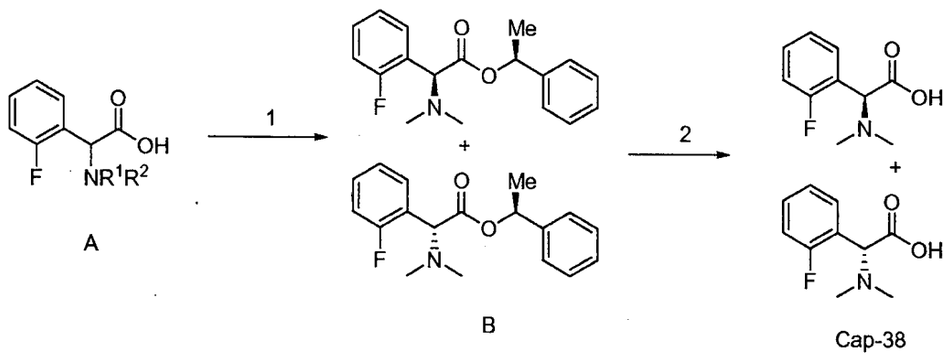


Etapa 1: 2-(quinolin-3-il)-2-(N,N-dimetilamino)-acetato de (R,S)-etilo: Una mezcla de N,N-dimetilaminoacetato de etilo (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) y tolueno (10 ml) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. 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 combinadas 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 instantánea (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del título (0.128 g, 17%) como un aceite naranja. RMN de ^1H (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, J

= 7.0 Hz, 3H). CLEM: Anal. Calculado para $C_{15}H_{18}N_2O_2$: 258; encontrado: 259 $(M+H)^+$.

Etapa 2: Ácido (R,S) 2-(quinolin-3-il)-2-(N,N-dimetilamino)acético: Se calentó una mezcla de 2-(quinolin-3-il)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.122 g, 0.472 mmol) y HCl 6M (3 ml) a 100 °C durante 12 horas. El solvente se eliminó a vacío proporcionando el diclorhidrato del compuesto del título (0.169 g, >100%) como una espuma amarillo claro. El material sin purificar se usó en las etapas siguientes sin purificación adicional. CLEM: Anal. Calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.

Cap-38



Etapa 1: 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo) y 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletil): A una mezcla de ácido (RS)-2-(dimetilamino)-2-(2-fluorofenil)acético (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) y (S)-1-feniletanol (2.09 g, 17.15 mmol) en CH_2Cl_2 (40 ml) se añadió EDCI (3.29 g,

17.15 mmol) y la mezcla se dejó agitando a temperatura ambiente durante 12 horas. El solvente 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 combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-50% de éter dietílico-hexano). La mezcla diastereomérica pura resultante se separó entonces por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando primero (R)-2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-1-fenetilo (0.501 g, 13%) y luego (S)-2-(dimetilamino)-2-(2-fluorofenil)-acetato de (S)-1-fenetilo (0.727 g. 18%), ambas como sus sales TFA. isómero (S,R): RMN de ^1H (400 MHz, CD_3OD) δ 7.65 - 7.70 (m, 1H), 7.55-7.60 (ddd, *J* = 9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, *J* = 6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, *J* = 6.5 Hz, 3H). CLEM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$; isómero (S,S): RMN de ^1H (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, *J* = 8.5, 1.5 Hz, 2H), 6.02 (q, *J* = 6.5 Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, *J* = 6.5 Hz, 3H). CLEM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301;

encontrado: 302 $(M+H)^+$.

Etapa 2: ácido (R)-2-(dimetilamino)-2-(2-fluorofenil)acético: Una mezcla de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo), sal TFA (1.25 g, 3.01 mmol) y 20% de $Pd(OH)_2/C$ (0.125 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (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 compuesto del título como un sólido incoloro (0.503 g, 98%). RMN de ^1H (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.

El isómero S se podía obtener a partir de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletilo), sal TFA de una forma similar.

Cap-39

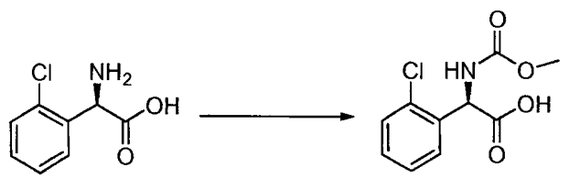


cap-39

Una mezcla de (R)-(2-clorofenil)glicina (0.300 g, 1.62 mmol), formaldehído (solución acuosa al 35%, 0.80 ml, 3.23 mmol) y 20% de $Pd(OH)_2/C$ (0.050 g) se sometió a hidrogenación a temperatura ambiente y presión atmosférica

(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-TFA al 0.1%) dando la sal TFA del compuesto del título ácido (R)-2-(dimetilamino)-2-(2-clorofenil)acético como un aceite incoloro (0.290 g, 55%). RMN de ^1H (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.

Cap-40

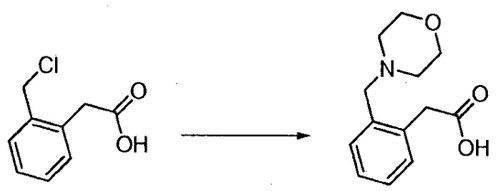


cap-40

A una solución enfriada en hielo de (R)-(2-clorofenil)glicina (1.00 g, 5.38 mmol) y NaOH (0.862 g, 21.6 mmol) en H_2O (5.5 ml) se añadió cloroformiato de metilo (1.00 ml, 13.5 mmol) gota a gota. La mezcla se dejó agitando a 0 °C durante 1 hora y luego se acidificó mediante la adición de HCl concentrado (2.5 ml). La mezcla se extrajo con acetato de etilo (2x) y la fase orgánica combinada se lavó (H_2O, salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío dando el compuesto del título ácido (R)-2-(metoxicarbonilamino)-2-(2-clorofenil)acético como una espuma

amarillo-naranja (1.31 g, 96%). RMN de ^1H (400 MHz, CD_3OD) δ 7.39 - 7.43 (m, 2H), 7.29 - 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). CLEM: Anal. Calculado para $C_{10}H_{10}ClNO_4$: 243; encontrado: 244 $(M+H)^+$.

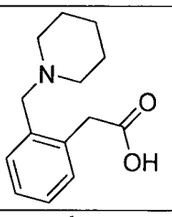
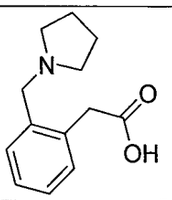
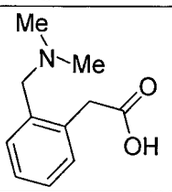
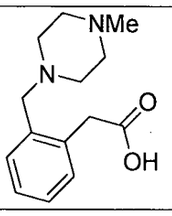
Cap-41



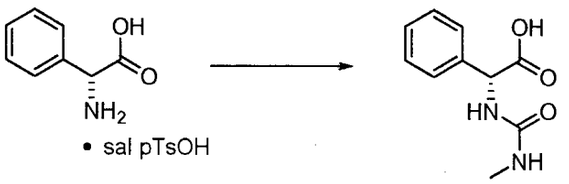
cap-41

A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2.00 g, 10.8 mmol) en THF (20 ml) se añadió morfolina (1.89 g, 21.7 mmol) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó entonces con acetato de etilo y se extrajo con H_2O (2x). La fase acuosa se liofilizó y el residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-10% de metanol-CH_2Cl_2) dando el compuesto del título ácido 2-(2-(morfolinometil)fenil)acético como un sólido incoloro (2.22 g, 87%). RMN de ^1H (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (s ancho, 4H), 3.68 (s, 2H), 3.14 (s ancho, 4H). CLEM: Anal. Calculado para $C_{13}H_{17}NO_3$: 235; encontrado: 236 $(M+H)^+$.

Los siguientes ejemplos se prepararon de igual modo usando el proceso descrito para Cap-41:

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

Cap-45a

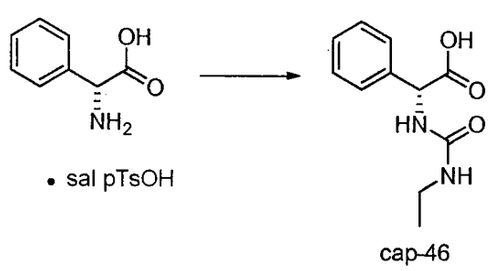


Cap-45a

Se añadió HMDS (1.85 ml, 8.77 mmol) a una suspensión de p-toluenosulfonato del ácido (R)-2-amino-2-fenilacético (2.83 g, 8.77 mmol) en CH_2Cl_2 (10 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió isocianato de metilo (0.5 g, 8.77 mmol) en una porción continuando la agitación durante 30 minutos. La reacción se

inactivó mediante adición de H_2O (5 ml) y se filtró el precipitado resultante, se lavó con H_2O y n-hexanos, y se secó a vacío. Se recuperó ácido (R)-2-(3-metilureido)-2-fenilacético (1.5 g; 82 %) como un sólido blanco y se usó sin purificación adicional. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.67 (s, 1H). CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_3$ 208.08 encontrado 209.121 $(M+H)^+$; HPLC PHENOMENEX® C-18 3.0 x 46 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, T_R = 1.38 min, índice de homogeneidad 90 %.

Cap-46

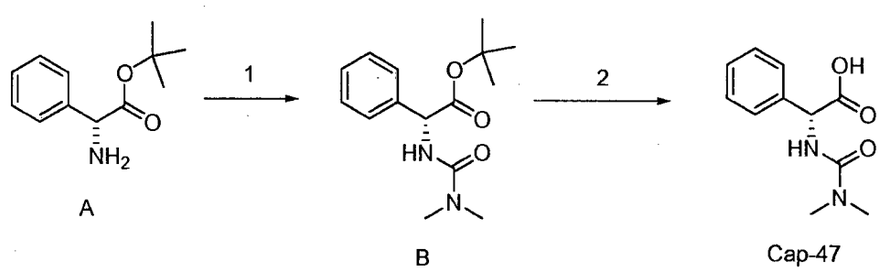


cap-46

El producto deseado se preparó de conformidad con el proceso descrito para *Cap*-45a. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 0.96 (t, *J*=7.17 Hz, 3H) 2.94 - 3.05 (m, 2H) 5.17 (d, *J*=7.93 Hz, 1H) 6.05 (t, *J*=5.19 Hz, 1H) 6.60 (d, *J*=7.63 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.68 (s, 1H). CLEM: Anal. Calculado para $C_{11}H_{14}N_2O_3$ 222.10 encontrado 223.15 $(M+H)^+$.

HPLC XTERRA® C-18 3.0 × 506 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.2% H_3PO_4, B = 10% de agua, 90% de metanol, 0.2% H_3PO_4, T_R = 0.87 min, índice de homogeneidad 90 %.

Cap-47

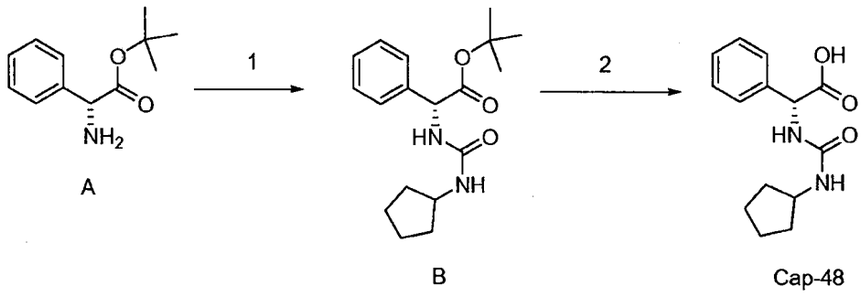


Etapa 1: 2-(3,3-dimetilureido)-2-fenilacetato de (R)-*terc*-butilo: A una solución agitada de (R)-terc-butil-2-amino-2-fenilacetato (1.0 g, 4.10 mmol) y base de Hunig (1.79 ml, 10.25 mmol) en DMF (40 ml) se añadió cloruro de dimetilcarbamoilo (0.38 ml, 4.18 mmol) gota a gota durante 10 minutos. Después 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). CLEM: Anal. Calculado para $C_{15}H_{22}N_2O_3$ 278.16 encontrado 279.23 $(M+H)^+$; HPLC PHENOMENEX® LUNA C-18 4.6 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, T_R = 2.26 min, índice de homogeneidad 97%.

Etapa 2: ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-*terc*-butilo (0.86 g, 3.10 mmol) en CH_2Cl_2 (250 ml) se añadió TFA (15 ml) gota a gota y la solución resultante se agitó a ta durante 3 horas. El compuesto deseado precipitó entonces en solución con una mezcla de EtOAC:Hexanos (5:20), se separó por filtración y se secó a presión reducida. Se aisló ácido (R)-2-(3,3-dimetilureido)-2-fenilacético como un sólido blanco (0.59g, 86%) y se usó sin purificación posterior. RMN de ^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). CLEM: Anal. Calculado para $C_{11}H_{14}N_2O_3$: 222.24; encontrado: 223.21 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.2% H_3PO_4, B = 10% de agua, 90% de metanol, 0.2% H_3PO_4, T_R = 0.75 min, índice de homogeneidad 93%.

Cap-48



Etapa 1: 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*terc*-butilo: A una solución agitada de clorhidrato del ácido (R)-2-amino-2-fenilacético (1.0 g, 4.10 mmol) y base de Hunig (1.0 ml, 6.15 mmol) en DMF (15 ml) se añadió isocianato de ciclopentilo (0.46 ml, 4.10 mmol) gota a gota y durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se suspendió en acetato de etilo. La fase orgánica se lavó con H_2O y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*terc*-butilo como un aceite opaco (1.32 g; 100 %) y se usó sin purificación posterior. RMN de ^1H (500 MHz, CD_3Cl-D) δ ppm 1.50 - 1.57 (m, 2H) 1.58 - 1.66 (m, 2H) 1.87 - 1.97 (m, 2H) 3.89 - 3.98 (m, 1H) 5.37 (s, 1H) 7.26 - 7.38 (m, 5H). CLEM: Anal. Calculado para $C_{18}H_{26}N_2O_3$ 318.19 encontrado 319.21 $(M+H)^+$; HPLC XTERRA® C-18 3.0 x 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.1%

de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, T_R = 2.82 min, índice de homogeneidad 96%.

Etapa 2: Ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*terc*-butilo (1.31 g, 4.10 mmol) en CH_2Cl_2 (25 ml) se añadió TFA (4 ml) y trietilsilano (1.64 ml; 10.3 mmol) gota a gota, y la solución resultante se agitó a temperatura ambiente durante 6 horas. Los componentes volátiles se eliminaron a presión reducida y el producto bruto se recristalizó en acetato de etilo/pentanos proporcionando ácido (R)-2-(3-ciclopentilureido)-2-fenilacético como un sólido blanco (0.69 g, 64%). RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 1.17 - 1.35 (m, 2H) 1.42 - 1.52 (m, 2H) 1.53 - 1.64 (m, 2H) 1.67 - 1.80 (m, 2H) 3.75 - 3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24 - 7.40 (m, 5H) 12.73 (s, 1H). CLEM: Anal. Calculado para $C_{14}H_{18}N_2O_3$: 262.31; encontrado: 263.15 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.2% H_3PO_4, B = 10% de agua, 90% de metanol, 0.2% H_3PO_4, T_R = 1.24 min, índice de homogeneidad 100%.

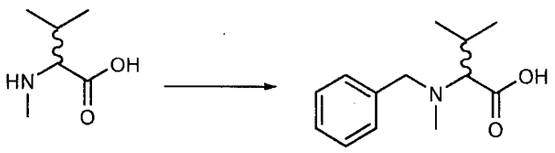
Cap-49



cap-49

A una solución agitada de ácido 2-(bencilamino)acético (2.0 g, 12.1 mmol) en ácido fórmico (91 ml) se añadió formaldehído (6.94 ml, 93.2 mmol). Después de cinco horas a 70 °C, la mezcla de reacción se concentró a presión reducida hasta 20 ml y precipitó un sólido blanco. Después de filtrar, las aguas madres se recogieron y se concentró además a presión reducida proporcionando el producto bruto. La purificación por HPLC preparativa de fase inversa (XTERRA® 30 X 100 mm, detección a 220 nm, Velocidad de flujo 35 ml/min, 0 a 35% de B durante 8 min; A = 90% de agua, 10 % de metanol, 0.1% de TFA, B = 10% de agua, 90 % de metanol, 0.1% de TFA) proporcionó el compuesto del título ácido 2-(bencil(metil)-amino)acético como su sal TFA (723 mg, 33%) como una cera incolora. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29 - 7.68 (m, 5H). CLEM: Análisis calculado para: $C_{10}H_{13}NO_2$ 179.09; Encontrado: 180.20 $(M+H)^+$.

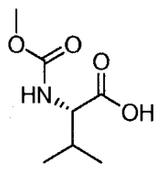
Cap-50



Cap-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico(0.50 g, 3.81 mmol) en agua (30 ml) se añadió K_2CO_3 (2.63 g, 19.1 mmol) y cloruro de bencilo (1.32 g, 11.4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se extrajo con acetato de etilo (30 ml x 2) y la fase acuosa se concentró a presión reducida proporcionando el producto bruto que se purificó por HPLC preparativa de fase inversa (XTERRA® 30 x 100mm, detección a 220 nm, Velocidad de flujo 40 ml/min, 20 a 80% de B durante 6 min; A = 90% de agua, 10 % de metanol, 0.1% de TFA, B = 10% de agua, 90 % de metanol, 0.1% de TFA) proporcionando ácido 2-(bencil(metil)amino)-3-metilbutanoico, sal TFA (126 mg, 19%) como una cera incolora. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33 - 2.48 (m, 1H) 2.54 - 2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29 - 7.65 (m, 5H). CLEM: Análisis calculado para: $C_{13}H_{19}NO_2$ 221.14; Encontrado: 222.28 $(M+H)^+$.

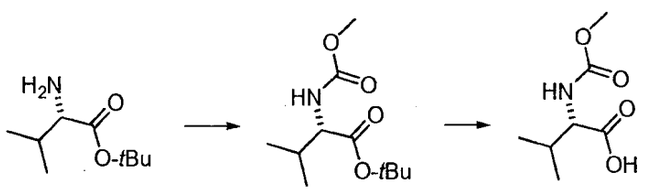
Cap-51



Ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico

Se añadió Na_2CO_3 (1.83g, 17.2 mmol) a una solución de NaOH (33 ml de 1M/H_2O, 33 mmol) de L-valina (3.9 g, 33.29 mmol) y la solución resultante se enfrió con baño de hielo-agua. Se añadió gota a gota durante 15 minutos cloroformiato de metilo (2.8 ml, 36.1 mmol), se retiró el baño de enfriamiento y la mezcla de reacción se agitó a temperatura ambiente durante 3.25 horas. La mezcla de reacción se lavó con éter (50 ml, 3x), y la fase acuosa se enfrió con un baño de hielo-agua y se acidificó con HCl concentrado hasta un pH de 1-2, y se extrajo con CH_2Cl_2 (50 ml, 3x). La fase orgánica se secó ($MgSO_4$) y se evaporó a vacío proporcionando *Cap*-51 como un sólido blanco (6 g). RMN de ^1H para el rotámero dominante (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, J = 8.6, 1H), 3.84 (dd, J = 8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; encontrado 176.0922.

Cap 51 (ruta alternativa)



Ácido (S)-metoxicarbonilamino)-3-metilbutanoico

Se añadió DIEA (137.5 ml, 0.766 mol) a una suspensión de clorhidrato de 2-amino-3-metilbutanoato de (*S*)-*terc*-butilo (75.0 g, 0.357 mol) en THF (900 ml), y la mezcla se enfrió hasta 0 °C (baño de hielo/agua). Se añadió gota a gota durante 45 minutos cloroformiato de metilo (29.0 ml, 0.375 mol), se retiró el baño de enfriamiento y la mezcla heterogénea se agitó a temperatura ambiente durante 3 h. El solvente se eliminó a presión reducida y el residuo se repartió entre EtOAc y agua (1 litro de cada uno). La fase orgánica se lavó con H_2O (1 l) y salmuera (1 l), se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El material bruto se hizo pasar a través de una almohadilla corto de gel de sílice (1 kg), eluyendo con hexanos (4 l) y EtOAc:hexanos 15:85 (4 l) proporcionando 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-*terc*-butilo como un aceite transparente (82.0 g, 99% de rendimiento). RMN de ^1H (500 MHz, DMSO-d_6, δ = 2.5 ppm) 7.34 (d, J = 8.6, 1 H), 3.77 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.05 (m, 1 H), 1.39 (s, 9 H), 0.83 - 0.92 (m, 6 H). RMN de ^{13}C (126

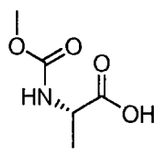
MHz, DMSO-d_6, δ = 39.2 ppm) 170.92, 156.84, 80.38, 60.00, 51.34, 29.76, 27.62, 18.92, 17.95, CL/EM: $[M+Na]^+$ 254.17.

Se añadieron ácido trifluoroacético (343 ml, 4.62 mol) y Et_3SiH (142 ml, 0.887 mol) secuencialmente a una solución de 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-*terc*-butilo (82.0 g, 0.355 mol) en CH_2Cl_2 (675 ml), y la mezcla se agitó a temperatura ambiente durante 4 h. El componente volátil se eliminó a presión reducida y el aceite resultante se trituró con éter de petróleo (600 ml) proporcionando un sólido blanco, que se filtró y se lavó con hexanos (500 ml) y éter de petróleo (500 ml). La recristalización en EtOAc/éter de petróleo proporcionó *Cap-51* como cristales a modo de escamas blancos (54.8 g, 88 % de rendimiento). PF = 108.5-109.5 °C. RMN de ^1H (500 MHz, DMSO-d_6, δ = 2.5 ppm) 12.52 (s, 1 H), 7.31 (d, J = 8.6, 1 H), 3.83 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.07 (m, 1 H), 0.86 (dd, J = 8.9. 7.0, 6 H). RMN de ^{13}C (126 MHz, DMSO-d_6, δ = 39.2 ppm) 173.30, 156.94, 59.48, 51.37, 29.52, 19.15, 17.98, CL/EM: $[M+H]^+$ = 176.11, Análisis calculado para $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Encontrado: C, 48.17; H, 7.55; N, 7.99. Rotación óptica: $[\alpha]_D$ = -4.16 (12.02 mg/ml; MeOH). Pureza

óptica: >99.5 % ee. Nota: la valoración de la pureza óptica se realizó en el derivado éster metílico de *Cap-51*, que se preparó según un protocolo de esterificación normalizado en $TMSCHN_2$ (benceno/MeOH). Condiciones del análisis de HPLC: columna, CHIRALPAK® AD-H (4.6 x 250mm, 5μm); solvente, heptano al 95%/IPA al 5% (isocrático); velocidad de flujo, 1 ml/min; temperatura, 35 °C; UV monitoreado a 205 nm.

[Nota: Cap 51 también se podía adquirir de Flamm.]

Cap-52 (Igual que Cap-12)



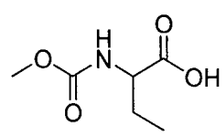
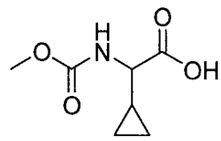
Ácido (S)-2-(metoxicarbonilamino)propanoico

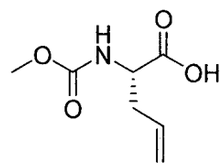
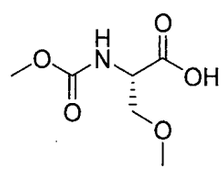
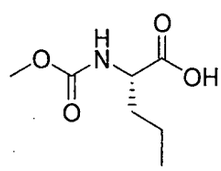
Cap-52 se sintetizó a partir de L-alanina de conformidad con el proceso descrito para la síntesis de *Cap*-51, Con fines caracterizadores, se purificó una porción del material bruto por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando *Cap*-52 como un aceite incoloro viscoso. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.49 (s ancho, 1H), 7.43 (d, J = 7.3, 0.88H), 7.09 (s ancho aparente, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

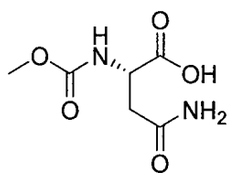
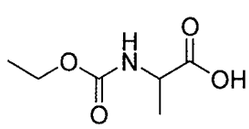
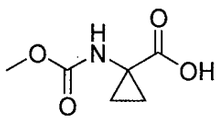
Cap-53 a Cap-64

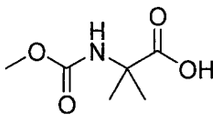
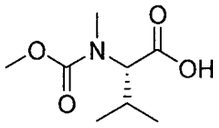
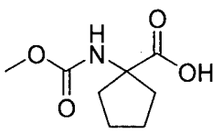
Cap-53 a *Cap*-64 se prepararon a partir de materiales partida apropiados de conformidad con el proceso

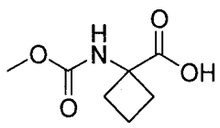
descrito para la síntesis de *Cap*-51, con las modificaciones indicadas si las hubiera.

Cap	Estructura	Datos
Cap-53a: (R) *Cap-53b*: (S) *(ácido (S)-2-(metoxicarbonilamino)-butanoico)*		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (s ancho, 1H), 7.4 (d, *J* = 7.9. 0.9H), 7.06 (s ap., *0*.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, *J* = 7.3, 3H). T_R = 0.77 minutos (Cond. II); CL/EM: Anal. Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06; encontrado 184.07, EMAR Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; encontrado 184.0592,
Cap-54a: (R) *Cap-54b*: (S) *(ácido (S)-2-ciclopropil-2-(metoxicarbonilamino)acético)*		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, *J* = 7.6, 0.9H), 7.25 (s ap., *0*.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). EMAR Calculado para $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; encontrado 174.0771

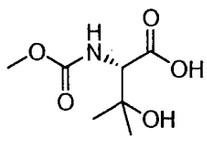
Cap	Estructura	Datos
Cap-55		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, *J* = 8.2, 0.9H), 7.07 (s ap., *0*.1H), 5.80-5.72 (m, 1H), 5.10 (d, *J* = 17.1, 1H), 5.04 (d, *J* = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2.29 (m, 1H).
Cap-56 *ácido (S)-3-metoxi-2-(metoxicarbonilamino)-propanoico*		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, *J* = 8.3, 0.9H), 6.96 (s ap., *0*.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H).
Cap-57		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, *J* = 7.7, 0.08H), 7.40 (d, *J* = 7.9. 0.76H), 7.19 (d, *J* = 8.2, 0.07H), 7.07 (d, *J* = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1.26 (m, 2H), 0.85 (t, *J* = 7.4, 3H). CL (Cond. II): T_R = 1.39 CL/EM: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176.09; encontrado 176.06.

Cap	Estructura	Datos
Cap-58		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (s ancho, 1H), 7.35 (s,1H), 7.31 (d, J = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, J = 15.5, 5.4, 1H), 2.43 (dd, J = 15.6, 8.0, 1H). T_R = 0.16 min (Cond. II); CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; encontrado 191.14.
Cap-59a: (R) *Cap-59b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.49 (s ancho, 1H), 7.40 (d, J = 7.3, 0.89H), 7.04 (s ancho, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, J = 7.3, 3H), 1.15 (t, J = 7.2, 3H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; encontrado 162.0771.
Cap-60		El material bruto se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando un aceite viscoso incoloro que cristalizó en un sólido blanco al exponerse a alto vacío. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.38 (s ancho, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (dos s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; encontrado 160.0604.

Cap	Estructura	Datos
Cap-61		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.27 (s ancho, 1H), 7.40 (s ancho, 1H), 3.50 (s, 3H), 1.32 (s, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; encontrado 162.0765.
Cap-62		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.74 (s ancho, 1H), 4.21 (d, *J* = 10.3, 0.6H), 4.05 (d, *J* = 10.0, 0.4H), 3.62/3.60 (dos singletes, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, *J* = 6.3, 3H), 0.81 (d, *J* = 6.6, 3H). CL/EM: Anal. Calculado para $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; encontrado 188.05.
Cap-63		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para el proceso general.] RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21 (s ancho, 1H), 7.42 (s ancho, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; encontrado 188.19.

Cap	Estructura	Datos
Cap-64		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para el proceso general.] RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.35 (s ancho, 1H), 7.77 (s, 0.82H), 7.56/7.52 (s ancho solapante, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

Cap-65

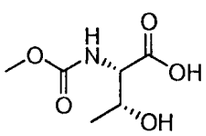


Se añadió cloroformiato de metilo (0.65 ml, 8.39 mmol) gota a gota durante 5 minutos a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 ml de 1M/H_2O, 8.2 mmol) y ácido (*S*)-2-amino-3-hidroxi-3-metilbutanoico (1.04 g, 7.81 mmol). La mezcla de reacción se agitó durante 45 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 3.75 horas. La mezcla de reacción se lavó con CH_2Cl_2, y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta una región de pH de 1-2, El componente volátil se eliminó a vacío y el residuo se suspendió en una mezcla 2:1 de MeOH/CH_2Cl_2 (15 ml) y se filtró, y el filtrado

se sometió a evaporación rotativa proporcionando *Cap*-65 como una espuma semiviscosa blanca (1.236 g). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 6.94 (d, *J* = 8.5, 0.9 H), 6.53 (s ancho, 0.1H), 3.89 (d, *J* = 8.8, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

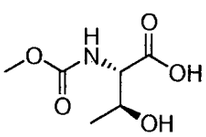
Cap-66 y -67 se prepararon a partir de materiales de partida disponibles comercialmente usando el proceso descrito para la síntesis de *Cap*-65.

Cap-66



RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (s ancho, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Nota: solo se indican las señales dominantes de NH]

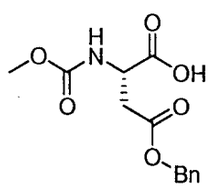
Cap-67



RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (s ancho, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (d ancho, *J* = 0.4, 0.05H), 6.86 (s ancho, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Nota: solo se indican las

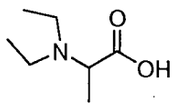
señales dominantes de NH]

Cap-68



Se añadió cloroformiato de metilo (0.38 ml, 4.9 mmol) gota a gota a una mezcla de NaOH 1N (ac) (9.0 ml, 9.0 mmol), $NaHCO_3$ 1M (ac) (9.0 ml, 9.0 mol), éster β-bencílico del ácido L-aspártico (1.0 g, 4.5 mmol) y dioxano (9 ml). La mezcla de reacción se agitó en condiciones ambientales durante 3 horas, y luego se lavó con acetato de etilo (50 ml, 3x). La fase acuosa se acidificó con HCl 12N hasta un pH ~ 1-2, y se extrajo con acetato de etilo (3 x 50 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron a vacío proporcionando *Cap*-68 como un aceite amarillo claro (1.37g; la masa es superior al rendimiento teórico, y el producto se usó sin purificación adicional). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.88 (s ancho, 1H), 7.55 (d, *J* = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, *J* = 12.8, 1H), 5.10 (d, *J* = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 16.2, 5.5, 1H), 2.71 (dd, *J* =16.2, 8.3, 1H). CL (Cond. II): T_R = 1.90 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; encontrado 282.12.

Cap-69a y Cap-69b



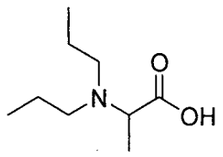
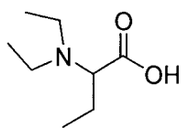
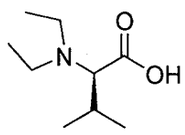
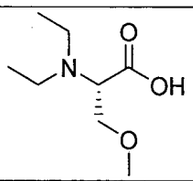
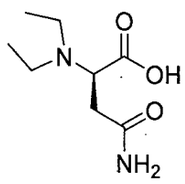
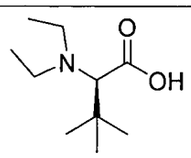
Cap-69a: (R)-enantiómero
Cap-69b: (S)-enantiómero

Se añadió $NaCNBH_3$ (2.416 g, 36.5 mmol) en lotes a una solución acuosa enfriada (~15°C) (17 ml)/MeOH (10 ml) de alanina (1.338 g, 15.0 mmol). Unos pocos minutos después se añadió gota a gota durante 4 minutos acetaldehído (4.0 ml, 71.3 mmol), se retiró entonces el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 6 horas. Se añadió más acetaldehído (4.0 ml) y la reacción se agitó durante 2 horas. Se añadió HCl concentrado lentamente a la mezcla de reacción hasta que el pH alcanzó ~ 1.5, y la mezcla resultante se calentó durante 1 hora a 40°C. La mayoría del componente volátil se eliminó a vacío y el residuo se purificó con una resina de intercambio iónico DOWEX® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado mezclando 18 ml de NH_4OH y 282 ml de agua) proporcionando *Cap*-69 (2.0 g) como un sólido higroscópico blando blanquecino. RMN de ^1H (DMSO-d_6, 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).

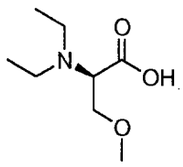
Cap-70 y Cap-74x

Cap-70 a *Cap-74x* se prepararon de conformidad con el proceso descrito para la síntesis de *Cap*-69 usando

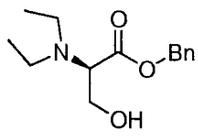
materiales de partida apropiados.

Cap-70a: (R) *Cap-70b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, J = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, J = 7.3, 3H), 0.85 (t, J = 7.5, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.13.
Cap-71a: (R) *Cap-71b*: (S)		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, J = 7.2, 6H), 0.91 (t, J = 7.3, 3H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; encontrado 160.06.
Cap-72		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, J = 7.1, 6H), 0.91 (d, J = 6.5, 3H), 0.85 (d, J = 6.5, 3H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.15.
Cap-73		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (s ancho, 1H), 3.77 (dd, J = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, J = 7.2, 6H).
Cap-74		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, J = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, J = 15.6, 7.0, 1H), 2.36 (dd, J = 15.4, 6.3, 1H), 1.09 (t, J = 7.2, 6H). T_R = 0.125 minutos (Cond. II); CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; encontrado 189.13.
Cap-74x		CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; encontrado 188.21

Cap-75



Cap-75, etapa a

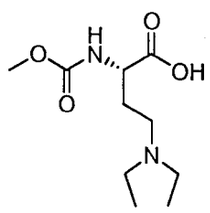


Se añadió $NaBH_3CN$ (1.6 g, 25.5 mmol) a una solución enfriada (baño de hielo/agua) en agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Se añadió acetaldehído (1.5 ml, 12.5 mmol) gota a gota durante 5 min, se retiró el baño de enfriamiento, y la mezcla de reacción se agitó en condiciones ambientales durante 2 horas. La reacción se inactivó cuidadosamente con HCl 12N y se concentró a vacío. El residuo se disolvió en agua y se purificó con una HPLC de fase inversa ($MeOH/H_2O$/TFA) proporcionando la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo como un aceite incoloro viscoso (1.9 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.73 (s ancho, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). CL/EM (Cond. II): T_R = 1.38 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; encontrado 252.19.

Cap-75

Se añadió NaH (0.0727 g, 1.82 mmol, 60%) a una solución enfriada (hielo-agua) en THF (3.0 ml) de la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo (0.3019 g, 0.8264 mmol) preparada antes, y la mezcla se agitó durante 15 min. Se añadió yoduro de metilo (56 µl, 0.90 mmol) y se continuó agitando durante 18 horas dejando que el baño se descongelara hasta condiciones ambiente. La reacción se inactivó con agua y se cargó en un cartucho MCX preacondicionado con MeOH (6 g) y se lavó con metanol seguido por elución del compuesto con NH_3 2N/Metanol. La eliminación del componente volátil a vacío proporcionó *Cap*-75, contaminado con ácido (R)-2-(dietilamino)-3-hidroxipropanoico, como un semisólido amarillo (100 mg). El producto se usó como tal sin purificación adicional.

Cap-76



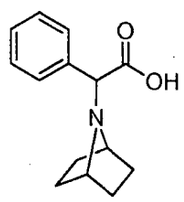
Se añadió $NaCNBH_3$ (1.60 g, 24.2 mmol) en cargas a una solución enfriada (~15 °C) en agua/MeOH (12 ml cada uno) de ácido (*S*)-4-amino-2-(*terc*-butoxicarbonilamino) butanoico (2.17 g, 9.94 mmol). Unos pocos minutos después se añadió acetaldehído (2.7 ml, 48.1 mmol) gota a gota durante 2 min,

se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 3.5 horas. Se añadió más acetaldehído (2.7 ml, 48.1 mmol) y la reacción se agitó durante 20.5 horas. Se eliminó a vacío la mayoría del componente MeOH, y la mezcla restante se trató con HCl concentrado hasta que su pH llegó a ~ 1.0 y luego se calentó durante 2 horas a 40 °C. El componente volátil se eliminó a vacío, y el residuo se trató con HCl 4 M/dioxano (20 ml) y se agitó en condiciones ambientales durante 7.5 horas. El componente volátil se eliminó a vacío y el residuo se purificó con resina de intercambio iónico DOWEX® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado a partir de 18 ml de NH_4OH y 282 ml de agua) proporcionando el intermediario ácido (S)-2-amino-4-(dietilamino)butanoico como un sólido blanquecino (1.73 g).

Se añadió cloroformiato de metilo (0.36 ml, 4.65 mmol) gota a gota durante 11 min a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 ml de 1M/H_2O, 4.6 mmol) y el producto anterior (802.4 mg). La mezcla de reacción se agitó durante 55 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 5.25 horas. La mezcla de reacción se diluyó con un volumen igual de agua y se lavó con CH_2Cl_2 (30 ml, 2x), y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta un pH en torno a 2, El componente

volátil se eliminó a vacío y el material bruto se desbasificó con resina MCX (6.0g; la columna se lavó con agua, y la muestra se eluyó con NH_3 2.0 M/MeOH) proporcionando *Cap*-76 impuro como un sólido blanquecino (704 mg). RMN de ^1H (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, J = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, J = 7.3, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; encontrado 233.24.

Cap-77*a* y -77*b*

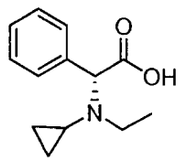


Cap-77a: enantiómero-1
Cap-77b: enantiómero-2

La síntesis de *Cap*-77 se llevó a cabo de conformidad con el proceso descrito para *Cap*-7 usando 7-azabiciclo[2.2.1]heptano para la etapa de desplazamiento SN_2, y efectuando la separación estereoisomérica del intermediario 2-(7-azabiciclo[2.2.1]heptan-7-il)-2-fenilacetato de bencilo usando las siguientes condiciones: el intermediario (303.7 mg) se disolvió en etanol, y la solución resultante se inyectó en una columna HPLC quiral (columna Chiracel AD-H, 30 x 250 mm, 5 um) eluyendo con 90% de CO_2-10% de EtOH a 70 ml/min, y una temperatura de 35 °C proporcionando 124.5 mg de estereoisómero-1 y 133.8 mg de estereoisómero-2. Estos ésteres bencílicos se sometieron a hidrogenación de

conformidad con la preparación de *Cap*-7 proporcionando *Cap*-77: RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (s ancho aparente, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). CL (Cond. I): T_R = 0.67 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; encontrado 232.18, EMAR: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; encontrado 232.1340,

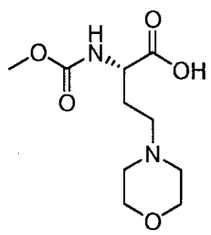
Cap-78



Se añadió $NaCNBH_3$ (0.5828 g, 9.27 mmol) a una mezcla de la sal HCl de ácido (*R*)-2-(etilamino)-2-fenilacético (un intermediario en la síntesis de *Cap*-3; 0.9923 mg, 4.60 mmol) y (1-etoxiciclopropoxi)trimetilsilano (1.640 g, 9.40 mmol) en MeOH (10 ml), y se calentó la mezcla semiheterogénea a 50 °C con un baño de aceite durante 20 horas. Se añadieron más (1-etoxiciclopropoxi)trimetilsilano (150 mg, 0.86 mmol) y $NaCNBH_3$ (52 mg, 0.827 mmol) y la mezcla de reacción se calentó otras 3.5 horas. Se dejó enfriar hasta temperatura ambiente y se acidificó ~ pH entorno a 2 con HCl concentrado, y la mezcla se filtró y el filtrado se evaporó en un evaporador rotatorio. El material bruto resultante se suspendió en *i*-PrOH (6 ml) y se calentó para efectuar la disolución y la parte no disuelta se separó por filtración y

el filtrado se concentró a vacío. Se purificó aproximadamente 1/3 del material bruto resultante con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando la sal TFA de *Cap*-78 como un aceite incoloro viscoso (353 mg). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz; después de intercambio de D_2O): δ 7.56-7.49 (m, 5H), 5.35 (S, 1H), 3.35 (m, 1H), 3.06 (s ancho aparente, 1H), 2.66 (m, 1H), 1.26 (t, J = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). CL (Cond. I): T_R = 0.64 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; encontrado 220.21, EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; encontrado 220.1343.

Cap-79

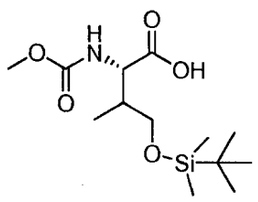


Se burbujeó ozono a través de una solución enfriada (-78 °C) en CH_2Cl_2 (5.0 ml) de *Cap*-55 (369 mg, 2.13 mmol) durante aproximadamente 50 min hasta que la mezcla de reacción alcanzó un tinte de color azul. Se añadió Me_2S (10 gotas de pipeta) y la mezcla de reacción se agitó durante 35 min. Se reemplazó el baño de -78 °C con un baño a -10 °C y se continuó agitando durante otros 30 min, y luego se eliminó el componente volátil a vacío proporcionando un aceite viscoso incoloro.

Se añadió $NaBH_3CN$ (149 mg, 2.25 mmol) a una solución en MeOH (5.0 ml) del material bruto anterior y morfolina (500 µl, 5.72 mmol) y la mezcla se agitó en condiciones ambientales durante 4 horas. Se enfrió hasta temperatura de hielo-agua y se trató con HCl concentrado para llevar el pH a ~2.0, y luego se agitó durante 2.5 horas. El componente volátil se eliminó a vacío, y el residuo se purificó con una combinación de resina MCX (lavado con MeOH; elución con NH_3 2.0 N/MeOH) y una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando *Cap*-79 que contenía una cantidad desconocida de morfolina.

Con el fin de consumir la morfolina contaminante, se disolvió el material anterior en CH_2Cl_2 (1.5 ml) y se trató con Et_3N (0.27 ml, 1.94 mmol) seguido por anhídrido acético (0.10 ml, 1.06 mmol) y se agitó en condiciones ambientales durante 18 horas. Se añadieron THF (1.0 ml) y H_2O (0.5 ml) y se continuó agitando durante 1.5 horas. El componente volátil se eliminó a vacío, y el residuo resultante se hizo pasar a través de resina MCX (lavado con MeOH; elución con NH_3 2.0 N/MeOH) proporcionando *Cap*-79 impuro como un aceite viscoso marrón, que se usó para la etapa siguiente sin purificación adicional.

Cap-80a y Cap-80b



Cap-80a: S/S-diastereómero
Cap-80b: S/R-diastereómero

Se añadió $SOCl_2$ (6.60 ml, 90.5 mmol) gota a gota durante 15 min a una mezcla enfriada (hielo-agua) de ácido (S)-3-amino-4-(benciloxi)-4-oxobutanoico (10.04g, 44.98 mmol) y MeOH (300 ml), se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 29 horas. Se eliminó la mayor parte del componente volátil a vacío y el residuo se repartió cuidadosamente entre EtOAc (150 ml) y solución saturada de $NaHCO_3$, La fase acuosa se extrajo con EtOAc (150 ml, 2x), y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 4-metil-2-aminosuccinato de (S)-1-bencilo como un aceite incoloro (9.706g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (t aparente, J = 6.6, 1H), 3.55 (s, 3H), 2.68 (dd, J = 15.9, 6.3, 1H), 2.58 (dd, J = 15.9, 6.8, 1H), 1.96 (s, 2H). CL (Cond. I): T_R = 0.90 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; encontrado 238.22.

Se añadió $Pb(NO_3)_2$ (6.06 g, 18.3 mmol) durante 1 minuto a una solución en CH_2Cl_2 (80 ml) de 4-metil-2-aminosuccinato de (S)-1-bencilo (4.50 g, 19.0 mmol), 9-bromo-

9-fenil-9*H*-fluoreno (6.44 g, 20.0 mmol) y Et_3N (3.0 ml, 21.5 mmol) y la mezcla heterogénea se agitó en condiciones ambientales durante 48 horas. La mezcla se filtró y el filtrado se trató con $MgSO_4$ y se filtró de nuevo y el filtrado final se concentró. El material bruto resultante se sometió a una purificación en BIOTAGE® (350 g gel de sílice, elución con CH_2Cl_2) proporcionando 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo como aceite incoloro muy viscoso (7.93 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, J = 12.4, 1H), 4.51 (d, J = 12.6, 1H), 3.78 (d, J = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, parcialmente traslapado con solvente). CL (Cond. I): T_R = 2.16 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; encontrado 478.19.

Se añadió LiHMDS (9.2 ml de 1.0 M/THF, 9.2 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) THF (50 ml) de 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo (3.907 g, 8.18 mmol) y se agitó durante ~1 horas. Se añadió MeI (0.57 ml, 9.2 mmol) gota a gota durante 8 min a la mezcla y se continuó agitando durante 16.5 horas dejando que el baño de enfriamiento se descongelara hasta temperatura ambiente. Después de inactivar con solución saturada de NH_4Cl (5 ml), se eliminó a vacío la mayor parte del componente orgánico y el residuo se repartió

entre CH_2Cl_2 (100 ml) y agua (40 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se purificó con un BIOTAGE® (350 g gel de sílice; 25% de EtOAc/hexanos) proporcionando 3.65 g de una mezcla de diastereoisómeros 2S/3S y 2S/3R de 4-metil 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de 1-bencilo en una relación ~1.0:0.65 (RMN de ^1H). La estereoquímica del isómero dominante no se determinó en este paso y la mezcla se sometió a la etapa siguiente sin separación. Datos parciales de RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): Diastereómero mayoritario, δ 4.39 (d, J = 12.3, 1H de CH_2), 3.33 (s, 3H, traslapado con señal de H_2O), 3.50 (d, J = 10.9, NH), 1.13 (d, J = 7.1, 3H); Diastereómero minoritario, δ 4.27 (d, J =12.3, 1H de CH_2), 3.76 (d, J = 10.9, NH), 3.64 (s, 3H), 0.77 (d, J = 7.0, 3H). CL (Cond. I): T_R = 2.19 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; encontrado 492.15.

Se añadió hidruro de diisobutilaluminio (20.57 ml de 1.0 M en hexanos, 20.57 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) en THF (120 ml) de 4-metil-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de (2S)-1-bencilo (3.37 g, 6.86 mmol) preparado antes y se agitó a -78 °C durante 20 horas. La mezcla de reacción se separó del baño de enfriamiento y se vertió rápidamente en H_3PO_4 ~1M/H_2O (250 ml) con agitación y la mezcla se extrajo con éter (100 ml, 2x). La fase orgánica combinada se lavó con salmuera, se secó

($MgSO_4$), se filtró y se concentró a vacío. Se preparó una malla de gel de sílice del material bruto y se sometió a cromatografía (25% de EtOAc/hexanos; elución por gravedad) proporcionando 1.1 g de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con alcohol bencílico, como un aceite incoloro viscoso y 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo que contenía el estereoisómero (2S,3R) como una impureza. La muestra anterior se volvió a someter a las mismas condiciones de purificación de cromatografía en columna proporcionando 750 mg de material purificado como una espuma blanca. [Nota: el isómero (2S, 3S) eluye antes que el isómero (2S,3R) en las condiciones anteriores]. Isómero (2S, 3S): RMN de ^1H (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, traslapado con la señal del solvente), 1.58 (m, 1H), 0.88 (d, J = 6.8, 3H). CL (Cond. I): T_R = 2.00 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; encontrado 464.22, Isómero (2S, 3R): RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (d, J = 7.5, 2H), 7.39-7.10 (m, 16H), 4.63 (d, J= 12.1, 1H), 4.50 (t aparente, J = 4.9, 1H), 4.32 (d, J = 12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, J = 9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, J = 6.8, 3H). CL (Cond. I): T_R = 1.92 min; CL/EM:

Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; encontrado 464.52.

Las asignaciones estereoquímicas relativas de los productos de reducción con DIBAL se hicieron basándose en estudios NOE llevados a cabo en derivados lactona preparados a partir de cada isómero usando el siguiente protocolo: Se añadió LiHMDS (50 µl de 1.0 M/THF, 0.05 mmol) a una solución enfriada (hielo-agua) en THF (2.0 ml) de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (62.7 mg, 0.135 mmol), y la mezcla de reacción se agitó a temperatura similar durante ~2 horas. El componente volátil se eliminó a vacío y el residuo se repartió entre CH_2Cl_2 (30 ml), agua (20 ml) y solución acuosa saturada de NH_4Cl (1 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se sometió a una purificación BIOTAGE® (40 g gel de sílice; 10-15% de EtOAc/hexanos) proporcionando (3S,4S)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona como una película incolora de sólido (28.1 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a (3S,4R)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona. Isómero (3S,4S)-lactona: RMN de ^1H (DMSO-d_6, 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 traslapado con la señal del solvente), 2.16 (m, 1H), 0.27 (d, J = 6.6, 3H). CL (Cond. I): T_R = 1.98 min; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.42, Isómero (3S,4R)-lactona: RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.89 (d, J = 7.6, 1H), 7.85 (d, J = 7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, J = 9.1, 4.8, 1H), 3.76 (d, J = 8.8, 1H), 2.96 (d, J = 3.0, NH), 2.92 (dd, J = 6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, J = 7.0, 3H). CL (Cond. I): T_R = 2.03 min; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.49.

Se añadieron TBDEM-Cl (48 mg, 0.312 mmol) seguido por imidazol (28.8 mg, 0.423 mmol) a una solución en CH_2Cl_2 (3 ml) de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (119.5 mg, 0.258 mmol), y la mezcla se agitó en condiciones ambientales durante 14.25 horas. La mezcla de reacción se diluyó entonces con CH_2Cl_2 (30 ml) y se lavó con agua (15 ml), y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó con una BIOTAGE® (40 g gel de sílice; 5% de EtOAc/hexanos) proporcionando 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con impurezas con base de TBDMS, como un aceite incoloro viscoso (124.4 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma

similar a 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo. Isómero (2S,3S)-silil éter: RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, J = 4.1, 1H), 7.80 (d, J = 4.0, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, J = 12.4, 1H), 4.42 (d, J = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, J = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, J = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). CL (Cond. 1, donde el tiempo de ejecución de prolongó hasta 4 min): T_R = 3.26 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; encontrado 578.40, Isómero (2S,3R)-silil éter: RMN de ^{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 horas, recargándose el balón 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

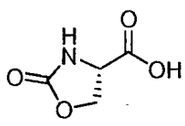
(750 ml). La fase orgánica combinada se concentró y se preparó una malla de gel de sílice a partir del material bruto resultante y se sometió a una cromatografía instantánea (mezcla 8:2:1 de EtOAc/i-PrOH/H_2O) proporcionando ácido (2S,3S)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico como un sólido apelusado blanco (325 mg). Se elaboró 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a ácido (2S,3R)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico. (Isómero 2S,3S)-amino ácido: RMN de ^1H (Metanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76 (dd, J = 10.5, 5.2, 1H), 3.73 (d, J = 3.0, 1H), 3.67 (dd, J = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, J = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44, Isómero (2S,3R)-amino ácido: RMN de ^1H (Metanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, J = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, J = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44.

Se añadieron agua (1 ml) y NaOH (0.18 ml de 1.0 M/H_2O, 0.18 mmol) a una mezcla de ácido (2S,3S)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico (41.9 mg, 0.169 mmol) y Na_2CO_3 (11.9 mg, 0.112 mmol), y se sometió a ultrasonidos durante aproximadamente 1 minuto para efectuar la disolución de los reactivos. La mezcla se enfrió entonces

con un baño de hielo-agua, se añadió cloroformiato de metilo (0.02 ml, 0.259 mmol) se durante 30 s y se continuó con agitación vigorosa a temperatura similar durante 40 minutos y luego a temperatura ambiente durante 2.7 horas. La mezcla de reacción se diluyó con agua (5 ml), se enfrió con baño de hielo-agua y se trató gota a gota con solución acuosa de HCl 1.0 N HCl (~0.23 ml). La mezcla se diluyó adicionalmente con agua (10 ml) y se extrajo con CH_2Cl_2 (15 ml, 2x). La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando *Cap*-80a como un sólido blanquecino. Se elaboró ácido (2S,3R)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico de forma similar a *Cap*-80b. *Cap*-80a: RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 12.57 (s ancho, 1H), 7.64 (d, J = 8.3, 0.3H), 7.19 (d, J = 8.8, 0.7H), 4.44 (dd, J = 8.1, 4.6, 0.3H), 4.23 (dd, J = 8.7, 4.4, 0.7H), 3.56/3.53 (dos singletes, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, traslapado con la señal de t-Bu), 0.79 (d, J = 7, 2.1H), 0.02/0.01/0.00 (tres singletes traslapados, 6H). CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado 328.46, *Cap*-80b: RMN de ^1H ($CDCl_3$, δ = 7.24 ppm, 400 MHz), 6.00 (d ancho, J = 6.8, 1H), 4.36 (dd, J = 7.1, 3.1, 1H), 3.87 (dd, J = 10.5, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, J = 10.6, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, J = 7.1, 3H), 0.90 (s, 9H), 0.08 (s, 6H). CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado

328.53, Los productos brutos se usaron sin purificación adicional.

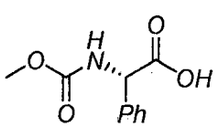
Cap-81



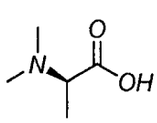
Se preparó de conformidad con el protocolo descrito por Falb et al. *Synthetic Communications* 1993, *23,* 2839.

Cap-82 a Cap-85

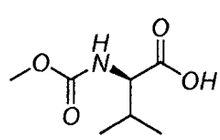
Se sintetizaron *Cap*-82 a *Cap*-85 a partir de los materiales de partida apropiados de conformidad con el proceso descrito para *Cap*-51 o *Cap*-13, Las muestras presentaron perfiles espectrales similares a los de sus estereoisómeros (es decir, *Cap*-4, *Cap*-13, *Cap*-51 y *Cap*-52, respectivamente).



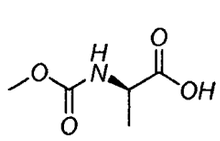
Cap-82



Cap-83

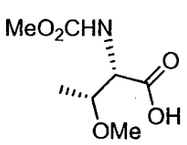


Cap-84



Cap-85

Cap-86

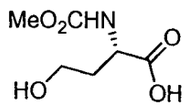


Ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico

A una mezcla de O-metil-L-treonina (3.0 g,

22.55 mmol), NaOH (0.902 g, 22.55 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (1.74 ml, 22.55 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 12 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2x250 ml) y MeOH al 10% en CH_2Cl_2 (250 ml) y las fases orgánicas combinadas se concentraron a vacío proporcionando un aceite incoloro (4.18 g, 97%) que fue de pureza suficiente para usar en las etapas siguientes. RMN de ^1H (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, *J* = 7.7 Hz, 3H). CLEM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 190 $(M-H)^-$.

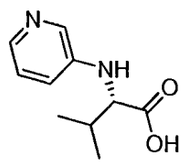
Cap-87



A una mezcla de L-homoserina (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (0.76 ml, 9.79 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 48 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2X250 ml) y las fases orgánicas combinadas se concentraron a vacío proporcionando un sólido incoloro (0.719 g, 28%) que fue de pureza suficiente para usar en las etapas siguientes. RMN de ^1H (400 MHz, $CDCl_3$) δ 4.23 (dd, *J* = 4.5, 9.1 Hz, 1H),

3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 - 2.14 (m, 1H), 1.82 - 1.89 (m, 1H). CLEM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 192 $(M+H)^+$.

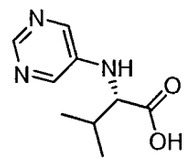
Cap-88



Se calentó una mezcla de L-valina (1.0 g, 8.54 mmol), 3-bromopiridina (1.8 ml, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) y CuI (169 mg, 0.887 mmol) en DMSO (10 ml) a 100°C durante 12h. La mezcla de reacción se enfrió hasta ta, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio iónico (Strata). La suspensión se dejó reposar durante 20 min y se cargó en 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 título se obtuvo como una espuma (1.02 g, 62%). RMN de ^1H (400 MHz, DMSO-d_6) δ 8.00 (s ancho, 1H), 7.68 - 7.71 (m, 1H), 7.01 (s ancho, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 5.75 (s ancho, 1H), 3.54 (s, 1H), 2.04 - 2.06 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). CLEM: Anal. Calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

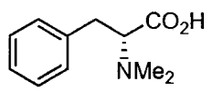
Cap-89



Se calentó a 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 título se obtuvo como una espuma (1.02 g, 62%). La RMN de ^1H (400 MHz, CD_3OD) mostró que la mezcla contenía valina y no se pudo estimar la pureza. El material se usó como tal en las posteriores reacciones. CLEM: Anal. Calculado para $C_9H_{13}N_3O_2$: 195; encontrado: 196 $(M+H)^+$.

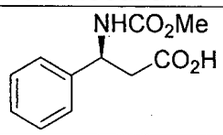
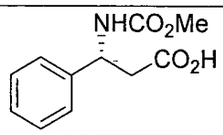
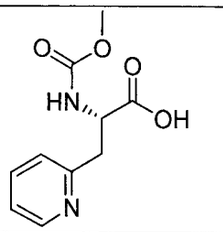
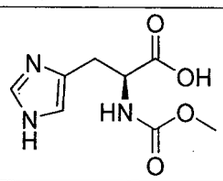
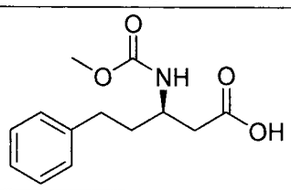
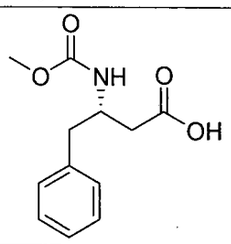
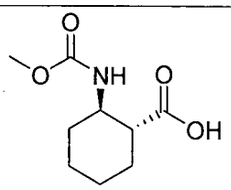
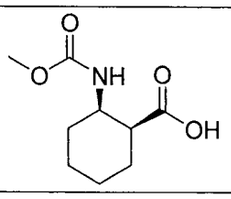
Cap-90

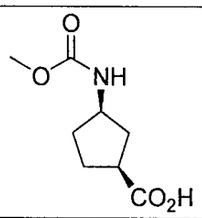
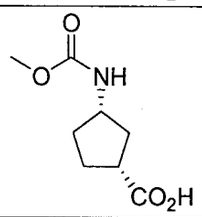
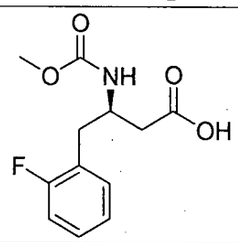
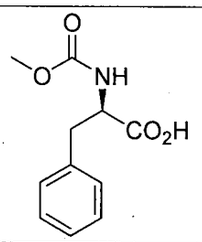
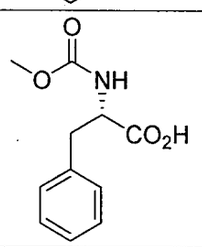
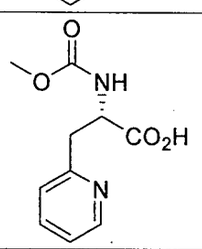


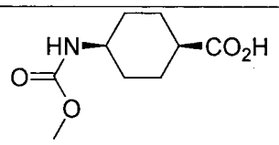
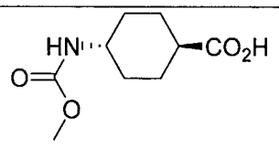
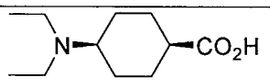
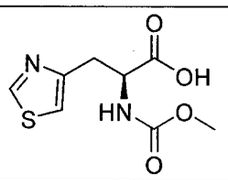
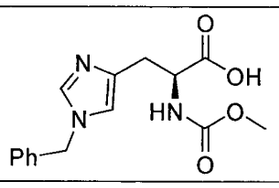
Se preparó *Cap*-90 de conformidad con el proceso descrito para la preparación de *Cap*-1, El material bruto se usó como tal en las etapas posteriores. CLEM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

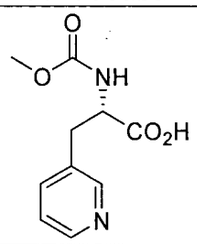
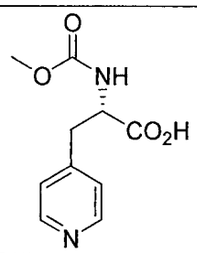
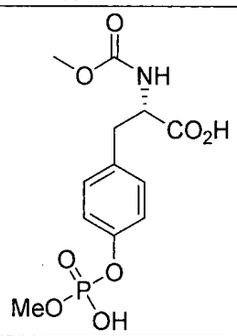
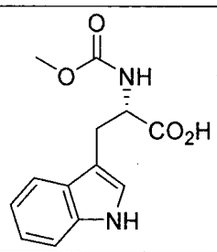
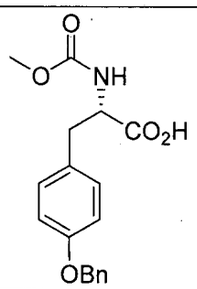
Cap-91 a Cap-116

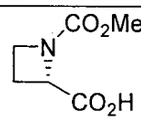
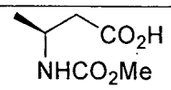
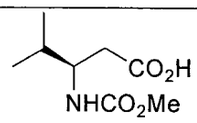
Los siguientes Caps se prepararon de conformidad con el proceso del usado para la preparación del Cap 51, a menos que se indique de otro modo:

Cap	Estructura	CLEM
Cap-91		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-92		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-93		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-94		CLEM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.
Cap-95		CLEM: Anal. Calculado para $C_{13}H_{17}NO_4$: 251; encontrado: 250 $(M-H)^-$.
Cap-96		CLEM: Anal. Calculado para $C_{12}H_{15}NO_4$: 237; encontrado: 236 $(M-H)^-$.
Cap-97		CLEM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 200 $(M-H)^-$.
Cap-98		CLEM: Anal. Calculado para C9H15NO4: 201; encontrado: 202 (M+H)+.

Cap	Estructura	CLEM
Cap-99		RMN de ^1H (400 MHz, CD_3OD) δ 3.88 - 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 - 1.94 (m, 3H), 1.45 - 1.71 (m, 2H).
Cap-99a		RMN de ^1H (400 MHz, CD_3OD) δ 3.88 - 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 - 1.94 (m, 3H), 1.45 - 1.71 (m, 2H).
Cap-100		CLEM: Anal. Calculado para $C_{12}H_{14}NO_4F$: 255; encontrado: 256 $(M+H)^+$.
Cap-101		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-102		CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$
Cap-103		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.

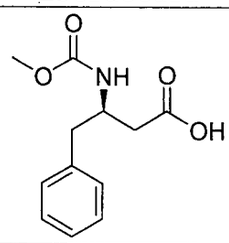
Cap	Estructura	CLEM
Cap-104		RMN de ^1H (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 - 3.53 (m, 1H), 2.66 - 2.69 y 2.44 - 2.49 (m, 1H), 1.91 - 2.01 (m, 2H), 1.62 - 1.74 (m, 4H), 1.51 - 1.62 (m, 2H).
Cap-105		RMN de ^1H (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 - 3.35 (m, 1H, parcialmente oscurecido por Solvente), 2.37 - 2.41 y 2.16 - 2.23 (m, 1H), 1.94 - 2.01 (m, 4H), 1.43 - 1.53 (m, 2H), 1.17 - 1.29 (m, 2H).
Cap-106	 Se preparó a partir de ácido cis-4-aminociclohexanocarboxílico y acetaldehído usando un proceso similar descrito para la síntesis de Cap-2, La sal HCl bruta se hizo pasar a través de MCX (lavado con $MeOH/H_2O/CH_2Cl_2$; elución con NH_3 2N /MeOH) proporcionando un aceite que se disolvió en CH_3CN/H_2O y se liofilizó proporcionando un sólido color castaño.	RMN de ^1H (400 MHz, CD_3OD) 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).
Cap-107		CLEM: Anal. Calculado para $C_8H_{10}N_2O_4S$: 230; encontrado: 231 $(M+H)^+$.
Cap-108		CLEM: Anal. Calculado para $C_{15}H_{17}N_3O_4$: 303; encontrado: 304 $(M+H)^+$.

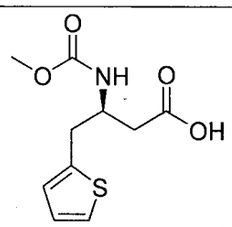
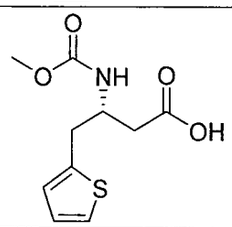
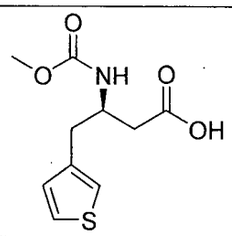
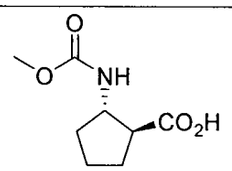
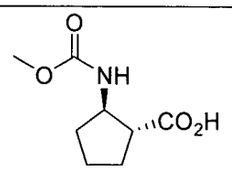
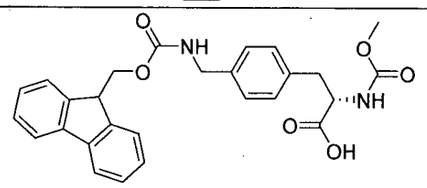
Cap	Estructura	CLEM
Cap-109		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-110		CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-111		CLEM: Anal. Calculado para $C_{12}H_{16}NO_8P$: 333; encontrado: 334 $(M+H)^+$.
Cap-112		CLEM: Anal. Calculado para $C_{13}H_{14}N_2O_4$: 262; encontrado: 263 $(M+H)^+$.
Cap-113		CLEM: Anal. Calculado para $C_{18}H_{19}NO_5$: 329; encontrado: 330 $(M+H)^+$.

Cap	Estructura	CLEM
Cap-114		RMN de ^{1}H (400 MHz, $CDCl_3$) δ 4.82 - 4.84 (m, 1H), 4.00 - 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s ancho, 2H)
Cap-115		RMN de ^{1}H (400 MHz, $CDCl_3$) δ 5.13 (s ancho, 1H), 4.13 (s ancho, 1H), 3.69 (s, 3H), 2.61 (d, *J* = 5.0 Hz, 2H), 1.28 (d, *J* = 9.1 Hz, 3H).
Cap-116		RMN de ^{1}H (400 MHz, $CDCl_3$) δ 5.10 (d, *J* = 8.6 Hz, 1H), 3.74 - 3.83 (m, 1H), 3.69 (s, 3H), 2.54 - 2.61 (m, 2H), 1.88 (sept, *J* = 7.0 Hz, 1H), 0.95 (d, *J* = 7.0 Hz, 6H).

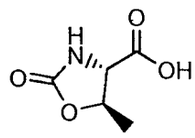
Cap-117 a Cap-123

Para la preparación de *Cap*-117 a *Cap*-123 los Boc aminoácidos se obtuvieron de suministradores comerciales y se desprotegieron por tratamiento con TFA al 25% en CH_2Cl_2. Después de completarse la reacción que se juzgó por CLEM se eliminaron los solventes a vacío y se carbamoiló la sal TFA correspondiente del aminoácido con cloroformiato de metilo de conformidad con el proceso descrito para el *Cap*-51.

Cap	Estructura	CLEM
Cap-117		CLEM: Anal. Calculado para $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$.

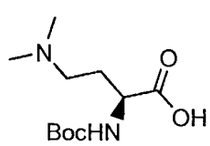
Cap	Estructura	CLEM
Cap-118		CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-119		CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-120		CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-121		RMN de ^1H (400 MHz, $CDCl_3$) δ 4.06 - 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 y 2.66 (s ancho, 1H), 1.86 - 2.10 (m, 3H), 1.64 - 1.76 (m, 2H), 1.44 - 1.53 (m, 1H).
Cap-122		El perfil de RMN de ^1H es similar al de su enantiómero, Cap-121.
Cap-123		CLEM: Anal. Calculado para $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$.

Cap-124



Se llevó a cabo la carbamoilación de la sal clorhidrato de éster *terc*-butílico de L-treonina de conformidad con el proceso para *Cap*-51, La mezcla de reacción bruta se acidificó con HCl 1N hasta pH~1 y la mezcla se extrajo con EtOAc (2X50 ml). Las fases orgánicas combinadas se concentraron a vacío dando un aceite incoloro que solidificó en reposo. La capa acuosa se concentró a vacío y la mezcla resultante de producto y sales inorgánicas del producto y sales inorgánicas se trituró con EtOAc-CH_2Cl_2-MeOH (1:1:0.1) y luego se concentró la fase orgánica a vacío dando un aceite incoloro que por CLEM se mostró que fue el producto deseado. Ambas tandas se reunieron dando 0.52 g de un sólido. RMN de ^1H (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). CLEM: Anal. Calculado para $C_5H_7NO_4$: 145; encontrado: 146 $(M+H)^+$.

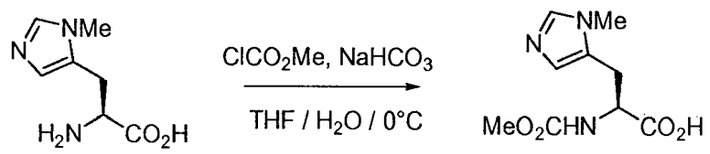
Cap-125



A una suspensión de $Pd(OH)_2$ (20%, 100 mg), formaldehído acuoso (37% en peso, 4 ml), ácido acético (0.5

ml) en metanol (15 ml) se añadió ácido (S)-4-amino-2-(*terc*-butoxicarbonilamino)butanoico (1 g, 4.48 mmol). La reacción se purgó varias veces con hidrógeno y se agitó durante la noche bajo un balón de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró a través de una almohadilla de tierra de diatomeas (CELITE®) y se eliminó el compuesto volátil a vacío. El material resultante bruto se usó como tal para la etapa siguiente. CLEM: Anal. Calculado para $C_{11}H_{22}N_2O_4$: 246; encontrado: 247 $(M+H)^+$.

Cap-126



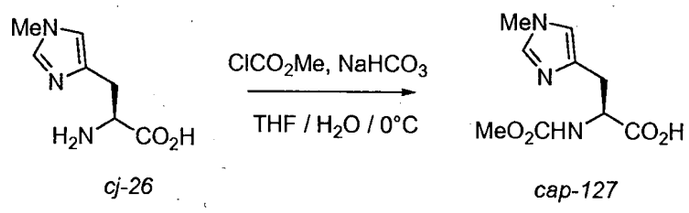
cj-25 *cap-126*

Este proceso es una modificación del que se usó para preparar *Cap*-51, A una suspensión de 3-metil-L-histidina (0.80 g, 4.70 mmol) en THF (10mL) y H_2O (10 ml) a 0°C se añadió $NaHCO_3$ (0.88 g, 10.5 mmol). La mezcla resultante se trató con $ClCO_2Me$ (0.40 ml, 5.20 mmol) y se dejó agitar la mezcla a 0°C. Después de agitar durante aproximadamente. 2h la CLEM no mostró material de partida. La reacción se acidificó hasta pH 2 con HCl 6 N.

Los solventes se eliminaron a vacío y el residuo se suspendió en 20 ml de MeOH al 20% en CH_2Cl_2, La mezcla se filtró y se concentró dando una espuma amarillo claro (1.21

g,). La CLEM y RMN de ^1H mostraron que el material fue una mezcla 9:1 del éster metílico y el producto deseado. Este material se suspendió en THF (10 ml) y H_2O (10 ml), se enfrió hasta 0°C y se añadió LiOH (249.1 mg, 10.4 mmol). Después de agitar aproximadamente 1h la CLEM mostró que no quedaba éster. Seguidamente la mezcla se acidificó con HCl 6N y los solventes se eliminaron a vacío. La CLEM y RMN de ^1H confirmaron la ausencia del éster. El compuesto del título se obtuvo como su sal HCl contaminada con sales inorgánicas (1.91 g, >100%). El compuesto se usó como tal en 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 solvente), 3.12 (dd, *J* = 9.0, 15.6 Hz, 1H). CLEM: Análisis calculado para $C_9H_{13}N_3O_4$: 227.09; encontrado: 228.09 $(M+H)^+$.

Cap-127



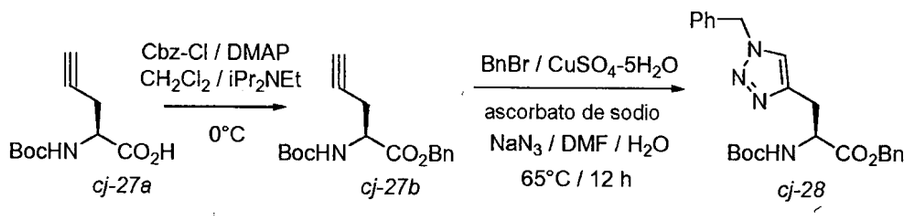
cj-26 *cap-127*

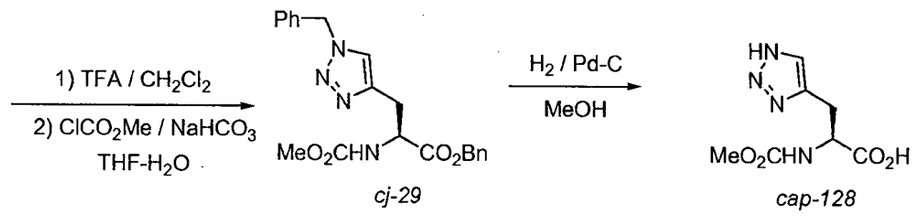
Se preparó *Cap*-127 de conformidad con el proceso para *Cap*-126 anterior partiendo de ácido (S)-2-amino-3-(1-metil-1H-imidazol-4-il)propanoico (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) y $ClCO_2Me$ (0.56 ml, 7.28 mmol). El

compuesto del título se obtuvo como su sal HCl (1.79 g, >100%) contaminado con sales inorgánicas. La CLEM y RMN de ^1H mostraron la presencia de aproximadamente 5% del éster metílico. La mezcla bruta se usó como tal sin purificación adicional. RMN de ^1H (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, *J* = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H).

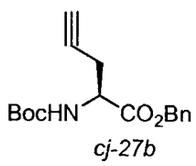
CLEM: Anal. Calculado para $C_9H_{13}N_3O_4$: 227.09; encontrado: 228 $(M+H)^+$.

Preparación de Cap-128





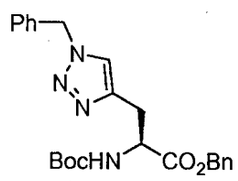
Etapa 1, Preparación de 2-(*terc*-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b).



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 instantánea (TLC 6:1 hex:EtOAc) dando el compuesto del título (1.30 g, 91%) como un aceite incoloro. RMN de ^1H (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d ancho, J = 8.1 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.48 - 4.53 (m, 1H), 2.68 - 2.81 (m, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.44 (s, 9H). CLEM: Anal. Calculado para $C_{17}H_{21}NO_4$: 303; encontrado: 304 $(M+H)^+$.

Etapa 2, Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(*terc*-butoxicarbonilamino)propanoato de (S)-bencilo (cj-28).



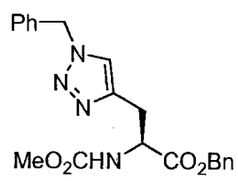
cj-28

A una mezcla de 2-(*terc*-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (0.50 g, 1.65 mmol), ascorbato sódico (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) y NaN_3 (0.13 g, 2.1 mmol) en DMF-H_2O (5 ml, 4:1) a ta se añadió BnBr (0.24 ml, 2.02 mmol) y la mezcla se calentó hasta 65°C. Después de 5 horas, la CLEM indicó baja conversión. Se añadió una porción adicional de NaN_3 (100 mg) y se continuó

calentando durante 12 horas. La reacción se vertió en EtOAc y H_2O y se agitó. Las fases se separaron y la fase acuosa se extrajo tres veces con EtOAc y las fases orgánicas combinadas se lavaron (H_2O x3, salmuera), se secaron (Na_2SO_4), se filtraron y concentraron. El residuo se purificó por cromatografía instantánea (BIOTAGE®, 40+M 0-5% de MeOH en CH_2Cl_2; TLC 3% de MeOH en CH_2Cl_2) proporcionando un aceite amarillo claro que solidificó en reposo (748.3 mg, 104%). La RMN fue consistente con el producto deseado pero sugirió la presencia de DMF. El material se usó como tal sin purificación adicional. RMN de ^1H (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27 - 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, *J* = 1.0, 5.3 Hz, 1H), 3.06 (dd, *J* = 5.3, 14.7 Hz), 2.96 (dd, *J* = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H).

CLEM: Anal. Calculado para $C_{24}H_{28}N_4O_4$: 436; encontrado: 437 $(M+H)^+$.

Etapa 3, Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (cj-29).



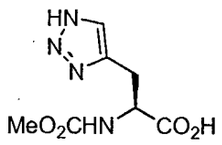
cj-29

Se añadió TFA (4 ml) a una solución de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(*terc*-

butoxicarbonilamino)propanoato de (S)-bencilo (0.52 g, 1.15 mmol) en CH_2Cl_2, La mezcla se dejó agitando a temperatura ambiente durante 2h. La mezcla se concentró a vacío dando un aceite incoloro que solidificó en reposo. Este material se disolvió en THF-H_2O y se enfrió hasta 0°C. Se añadió $NaHCO_3$ sólido (0.25 g, 3.00 mmol) seguido por $ClCO_2Me$ (0.25 ml, 3.25 mmol). Después de agitar durante 1.5h la mezcla se acidificó hasta pH~2 con HCl 6N y luego se vertió en H_2O-EtOAc. Las capas orgánicas se separaron y se extrajo la capa acuosa 2x con EtOAc. Las capas orgánicas combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío dando un aceite incoloro (505.8 mg, 111%, la RMN sugirió la presencia de una impureza no identificada) que solidificó en reposo en la bomba. El material se usó como tal sin purificación posterior. RMN de ^1H (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.27 - 7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 4.32 - 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J = 5.6, 14.7 Hz, 1H), 2.98 (dd, J = 9.6, 14.7 Hz, 1H). CLEM: Anal. Calculado para $C_{21}H_{22}N_4O_4$: 394; encontrado: 395 $(M+H)^+$.

Etapa 4, Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-

il)propanoico (*Cap*-128).

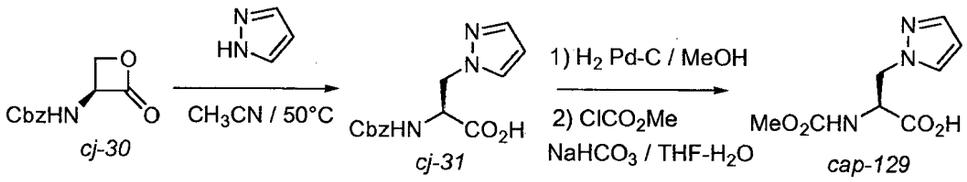


Cap-128

Se sometió 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (502 mg, 1.11 mmol) a hidrogenación en presencia de Pd-C (82 mg) en MeOH (5 ml) a presión atmosférica durante 12h. La mezcla se filtró a través de tierra de diatomeas (CELITE®) y se concentró a vacío. Se obtuvo ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico como una goma incolora (266 mg, 111%) que estaba contaminada con aproximadamente 10% del éster metílico. El material se usó sin purificación adicional.

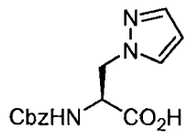
RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.78 (s ancho, 1H), 7.59 9s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 4.19 - 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, *J* = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, *J* = 9.9, 15.0 Hz, 1H). CLEM: Anal. Calculado para $C_7H_{10}N_4O_4$: 214; encontrado: 215 $(M+H)^+$.

Preparación de Cap-129



Etapa 1, Preparación de ácido (S)-2-

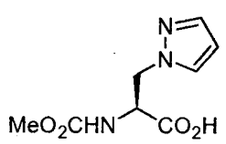
(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico(cj-31).



cj-31

Se calentó una suspensión de 2-oxooxetan-3-ilcarbamato de (S)-bencilo (0.67 g, 3.03 mmol) y pirazol (0.22 g, 3.29 mmol) en CH_3CN (12 ml) a 50°C durante 24h. La mezcla se enfrió hasta TA durante la noche y el sólido se filtró proporcionando ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (330.1 mg). El filtrado se concentró a vacío y luego se trituró con una pequeña cantidad de CH_3CN (aproximadamente 4 ml) proporcionando una segunda tanda (43.5 mg). Rendimiento total 370.4 mg (44%). P.f. 165.5 - 168°C. p.f. lit 168.5 - 169.5 [Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105]. RMN de ^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). CLEM: Anal. Calculado para $C_{14}H_{15}N_3O_4$: 289; encontrado: 290 $(M+H)^+$.

Etapa 2, Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (*Cap*-129).

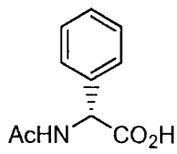


cap-129

Se sometió ácido (S)-2-(benciloxicarbonilamino)-3-

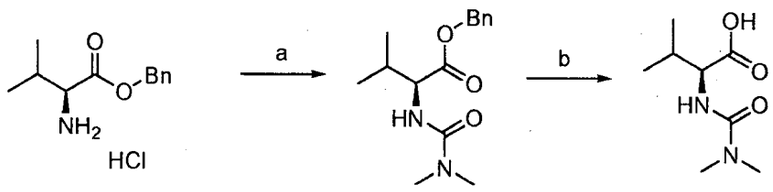
(1H-pirazol-1-il)propanoico (0.20 g, 0.70 mmol) a hidrogenación en presencia de Pd-C (45 mg) en MeOH (5 ml) a presión atmosférica durante 2h. El producto parecía ser insoluble en MeOH, por tanto se diluyó la mezcla de reacción con 5 ml de H_2O y unas pocas gotas de HCl 6N. La solución homogénea se filtró a través de tierra de diatomeas (CELITE®), y el MeOH se eliminó a vacío. La solución restante se congeló y se liofilizó dando una espuma amarilla (188.9 mg). Este material se suspendió en THF-H_2O (1:1, 10 ml) y luego se enfrió hasta 0°C. A la mezcla fría se añadió $NaHCO_3$ (146.0 mg, 1.74 mmol) cuidadosamente (generación de CO_2). Después de cesar la generación de gas (aproximadamente 15 min) se añadió $ClCO_2Me$ (0.06 ml, 0.78 mmol) gota a gota. La mezcla se dejó agitando durante 2 horas y se acidificó hasta pH~2 con HCl 6N y se vertió en EtOAc. Las fases se separaron y la fase acuosa se extrajo con EtOAC (x5). Las fases orgánicas combinadas se lavaron (salmuera), se secaron (Na_2SO_4), se filtraron y concentraron dando el compuesto del título 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). CLEM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.

Cap-130



Se preparó *Cap*-130 por acilación de (R)-fenilglicina disponible comercialmente de forma análoga al proceso dado en: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285,

Cap-131

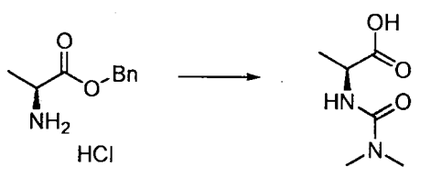


Etapa a: Se añadió cloruro de dimetilcarbamoilo (0.92 ml, 10 mmol) lentamente a una solución de clorhidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2.44 g; 10 mmol) y base de Hunig (3.67 ml, 21 mmol) en THF (50 ml). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16 horas) y se concentró a presión reducida. El residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El aceite amarillo resultante se purificó por cromatografía instantánea, eluyendo con acetato de etilo:hexanos (1:1). Las fracciones recogidas se concentraron a vacío proporcionando

2.35 g (85%) de aceite transparente. RMN de. ^{1}H (300 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.95 Hz, 3H), 0.89 (d, *J*=6.59 Hz, 3H), 1.98-2.15 (m, 1H), 2.80 (s, 6H), 5.01-5.09 (m, *J*=12.44 Hz, 1H), 5.13 (d, *J*=12.44 Hz, 1H), 6.22 (d, *J*=8.05 Hz, 1H), 7.26-7.42 (m, 5H). CL (Cond. 1): T_R = 1.76 min; EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; encontrado 279.03.

Etapa b: A una solución en MeOH (50 ml) del intermediario preparado antes (2.35 g; 8.45 mmol) se añadió Pd/C (10%; 200 mg) y la suspensión negra resultante se llenó con N_2 (3x) y se colocó en 10.13 kPa de H_2, La mezcla se agitó a temperatura ambiente durante la noche y se filtró a través de un filtro de microfibra para separar el catalizador. La solución transparente resultante se concentró entonces a presión reducida obteniendo 1.43 g (89%) de *Cap-131* como espuma blanca, que se usó sin purificación posterior. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.87 (d, *J*=4.27 Hz, 3H), 0.88 (d, *J*=3.97 Hz, 3H), 1.93-2.11 (m, 1H), 2.80 (s, 6H), 3.90 (dd, *J*=8.39, 6.87 Hz, 1H), 5.93 (d, *J*=8.54 Hz, 1H), 12.36 (s, 1H). CL (Cond. 1): T_R = 0.33 min; EM: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; encontrado 189.04.

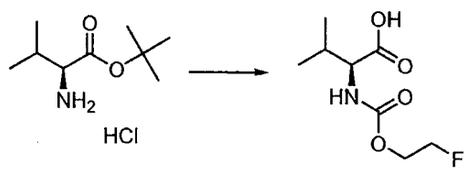
Cap-132



Cap-132 se preparó a partir de clorhidrato de 2-

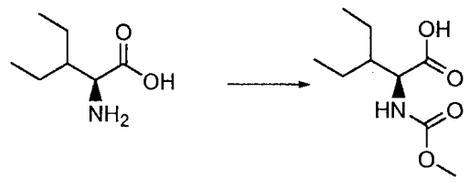
aminopropanoato de (S)-bencilo de conformidad con el proceso descrito para *Cap-131,* RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (ct, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). CL (Cond. 1): T_R = 0.15 min; EM: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; encontrado 161.00.

Cap-133



Cap-133 se preparó a partir de clorhidrato de 2-amino-3-metilbutanoato de (S)-*terc*-butilo y cloroformiato de 2-fluoroetilo de conformidad con el proceso descrito para *Cap-47,* RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.54 (m, 1H), 4.59-4.65 (m, 1H), 7.51 (d, *J* = 8.54 Hz, 1H), 12.54 (s, 1H).

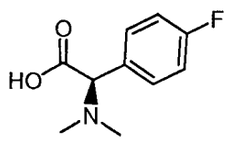
Cap-134



Cap-134 se preparó a partir de (S)-dietil alanina y cloroformiato de metilo de conformidad con el proceso descrito para *Cap-51,* RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63

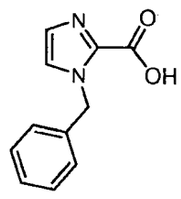
(m, 3H), 4.09 (dd, *J* = 8.85, 5.19 Hz, 1H), 7.24 (d, *J* = 8.85 Hz, 1H), 12.55 (s, 1H). CL (Cond. 2): T_R = 0.66 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$: 204.12; encontrado 204.02.

Cap-135



Una solución de ácido D-2-amino-(4-fluorofenil)acético (338 mg, 2.00 mmol), HCl 1*N* en éter dietílico (2.0 ml, 2.0 mmol) y formalina (37%, 1 ml) en metanol (5 ml) se sometió a hidrogenación bajo un 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 *Cap-135* como una espuma blanca (316 mg, 80%). RMN de ^1H (300 MHz, MeOH-d_4) δ 7.59 (dd, *J* = 8.80, 5.10 Hz, 2H), 7.29 (t, *J* = 8.6 Hz, 2H), 5.17 (s, 1H), 3.05 (s muy ancho, 3H), 2.63 (s muy ancho, 3H); T_R = 0.19 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; encontrado: 198.10.

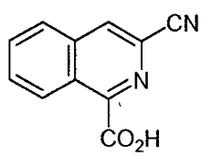
Cap-136



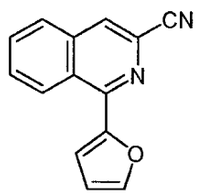
A una suspensión enfriada (-50 °C) de 1-bencil-1*H*-

imidazol (1.58 g, 10.0 mmol) en éter dietílico anhidro (50 ml) en nitrógeno se añadió n-butil litio (2.5 M en hexanos, 4.0 ml, 10.0 mmol) gota a gota. Después de agitar durante 20 minutos a -50 °C, se hizo burbujear dióxido de carbono (pasado a través de Drierite) en la mezcla de reacción durante 10 minutos antes de dejar calentar hasta 25°C. El precipitado pesado que se formó al añadir dióxido de carbono a la mezcla de reacción se filtró proporcionando un sólido blanco higroscópico que se recogió en agua (7 ml), se acidificó hasta pH = 3, se enfrió y se indujo a cristalizar con raspado. La filtración de este precipitado dio un sólido blanco que se suspendió en metanol, se trató con HCl 1*N*/éter dietílico (4 ml) y se concentró a vacío. La liofilización del residuo en agua (5 ml) proporcionó la sal HCl de *Cap-136,* 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); T_R = 0.51 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; encontrado: 203.11.

Cap-137

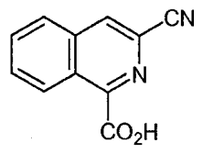


Cap-137, etapa a



Una suspensión de 1-cloro-3-cianoisoquinolina (188 mg, 1.00 mmol; preparada de conformidad con el proceso del documento WO 2003/099274) (188 mg, 1.00 mmol), fluoruro de cesio (303.8 mg, 2.00 mmol), dicloruro de bis(tri-*terc*-butilfosfina)paladio (10 mg, 0.02 mmol) y 2-(tributilestannil)furano (378 µl, 1.20 mmol) en dioxano anhidro (10 ml) en nitrógeno se calentó a 80 °C durante 16 horas de enfriar hasta 25°C y se trató con solución acuosa saturada de fluoruro potásico con agitación vigorosa durante 1 h. La mezcla se repartió entre acetato de etilo y la fase orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación del residuo sobre gel de sílice (elución con acetato de etilo de 0% a 30%/hexanos) proporcionó *Cap-137, etapa a* como un sólido blanco que se usó como tal (230 mg, 105%). T_R = 1.95 min (Condiciones de EM-W2); índice de homogeneidad del 90%; EMBR: Análisis calculado para $[M+H]^+$ $C_{14}H_8N_2O$: 221.07; encontrado: 221.12.

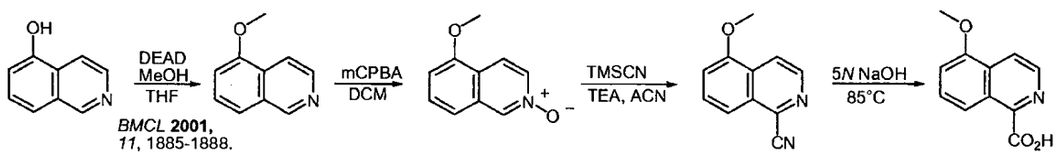
Cap-137



A una suspensión de *Cap-137, etapa a*, (110 mg, 0.50 mmol) y peryodato sódico (438 mg, 2.05 mmol) en tetracloruro de carbono (1 ml), acetonitrilo (1 ml) y agua (1.5 ml) se añadió tricloruro de rutenio hidratado (2 mg, 0.011 mmol). La mezcla se agitó a 25 °C durante 2 h y luego se repartió entre diclorometano y agua. La fase acuosa se separó, se extrajo dos veces más con diclorometano y se secaron los extractos reunidos sobre Na_2SO_4, se filtraron y concentraron. La trituración del residuo con hexanos proporcionó *Cap-137* (55 mg, 55%) como un sólido de color grisáceo. T_R = 1.10 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_8N_2O_2$: 200.08; encontrado: 200.08.

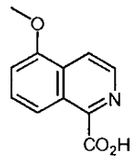
Caps 138 a 158

Estrategia de síntesis. Proceso A.

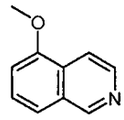


BMCL **2001**, *11*, 1885-1888.

Cap-138



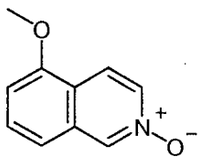
Cap-138, etapa a



A una suspensión agitada de 5-hidroxiisoquinolina (preparada de conformidad con el proceso 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 *Cap-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); T_R = 0.66 min (Cond. D2); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO$: 160.08;

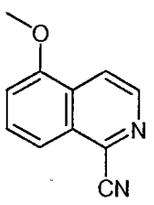
encontrado 160.1.

Cap-138, etapa b



A una solución agitada de *Cap-138, etapa a* (2.34 g, 14.7 mmol) en diclorometano anhidro (50 ml) a temperatura ambiente se añadió ácido *meta*-cloroperbenzoico (77%, 3.42 g, 19.8 mmol) en una porción. Después de agitar durante 20 horas, se añadió carbonato potásico en polvo (2.0 g) y la mezcla se agitó durante 1 hora a temperatura ambiente antes de que se filtrara y concentrara proporcionando *Cap-138, etapa b* como un sólido amarillo pálido que fue suficientemente puro para usarse posteriormente (2.15 g, 83%). RMN de ^{1}H ($CDCl_3$, 400 MHz) δ 8.73 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 7.3, 1.7 Hz, 1H), 8.04 (d, J=7.1 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.00 (s, 3H); T_R = 0.92 min, (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO_2$: 176.07; encontrado: 176.0.

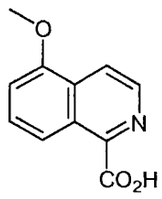
Cap-138, etapa c



A una solución agitada de *Cap-138, etapa b* (0.70 g,

4.00 mmol) y trietilamina (1.1 ml, 8.00 mmol) en acetonitrilo seco (20 ml) a temperatura ambiente en nitrógeno se añadió cianuro de trimetilsililo (1.60 ml, 12.00 mmol). La mezcla se calentó a 75°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 solvente. El residuo se sometió a cromatografía instantánea sobre gel de sílice (elución con acetato de etilo al 5%/hexanos) hasta acetato de etilo al 25%/en hexanos proporcionando *Cap-138, etapa c* (498.7 mg) como un sólido blanco cristalino junto con 223 mg de más *Cap-138, etapa c* recuperado del filtrado. RMN de ^1H ($CDCl_3$, 500 MHz) δ 8.63 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 4.04 (s, 3H); T_R = 1.75 min, (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; encontrado: 185.10.

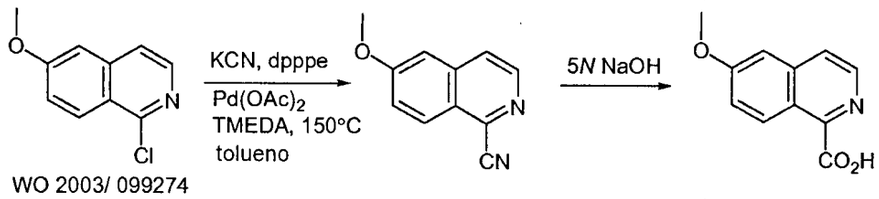
Cap-138



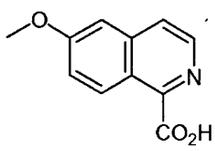
Se trató *Cap-138, etapa c* (0.45 g, 2.44 mmol) con solución de hidróxido sódico 5*N* (10 ml) y la suspensión resultante

se calentó a 85°C durante 4 h, se enfrió hasta 25°C, se diluyó con diclorometano y se acidificó con ácido clorhídrico 1*N*. La fase orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, se concentró hasta ¼ del volumen y se filtró proporcionando *Cap-138* como un sólido amarillo (0.44 g, 88.9%). RMN de ^1H (DMSO-d_6, 400 MHz) δ 13.6 (s ancho, 1H), 8.56 (d, *J* = 6.0 Hz, 1H), 8.16 (d, *J* = 6.0 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H); T_R = 0.70 min (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.

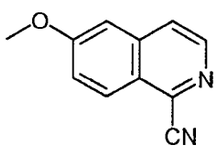
Estrategia de síntesis. Proceso B (derivado de *Tetrahedron Letters*, **2001**, *42*, 6707).



Cap-139



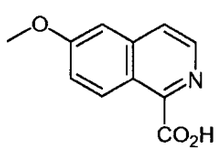
Cap-139, etapa a



A un vial a rosca de pared gruesa que contenía una

suspensión desgasificada en argón de 1-cloro-6-metoxiisoquinolina (1.2 g, 6.2 mmol; preparado de conformidad con el proceso 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 *Cap-139, etapa a* como un sólido blanco (669.7 mg). RMN de ^1H ($CDCl_3$, 500 MHz) δ 8.54 (d, *J* = 6.0 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 3H); T_R = 1.66 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; encontrado: 185.20,

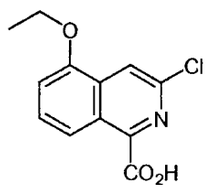
Cap-139



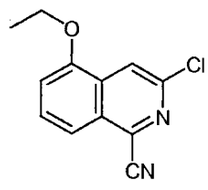
Cap-139 se preparó a partir de la hidrólisis básica de *Cap-139, etapa a* con NaOH 5*N* de conformidad con el proceso

descrito para *Cap-138,* RMN de ^{1}H (400 MHz, DMSO-d_6) δ 13.63 s muy ancho, 1H), 8.60 (d, *J* = 9.3 Hz, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 5.9 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H); T_R = 0.64 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.

Cap-140



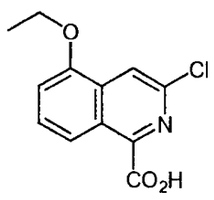
Cap-140, etapa a



A una mezcla agitada vigorosamente de 1,3-dicloro-5-etoxiisoquinolina (482 mg, 2.00 mmol; preparada de conformidad con el proceso del documento WO 2005/051410), acetato de paladio (II) (9 mg, 0.04 mmol), carbonato sódico (223 mg, 2.10 mmol) y 1,5-bis(difenilfosfino)pentano (35 mg, 0.08 mmol) en dimetilacetamida seca (2 ml) a 25 °C en nitrógeno se añadió N,N,N',N'-tetrametiletilendiamina (60 ml, 0.40 mmol). Después de 10 min, la mezcla se calentó hasta 150

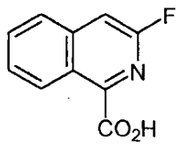
°C, y luego se añadió una solución patrón de acetona cianohidrina (preparada a partir de 457 µl de acetona cianohidrina en 4.34 ml de DMA) en porciones de 1 ml durante 18 h usando una bomba de jeringa. La mezcla se repartió entonces entre acetato de etilo y agua y se separó la fase orgánica, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con acetato de etilo al 10%/hexanos hasta acetato de etilo al 40%/hexanos proporcionando *Cap-140, etapa a* como un sólido amarillo (160 mg, 34%). T_R = 2.46 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; encontrado: 233.08.

Cap-140

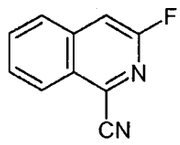


Cap-140 se preparó por la hidrólisis ácida de *Cap-140, etapa a* con HCl 12*N* como se describe en el proceso para la preparación de *Cap 141,* descrito más adelante. T_R = 2.24 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; encontrado: 252.02.

Cap-141

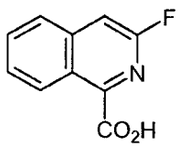


Cap-141, etapa a



Cap-141, etapa a se preparó a partir de 1-bromo-3-fluoroisoquinolina (preparada a partir de 3-amino-1-bromoisoquinolina usando el proceso esbozado en *J. Med. Chem.* **1970**, *13*, 613) como se describe en el proceso para la preparación de *Cap-140, etapa a* (*vide supra*). RMN de ^{1}H (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.83 (t, *J* = 7.63 Hz, 1H), 7.77-7.73 (m, 1H), 7.55 (s, 1H); T_R = 1.60 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_6FN_2$: 173.05; encontrado: 172.99.

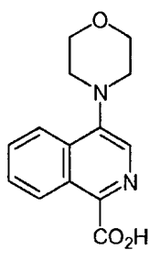
Cap-141



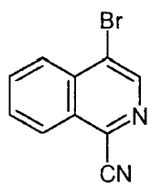
Se trató *Cap-141, etapa a* (83 mg, 0.48 mmol) con HCl 12*N* (3 ml) y la suspensión resultante se calentó a 80 °C durante 16 h antes de enfriar hasta temperatura ambiente y se

diluyó con agua (3 ml). La mezcla se agitó durante 10 min y luego se filtró proporcionando *Cap-141* como un sólido blanquecino (44.1 mg, 48%). El filtrado se diluyó con diclorometano y se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró proporcionando más *Cap-141* que fue suficientemente puro para usarlo posteriormente (29.30 mg, 32%). RMN de ^1H (DMSO-d_6, 500 MHz) δ 14.0 (s ancho, 1H), 8.59-8.57 (m, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.88-7.85 (m, 2H), 7.74-7.71 (m, 1H); T_R = 1.33 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 191.97.

Cap-142



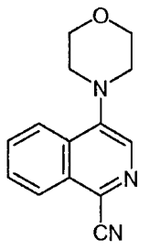
Cap-142, etapa a



Cap-142, etapa a se preparó a partir de N-óxido de 4-bromoisoquinolina como se describe en el proceso en dos etapas para la preparación de *Cap-138, etapas b y c*. T_R = 1.45 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97;

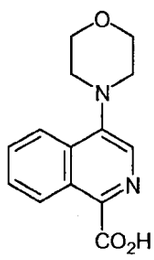
encontrado: 233.00.

Cap-142, etapa b



A una suspensión desgasificada en argón de *Cap-142, etapa a* (116 mg, 0.50 mmol), fosfato potásico tribásico (170 mg, 0.80 mmol), acetato de paladio (II) (3.4 mg, 0.015 mmol) y 2-(diciclohexilfosfino)bifenilo (11 mg, 0.03 mmol) en tolueno anhidro (1 ml) se añadió morfolina (61 µl, 0.70 mmol). La mezcla se calentó a 100 °C durante 16 h, se enfrió hasta 25 °C 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 *Cap-142, etapa b* (38 mg, 32%) como un sólido amarillo, que se llevó a etapas posteriores directamente. T_R = 1.26 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; encontrado: 240.13.

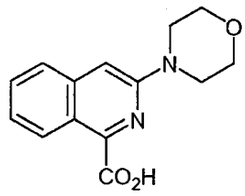
Cap-142



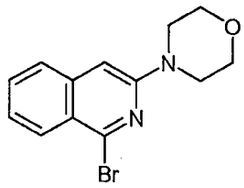
Cap-142 se preparó a partir de *Cap-142, etapa b* con

hidróxido sódico 5*N* como se describe en el proceso para *Cap-138*, T_R = 0.72 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; encontrado: 259.08.

Cap-143



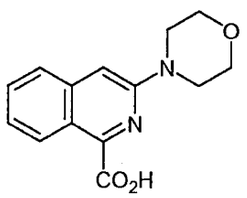
Cap-143, etapa a



A una solución agitada de 3-amino-1-bromoisoquinolina (444 mg, 2.00 mmol) en dimetilformamida anhidra (10 ml) se añadió hidruro sódico (60%, sin lavar, 96 mg, 2.4 mmol) en una porción. 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 5h y a 75 °C durante 72 h antes de enfriar hasta 25 °C, se inactivó con solución saturada de cloruro amónico y se diluyó con acetato de etilo. La fase orgánica se separó, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La

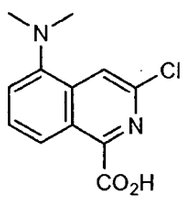
purificación del residuo sobre gel de sílice eluyendo con acetato de etilo al 0% a 70%/hexanos proporcionó *Cap-143, etapa a* como un sólido amarillo (180 mg, 31%). T_R = 1.75 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; encontrado: 293.04.

Cap-143

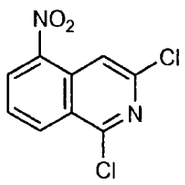


A una solución fría (-60 °C) de *Cap-143, etapa a* (154 mg, 0.527 mmol) en tetrahidrofurano anhidro (5 ml) se añadió una solución de *n*-butil litio en hexanos (2.5 M, 0.25 ml, 0.633 mmol). Después de 10 min, se burbujeó dióxido de carbono en la mezcla de reacción durante 10 minutos antes que se inactivara con HCl 1N y se dejó calentar hasta 25°C. La mezcla se extrajo entonces con diclorometano (3 x 30 ml) y los extractos orgánicos reunidos se concentraron a vacío. La purificación del residuo por una HPLC de fase inversa (MeOH/agua/TFA) proporcionó *Cap-143* (16 mg, 12%). T_R = 1.10 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; encontrado: 259.08,

Cap-144

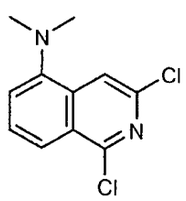


Cap-144, etapa a



Se añadió 1,3-dicloroisoquinolina (2.75 g, 13.89 mmol) en pequeñas porciones a una solución fría (0 °C) de ácido nítrico fumante (10 ml) y ácido sulfúrico concentrado (10 ml). La mezcla se agitó a 0°C durante 0.5 horas antes de que se calentara gradualmente hasta 25°C a la que se agitó durante 16 horas. La mezcla se vertió entonces en un vaso de precipitados que contenía hielo triturado y agua y la suspensión resultante se agitó durante 1 hora a 0°C antes de que se filtrara proporcionando *Cap-144, etapa a* (2.73 g, 81%) como un sólido amarillo que se usó directamente. T_R = 2.01 min. (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; encontrado: 242.92.

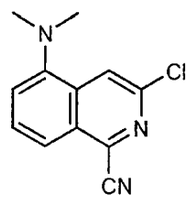
Cap-144, etapa b



Se suspendió *Cap-144, etapa a* (0.30 g, 1.23 mmol)

en metanol (60 ml) y se trató con óxido de platino (30 mg) y la suspensión se sometió a hidrogenación de Parr a 48.26 kPa de H_2 durante 1.5 h. A continuación, se añadieron formalina (5 ml) y más óxido de platino (30 mg) y la suspensión se volvió a someter a hidrogenación de Parr a 310.26 kPa de H_2 durante 13 h. A continuación se sometió a filtración por succión a través de tierra de diatomeas (CELITE®) y se concentró hasta ¼ de su volumen. La filtración por succión del precipitado proporcionó el compuesto del título 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%/hexanos proporcionando *Cap-144, etapa b* (231 mg, 78%) como un sólido amarillo pálido. T_R = 2.36 min (Condiciones-D1); índice de homogeneidad del 95%; RMN de ^1H (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 2.88 (s, 6H); CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.03; encontrado: 241.02, EMAR: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.0299; encontrado: 241.0296.

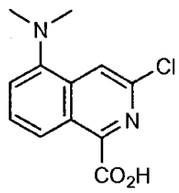
Cap-144, etapa c



Cap-144, etapa c se preparó a partir de *Cap-144, etapa b* de conformidad con el proceso descrito para la preparación de *Cap-139, etapa a*. T_R = 2.19 min (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.06; encontrado:

232.03, EMAR: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.0642; encontrado: 232.0631.

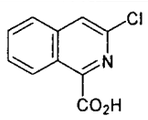
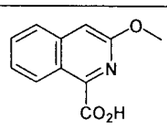
Cap-144

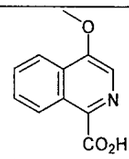
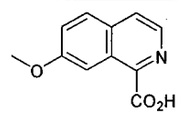
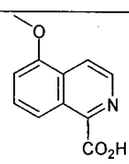
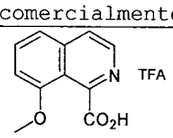


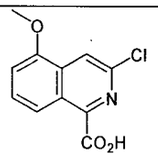
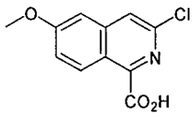
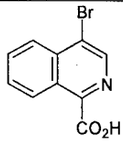
Cap-144 se preparó de conformidad con el proceso descrito para *Cap-141*, T_R = 2.36 min (Condiciones-D1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; encontrado: 238.09.

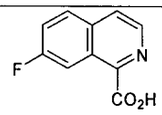
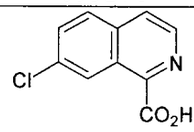
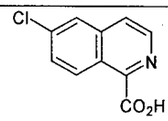
Caps-145 a 162

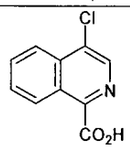
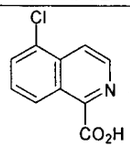
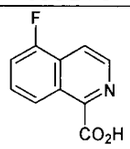
Se prepararon *Caps-145* a *162* a partir de las 1-cloroisoquinolinas apropiadas de conformidad con el proceso descrito para la preparación de *Cap-138* (Proceso A) o *Cap-139* (Proceso B) a no ser que se describa de otro modo más adelante.

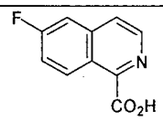
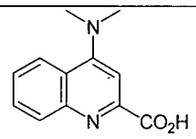
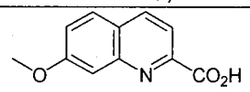
Cap n°	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-145	 Preparado a partir de 1,3-dicloroisoquinolina disponible comercialmente	B	12*N* HCl	1.14 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.00.
Cap-146	 Preparado a partir de 3-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	1.40 min (Condiciones-D1); 95% ; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.06.

Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-147	 Preparado a partir de 1-cloro-4-hidroxiisoquinolina disponible comercialmente	B	NaOH 5N	0.87 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.
Cap-148	 Preparado a partir de 7-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0.70 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.
Cap-149	 Preparado a partir de 5-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0.70 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.
Cap-150	 Preparado a partir de 8-metoxi-1-cloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	A	HCl 12N	0.26 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.04.

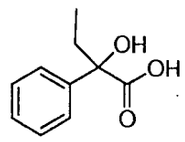
Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-151 ácido 3-cloro-5-metoxiisoquinolin-1-carboxílico	 Preparado a partir de 5-metoxi-1,3-dicloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2005 / 051410.	B	HCl 12N	1.78 min (Condiciones-D1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; encontrado: 238.09.
Cap-152	 Preparado a partir de 6-metoxi-1,3-dicloroisoquinolina disponible comercialmente	B	HCl 12N	1.65 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00; encontrado: 238.09.
Cap-153	 Preparado a partir de 4-bromoisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/ 062241	A	HCl 6N	1.18 min (Condiciones de EM-W1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; encontrado: 251.95.

Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-154	 Preparado a partir de 7-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	B	NaOH 5N	0.28 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 192.03.
Cap-155	 Preparado a partir de 1,7-dicloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	B	NaOH 5N	0.59 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.00.
Cap-156	 Preparado a partir de 1,6-dicloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	B	NaOH 5N	0.60 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.03.

Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-157	 Preparado a partir de 1,4-dicloroisoquinolina que se puede sintetizar siguiendo el proceso del documento WO 2003/062241	B	HCl 12N	1.49 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{17}ClNO$: 208.02; encontrado: 208.00.
Cap-158	 Preparado a partir de 1,5-dicloroisoquinolina que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	B	NaOH 5N	0.69 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.01.
Cap-159	 Preparado a partir de 5-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	B	NaOH 5N	0.41 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 192.03.

Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-160	 Preparado a partir de 6-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el proceso del documento WO 2003/099274	B	NaOH 5N	0.30 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 192.03.
Cap-161	 Preparado a partir de ácido 4-bromoquinolin-2-carboxílico y dimetilamina (DMSO, 100 °C)	--	--	0.70 min (Cond. D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217.10; encontrado: 217.06.
Cap-162	 Preparado a partir de *m*-anisidina siguiendo el proceso descrito en *J. Hetero. Chem.* **1993**, 17 y *Heterocycles*, **2003**, *60*, 953.	--	--	0.65 min (Condiciones-M3); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 203.94.

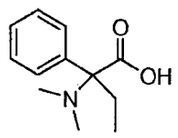
Cap-163



A una solución de ácido 2-cetobutírico (1.0 g, 9.8 mmol) en éter dietílico (25 ml) se añadió gota a gota bromuro de fenilmagnesio (22 ml, 1M en THF). La reacción se agitó a

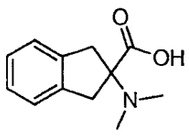
~25 °C en nitrógeno durante 17.5h. La reacción se acidificó con HCl 1N y el producto se extrajo con acetato de etilo (3 x 100 ml). La fase orgánica combinada se lavó con agua seguido por salmuera y se secó sobre $MgSO_4$, Después de concentrar a vacío se obtuvo un sólido blanco. El sólido se recristalizó en hexanos/acetato de etilo proporcionando *Cap-163* como agujas blancas (883.5 mg). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.71 (s ancho, 1 H), 7.54-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 5.52-5.39 (s ancho, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 0.79 (t ap, J = 7.4 Hz, 3H).

Cap-164



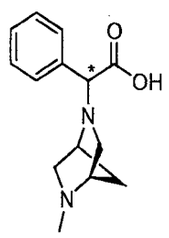
Se expuso a H_2 a 344.74 kPa en un frasco de Parr durante 42 horas una mezcla de ácido 2-amino-2-fenilbutírico (1.5 g, 8.4 mmol), formaldehído (14 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (0.5 mg) en MeOH (40 ml). La reacción se filtró sobre CELITE® y se concentró a vacío, el residuo se suspendió en MeOH (36 ml) y el producto se purificó con una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de *Cap-164* como un sólido blanco (1.7 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.54-7.47 (m, 5H), 2.63 (m, 1H), 2.55 (s, 6H), 2.31 (m, 1H), 0.95 (t ap, J = 7.3 Hz, 3H).

Cap-165



A una mezcla de ácido 2-amino-2-indanocarboxílico (258.6 mg, 1.46 mmol) y ácido fórmico (0.6 ml, 15.9 mmol) en 1,2-dicloroetano (7 ml) se añadió formaldehído (0.6 ml, 37% en agua). La mezcla se agitó a ~25 °C durante 15 min luego se calentó a 70 °C durante 8h. El componente volátil se eliminó a vacío y el residuo se disolvió en DMF (14 ml) y se purificó por una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de *Cap-165* como un aceite viscoso (120.2 mg). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; encontrado: 206.07.

Cap-166a y -166b

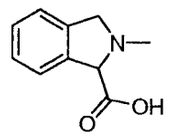


Cap-166a: Diastereómero-1
Cap-166b: Diastereómero-2

Caps-166a y *-166b* se prepararon a partir de (1S, 4S)-(+)-2-metil-2.5-diazabiciclo[2.2.1]heptano (2HBr) de conformidad con el proceso descrito para la síntesis de *Cap-7a y Cap-7b*, con la salvedad de que se separó el éster

bencílico intermediario usando una columna semipreparativa CHIRALCEL®OJ, 20 x 250 mm, 10 µm eluyendo con una mezcla 85:15 de heptano/etanol a 10 ml/min de velocidad de flujo de elución durante 25 min. *Cap-166b*: RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H), 7.27-7.19 (m, 3H), 4.09 (s, 1H), 3.34 (s ancho ap, 1H), 3.16 (s ancho ap, 1H), 2.83 (d, *J*=10.1 Hz, 1H), 2.71 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H), 1.77 (d, J = 9.8 Hz, 1H), 1.63 (d, J = 9.8 Hz, 1H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; encontrado: 247.11.

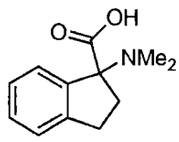
Cap-167



Se agitó una solución de ácido Boc-1,3-dihidro-2H-isoindol carboxílico racémico (1.0g, 3.8 mmol) en TFA al 20%/CH_2Cl_2 a ~25 °C durante 4h. Se eliminó todo el componente volátil a vacío. Se expuso una mezcla del material bruto resultante, formaldehído (15 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (10 mg) en MeOH a H_2 (275.71 kPa) en un frasco de Parr durante 23 h. La mezcla de reacción se filtró sobre CELITE® y se concentró a vacío proporcionando *Cap-167* como una espuma amarilla (873.5 mg). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, J = 14 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.07 (s, 3H). CL/EM:

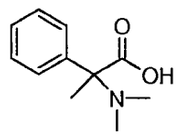
Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; encontrado: 178.65.

Cap-168



Se preparó *Cap-168* racémico a partir de ácido Boc-aminoindano-1-carboxílico racémico de conformidad con el proceso descrito para la preparación de *Cap-167*, El producto bruto se usó como tal.

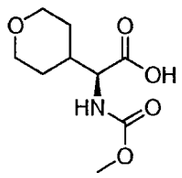
Cap-169



Se colocó una mezcla de clorhidrato de ácido 2-amino-2-fenilpropanoico (5.0 g, 2.5 mmol), formaldehído (15 ml, 37% en agua), HCl 1N (15 ml) y Pd al 10%/C (1.32 g) en MeOH (60 ml) en un frasco de Parr y se agitó en hidrógeno (379.11 kPa) durante 4 días. La mezcla de reacción se filtró sobre Celite y se concentró a vacío. El residuo se suspendió en MeOH y se purificó por HPLC preparativa de fase inversa (MeOH/agua/TFA) proporcionando la sal TFA de *Cap-169* como un semisólido viscoso (2.1 g). RMN de ^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). CL/EM: Análisis

calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; encontrado: 194.12.

Cap-170

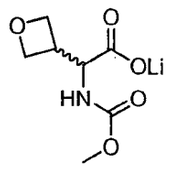


Ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético

A ácido (*S*)-2-amino-2-(tetrahidro-2*H*-piran-4-il)acético (505 mg; 3.18 mmol; obtenido de Astatech) en agua (15ml) se añadió carbonato sódico (673 mg; 6.35 mmol) y la mezcla resultante se enfrió hasta 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 combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando *Cap-170* un residuo incoloro. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 12.65 (1 H, s ancho), 7.44 (1 H, d, *J*=8.24 Hz), 3.77 - 3.95 (3 H, m), 3.54 (3 H, s), 3.11 - 3.26 (2 H, m), 1.82 - 1.95 (1 H, m), 1.41 - 1.55 (2 H, m), 1.21 - 1.39 (2 H, m); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{16}NO_5$: 218.1; encontrado

218.1,

Cap-171

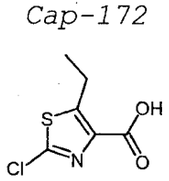


Una solución de 2-(benciloxicarbonilamino)-2-(oxetan-3-iliden)acetato de metilo (200 mg, 0.721 mmol; Il Farmaco (2001), 56, 609-613) en acetato de etilo (7 ml) y CH_2Cl_2 (4.00 ml) se desgasificó burbujeando nitrógeno durante 10min. Se añadieron entonces dicarbonato de dimetilo (0.116 ml, 1.082 mmol) y Pd/C (20 mg, 0.019 mmol), la mezcla de reacción se ajustó bajo un 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 sulfúrico y 100 ml de agua) indicó la conversión completa. La reacción se filtró a través de CELITE® y se concentró. El residuo se purificó por BIOTAGE® (cada con diclorometano en 25 de muestra; elución en columna 25S con diclorometano para 3CV luego 0 a 5% de MeOH/diclorometano sobre 250ml luego mantenido a 5% de MeOH/diclorometano para 250 ml; 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,

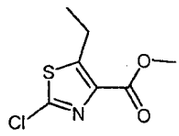
CLOROFORMO-D) δ ppm 3.29 - 3.40 (m, *J*=6.71 Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, *J*=6.41 Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (s ancho, 1 H). CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; encontrado 204.0.

Se añadió a 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo (50 mg, 0.246 mmol) en THF (2 ml) y agua (0.5 ml) hidróxido de litio monohidratado (10.33 mg, 0.246 mmol). La solución resultante se dejó agitando durante la noche a temperatura ambiente. La TLC (1:1 EA/Hex; tinción de Hanessian [1g de $Ce(NH_4)_2SO_4$, 6 g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua]) indicó que quedaba ~10% de material de partida. Se añadieron otros 3 mg de LiOH y se dejó agitando durante la noche momento en el que la TLC mostró que no quedaba material de partida. Se concentró a vacío y se colocó en alto vacío durante la noche proporcionando 55 mg de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de litio como un sólido incoloro. RMN de ^1H (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

Cap-172



Cap-172, etapa a



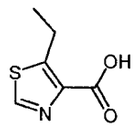
La siguiente etapa de diazotación se adaptó de Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: Se añadió una solución de $NaNO_2$ (166 mg, 2.4 mmol) en agua (0.6 ml) a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1.0 mmol), $CuSO_4 \cdot 5H_2O$ (330 mg, 1.32 mmol), NaCl (260 mg, 4.45 mmol) y H_2SO_4 (5.5 ml) en agua (7.5 ml). La mezcla se agitó a 0 °C durante 45 min y se dejó calentar hasta temperatura ambiente donde se agitó durante otra 1 h antes de añadir CuCl (118 mg). Esta mezcla se agitó de nuevo a temperatura ambiente durante 16 h antes de diluirse con salmuera y extraerse con éter dos veces. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 2-cloro-5-etiltiazol-4-carboxilato de metilo (es decir, *Cap-172, etapa a*) (175 mg, 85%) como un aceite naranja (80% de pureza) que se usó directamente en la siguiente reacción. T_R = 1.99 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_7H_9ClNO_2S$: 206.01; encontrado: 206.05.

Cap-172

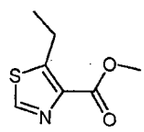
A una solución de 2-cloro-5-etiltiazol-4-

carboxilato de metilo (175 mg) en THF/H_2O/MeOH (20 ml/ 3 ml/ 12 ml) se añadió LiOH (305 mg, 12.76 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando *Cap-172* (60 mg, 74%) como un sólido rojo que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 13.03-13.42 (1 H, m), 3.16 (2 H, q, J = 7.4 Hz), 1.23 (3 H, t, J = 7.5 Hz). T_R = 1.78 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_6H_7ClNO_2S$: 191.99; encontrado: 191.99.

Cap-173



Cap-173, etapa a



La siguiente etapa de diazotación se adaptó de Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: Se añadió una solución de $NaNO_2$ (150 mg, 2.17 mmol) en agua (1.0 ml) gota a gota a una solución agitada, fría (0 °C) de 2-

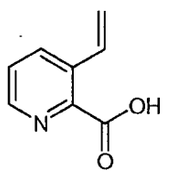
amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1.0 mmol) en H_3PO_2 al 50% (3.2 ml). La mezcla se agitó a 0 °C durante 1 h y se dejó calentar hasta temperatura ambiente donde se agitó durante otras 2h. Después de volver a enfriar hasta 0 °C, la mezcla se trató lentamente con una solución de NaOH (85 mg) en agua (10 ml). La mezcla se diluyó entonces con solución saturada de $NaHCO_3$ y se extrajo dos veces con éter. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 5-etiltiazol-4-carboxilato de metilo (es decir, *Cap-173, etapa a*) (134 mg, 78%) como un aceite naranja (85% de pureza) que se usó directamente en la siguiente reacción. T_R = 1.58 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_7H_{10}NO_2S$: 172.05; encontrado: 172.05.

Cap-173

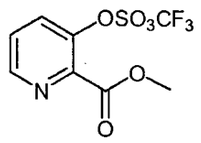
A una solución de 5-etiltiazol-4-carboxilato de metilo (134 mg) en THF/H_2O/MeOH (18 ml/ 2.7 ml/ 11 ml) se añadió LiOH (281 mg, 11.74 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando *Cap-173* (90 mg, 73%) como un sólido naranja que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 12.74-13.04 (1 H, m), 3.20 (2 H, q, *J* = 7.3

Hz), 1.25 (3 H, t, *J* = 7.5 Hz). T_R = 1.27 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_6H_8NO_2S$: 158.03; encontrado: 158.04.

Cap-174



Cap-174, etapa a



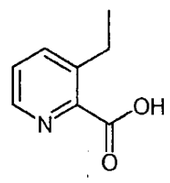
Se añadió anhídrido tríflico (5.0 g, 18.0 mmol) gota a gota a una solución fría (0 °C) de 3-hidroxipicolinato de metilo (2.5 g, 16.3 mmol) y TEA (2.5 ml, 18.0 mmol) en CH_2Cl_2 (80 ml). La mezcla se agitó a 0 °C durante 1h antes de dejar calentar hasta temperatura ambiente, momento en el que se agitó durante una hora más. La mezcla se inactivó entonces con solución saturada de $NaHCO_3$ (40 ml) y la fase orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró dando 3-(trifluorometilsulfoniloxi)picolinato de metilo (*es decir, Cap-174, etapa a*) (3.38 g, 73%) como un aceite marrón oscuro (>95% de pureza) que se usó directamente sin purificación posterior. RMN de ^1H (300 MHz, $CDCl_3$) δ ppm 8.72-8.79 (1 H, m), 7.71 (1 H, d, *J* = 1.5 Hz), 7.58-7.65 (1 H, m), 4.04 (3 H, s). T_R = 1.93 min (Condición-MD1); CL/EM:

Análisis calculado para $[M+H]^+$ $C_8H_7F_3NO_5S$: 286.00; encontrado: 286.08.

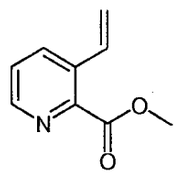
Cap-174

A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (570 mg, 2.0 mmol) en DMF (20 ml) se añadió LiCl (254 mg, 6.0 mmol), tributil(vinil)estanano (761 mg, 2.4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0.06 mmol). La mezcla se calentó a 100 °C durante la noche antes d añadir una solución saturada de KF (20 ml) a la mezcla de reacción a temperatura ambiente. Esta mezcla se agitó durante 4 h antes de filtrar a través de CELITE® y la almohadilla de CELITE® se lavó con acetato de etilo. La fase acuosa del filtrado se separó entonces y se concentró a vacío. El residuo se trató con HCl 4*N* en dioxanos (5 ml) y la mezcla resultante se extrajo con metanol, se filtró y se evaporó proporcionando *Cap-174* (260 mg) como un sólido verde que estaba ligeramente contaminado con sales inorgánicas pero que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 8.21 (1 H, d, *J* = 3.7 Hz), 7.81-7.90 (1 H, m), 7.09 (1 H, dd, *J* = 7.7, 4.8 Hz), 6.98 (1 H, dd, *J* = 17.9, 11.3 Hz), 5.74 (1 H, dd, *J* = 17.9, 1.5 Hz), 5.20 (1 H, d, *J* = 11.0 Hz). T_R = 0.39 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_8NO_2$: 150.06; encontrado: 150.07.

Cap-175



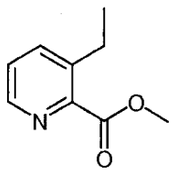
Cap-175, etapa a



A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (*es decir, Cap-174, etapa a*) (570 mg, 2.0 mmol), un intermediario en la preparación de *Cap-174,* en DMF (20 ml) se añadió LiCl (254 mg, 6.0 mmol), tributil(vinil)estanano (761 mg, 2.4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0.06 mmol). La mezcla se calentó a 100 °C durante 4 h antes de eliminar el solvente a vacío. El residuo se suspendió en acetonitrilo (50 ml) y hexanos (50 ml) y la mezcla resultante se lavó dos veces con hexanos. Se separó entonces la fase de acetonitrilo, se filtró a través de CELITE® y se evaporó. La purificación del residuo por cromatografía instantánea en un aparato Horizon (elución con gradiente de acetato de etilo al 25% en hexanos hasta acetato de etilo al 65% en hexanos) proporcionó 3-vinilpicolinato de metilo (es decir, *Cap-175, etapa a*) (130 mg, 40%) como un aceite amarillo. RMN de ^{1}H (300 MHz, $CDCl_3$) δ ppm 8.60 (1 H, dd, *J* = 4.6, 1.7 Hz), 7.94

(1 H, d, J = 7.7 Hz); 7.33-7.51 (2 H, m), 5.72 (1 H, d, J = 17.2 Hz), 5.47 (1 H, d, J = 11.0 Hz), 3.99 (3 H, s). T_R = 1.29 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{10}NO_2$: 164.07; encontrado: 164.06.

Cap-175, etapa b



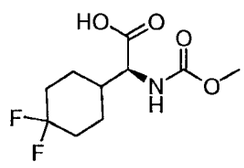
Se añadió paladio sobre carbón (10%, 25 mg) a una solución de 3-vinilpicolinato de metilo (120 mg, 0.74 mmol) en etanol (10 ml). La suspensión se agitó a temperatura ambiente en una atmósfera de hidrógeno durante 1 h antes de filtrar a través de CELITE® y se lavó la almohadilla de CELITE® con metanol. El filtrado se concentró hasta sequedad proporcionando 3-etilpicolinato de metilo (es decir, *Cap-175, etapa b*) que se llevó directamente a la siguiente reacción. T_R = 1.15 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{12}NO_2$: 166.09; encontrado: 166.09.

Cap-175

A una solución de 3-etilpicolinato de metilo en THF/H_2O/MeOH (5 ml/ 0.75 ml/ 3 ml) se añadió LiOH (35 mg, 1.47 mmol). La mezcla se agitó a temperatura ambiente durante 2 días antes de añadir más LiOH (80 mg). Después de otras 24 horas más a temperatura ambiente, la mezcla se filtró y el solvente se eliminó a vacío. El residuo se trató entonces con

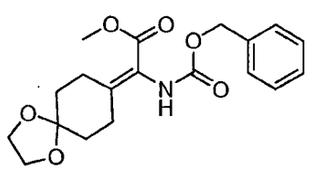
HCl 4*N* en dioxanos (5 ml) y la suspensión resultante se concentró hasta sequedad proporcionando *Cap-175* como un sólido amarillo que se usó sin purificación posterior. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 8.47 (1 H, dd, *J* = 4.8, 1.5 Hz), 7.82-7.89 (1 H, m), 7.53 (1 H, dd, *J* = 7.7, 4.8 Hz), 2.82 (2 H, q, *J* = 7.3 Hz), 1.17 (3 H, t, *J* = 7.5 Hz). T_R = 0.36 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{10}NO_2$: 152.07; encontrado: 152.10.

Cap-176



Ácido (S)-2(4,4-difluorociclohexil)-2-(metoxicarbonilamino)acético

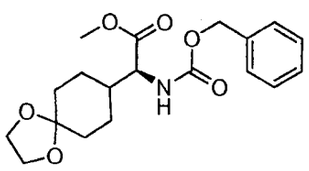
Cap-176, etapa a



Se añadió una solución de 1,4-dioxaspiro[4.5]decan-8-ona (15 g, 96 mmol) en EtOAc (150 ml) a una solución de 2-(benciloxicarbonilamino)-2-(dimetoxifosforil)acetato de metilo (21.21 g, 64.0 mmol) en 1,1,3,3-tetrametilguanidina (10.45 ml, 83 mmol) y EtOAc (150 ml). La solución resultante se agitó a temperatura ambiente durante 72 h y luego se diluyó con EtOAc (25 ml). La fase orgánica se lavó con HCl 1N

(75 ml), H_2O (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por BIOTAGE® (EtOAc al 5% hasta 25 %/Hexanos; 300g columna). Las fracciones reunidas que contenían el producto se concentraron entonces a vacío y el residuo se volvió a cristalizar en hexanos/EtOAc dando cristales blancos que corresponden a 2-(benciloxicarbonilamino)-2-(1,4-dioxaspiro[4.5]decan-8-iliden)acetato de metilo (6.2 g) RMN de ^1H (400 MHz, $CDCl_3$-*d*) δ ppm 7.30 - 7.44 (5 H, m), 6.02 (1 H, s ancho), 5.15 (2 H, s), 3.97 (4 H, s), 3.76 (3 H, s ancho), 2.84 - 2.92 (2 H, m), 2.47 (2 H, t, *J*=6.40 Hz), 1.74 - 1.83 (4 H, m). CL (Cond. OL1): T_R = 2.89 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745.21; encontrado: 745.47

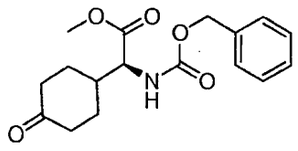
Cap-176, etapa b



Se preparó el éster *Cap-176, etapa b* a partir del alqueno *Cap-176, etapa a* de conformidad con el proceso de Burk, M. J.; Gross, M. F, y Martinez J. P. (*J. Am. Chem. Soc.*, **1995**, *117*, 9375-9376 y referencias en el mismo): Se cargó una botella a alta presión de 500 ml con el alqueno *Cap 176, etapa a* (3.5 g, 9.68 mmol) en MeOH desgasificado (200 ml) en una capa de N_2, La solución se cargó entonces con tetrafluoroborato de (-)-1,2-bis((2S,5S)-2,5-

dimetilfosfolano)etano(ciclooctadieno)rodio (I) (0.108 g, 0.194 mmol) y la mezcla resultante se cubrió con N_2 (3x) y se cargó con H_2 (3x). La solución se agitó vigorosamente a 482 kPa de H_2 a temperatura ambiente durante 72 h. El solvente se eliminó a presión reducida y el residuo que quedó se suspendió en EtOAc. La solución pardusca se filtró entonces a través de una almohadilla de gel de sílice y se eluyó con EtOAc. El solvente se concentró a vacío proporcionando un aceite transparente que correspondía al éster *Cap-176, etapa b* (3.4 g), RMN de ^1H (500 MHz, $CDCl_3$-*d*) δ ppm 7.28 - 7.43 (5 H, m), 5.32 (1 H, d, *J*=9.16 Hz), 5.06 - 5.16 (2 H, m), 4.37 (1 H, dd, *J*=9.00, 5.04 Hz), 3.92 (4 H, t, *J*=3.05 Hz), 3.75 (3 H, s), 1.64 - 1.92 (4 H, m), 1.37 - 1.60 (5 H, m). CL (Cond. OL1): T_R = 1.95 min. CL/EM: Análisis calculado para $[M+H]^+$ $C_{19}H_{26}NO_6$: 364.18; encontrado: 364.27.

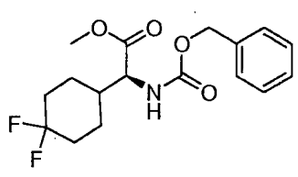
Cap-176, etapa c



Se disolvió el éster *Cap 176, etapa b* (4.78 g, 13.15 mmol) en THF (15 ml) seguido por la adición secuencial de agua (10 ml), ácido acético glacial (26.4 ml, 460 mmol) y ácido dicloroacético (5.44 ml, 65.8 mmol). La mezcla resultante se agitó durante 72 h a temperatura ambiente, y la reacción se inactivó mediante la adición lente de Na_2CO_3

sólido con agitación vigorosa hasta que no fue visible la generación de gas. El producto bruto se extrajo en acetato de etilo al 10%-diclorometano y las fases orgánicas se reunieron, se secaron ($MgSO_4$), se filtraron y concentraron. El residuo resultante se purificó por BIOTAGE® (EtOAc al 0 hasta 30%/Hex; 25 g de columna) proporcionando la cetona *Cap 176, etapa c* (3.86g) como un aceite transparente. RMN de ^1H (400 MHz, $CDCl_3$-*d*) δ ppm 7.28 - 7.41 (5 H, m), 5.55 (1 H, d, *J*=8.28 Hz), 5.09 (2 H, s), 4.46 (1 H, dd, *J*=8.16, 5.14 Hz), 3.74 (3 H, s), 2.18 - 2.46 (5 H, m), 1.96 - 2.06 (1 H, m), 1.90 (1 H, ddd, *J*=12.99, 5.96, 2.89 Hz), 1.44 - 1.68 (2 H, m, *J*=12.36, 12.36, 12.36, 12.36, 4.77 Hz). CL (Cond. OL1): T_R = 1.66 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342.13; encontrado: 342.10.

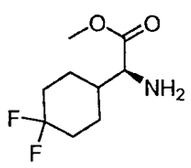
Cap-176, etapa d



Se añadió Deoxo-Fluor® (3.13 ml, 16.97 mmol) a una solución de la cetona *Cap-176, etapa c* (2.71 g, 8.49 mmol) en CH_2Cl_2 (50 ml) seguido por la adición de una cantidad catalítica de EtOH (0.149 ml, 2.55 mmol). La solución amarillenta resultante se agitó a ta durante la noche. La reacción se inactivó mediante la adición de $NaHCO_3$ acuoso saturado (25 ml) y la mezcla se extrajo con EtOAc (3X75 ml)).

Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se secaron dando un aceite amarillento. El residuo se purificó por cromatografía en BIOTAGE® (EtOAc al 2% hasta 15%/Hex; 90g de columna) y se recuperó un sólido blanco correspondiente al difluoruro de difluoro aminoácido *Cap 176, etapa d* (1.5 g). RMN de ^1H (400 MHz, $CDCl_3$-*d*) δ ppm 7.29 - 7.46 (5 H, m), 5.34 (1 H, d, *J*=8.28 Hz), 5.12 (2 H, s), 4.41 (1 H, dd, *J*=8.66, 4.89 Hz), 3.77 (3 H, s), 2.06 - 2.20 (2 H, m), 1.83 - 1.98 (1 H, m), 1.60 - 1.81 (4 H, m), 1.38 - 1.55 (2 H, m). RMN de ^{19}F (376 MHz, $CDCl_3$-*d*) δ ppm -92.15 (1 F, d, *J*=237.55 Hz), -102.44 (1 F, d, *J*=235.82 Hz). CL (Cond. OL1): T_R = 1.66 min. CL/EM: Análisis calculado para $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705.28; encontrado: 705.18.

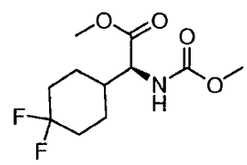
Cap-176, etapa e



Se disolvió el difluoruro *Cap 176, etapa d* (4 g, 11.72 mmol) en MeOH (120 ml) y se cargó con Pd/C (1.247 g, 1.172 mmol). Se inyectó en la suspensión N_2 (3x) y la mezcla de reacción se colocó bajo una presión de 101 kPa de H_2 (balón). La mezcla se agitó a temperatura ambiente durante 48 h. La suspensión se filtró entonces a través de una almohadilla de CELITE® y se concentró a vacío dando un aceite que corresponde al aminoácido *Cap-176, etapa e* (2.04 g) y que

se usó sin purificación posterior. RMN de ^{1}H (400 MHz, *DMSO-d_6*) δ ppm 3.62 (3 H, s), 3.20 (1 H, d, *J*=5.77 Hz), 1.91 - 2.09 (2 H, m), 1.50 - 1.88 (7 H, m), 1.20 - 1.45 (2 H, m). RMN de ^{19}F (376 MHz, *DMSO-d_6*) δ ppm -89.39 (1 F, d, *J*=232.35 Hz), -100.07 (1 F, d, *J*=232.35 Hz). RMN de ^{13}C (101 MHz, *DMSO-d_6*) δ ppm 175.51 (1 C, s), 124.10 (1 C, t, *J*=241.21, 238.90 Hz), 57.74 (1 C, s), 51.39 (1 C, s), 39.23 (1 C, s ancho), 32.02 - 33.83 (2 C, m), 25.36 (1 C, d, *J*=10.02 Hz), 23.74 (1 C, d, *J*=9.25 Hz). CL (Cond. OL2): T_R = 0.95 min. CL/EM: Análisis calculado para $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415.22; encontrado: 415.40.

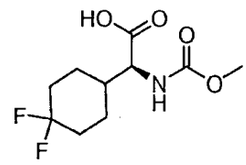
Cap-176, etapa f



Se añadió cloroformiato de metilo (1.495 ml, 19.30 mmol) a una solución de aminoácido *Cap 176, etapa e* (2 g, 9.65 mmol) y DIEA (6.74 ml, 38.6 mmol) en CH_2Cl_2 (100 ml). La solución resultante se agitó a ta durante 3 h y se eliminaron los volátiles a presión reducida. El residuo se purificó por BIOTAGE® (EtOAc al 0% hasta 20%/Hex; 90 g de columna). Se recuperó un aceite transparente que solidificó en reposo a vacío y que correspondía al carbamato *Cap-176, etapa f* (2.22 g). RMN de ^{1}H (500 MHz, $CDCl_3$-*d*) δ ppm 5.27 (1 H, d, *J*=8.55 Hz), 4.39 (1 H, dd, *J*=8.85, 4.88 Hz), 3.77 (3 H, s), 3.70 (3

H, s), 2.07 - 2.20 (2 H, m), 1.84 - 1.96 (1 H, m), 1.64 - 1.82 (4 H, m), 1.39 - 1.51 (2 H, m). RMN de ^{19}F (471 MHz, $CDCl_3$-*d*) δ ppm -92.55 (1 F, d, *J*=237.13 Hz), -102.93 (1 F, d, *J*=237.12 Hz). RMN de ^{13}C (126 MHz, $CDCl_3$-*d*) δ ppm 171.97 (1 C, s), 156.69 (1 C, s), 119.77 - 125.59 (1 C, m), 57.24 (1 C, s ancho), 52.48 (1 C, s ancho), 52.43 (1 C, s), 39.15 (1 C, s), 32.50 - 33.48 (2 C, m), 25.30 (1 C, d, *J*=9.60 Hz), 24.03 (1 C, d, *J*=9.60 Hz). CL (Cond. OL1): T_R = 1.49 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288.10; encontrado: 288.03.

Cap-176

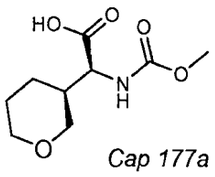


Ácido (S)-2(4,4-difluorociclohexil)-2-(metoxicarbonilamino)acético

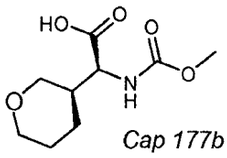
Se añadió una solución de LiOH (0.379 g, 15.83 mmol) en agua (25 ml) a una solución de carbamato *Cap-176, etapa f* (2.1 g, 7.92 mmol) en THF (75 ml) y la mezcla resultante se agitó a temperatura ambiente durante 4 h. Se eliminó el THF a vacío y la fase acuosa restante se acidificó con solución de HCl 1N (2 ml) y luego se extrajo con EtOAc (2 X 50 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron dando una espuma que correspondía al *Cap-176* (1.92 g). RMN de ^1H (400 MHz, *DMSO-d*$_6$) δ ppm 12.73 (1 H, s),

7.50 (1 H, d, *J*=8.78 Hz), 3.97 (1 H, dd, *J*=8.53, 6.02 Hz), 3.54 (3 H, s), 1.92 - 2.08 (2 H, m), 1.57 - 1.90 (5 H, m), 1.34 - 1.48 (1 H, m), 1.27 (1 H, qd, *J*=12.72, 3.26 Hz). RMN de ^{19}F (376 MHz, *DMSO-d*$_6$) δ ppm -89.62 (1 F, d, *J*=232.35 Hz), -99.93 (1 F, d, *J*=232.35 Hz). CL (Cond. OL2): T_R = 0.76 min. CL/EM: Análisis calculado para $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250.09; encontrado: 250.10.

Cap-177a y 177b

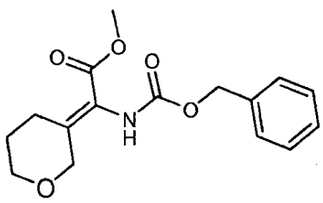


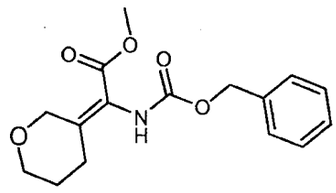
Cap 177a



Cap 177b

Cap-177a y 177b, etapa a



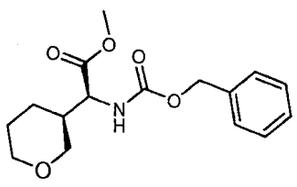


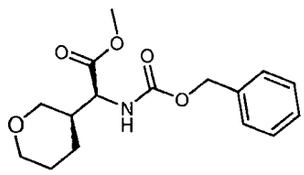
Se añadió 1,1,3,3-tetrametilguanidina (0.985 ml, 7.85 mmol) a una solución agitada de 2-(benciloxicarbonilamino)-2-(dimetoxifosforil)acetato de metilo (2.0 g, 6.0 mmol) en EtOAc (40 ml) y la mezcla se agitó a ta bajo N_2 durante 10 min. A continuación se añadió dihidro-2H-piran-3(4H)-ona [23462-75-1] (0.604 g, 6.04 mmol) y la mezcla se agitó a ta durante 16 h. La mezcla de reacción se enfrió entonces en el frigorífico 10 minutos y se

neutralizó con ácido cítrico acuoso (1.5 g en 20 ml de agua). Las dos fases se repartieron y la fase orgánica se lavó con HCl acuoso 0.25 N y salmuera, y luego se secó ($MgSO_4$) y se concentró hasta un aceite incoloro. El material bruto se purificó por cromatografía sobre sílice instantánea (solvente de carga: DCM, eluido con EtOAc/Hexanos, gradiente desde 20% hasta 30% de EtOAc) proporcionando dos productos isoméricos: El primer producto que eluyó fue (Z)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo (490 mg) (sólido blanco), y el segundo fue (E)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo (433 mg) (sólido blanco). Tiempo de retención de CL-EM 1.398 min (para el isómero Z) y 1.378 min (para el isómero E); m/z 304.08 (para el isómero Z) y 304.16 (para el isómero E) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH

al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) (para el isómero Z) δ ppm 7.30 - 7.44 (m, 5 H), 6.18 (s ancho, 1 H), 5.10 - 5.17 (m, 2 H), 4.22 (s, 2 H), 3.78 (s ancho, 3 H), 2.93 - 3.02 (m, 2 H), 1.80 (dt, *J*=11.7, 5.8 Hz, 2 H), 1.62 (s, 2 H). RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) (para el isómero E) δ ppm 7.31 - 7.44 (m, 5 H), 6.12 (s ancho, 1 H), 5.13 - 5.17 (m, 2 H), 4.64 (s ancho, 2 H), 3.70 - 3.82 (m, 5 H), 2.49 (t, *J*=6.5 Hz, 2 H), 1.80 (s ancho, 2 H). (Nota: la regioquímica absoluta se determinó por los desplazamientos de la RMN de ^{1}H y las constantes de acoplamiento).

Cap-177a y 177b, etapa b





Se añadió (-)-1,2-bis((2S,5S)-2,5-dimetilfosfolano)etano(ciclooctadieno)-rodio(I)tetrafluoroborato (28.2 mg, 0.051 mmol) a una solución agitada de (Z)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo (310 mg, 1.015 mmol) en MeOH (10 ml) y la mezcla se aspiró por succión con N_2, seguido por H_2, y a continuación se agitó la reacción bajo H_2 (4.136 x 10^5 Pa) a ta durante 2d. La mezcla de reacción se concentró y el residuo se purificó por cromatografía sobre

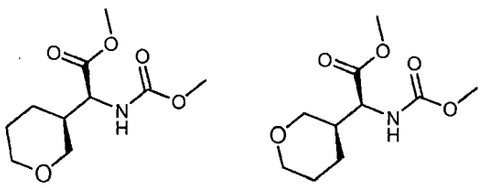
sílice instantánea (solvente de carga: DCM, eluido con EtOAc al 20% en hexanos) proporcionando (S)-2-(benciloxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (204 mg) como un aceite incoloro. Tiempo de retención de CL-EM 1.437 min; m/z 307.89 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 7.30 - 7.46 (m, 5 H), 5.32 (d, *J*=8.8 Hz, 1 H), 5.12 (s, 2 H), 4.36 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.98 (m, 2 H), 3.77 (s, 3 H), 3.28 - 3.37 (m, 1 H), 3.23 (dd, *J*=11.3, 10.5 Hz, 1 H), 2.04 - 2.16 (m, 1 H), 1.61 - 1.75 (m, 3 H), 1.31 - 1.43 (m, 1 H).

El otro estereoisómero ((E)-2-

(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo) (360 mg, 1.18 mmol) se redujo de una forma similar proporcionando (S)-2-(benciloxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo (214 mg) como un aceite incoloro. Tiempo de retención de CL-EM 1.437 min; m/z 308.03 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 7.30 - 7.44 (m, 5 H), 5.31 (d, *J*=9.0 Hz, 1 H), 5.12 (s, 2 H), 4.31 (dd, *J*=8.7, 6.9 Hz, 1 H), 3.80 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.37 (td, *J*=10.8, 3.5 Hz, 1 H), 3.28 (dd, *J*=11.3, 9.8 Hz, 1 H), 1.97 - 2.10 (m, 1 H), 1.81 (d, *J*=11.5 Hz, 1 H), 1.61 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1

H).

Cap-177a y 177b, etapa c



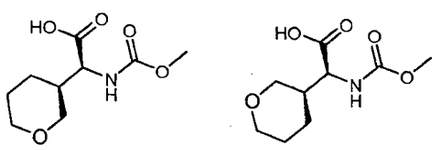
Se añadió Pd al 10%/C (69.3 mg, 0.065 mmol) a una solución de (S)-2-(benciloxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (200 mg, 0.651 mmol) y dicarbonato de dimetilo [4525-33-1] (0.104 ml, 0.976 mmol) en MeOH (10 ml). La mezcla de reacción se evacuó por succión con N_2, seguido por H_2, y luego se agitó la reacción bajo H_2 (3.79 x 10^5 Pa) a ta durante 5 h. La mezcla de reacción se filtró a través de una almohadilla de CELITE®/sílice y el filtrado se concentró hasta un aceite incoloro. El aceite bruto se purificó por cromatografía sobre sílice instantánea (solvente de carga: DCM, eluido con EtOAc al 30% en hexanos) proporcionando el producto (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (132 mg) como aceite incoloro. Tiempo de retención de CL-EM 0.92 min; m/z 231.97 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de

solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 5.24 (d, *J*=8.5 Hz, 1 H), 4.34 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.97 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.29 - 3.38 (m, 1 H), 3.23 (dd, *J*=11.2, 10.4 Hz, 1 H), 2.03 - 2.14 (m, 1 H), 1.56 - 1.75 (m, 3 H), 1.32 - 1.43 (m, 1 H).

Se transformó otro diastereómero ((S)-2-(benciloxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo) de una forma similar proporcionando (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo como un aceite incoloro. Tiempo de retención de CL-EM 0.99 min; m/z 231.90 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un

tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 5.25 (d, *J*=8.0 Hz, 1 H), 4.29 (dd, *J*=8.4, 7.2 Hz, 1 H), 3.82 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.37 (td, *J*=10.8, 3.3 Hz, 1 H), 3.28 (t, *J*=10.5 Hz, 1 H), 1.96 - 2.08 (m, 1 H), 1.81 (dd, *J*=12.9, 1.6 Hz, 1 H), 1.56 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

Cap-177a y 177b, etapa d



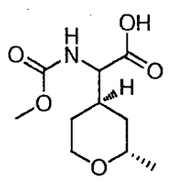
A una solución de (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (126 mg, 0.545 mmol) en THF (4 ml) agitando a ta se añadió una solución de LiOH 1M (1.090 ml, 1.090 mmol) en agua. La reacción se agitó a ta durante 3h, se neutralizó con HCl 1M (1.1 ml) y se extrajo con EtOAc (3x 10 ml). Los orgánicos se secaron, se filtraron y se concentraron proporcionando ácido (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acético (*Cap-177a*) (125 mg) como un aceite incoloro transparente. Tiempo de retención de CL-EM 0.44 min; m/z

218.00 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 5.28 (d, *J*=8.8 Hz, 1 H), 4.38 (dd, *J*=8.7, 5.6 Hz, 1 H), 3.96 - 4.04 (m, 1 H), 3.91 (d, *J*=11.0 Hz, 1 H), 3.71 (s, 3 H), 3.33 - 3.41 (m, 1 H), 3.24 - 3.32 (m, 1 H), 2.10 - 2.24 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.63 - 1.71 (m, 2 H), 1.35 - 1.49 (m, 1 H).

Se transformó otro diastereómero ((S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo) de una forma similar proporcionando ácido (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acético (*Cap-177b)* como un

aceite incoloro. Tiempo de retención de CL-EM 0.41 min; m/z 217.93 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de 100% de solvente A/0% de solvente B hasta 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato amónico 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 6.18 (s ancho, 1 H), 5.39 (d, *J*=8.5 Hz, 1 H), 4.27 - 4.37 (m, 1 H), 3.82 - 3.96 (m, 2 H), 3.72 (s, 3 H), 3.42 (td, *J*=10.8, 3.3 Hz, 1 H), 3.35 (t, *J*=10.4 Hz, 1 H), 2.01 - 2.18 (m, 1 H), 1.90 (d, *J*=11.8 Hz, 1 H), 1.59 - 1.76 (m, 2 H), 1.40 - 1.54 (m, 1 H).

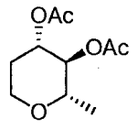
Cap-178



Ácido 2-(metoxicarbonilamino)-2-((2R,4S)-2-metiltetrahidro-

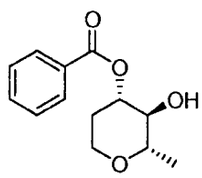
2H-piran-4-il)acético

Cap-178, etapa a



A una solución de diacetato de (2S,3S,4S)-2-metil-3,4-dihidro-2H-piran-3,4-diilo (5 g, 23.34 mmol) en 20 ml de MeOH en un depósito de hidrogenación se añadió Pd/C (150 mg, 0.141 mmol). La mezcla resultante se sometió a hidrogenación a 2.757 x 10^5 Pa en un agitador de Parr durante 1 hora. La mezcla se filtró a continuación y el filtrado se concentró dando *Cap-178, etapa a* (5.0 g) como un aceite transparente, que solidificó en reposo. RMN de ^{1}H (500 MHz, *CLOROFORMO-d*) δ ppm 4.85 - 4.94 (1 H, m), 4.69 (1 H, t, *J*=9.46 Hz), 3.88 - 3.94 (1 H, m), 3.44 (1 H, td, *J*=12.21, 1.83 Hz), 3.36 (1 H, dq, *J*=9.42, 6.12 Hz), 2.03 - 2.08 (1 H, m), 2.02 (3 H, s), 2.00 (3 H, s), 1.70 - 1.80 (1 H, m), 1.16 (3 H, d, *J*=6.10 Hz).

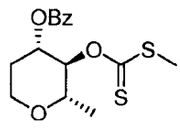
Cap-178, etapa b



A una solución de *Cap-178, etapa a* (5.0 g, 23 mmol) en 50 ml de MeOH se añadieron varias gotas de metóxido sódico. Después de agitar a temperatura ambiente durante 30 min, se añadió metóxido sódico (0.1 ml, 23.12 mmol) y la solución se

agitó a temperatura ambiente durante la noche. El solvente se eliminó entonces a vacío. El residuo se diluyó con benceno y se concentró dando el diol correspondiente como un sólido amarillo. El sólido se disolvió en 50 ml de piridina y a esta solución a -35°C se añadió cloruro de benzoilo (2.95 ml, 25.4 mmol) gota a gota. La mezcla resultante se agitó a -35 °C durante 1 hora y luego a temperatura ambiente durante la noche. La mezcla se diluyó con Et_2O y se lavó con agua. La fase acuosa se extrajo con EtOAc (2X). Las fases orgánicas combinadas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía instantánea (gel de sílice, EtOAc al 5%-15%/Hex) dando *Cap-178, etapa b* (4.5 g) como aceite transparente que cristalizó lentamente tras reposo prolongado. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{13}H_{16}NaO_4$ 259.09; encontrado 259.0; RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 8.02 - 8.07 (2 H, m), 7.55 - 7.61 (1 H, m), 7.45 (2 H, t, *J*=7.78 Hz), 5.01 (1 H, ddd, *J*=11.44, 8.70, 5.49 Hz), 3.98 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.54 (1 H, td, *J*=12.36, 2.14 Hz), 3.41 (1 H, t, *J*=9.00 Hz), 3.31 - 3.38 (1 H, m), 2.13 - 2.19 (1 H, m), 1.83 - 1.94 (1 H, m), 1.36 (3 H, d, *J*=5.80 Hz).

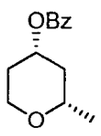
Cap-178, etapa c



A una mezcla de NaH (1.143 g, 28.6 mmol) (60% en

aceite mineral) en 6 ml de CS_2 se añadió *Cap-178, etapa b* (4.5 g, 19 mmol) en 40 ml de CS_2 gota a gota durante 15 min. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La mezcla viró a color naranja claro con algo de sólido. Se añadió gota a gota entonces MeI (14.29 ml, 229 mmol) durante 20 min. La mezcla se agitó entonces a temperatura ambiente durante la noche. La reacción se inactivó cuidadosamente con solución saturada de NH_4Cl. La mezcla se extrajo con EtOAc (3X). Las fases orgánicas combinadas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía instantánea (gel de sílice, EtOAc al 6%/Hex) dando *Cap-178, etapa c* (3.13 g) como aceite transparente. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{15}H_{18}NaO_4S_2$ 349.05; encontrado 349.11; RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7.94 - 8.00 (2 H, m), 7.50 - 7.58 (1 H, m), 7.41 (2 H, t, *J*=7.78 Hz), 5.96 (1 H, t, *J*=9.46 Hz), 5.28 (1 H, ddd, *J*=11.37, 9.38, 5.49 Hz), 4.02 (1 H, ddd, *J*=11.98, 4.96, 1.68 Hz), 3.54 - 3.68 (2 H, m), 2.48 (3 H, s), 2.31 (1 H, dd), 1.88 - 1.99 (1 H, m), 1.28 (3 H, d).

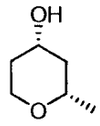
Cap-178, etapa d



A una mezcla de *Cap-178, etapa c* (3.13 g, 9.59 mmol) y AIBN (120 mg, 0.731 mmol) en 40 ml de benceno a 80 °C

se añadió hidruro de tri-n-butilestaño (10.24 ml, 38.4 mmol). La mezcla resultante se agitó a temperatura de reflujo durante 20 min y luego se enfrió hasta temperatura ambiente. La mezcla se diluyó con éter dietílico y se añadieron 100 ml de solución acuosa de KF (10 g) y la mezcla se agitó vigorosamente durante 30 min. Se separaron entonces las dos fases y la fase acuosa se extrajo con EtOAc (2X). La fase orgánica se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía instantánea (gel de sílice, desactivada con Et_3N al 3% en Hexanos y se inyectó Et_3N al 3% en Hexanos para eliminar el derivado de tributilestaño y luego se eluyó con EtOAc al 15%/Hex) dando *Cap-178, etapa d* (1.9 g) como aceite transparente. RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7.98 - 8.07 (2 H, m), 7.52 - 7.58 (1 H, m), 7.43 (2 H, t, *J*=7.63 Hz), 5.08 - 5.17 (1 H, m), 4.06 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.50 - 3.59 (2 H, m), 2.08 - 2.14 (1 H, m), 1.99 - 2.06 (1 H, m), 1.69 - 1.80 (1 H, m), 1.41 - 1.49 (1 H, m), 1.24 (3 H, d, *J*=6.10 Hz).

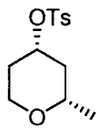
Cap-178, etapa e



A una mezcla de *Cap-178, etapa d* (1.9 g, 8.63 mmol) en 10 ml de MeOH se añadió metóxido sódico (2 ml, 4.00 mmol) (2 M en metanol). La mezcla resultante se agitó a temperatura ambiente durante 5 horas. El solvente se eliminó a vacío. La

mezcla se neutralizó con solución saturada de NH_4Cl y se extrajo con EtOAc (3X). Las fases orgánicas se secaron con $MgSO_4$ y se concentraron dando *Cap-178, etapa e* (0.8 g) como aceite transparente. El producto se usó en la etapa siguiente sin purificación posterior. RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 4.01 (1 H, ddd, *J*=11.80, 5.02, 1.76 Hz), 3.73 - 3.83 (1 H, m), 3.36 - 3.46 (2 H, m), 1.92 - 2.00 (1 H, m), 1.88 (1 H, m), 1.43 - 1.56 (1 H, m), 1.23 (3 H, d), 1.15 - 1.29 (1 H, m).

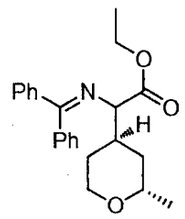
Cap-178, etapa f



Se añadió cloruro de tosilo (2.63 g, 13.77 mmol) a una solución de *Cap-178, etapa e* (0.8 g, 6.89 mmol) y piridina (2.23 ml, 27.5 mmol) en 100 ml de CH_2Cl_2, La mezcla resultante se agitó a temperatura ambiente durante 3 días. Se añadieron entonces 10 ml de agua a la mezcla de reacción y la mezcla se agitó a temperatura ambiente durante una hora. Se separaron las dos fases y la fase orgánica se lavó con agua y solución acuosa 1 N de HCl. La fase orgánica se secó con $MgSO_4$ y se concentró dando *Cap-178, etapa f* (1.75 g) como un sólido amarillo claro. El producto se usó en la etapa siguiente sin purificación posterior. Análisis calculado para $[M+H]^+$ $C_{13}H_{19}O_4S$ 271.10; encontrado 270.90; RMN de ^1H (500 MHz,

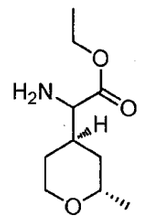
CLOROFORMO-d) δ ppm 7.79 (2 H, d, *J*=8.24 Hz), 7.34 (2 H, d, *J*=7.93 Hz), 4.53 - 4.62 (1 H, m), 3.94 (1 H, ddd, *J*=12.13, 4.96, 1.83 Hz), 3.29 - 3.41 (2 H, m), 2.45 (3 H, s), 1.90 - 1.97 (1 H, m), 1.79 - 1.85 (1 H, m), 1.64 - 1.75 (1 H, m), 1.38 - 1.48 (1 H, m), 1.17 (3 H, d, *J*=6.10 Hz).

Cap-178, etapa g



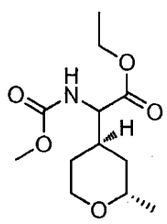
En un tubo de microondas se colocó 2-(difenilmetilenamino)acetato de etilo (1.6 g, 5.92 mmol) y *Cap-178, etapa f* (1.6 g, 5.92 mmol). Se añadieron 10 ml de tolueno. El tubo se selló y se añadió gota a gota bajo N_2 LiHMDS (7.1 ml, 7.10 mmol) (1 N en tolueno). La solución marrón oscura resultante se calentó a 100 °C bajo radiación de microondas durante 6 horas. A la mezcla se añadió entonces agua y la mezcla se extrajo con EtOAc (3X). Las fases orgánicas combinadas se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron dando una mezcla diastereomérica de *Cap-3, etapa g* (3.1 g) como un aceite naranja. La mezcla bruta se sometió a la etapa siguiente sin separación. CL/EM: Análisis calculado para $[M+H]^+$ $C_{23}H_{28}NO_3$ 366.21; encontrado 366.3.

Cap-178, etapa h



A una solución de la mezcla diastereomérica de *Cap-178* de etilo, *etapa g* en 20 ml de THF se añadió HCl (30 ml, 60.0 mmol) (2 N acuoso). La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla se extrajo con EtOAc y la fase acuosa se concentró dando una sal HCl de *Cap-178, etapa h* (1.9 g) como un aceite naranja. La sal se usó en la etapa siguiente sin purificación posterior. CL/EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{20}NO_3$ 202.14; encontrado 202.1.

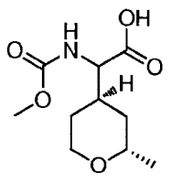
Cap-178, etapa i



Se agitó una solución de 1.9 g *Cap-178, etapa h* (sal HCl), DiPEA (4.19 ml, 24.0 mmol) y cloroformiato de metilo (1.24 ml, 16.0 mmol) en 20 ml de CH_2Cl_2 a temperatura ambiente durante 1 hora. La mezcla se diluyó con CH_2Cl_2 y se lavó con agua. La fase orgánica se secó con Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía

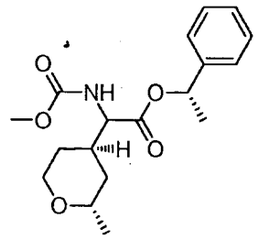
instantánea (gel de sílice, EtOAc al 0-20%/Hex) dando *Cap-178, etapa i* (1.1 g) como un aceite amarillo. Análisis calculado para $[M+Na]^+$ $C_{12}H_{21}NNaO_5$ 282.13; encontrado 282.14; RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 5.16 (1 H, s ancho), 4.43 - 4.58 (1 H, m), 4.17 - 4.28 (2 H, m), 3.89 - 4.03 (1 H, m), 3.72 - 3.78 (2 H, m), 3.67 - 3.72 (3 H, m), 2.07 - 2.19 (1 H, m), 1.35 - 1.77 (4 H, m), 1.30 (3 H, td, *J*=7.09, 2.89 Hz), 1.19 (3 H, d, *J*=6.53 Hz).

Cap-178, etapa j



A una mezcla de *Cap-178, etapa i* (1.1 g, 4.2 mmol) en 5 ml de THF y 2 ml de agua se añadió LiOH (6.36 ml, 12.7 mmol) (2 N ac.). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se neutralizó entonces con HCl acuoso 1 N y se extrajo con EtOAc (3X). Las fases orgánicas combinadas se secaron con $MgSO_4$ y se concentraron dando *Cap-178, etapa j* (0.8 g) como un aceite transparente. CL/EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; encontrado 232.1; RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 5.20 (1 H, d, *J*=8.28 Hz), 4.54 (1 H, t, *J*=8.16 Hz), 3.95 - 4.10 (1 H, m), 3.66 - 3.85 (5 H, m), 2.15 - 2.29 (1 H, m), 1.41 - 1.85 (4 H, m), 1.23 (3 H, dd, *J*=6.53, 1.76 Hz).

Cap-178, etapa k

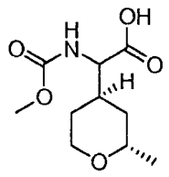


A una solución de *Cap-178, etapa j* (240 mg, 1.04 mmol), (S)-1-feniletanol (0.141 ml, 1.142 mmol) y EDC (219 mg, 1.14 mmol) en 10 ml de CH_2Cl_2 se añadió DMAP (13.95 mg, 0.114 mmol). La solución resultante se agitó a temperatura ambiente durante la noche y el solvente se eliminó a vacío. El residuo se recogió en EtOAc, se lavó con agua, se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía (gel de sílice, EtOAc al 0-15%/Hexanos) dando *Cap-178, etapa k* como una mezcla de dos diastereómeros. La mezcla se separó por HPLC quiral (columna CHIRALPAK® AS, 21 x 250 mm, 10 um) eluyendo con dietilamina al 90%/heptano al 0.1% /EtOH al 10% a 15 ml/min dando *Cap-178, estereoisómero 1 de la etapa k* (eluye primero) y *Cap-178, estereoisómero 2 de la etapa k* (eluye segundo) *como* sólido blancos. La estereoquímica de los dos isómeros no se determinó.

Cap-178, estereoisómero 1 de la etapa k (130 mg): CL/EM: Análisis calculado para $[M+Na]^+$ $C_{18}H_{25}NNaO_5$ 358.16; encontrado 358.16; RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7.28 - 7.38 (5 H, m), 5.94 (1 H, q, *J*=6.71 Hz), 5.12 (1 H, d, *J*=9.16 Hz), 4.55 (1 H, t, *J*=9.00 Hz), 3.72 - 3.81 (1 H, m),

3.67 (3 H, s), 3.60 - 3.70 (2 H, m), 1.98 - 2.08 (1 H, m), 1.59 (3 H, d, *J*=6.71 Hz), 1.38 - 1.47 (2 H, m), 1.30 (2 H, t, *J*=5.34 Hz), 0.93 (3 H, d, *J*=6.41 Hz).

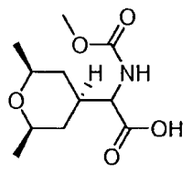
Cap-178, estereoisómero 1



Ácido 2-(metoxicarbonilamino)-2-((2R,4S)-2-metiltetrahidro-2H-piran-4-il)acético

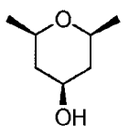
A una solución de *Cap-178, estereoisómero 1 de la etapa k* (ácido (S)-2-(metoxicarbonilamino)-2-((2S,4R)-2-metiltetrahidro-2H-piran-4-il)acético) (150 mg, 0.447 mmol) en 10 ml de EtOH se añadió Pd/C (20 mg, 0.188 mmol) y la mezcla se sometió a hidrogenación en un agitador de Parr a 2.757 x 10^5 Pa durante la noche. La mezcla se filtró a continuación y el filtrado se concentró dando *Cap-178, estereoisómero 1* (100 mg) como un sólido blanco pegajoso. CL/EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; encontrado 232.1; RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 5.14 - 5.27 (1 H, m), 4.51 (1 H, t, *J*=8.39 Hz), 3.90 - 4.07 (1 H, m), 3.60 - 3.83 (5 H, m), 2.06 - 2.27 (1 H, m), 1.45 - 1.77 (4 H, m), 1.21 (3 H, d, *J*=6.41 Hz).

Cap-179



179 estereoisómero 1
179 estereoisómero 2

Cap-179, etapa a

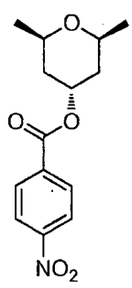


Se disolvió 2,6-dimetil-4H-piran-4-ona (10 g, 81 mmol) en etanol (125 ml) y se añadió Pd/C (1 g, 0.94 mmol). La mezcla se sometió a hidrogenación en un agitador de Parr bajo H_2 (0.325 g, 161 mmol) (4.825×10^5 Pa) a temperatura ambiente durante 12 horas. El catalizador se filtró a través de una almohadilla de CELITE® y se lavó con etanol. El filtrado se concentró a vacío y le residuo se purificó por BIOTAGE® (EtOAc 2% a 25 %/Hex; columna de 160 g). Se aislaron dos fracciones de aceites transparentes. La primera que eluye corresponde a (2R,6S)-2,6-dimetildihidro-2H-piran-4(3H)-ona (1.8 g, 14.04 mmol, 17.43 % de rendimiento) mientras que la segunda corresponde a *Cap-179, etapa a* (1.8 g).

Datos de (2R,6S)-2,6-dimetildihidro-2H-piran-4(3H)-ona: RMN de ^{1}H (500 MHz, *CLOROFORMO-d*) δ ppm 3.69 (2 H, ddd, *J*=11.29, 5.95, 2.29 Hz), 2.24 - 2.36 (2 H, m), 2.08 - 2.23 (2 H, m), 1.18 - 1.34 (6 H, m); ^{13}C NMR (126 MHz, *CLOROFORMO-d*) δ ppm 206.96 (1 C, s ancho), 72.69 (2 C, s), 48.70 (2 C, s), 21.72 (2 C, s).

Datos de Cap-179, etapa a: RMN de ^{1}H (500 MHz, *CLOROFORMO-d*) δ ppm 3.69 - 3.78 (1 H, m), 3.36 - 3.47 (2 H, m), 2.10 (1 H, s ancho), 1.88 (2 H, dd, *J*=12.05, 4.73 Hz), 1.19 (6 H, d, *J*=6.10 Hz), 1.10 (2 H, q, *J*=10.70 Hz); ^{13}C NMR (126 MHz, *CLOROFORMO-d*) δ ppm 71.44 (2 C, s), 67.92 (1 C, s), 42.59 (2 C, s), 21.71 (2 C, s).

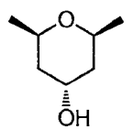
Cap-179, etapa b



Se añadió gota a gota DEAD (2.311 ml, 14.59 mmol) a una solución de *Cap-179, etapa a* (0.38 g, 2.92 mmol), ácido 4-nitrobenzoico (2.195 g, 13.14 mmol) y Ph_3P (3.83 g, 14.59 mmol) en benceno (25 ml). Se detectó generación de calor y la solución ámbar resultante se agitó a temperatura ambiente durante 6 horas. El solvente se eliminó a presión reducida y el residuo se purificó mediante BIOTAGE® (EtOAc al 0 a 15%/Hex; columna de 80 g). Se aisló un sólido blanco que corresponde a *Cap-179, etapa b* (0.77 g). CL/EM: Análisis calculado para $[M]^+$ $C_{14}H_{17}NO_5$: 279.11; encontrado 279.12, RMN de ^{1}H (500 MHz, *CLOROFORMO-d*) δ ppm 8.27 - 8.32 (2 H, m), 8.20 - 8.24 (2 H, m), 5.45 (1 H, quin, *J*=2.82 Hz), 3.92 (2 H, dqd, *J*=11.90, 6.10, 6.10, 6.10, 1.53 Hz), 1.91 (2 H, dd,

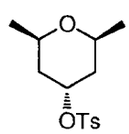
J=14.80, 2.29 Hz), 1.57 (3 H, dt, *J*=14.65, 3.05 Hz), 1.22 (6 H, d, *J*=6.10 Hz).

Cap-179, etapa c



Se añadió una solución de LiOH (0.330 g, 13.8 mmol) en agua (8 ml) a una solución de *Cap-179, etapa b* (0.77 g, 2.76 mmol) en THF (30 ml) y la mezcla resultante se agitó a temperatura ambiente durante 16 h. Se eliminó el THF a presión reducida y la fase acuosa se diluyó con más agua (20 ml) y se extrajo con EtOAc (3 X 15 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. Se recuperó un residuo oleoso con un sólido blanco. La mezcla se trituró con hexanos y el sólido se separó por filtración proporcionando un aceite transparente que corresponde a *Cap-179, etapa c* (0.34 g, 2.61 mmol, 95 % de rendimiento). RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 4.21 (1 H, quin, *J*=2.82 Hz), 3.87 - 3.95 (2 H, m), 1.72 (1 H, s ancho), 1.63 (2 H, dd, *J*=14.34, 2.14 Hz), 1.39 - 1.47 (2 H, m), 1.17 (6 H, d, *J*=6.41 Hz).

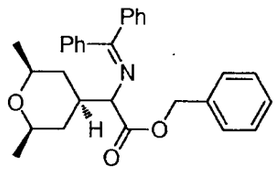
Cap-179, etapa d



Se añadió cloruro de tosilo (3.98 g, 20.89 mmol) a una solución de *Cap-179, etapa c* (1.36 g, 10.5 mmol) y

piridina (3.38 ml, 41.8 mmol) en CH_2Cl_2 (150 ml) a temperatura ambiente y se agitó durante 24 horas y luego se concentró hasta un aceite amarillo. El residuo que queda se añadió a piridina (20 ml) y agua (30 ml) y la mezcla resultante se agitó a temperatura ambiente durante 1 1/2 h. La mezcla se extrajo con Et_2O (75 ml) y la fase orgánica separada se lavó concienzudamente con HCl acuoso 1 N (4 X 50 ml). La fase orgánica se secó a continuación ($MgSO_4$), se filtró y se concentró. Se aisló un sólido blanco que corresponde a *Cap-179, etapa d* (2.2 g). CL/EM: Análisis calculado para $[2M+H]^+$ $C_{28}H_{41}O_8S_2$: 569.22; encontrado 569.3, RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 7.80 (2 H, d, *J*=8.28 Hz), 7.35 (2 H, d, *J*=8.03 Hz), 4.89 (1 H, quin, *J*=2.82 Hz), 3.77 - 3.88 (2 H, m), 2.46 (3 H, s), 1.77 (2 H, dd, *J*=14.93, 2.89 Hz), 1.36 (2 H, ddd, *J*=14.31, 11.54, 2.76 Hz), 1.13 (6 H, d, *J*=6.27 Hz).

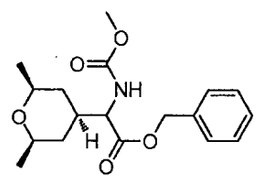
Cap-179, etapa e



Se añadió LiHMDS (4.30 ml, 4.30 mmol) a una solución de *Cap-179, etapa d* (1.02 g, 3.59 mmol) y 2-(difenilmetilenamino)acetato de bencilo (1.181 g, 3.59 mmol) en tolueno (25 ml) a temperatura ambiente en un vial de microondas sellado y la mezcla resultante se agitó entonces durante 5 h a 100 °C bajo radiación de microondas. La

reacción se inactivó con agua (10 ml), se extrajo con EtOAc, se lavó con agua, se secó sobre $MgSO_4$, se filtró y se concentró a vacío. El residuo se purificó por BIOTAGE® (EtOAc al 0% a 6%/Hex; columna de 80 g) y se aisló un aceite amarillo que correspondía a *Cap-179, etapa e* (1.2 g). Análisis calculado para $[2M+Na]^+$ $C_{58}H_{62}N_2NaO_6$: 905.45; encontrado 905.42, RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 7.64 - 7.70 (4 H, m), 7.29 - 7.44 (29 H, m), 7.06 (4 H, dd, *J*=7.65, 1.63 Hz), 5.18 (2 H, d, *J*=2.01 Hz), 3.89 (2 H, d, *J*=6.53 Hz), 3.79 - 3.87 (1 H, m), 3.46 (5 H, dquind, *J*=11.26, 5.87, 5.87, 5.87, 5.87, 1.88 Hz), 2.47 (2 H, s), 2.35 - 2.46 (2 H, m), 1.78 (1 H, dd, *J*=14.81, 3.01 Hz), 1.62 - 1.65 (1 H, m), 1.61 (2 H, s), 1.36 - 1.43 (3 H, m), 1.19 (7 H, d, *J*=6.27 Hz), 1.14 (11 H, dd, *J*=6.15, 2.89 Hz), 0.86 - 0.96 (3 H, m).

Cap-179, etapa f (estereoisómero 1 y estereoisómero 2)



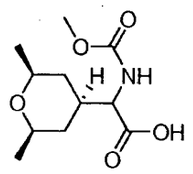
Se disolvió *Cap-179, etapa d* (2.08 g, 4.71 mmol) en THF (100 ml) y se trató con HCl 2 N (9.42 ml, 18.84 mmol). La solución transparente resultante se agitó a temperatura ambiente durante 4 h y luego se eliminó el THF a presión reducida. La fase acuosa que quedó se extrajo con hexanos (3 X 20 ml) y, después de diluir con H_2O (20 ml), se basificó la fase acuosa con NaOH 1 N hasta pH = 10 y se extrajo con EtOAc

(3 x 10 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo resultante se recogió en CH_2Cl_2 (100 ml) y se cargó con DIEA (2.468 ml, 14.13 mmol) y cloroformiato de metilo (0.401 ml, 5.18 mmol). La solución resultante se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se inactivó con agua (10 ml) y la fase orgánica se eliminó a presión reducida. La fase acuosa se extrajo entonces con EtOAc (3 x 10 ml) y las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por BIOTAGE® (EtOAc al 10%/Hex; columna de 25 g). Se recuperó un aceite incoloro transparente que correspondía a *Cap-179, etapa f* (1.05 g). CL/EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{26}NO_5$: 336.18; encontrado 336.3, RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7.32 - 7.40 (5 H, m), 5.26 (1 H, d, *J*=8.24 Hz), 5.13 - 5.24 (2 H, m), 4.36 (1 H, dd, *J*=8.85, 4.88 Hz), 3.68 (3 H, s), 3.32 - 3.46 (2 H, m), 2.02 - 2.14 (1 H, m), 1.52 (1 H, d, *J*=12.82 Hz), 1.32 (1 H, d, *J*=12.51 Hz), 1.11 - 1.18 (6 H, m), 0.89 - 1.07 (2 H, m).

Se desarrolló un proceso de SFC quiral para separar la mezcla de estereoisómeros usando metanol al 12% como modificador en una columna CHIRALPAK® AD-H (30 x 250mm, 5µm) (Temp = 35 °C, Presión = 150 x 10^5 Pa, Longitud de onda = 210 nm, Velocidad de flujo = 70 ml/min durante 8 min, solvente A = CO_2, solvente B = MeOH). Los dos isómeros separados, *Cap-179*

etapa f (estereoisómero 1) (eluye primero) *y Cap-179 etapa f (estereoisómero 2)* (eluye segundo) mostraron los mismos datos analíticos que la mezcla correspondiente (véase más arriba).

Cap-179



179 estereoisómero-1
179 estereoisómero-2

ácido 2-((2R,4r,6S)-2,6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético

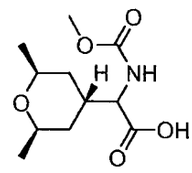
Se disolvió *Cap-179 etapa f (estereoisómero 1)* (0.35 g, 1.044 mmol) en MeOH (50 ml) en un aparato de Parr y se cargó con Pd/C (0.111 g, 1.044 mmol). La suspensión se colocó entonces en un agitador de Parr y se inyectó N_2 (3X) a la mezcla, se colocó bajo 2.757 x 10^5 Pa de H_2 (2.104 mg, 1.044 mmol) y se agitó a temperatura ambiente durante 2 h. El catalizador se separó por filtración a través de una almohadilla de CELITE® y el solvente se eliminó a presión reducida, proporcionando un sólido ámbar que corresponde a *Cap-179 estereoisómero 1* (0.25 g, 1.019 mmol, 98 % de rendimiento). RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 12.74 (4 H, s ancho), 7.35 (4 H, d, *J*=6.10 Hz), 3.85 (4 H, s ancho), 3.53 (3 H, s), 3.35 (2 H, ddd, *J*=15.95, 9.99, 6.10 Hz), 1.97 (1 H, s ancho), 1.48 (2 H, t, *J*=13.28 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.82 - 1.00 (2 H, m)

Se obtuvo *Cap-179 estereoisómero 2* de conformidad

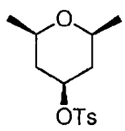
con el proceso usado para preparar *Cap-179 estereoisómero 1* usando *Cap-179 etapa f (estereoisómero 1)* como material de partida. *Cap-179 estereoisómero 2*: RMN de ^{1}H (500 MHz, *DMSO-d$_6$*) δ ppm 12.50 (1 H, s ancho), 7.31 (1 H, s ancho), 3.84 (1 H, t, *J*=7.32 Hz), 3.53 (3 H, s), 3.29 - 3.41 (2 H, m), 1.99 (1 H, s), 1.48 (2 H, t, *J*=14.34 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.95 (1 H, q, *J*=12.21 Hz), 0.87 (1 H, q, *J*=11.80 Hz).

Cap-180

Mezcla de reacción



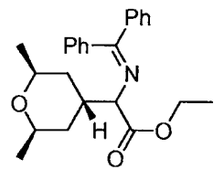
Cap-180, etapa a



Se añadió cloruro de tosilo (4.39 g, 23.0 mmol) a una solución de *Cap-179, etapa a* (1.50 g, 11.5 mmol) y piridina (3.73 ml, 46.1 mmol) en CH_2Cl_2 (50 ml) a temperatura ambiente y se agitó durante 2 días. La reacción se diluyó con CH_2Cl_2, se lavó con agua y luego con HCl 1 N. La fase orgánica se secó ($MgSO_4$) y se concentró hasta un aceite amarillo que se purificó por BIOTAGE® (EtOAc al 5% a 20%/Hex; columna de 40 g). Se aisló un aceite transparente que solidificó a vacío y que corresponde a *Cap-180-2a* (2.89 g). CL/EM: Análisis calculado para $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$: 591.21; encontrado 591.3,

RMN de ^{1}H (500 MHz, *CLOROFORMO-d*) δ ppm 7.80 (2 H, d, *J*=8.24 Hz), 7.35 (2 H, d, *J*=7.93 Hz), 4.59 (1 H, tt, *J*=11.37, 4.96 Hz), 3.36 - 3.46 (2 H, m), 2.46 (3 H, s), 1.91 (2 H, dd, *J*=12.05, 5.04 Hz), 1.37 (2 H, dt, *J*=12.67, 11.52 Hz), 1.19 (6 H, d, *J*=6.10 Hz).

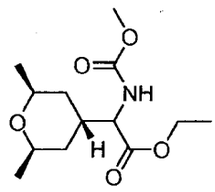
Cap-180, etapa b



Se añadió LiHMDS 1 N (7.09 ml, 7.09 mmol) a una solución de *Cap 180, etapa a* (1.68 g, 5.91 mmol) y 2-(difenilmetilenamino)acetato de etilo (1.579 g, 5.91 mmol) en tolueno (30 ml) a temperatura ambiente y la mezcla resultante se agitó entonces durante 16 h a 85 °C. La reacción se inactivó con agua (50 ml), se extrajo con EtOAc, se lavó con agua, se secó sobre $MgSO_4$, se filtró y se concentró en vacuo. El residuo se purificó por BIOTAGE® (EtOAc al 0% a 15%/Hex; columna de 40 g). Se aisló un aceite amarillento transparente que corresponde a *Cap-180, etapa b* (mezcla de estereoisómeros) (0.64 g). CL/EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{30}NO_3$: 380.22; encontrado 380.03, RMN de ^{1}H (400 MHz, *CLOROFORMO-d*) δ ppm 7.64 - 7.70 (2 H, m), 7.45 - 7.51 (3 H, m), 7.38 - 7.44 (1 H, m), 7.31 - 7.37 (2 H, m), 7.13 - 7.19 (2 H, m), 4.39 (1 H, d, *J*=10.54 Hz), 4.16 - 4.26 (2 H, m), 3.29 - 3.39 (1 H, m), 2.93 - 3.03 (1 H, m), 2.70 (1 H, m,

J=9.41, 4.14 Hz), 1.42 - 1.49 (2 H, m), 1.31 - 1.37 (1 H, m), 1.29 (4 H, t, *J*=7.15 Hz), 1.04 (6 H, dd, *J*=7.78, 6.27 Hz).

Cap-180, etapa c

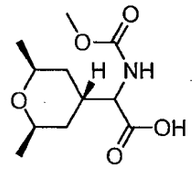


Se disolvió *Cap 180, etapa b* (0.36 g, 0.949 mmol) en THF (10 ml) y se trató con HCl 2 N (1.897 ml, 3.79 mmol). La solución transparente resultante se agitó a temperatura ambiente durante 20 h y se eliminó el THF a presión reducida. La fase acuosa que quedó se extrajo con hexanos (3 X 20 ml) y, después de diluir con H_2O (20 ml), se basificó la fase acuosa con NaOH 1 N hasta pH = 10 y se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo resultante se recogió en CH_2Cl_2 (10.00 ml) y se cargó con DIEA (0.497 ml, 2.85 mmol) y cloroformiato de metilo (0.081 ml, 1.044 mmol). La solución resultante se agitó a temperatura ambiente durante 2 h y la mezcla de reacción se inactivó con agua (10 ml) y la fase orgánica se eliminó a presión reducida. La fase acuosa se extrajo con EtOAc (3 x 10 ml) y las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron. Se recuperó un sólido ámbar que corresponde a *Cap-180, etapa c* (0.21 g) y se usó sin purificación

posterior. CL/EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{24}NO_5$: 273.17; encontrado 274.06, RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 5.20 (1 H, d, *J*=8.03 Hz), 4.59 (1 H, t, *J*=10.16 Hz), 4.11 - 4.27 (3 H, m), 3.69 - 3.82 (2 H, m), 3.64 (3 H, s), 1.95 - 2.07 (1 H, m), 1.63 (1 H, d, *J*=13.80 Hz), 1.41 (2 H, dd, *J*=8.03, 4.02 Hz), 1.31 - 1.37 (1 H, m), 1.26 (3 H, t, *J*=7.15 Hz), 1.16 (1 H, d, *J*=6.27 Hz), 1.12 (6 H, dd, *J*=6.15, 3.89 Hz).

Cap-180

Mezcla racémica

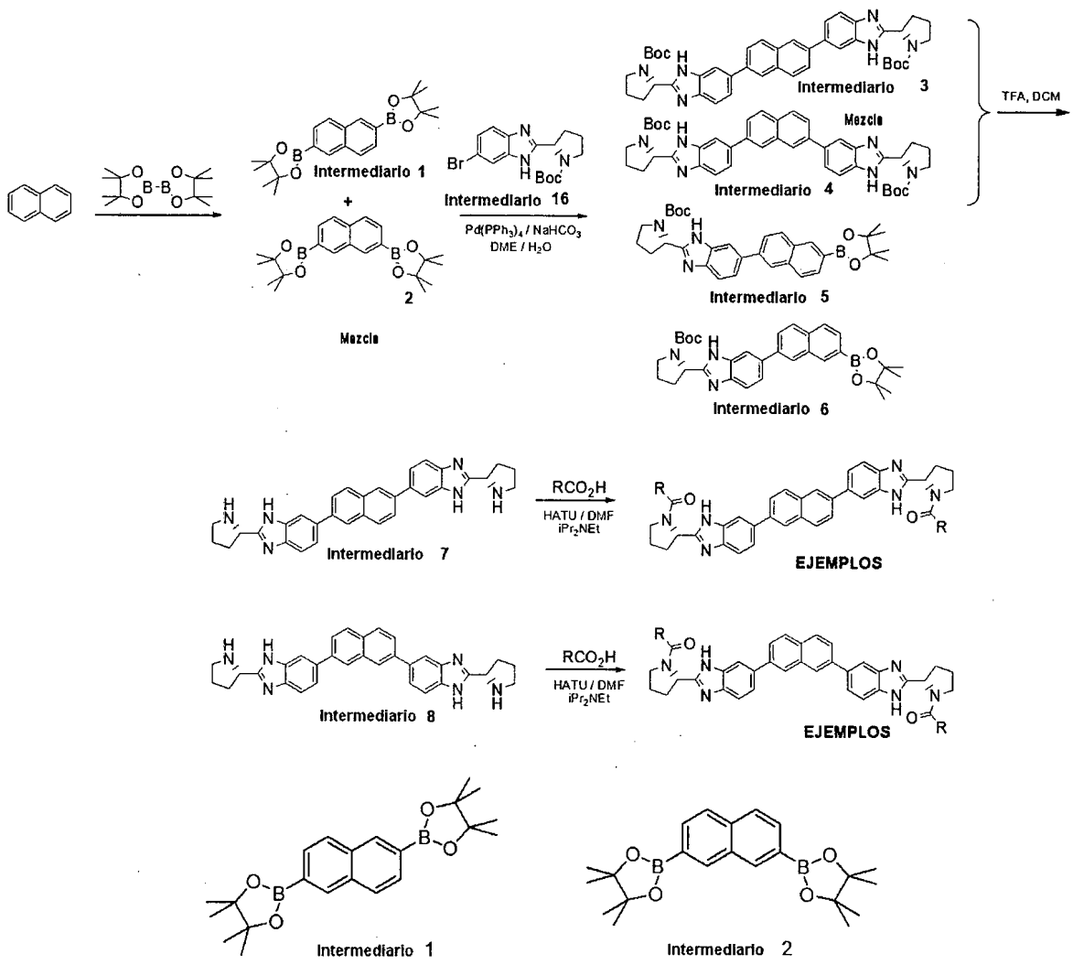


Se disolvió *Cap-180, etapa c* (0.32 g, 1.2 mmol) en THF (10 ml) y se cargó con LiOH (0.056 g, 2.342 mmol) en agua (3.33 ml) a 0 °C. La solución resultante se agitó a ta durante 2 h. Se eliminó el THF a presión reducida y el residuo que quedó se diluyó con agua (15 ml) y se lavó con Et_2O (2 x 10 ml). La fase acuosa se acidificó seguidamente con HCl 1 N hasta pH ~ 2 y se extrajo con EtOAc (3 x 15 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío proporcionando *Cap-180 (mezcla de estereoisómeros)* (0.2 g) como una espuma blanca. CL/EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{20}NO_5$: 246.13; encontrado 246.00, RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm

5.14 (1 H, d, *J*=9.03 Hz), 4.65 (1 H, t, *J*=9.91 Hz), 3.63 - 3.89 (5 H, m), 1.99 - 2.13 (1 H, m), 1.56 - 1.73 (2 H, m), 1.48 - 1.55 (1 H, m), 1.35 - 1.48 (1 H, m), 1.27 (1 H, s ancho), 1.17 (6 H, d, *J*=6.02 Hz).

INTERMEDIARIOS

Esquema de reacción 1



Literature ChemComm; 2005, páginas 2172-2174

Mezcla de Intermediario 1

2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno

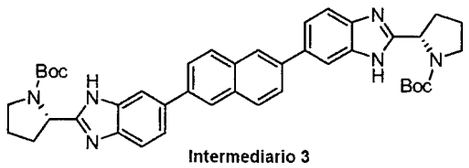
e Intermediario 2

2.7-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno

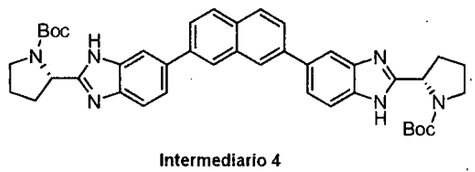
A una solución desgasificada de naftaleno (19.34 g, 151 mmol) y bis(pinacolato)diboro (84 g, 330 mmol) en ciclohexano (500 ml) se añadió 4,4'-di-*terc*-butil-2,2'-dipiridilo (4.05 g, 15.1 mmol) y di-μ-metoxibis(1,5-ciclooctadieno)diiridio (I) (5.0 g, 7.5 mmol). El matraz se selló y se calentó a 80°C durante 16 horas después se dejó enfriar a temperatura ambiente. El color de la reacción se volvió rojo oscuro tras calentamiento. El componente volátil se retiró en el vacío y el material resultante se purificó con cromatografía instantánea (la muestra se cargó seca en gel de sílice y se eluyó con acetato de etilo al 0-100%/tolueno) proporcionando una mezcla de 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno y 2,7-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (54.57 g, rendimiento del 95%, proporción 1.5:1) en forma de sólido blanco.

Intermediario 1: RMN de ^{1}H (500 MHz, benzeno-d_6) δ ppm 8.70 (s, 2H), 8.16 (d, *J*=8.2 Hz, 2H), 7.75 (d, *J*=8.2 Hz, 2H), 1.15 (s, 24H).

Intermediario 2: RMN de ^{1}H (500 MHz, benzeno-d_6) δ ppm 8.77 (s, 2H), 8.22 (d, *J*=8.2 Hz, 2H), 7.66 (d, *J*=8.2 Hz, 2H), 1.15 (s, 24H).



Intermediario 3



Intermediario 4

Mezcla de Intermediario 3

2,2'-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-terc-butilo

e Intermediario 4

2,2'-(5,5'-(naftaleno-2,7-diil)bis(1H-benzo[d]imidazol-5,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-terc-butilo

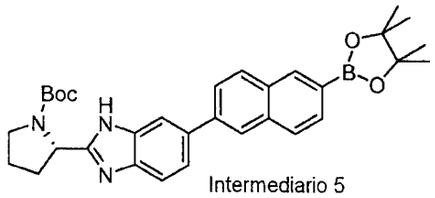
A una mezcla de 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno y 2,7-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (1.5:1) (1.25 g, 3.29 mmol) y 2-(6-bromo-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (3.01 g, 8.22 mmol) en 1,2-dimetoxietano (50 ml) y agua (12.5 ml) se añadió $NaHCO_3$ (1.38 g, 16.4 mmol). La mezcla de reacción se desgasificó en el vacío y se purgó con flujo de nitrógeno. Se añadió $Pd(Ph_3P)_4$ (190 mg, 0.164 mmol) y el matraz a presión se tapó y se calentó con un baño de aceite a 85°C durante 16 horas. El componente volátil se retiró en el vacío. Se fraccionó el residuo entre acetato de etilo y agua. Se separaron las fases y se extrajo la fase acuosa varias veces con acetato de etilo. Las fases orgánicas combinadas se filtraron a través de una almohadilla corto de tierra de diatomeas (CELITE®) y

el filtrado se secó (Na_2SO_4), se filtró y se concentró en el vacío. El material resultante se purificó por cromatografía instantánea (la muestra se cargó en seco en gel de sílice y se eluyó con acetato de etilo al 10-100%/CH_2Cl_2) después se cargó con (metanol al 10%/CH_2Cl_2) proporcionando una mezcla de 2,2'-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-*terc*-butilo y 2,2'-(5,5'-(naftaleno-2,7-diil)bis(1H-benzo[d]imidazol-5,2-iil))dipirrolidina-1-carboxilato de (2S,2'S)-*terc*-butilo (622 mg, rendimiento del 27.1%) en forma de sólido naranja que se usa sin purificación adicional. Se purificó una alícuota por una HPLC de fase reversa (agua/acetonitrilo/TFA) proporcionando una muestra analítica de cada intermediario en forma de una sal de TFA.

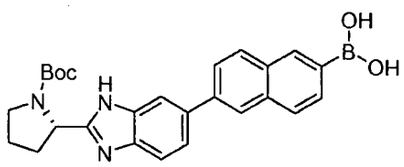
Datos analíticos para el Intermediario 3: Tiempo de retención de CL-EM 1.46 min; calculado para $C_{42}H_{46}N_6O_4$: 698.36 encontrado m/z 699.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue

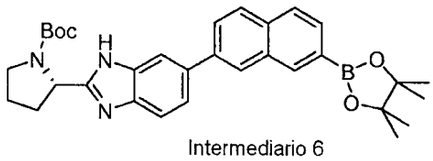
acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (sal de TFA, 500 MHz, MeOD) δ ppm 8.28 (s ancho, 2H), 8.13 (t, *J*=8.7 Hz, 4H), 8.05 (t, *J*=8.4 Hz, 2H), 7.92 (dd, *J*=14.8, 8.7 Hz, 3H), 5.20 - 5.36 (m, 2H), 3.70 - 3.84 (m, 2H), 3.57 - 3.70 (m, 2H), 2.54 - 2.70 (m, 2H), 2.18 - 2.28 (m, 2H), 2.14 (quintete, *J*=6.9 Hz, 4H), 1.50 (s, 9H), 1.23 (s, 9H).

Datos analíticos para el Intermediario 4: Tiempo de retención de CL-EM 1.52 min; calculado para $C_{42}H_{46}N_6O_4$: 698.36 encontrado m/z 699.24 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (sal de TFA, 500 MHz, MeOD) δ ppm 8.33 (s ancho, 2H), 7.98 - 8.17 (m, 6H), 7.83 - 7.98 (m, 4H), 5.18 - 5.35 (m, 2H), 3.71 - 3.83 (m, 2H), 3.57 - 3.70 (m, 2H), 2.63 (s ancho, 2H), 2.19 - 2.28 (m, 2H), 2.07 - 2.18 (m, 4H), 1.50 (s, 9H), 1.22 (s, 9H).

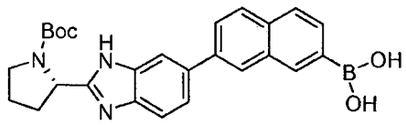


Intermediario 5





Intermediario 6



Intermediarios de ácido borónico

Mezcla de Intermediario 5

2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato trifluoroacetato de (S)-terc-butilo

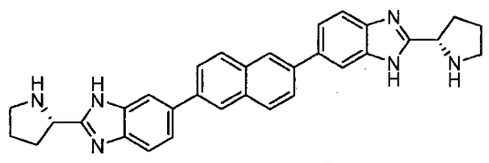
e Intermediario 6

2-(6-(7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato trifluoroacetato de (S)-terc-butilo

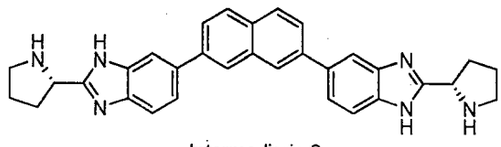
Después de purificación por cromatografía instantánea, la reacción anterior proporcionó también una mezcla de 2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato trifluoroacetato de (S)-*terc*-butilo y 2-(6-(7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (658 mg). Durante la separación de HPLC (amortiguador de TFA) los ésteres bóricos parcialmente

hidrolizados proporcionaron la misma mezcla que los intermediarios de ácido bórico.

Tiempo de retención de CL-EM 1.34 min (ácidos bóricos) y de 2.05 min (ésteres bóricos); calculado para (ácidos bóricos) $C_{26}H_{28}BN_3O_4$: 457.22 encontrado m/z 458.14 $[M+H]^+$. Para (ésteres bóricos) $[M+H]^+$ $C_{32}H_{38}BN_3O_4$: 539.3 encontrado m/z 490.16 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%.



Intermediario 7



Intermediario 8

Intermediario 7

2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno

e Intermediario 8

2,7-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno

Una mezcla de 2,2'-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-*terc*-butilo y 2,2'-(5,5'-(naftaleno-2,7-diil)bis(1H-benzo[d]imidazol-5,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-*terc*-butilo (594 mg, 0.162 mmol) y TFA (2 ml) en CH_2Cl_2 (10 ml) se agitó en condiciones ambientales durante 3 horas. El componente volátil se retiró en el vacío y la materia prima se purificó por una HPLC en fase reversa (agua/acetonitrilo/TFA) proporcionando una sal de TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (434 mg) en forma de sólido amarillo y una sal de TFA de 2,7-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (204.8 mg) en forma de sólido amarillo.

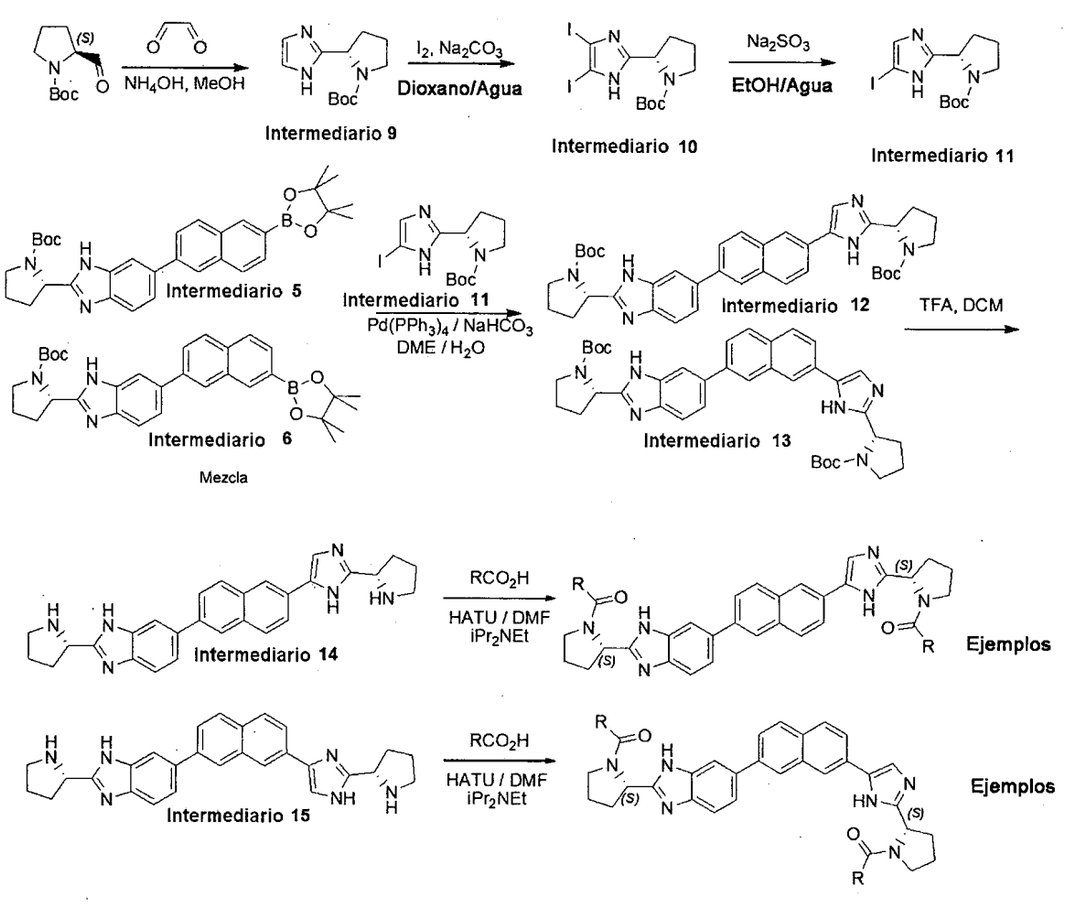
Datos analíticos para el Intermediario 7: Tiempo de retención de CL-EM 1.05 min; calculado para $C_{32}H_{30}N_6$ 498.25

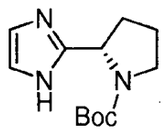
encontrado m/z 499.21 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.06 (d, J=8.6 Hz, 1H), 8.00 (s, 1H), 7.84 - 7.92 (m, 1H), 7.73 - 7.81 (m, 2H), 5.08 (t, J=7.6 Hz, 1H), 3.56 - 3.66 (m, 1H), 3.48 - 3.56 (m, 1H), 2.62 - 2.71 (m, 1H), 2.36 - 2.47 (m, 1H), 2.19 - 2.36 (m, 2H).

Datos analíticos para el Intermediario 8: Tiempo de retención de CL-EM 1.11 min; calculado para $C_{32}H_{30}N_6$ 498.25 encontrado m/z 499.20 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%,

un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.23 (s, 2H), 8.01 (m, 4H), 7.82 - 7.89 (m, 2H), 7.69 - 7.82 (m, 4H), 5.08 (t, *J*=7.6 Hz, 2H), 3.57 - 3.66 (m, 2H), 3.48 - 3.57 (m, 2H), 2.60 - 2.73 (m, 2H), 2.37 - 2.48 (m, 2H), 2.19 - 2.36 (m, 4H).

Esquema de reacción 2





Intermediario 9

2-(1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

Se añadió gota a gota glioxal (2.0 ml del 40% en agua) durante 11 minutos a una solución de metanol de NH_4OH (32 ml) y (S)-Boc-prolinal (8.56 g, 43.0 mmol) y la reacción se agitó a temperatura ambiente durante 19 horas. El componente volátil se retiró en el vacío y el residuo se purificó por una cromatografía instantánea (gel de sílice, acetato de etilo) seguido por una recristalización (acetato de etilo, temperatura ambiente) proporcionando 2-(1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo en forma de un sólido mullido blanco (4.43 g, 18.6 mmol, rendimiento del 43%).

RMN de ^1H (DMSO-d_6, 400 MHz) δ ppm 11.68/11.59 (sa, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35 - 3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H), CLEM. TR = 0.87 min; índice de homogeneidad >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; encontrado 238.22, El compuesto mostró tener un ee del 98.9% cuando se analizó en las condiciones de HPLC quiral destacadas a continuación.

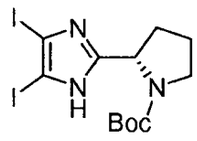
Columna: CHIRALPAK® AD, 10 µm, 4.6 x 50 mm

solvente: 1.7% de etanol/heptano (isocrático)

Velocidad de flujo: 1 ml/min

Longitud de onda: bien 220 ó 256 nm

Tiempo de retención relativo: 3.25 min (*R*), 5.78 minutos (*S*)



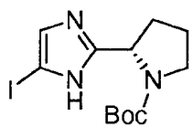
Intermediario 10

2-(4,5-diyodo-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

Se añadió yodo (16.17 g, 63.7 mmol) a una solución de 2-(1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (6.87 g, 29.0 mmol) y carbonato de sodio (9.21 g, 87 mmol) en dioxano (72 ml) y agua (72 ml) a temperatura ambiente. El matraz se recubrió con papel de aluminio y se agitó durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo y una solución acuosa saturada de tiosulfato de sodio. La mezcla se agitó durante 15 minutos y las fases se separaron. La fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron en el vacío proporcionando 2-(4,5-diyodo-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (12.5 g al 88%) en forma de un

sólido canela.

Tiempo de retención de CL-EM 1.40 min; calculado para $C_{12}H_{17}I_2N_3O_2$ 488.94 encontrado m/z 489.96 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 4.72 - 4.84 (m, 1H), 3.58 - 3.70 (m, 1H), 3.43 - 3.54 (m, 1H), 2.36 (s ancho, 1H), 1.88 - 2.08 (m, 3H), 1.47 (s ancho, 3H), 1.27 (s ancho, 6H).



Intermediario 11

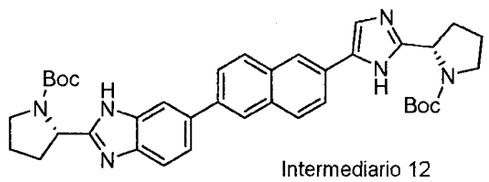
2-(5-yodo-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

Se añadió sulfito de sodio (10.31 g, 82 mmol) a una solución de 2-(4,5-diyodo-1H-imidazol-2-il)pirrolidina-1-

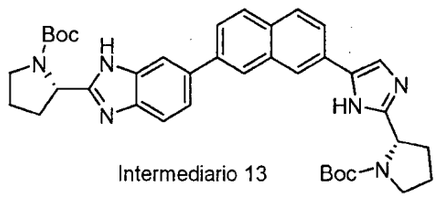
carboxilato de (S)-*terc*-butilo (4.0 g, 8.2 mmol) en etanol (75 ml) y agua (75 ml). La suspensión se calentó con un baño de aceite a 100°C durante 4 horas y a 90°C durante 16 h. La reacción se diluyó con acetato de etilo y agua. Se separaron las fases y se extrajo la fase acuosa varias veces con acetato de etilo. Los extractos orgánicos combinados se secaron (salmuera, Na_2SO_4), se filtraron y se concentraron en el vacío. El residuo se purificó por una cromatografía instantánea (la muestra se cargó en seco en gel de sílice y se eluyó con, acetato de etilo al 0 a 40%/CH_2Cl_2) proporcionando 2-(5-yodo-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (2.17 g, al 73.1%) en forma de un sólido blanco.

Tiempo de retención de CL-EM 0.930 min; calculado para $C_{12}H_{18}IN_3O_2$ 363.04 encontrado m/z 364.06 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al

10%/TFA al 0.1%. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7.52-7.64 (m, 1H), 4.95 - 5.10 (m, 1H), 3.57 - 3.70 (m, 1H), 3.47 - 3.57 (m, 1H), 2.37 - 2.55 (m, 1H), 1.94 - 2.10 (m, 3H), 1.46 (s, 4H), 1.27 (s, 5H).



Intermediario 12



Intermediario 13

Mezcla de Intermediario 12

2-(5-(6-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

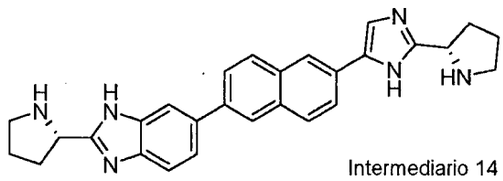
e Intermediario 13

2-(5-(7-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

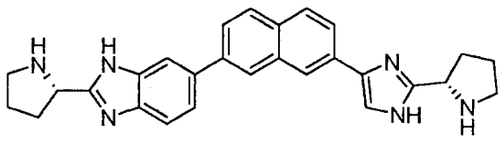
A una mezcla de 2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato trifluoroacetato de (S)-*terc*-butilo y de 2-(6-(7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-

carboxilato trifluoroacetato de (S)-*terc*-butilo (560 mg, 0.980 mmol) y de 2-(5-iodo-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (463 mg, 1.27 mmol) en 1,2-dimetoxietano (11.2 ml) y agua (2.8 ml) se añadió $NaHCO_3$ (412 mg, 4.90 mmol). La mezcla de reacción se desgasificó en el vacío durante 5 minutos y se purgó con flujo de nitrógeno. Se añadió $Pd(Ph_3P)_4$ (57 mg, 0.049 mmol) y el matraz a presión se tapó y se calentó con un baño de aceite a 100°C durante 16 horas. El componente volátil se retiró en el vacío. El residuo se fraccionó entre acetato de etilo y agua y la fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas combinadas se secaron (salmuera, Na_2SO_4), se filtraron y se concentraron en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel de sílice y se eluyó con acetato de etilo al 50-100%/hexanos) proporcionando una mezcla parcialmente purificada de productos que se purificaron adicionalmente por una HPLC de fase reversa (agua/acetonitrilo/TFA) proporcionando una mezcla de una sal de TFA de 2-(5-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo y una sal de TFA de 2-(5-(7-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (74 mg).

Tiempo de retención de CL-EM 1.32 min; calcd. para $[M+H]^+$ $C_{38}H_{44}N_6O_4$ 648.34 encontrado m/z 649.20 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Esta mezcla se usó sin purificación adicional.



Intermediario 14



Intermediario 15

Intermediario 14

2-((S)-pirrolidin-2-il)-6-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-benzo[d]imidazol

y

Intermediario 15

2-((S)-pirrolidin-2-il)-6-(7-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)-1H-benzo[d]imidazol

Una mezcla de 2-(5-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo y 2-(5-(7-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo como sales de TFA (74 mg) y TFA (2 ml) en CH_2Cl_2 (10 ml) se agitó en condiciones ambientales durante 4 horas. El componente volátil se retiró en el vacío. La materia prima se purificó por una HPLC de fase reversa (agua al 0 a 50%/acetonitrilo/TFA) proporcionando una sal de TFA de 2-((S)-pirrolidin-2-il)-6-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-benzo[d]imidazol (32 mg, al 31%) en forma de aceite amarillo y una sal de TFA de 2-((S)-pirrolidin-2-il)-6-(7-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)-1H-benzo[d]imidazol (16 mg) en forma de aceite amarillo.

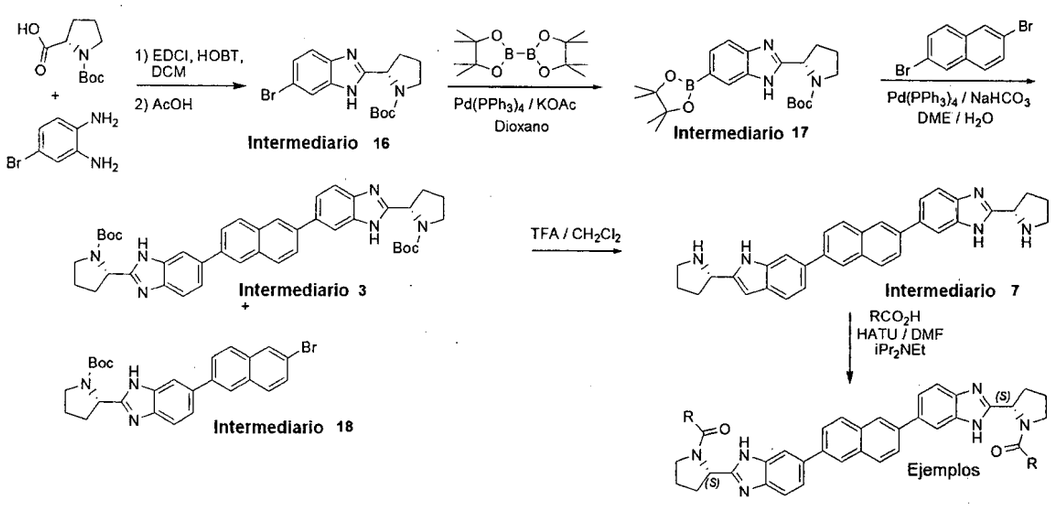
Datos analíticos para el Intermediario 14: Tiempo de retención de CL-EM 0.081 min; calculado para $C_{38}H_{28}N_6$ 448.24 encontrado m/z 449.20 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un

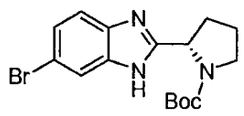
detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.17 (s, 1H), 8.03 (d, *J*=3.7 Hz, 1H), 8.01 (s, 2H), 7.92 - 7.97 (m, 1H), 7.87 7.92 (m, 1H), 7.75 - 7.80 (m, 3H), 5.11 (t, *J*=7.8 Hz, 1H), 4.99 (t, *J*=7.9 Hz, 1H), 3.49 - 3.69 (m, 4H), 2.56 - 2.76 (m, 2H), 2.41 - 2.52 (m, 2H), 2.21 - 2.41 (m, 4H).

Datos analíticos para el Intermediario 15: Tiempo de retención de CL-EM 0.87 min; calculado para $C_{38}H_{28}N_6$ 448.24 encontrado m/z 449.21 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B

fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.39 (s, 1H), 8.19 (s, 1H), 7.97 - 8.04 (m, 3H), 7.91 (d, *J*=8.6 Hz, 1H), 7.87 (d, *J*=8.6 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 2H), 5.12 (t, *J*=7.6 Hz, 1H), 5.04 (t, *J*=8.1 Hz, 1H), 3.50 - 3.68 (m, 4H), 2.60 - 2.74 (m, 2H), 2.41 - 2.55 (m, 2H), 2.21 - 2.41 (m, 4H).

Esquema de reacción 3





Intermediario 16

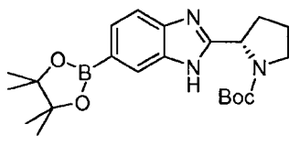
2-(6-bromo-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

Se añadió EDCI·HCl (16.9 g, 88.0 mmol) a una mezcla de 4-bromobenceno-1,2-diamina (15.0 g, 80.0 mmol), N-Boc-L-prolina (18.13 g, 84.0 mmol) y 1-hidroxibenzotriazol (12.28 g, 80.0 mmol) en CH_2Cl_2 (500 ml) y se agitó en condiciones

ambientales durante 16 horas. La mezcla se diluyó después con agua. El precipitado blanco se filtró aparte y las fases se separaron. La fase orgánica se lavó con agua, se secó (salmuera; Na_2SO_4), se filtró y se concentró en el vacío proporcionando una espuma marrón. Se añadió ácido acético (300 ml) a la espuma y la mezcla se calentó a 85°C (temperatura del baño) durante 5 horas. El componente volátil se retiró en el vacío y el residuo se disolvió en EtOAc, se lavó con agua y la fase orgánica se secó (Na_2SO_4), se filtró y se concentró en el vacío. La materia prima resultante se sometió a cromatografía instantánea (gel de sílice; EtOAc al 0-37%/CH_2Cl_2). El material parcialmente puro se volvió a someter a cromatografía instantánea (gel de sílice; EtOAc al 20-35%/CH_2Cl_2) proporcionando 2-(6-bromo-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (17.98 g, rendimiento del 61.2%) en forma de espuma amarilla.

Tiempo de retención de CL-EM 1.23 min; calculado para $C_{16}H_{20}BrN_3O_2$: 365.07 encontrado m/z 368.07 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un

tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7.59 - 7.75 (m, 1H), 7.38 - 7.53 (m, 1H), 7.31 - 7.38 (m, 1H), 5.04-5.09 (m, 0.3H), 4.94 - 5.00 (m, 0.7H), 3.68 - 3.76 (m, 1H), 3.50 - 3.59 (m, 1H), 2.34 - 2.51 (m,, 1H), 1.95 - 2.12 (m, 3H), 1.47 (sa, 3H), 1.15 (s, 6H).



Intermediario 17

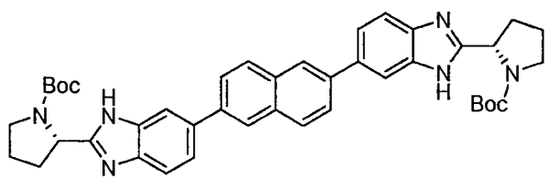
2-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

A un matraz conteniendo una mezcla de 2-(6-bromo-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (4.5 g, 12 mmol) y bis(pinacolato)diboro (6.55 g, 25.8 mmol) en 1,4-dioxano (50 ml) se añadió acetato de potasio (3.01 g, 30.7 mmol). El matraz de reacción se desgasificó en el vacío durante 5 minutos y se purgó después con nitrógeno. Se añadió el catalizador $Pd(Ph_3P)_4$ (710 mg, 0.614 mmol) y el matraz se tapó y se calentó con un baño de

aceite a 85°C (temperatura del baño) durante 16 horas. La mezcla de reacción se concentró en el vacío. La materia prima se fraccionó entre CH_2Cl_2 y una solución de $NaHCO_3$ saturada y la fase acuosa se extrajo con CH_2Cl_2, La fase orgánica combinada se secó (salmuera, Na_2SO_4), se filtró y se concentró en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel de sílice y se eluyó con acetato de etilo al 10-50%/CH_2Cl_2) proporcionando 2-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (2.80 g, rendimiento del 55%) en forma de sólido blanco.

Tiempo de retención de CL-EM 1.493 min; calculado para $C_{22}H_{32}BN_3O_4$: 413.25 encontrado m/z 414.23 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (400 MHz, MeOD) δ ppm 7.81 - 8.08

(m, 1H), 7.40 - 7.68 (m, 2H), 4.95 - 5.13 (m, 1H), 3.68 - 3.79 (s ancho, 1H), 3.48 - 3.60 (s ancho, 1H), 2.35 - 2.52 (s ancho, 1H), 1.95-2.15 (m, 3H), 1.46 (s, 3H), 1.37 (s, 12H), 1.13 (s, 6H).



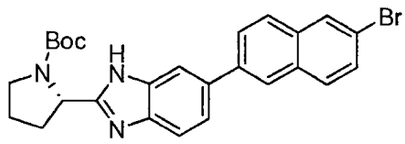
Intermediario 3

2-(5-(6-(2-(1-(terc-butoxicarbonil)-2-pirrolidinil)-1H-benzimidazol-6-il)-2-naftil)-1H-benzimidazol-2-il)-1-pirrolidinacarboxilato de terc-butilo

A una mezcla de 2-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (1.29 g, 33.1 mmol) y 2,6-dibromonaftaleno (446 mg, 1.56 mmol) en 1,2-dimetoxietano (20 ml) y agua (6 ml) se añadió $NaHCO_3$ (787 mg, 9.36 mmol). La mezcla de reacción se desgasificó en el vacío durante 10 minutos y se purgó con flujo de nitrógeno. Se añadió el catalizador $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol) y el matraz se tapó y se calentó con un baño de aceite a 100°C durante 16 horas. El componente volátil se retiró en el vacío. El residuo se fraccionó entre CH_2Cl_2 y agua y las fases se separaron. La fase acuosa se extrajo varias veces con CH_2Cl_2 y las fases orgánicas combinadas se secaron (salmuera, Na_2SO_4), se

filtraron y se concentraron en el vacío. El material resultante se purificó con cromatografía en matraz (la muestra se cargó en seco en gel de sílice y se eluyó con acetato de etilo al 0-70%/CH_2Cl_2) proporcionando 2-(5-(6-(2-(1-(*terc*-butoxicarbonil)-2-pirrolidinil)-1H-benzimidazol-6-il)-2-naftil)-1H-benzimidazol-2-il)-1-pirrolidinacarboxilato de *terc*-butilo (605 mg) en forma de sólido amarillo.

Tiempo de retención de CL-EM 1.46 min; calculado para $C_{42}H_{46}N_6O_4$: 698.36 encontrado m/z 699.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 minuto y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.28 (s ancho, 2H), 8.13 (t, *J*=8.7 Hz, 4H), 8.05 (t, *J*=8.4 Hz, 2H), 7.92 (dd, *J*=14.8, 8.7 Hz, 4H), 5.20 - 5.36 (m, 2H), 3.70 - 3.84 (m, 2H), 3.57 - 3.70 (m, 2H), 2.54 - 2.70 (m, 2H), 2.18 - 2.28 (m, 2H), 2.14 (quintete, *J*=6.9 Hz, 4H), 1.50 (s, 9H), 1.23 (s, 9H).



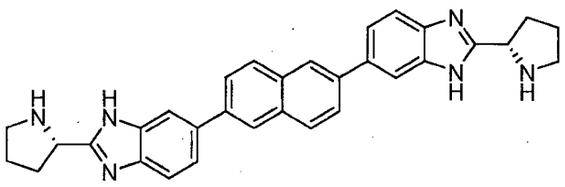
Intermediario 18

(2S)-2-(5-(6-bromo-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinacarboxilato de terc-butilo

La reacción anterior también proporcionó (2S)-2-(5-(6-bromo-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinacarboxilato de *terc*-butilo (519 mg) en forma de sólido amarillo.

Tiempo de retención de CL-EM 1.88 min; calculado para $C_{26}H_{26}BrN_3O_2$: 491.12 encontrado m/z 494.04 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.21 (d, *J*=8.6 Hz, 1H), 8.05 - 8.14 (m, 2H), 7.93 - 8.05 (m, 2H), 7.82 - 7.93 (m, 3H), 7.57 - 7.67 (m, 1H), 5.28 (s ancho, 1H), 3.98

(s, 1H), 3.70 - 3.80 (m, 1H), 3.57 - 3.70 (m, 1H), 2.54 - 2.71 (m, 1H), 2.17 - 2.29 (m, 1H), 2.09 - 2.17 (m, 2H), 1.49 (s, 4H), 1.22 (s, 5H).



Intermediario 7

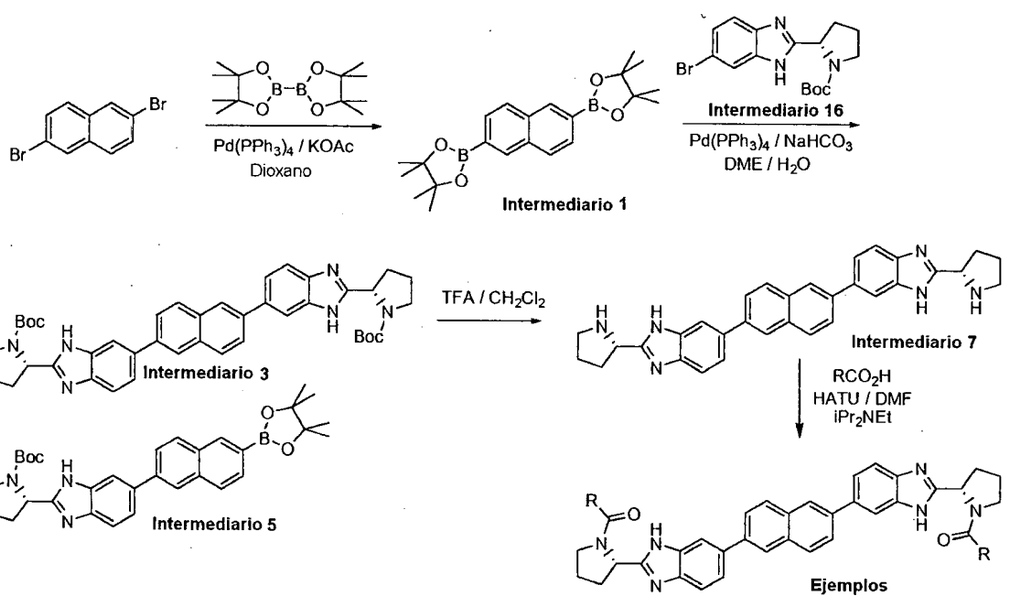
5,5'-(2,6-naftalenodiil)bis(2-(2-pirrolidinil)-1H-benzimidazol)

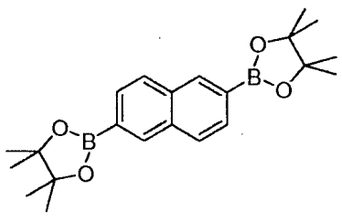
Una mezcla de 2-(5-(6-(2-(1-(*terc*-butoxicarbonil)-2-pirrolidinil)-1H-benzimidazol-6-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinacarboxilato de *terc*-butilo (591 mg, 0.844 mmol) y TFA (2 ml) en CH_2Cl_2 (10 ml) se agitó en condiciones ambientales durante 2 horas. El componente volátil se retiró en el vacío y el material resultante se cargó en una columna de MCX, se purgó con flujo de metanol, se liberó con elución de NH_3 2.0 M/metanol) y se concentró proporcionando 5,5'-(2,6-naftalenodiil)bis(2-(2-pirrolidinil)-1H-benzimidazol) (419 mg) en forma de un sólido canela.

Tiempo de retención de CL-EM 1.02 min; calculado para $C_{33}H_{31}N_5$: 498.25 encontrado m/z 499.25 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x

50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.06 (d, J=8.6 Hz, 1H), 8.00 (s, 1H), 7.84 - 7.92 (m, 1H), 7.73 - 7.81 (m, 2H), 5.08 (t, J=7.6 Hz, 1H), 3.56 - 3.66 (m, 1H), 3.48 - 3.56 (m, 1H), 2.62 - 2.71 (m, 1H), 2.36 - 2.47 (m, 1H), 2.19 - 2.36 (m, 2H).

Esquema de reacción 4





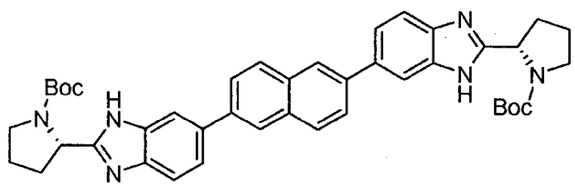
Intermediario 1

2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno

Un matraz a presión conteniendo una mezcla de 2,6-dibromonaftaleno (8.0 g, 28 mmol), bis(pinacolato)diboro (21.3 g, 84.0 mmol), acetato de potasio (3.01 g, 30.7 mmol) y 1,4-dioxano (50 ml) se desgasificó en el vacío durante 5 minutos y se purgó con nitrógeno. Se añadió el catalizador $Pd(Ph_3P)_4$ (710 mg, 0.614 mmol). El matraz se tapó y se calentó con un baño de aceite a 85°C (temperatura del baño) durante 16 horas. La mezcla de reacción se concentró en el vacío y la materia prima se fraccionó entre CH_2Cl_2 y una solución de $NaHCO_3$ saturada. La fase acuosa se extrajo con CH_2Cl_2 y las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel de sílice se eluyó con CH_2Cl_2 al 50-100%/Hexanos) proporcionando 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno contaminado con bis(pinacolato)diboro. El sólido se disolvió en CH_2Cl_2 y se añadió metanol hasta que se observó precipitación. El precipitado se recogió por filtración proporcionando 2,6-

bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (5.1 g, rendimiento al 48%) en forma de sólido blanco.

RMN de ^{1}H (500 MHz, BENCENO-d_6) δ ppm 8.70 (s, 2H), 8.16 (d, *J*=8.2 Hz, 2H), 7.75 (d, *J*=8.2 Hz, 2H), 1.15 (s, 24H).



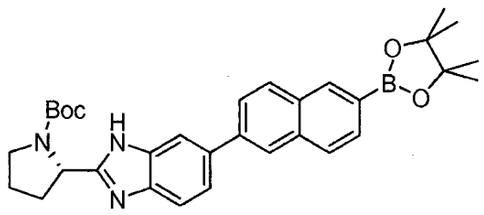
Intermediario 3

2,2'-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-terc-butilo

A una mezcla de 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (2.0 g, 5.3 mmol) y 2,6-dibromonaftaleno de (S)-*terc*-butilo (2.89 g, 7.89 mmol) en 1,2-dimetoxietano (42.1 l) y agua (10.5 ml) se añadió $NaHCO_3$ (2.21 g, 26.3 mmol). La mezcla de reacción se desgasificó en el vacío y se purgó con flujo de nitrógeno. Se añadió el catalizador $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol). El matraz se tapó y se calentó con un baño de aceite a 100°C durante 16 horas. El componente volátil se eliminó en el vacío y el residuo se fraccionó entre acetato de etilo y agua. Se separaron las fases y se extrajo la fase acuosa varias veces con acetato de etilo. Las fases orgánicas combinadas se filtraron a través de una almohadilla corto de tierra de diatomeas (CELITE®) y

el filtrado se secó (Na_2SO_4), se filtró y se concentró en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel de sílice y se eluyó con acetato de etilo al 0-100%/hexanos) proporcionando 2,2-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil)dipirrolidina-1-carboxilato de (2S,2'S)-*terc*-butilo (761 mg, rendimiento del 21%) en forma de sólido naranja.

Tiempo de retención de CL-EM 1.46 min; calculado para $C_{42}H_{46}N_6O_4$: 698.36 encontrado m/z 699.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 minuto y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) □ ppm 8.28 (s ancho, 2H), 8.13 (t, *J*=8.7 Hz, 4H), 8.05 (t, *J*=8.4 Hz, 2H), 7.92 (dd, *J*=14.8, 8.7 Hz, 4H), 5.20 - 5.36 (m, 2H), 3.70 - 3.84 (m, 2H), 3.57 - 3.70 (m, 2H), 2.54 - 2.70 (m, 2H), 2.18 - 2.28 (m, 2H), 2.09 - 2.19 (m, 4H), 1.50 (s, 9H), 1.23 (s, 9H).



Intermediario 5

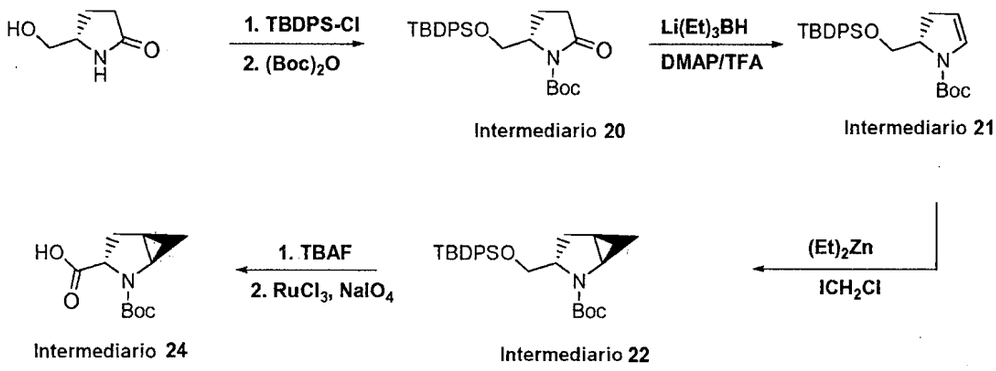
2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

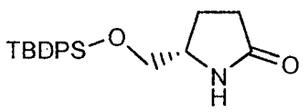
La reacción anterior también proporcionó 2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato trifluoroacetato de (S)-*terc*-butilo (1.58 g, rendimiento del 56%) en forma de sólido canela.

Tiempo de retención de CL-EM 1.46 min; calculado para $C_{32}H_{38}BN_3O_4$: 539.3 encontrado m/z 540.24 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al

10%/TFA al 0.1%.

Esquema de reacción 5



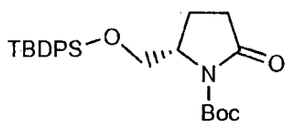


Intermediario 19

(S)-5-((terc-butildifenilsililoxi)metil)pirrolidin-2-ona

A una solución de (*S*)-5-(hidroximetil)pirrolidin-2-ona (10 g, 87 mmol) en CH_2Cl_2 (50 ml) se añadió *terc*-butilclorodifenilsilano (25.6 g, 93 mmol), Et_3N (12.1 ml, 87 mmol) y DMAP (1.06 g, 8.7 mmol). La mezcla se agitó a temperatura ambiente hasta que la pirrolidinona inicial se consumió completamente y después se diluyó con CH_2Cl_2 (50 ml) y se lavó con agua (50 ml). La materia prima se secó (Na_2SO_4), se filtró, se evaporó en el vacío y la materia prima se sometió a cromatografía instantánea (gel de sílice; al 30 a 100% de EtOAc/hexanos) proporcionando (S)-5-((*terc*-butildifenilsililoxi)metil)pirrolidin-2-ona (22.7 g, rendimiento del 74%) en forma de un aceite incoloro.

EM/CL $(M+H)^+$ = 354.58, RMN de ^1H (400 MHz, DMSO-d_6) δ 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).



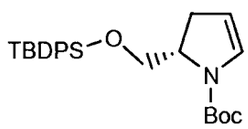
Intermediario 20

2-((terc-butildifenilsililoxi)metil)-5-oxopirrolidina-1-carboxilato de (S)-terc-butilo

Se añadió dicarbonato de di-*terc*-butilo (38.5 g, 177 mmol) por partes en forma de un sólido durante 10 minutos a una solución de (S)-5-((*terc*-butildifenilsililoxi)metil)pirrolidin-2-ona (31.2 g, 88.3 mmol), Et_3N (8.93 g, 88 mmol) y DMAP (1.08 g, 8.83 mmol) en CH_2Cl_2 (200 ml) y la mezcla de reacción se agitó durante 18 horas a 24°C. La mayoría del material volátil se eliminó en el vacío y la materia prima se purificó por cromatografía en gel de sílice (EtOAc al 20%/hexanos a EtOAc al 50%/hexanos) proporcionando 2-((*terc*-butildifenilsililoxi)metil)-5-oxopirrolidina-1-carboxilato de (S)-*terc*-butilo (32.65 g, rendimiento del 82%) en forma de un sólido blanco.

EM/CL $(M-Boc+H)^+$ = 354.58, RMN de ^1H (400 MHz, DMSO-d_6) δ 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).



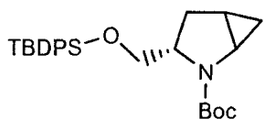
Intermediario 21

2-((terc-butildifenilsililoxi)metil)-2,3-dihidro-1H-pirrol-1-carboxilato de (S)-terc-butilo

Un matraz de tres cuellos equipado con un termómetro y una entrada de nitrógeno se cargó con 2-((*terc*-butildifenilsililoxi)metil)-5-oxopirrolidina-1-carboxilato de (S)-*terc*-butilo (10.05 g, 22.16 mmol) y tolueno (36 ml) y se disminuyó en un baño de enfriamiento de -55°C. Cuando la temperatura interna de la mezcla alcanzó -50°C, se añadió gota a gota trietilborohidruro de litio (23 ml de 1.0 M/THF, 23 mmol) durante 30 min y la mezcla se agitó durante 35 min manteniendo mientras la temperatura interna entre -50°C y -45°C. La base de Hunig (16.5 ml, 94 mmol) se añadió gota a gota durante 10 min. Después, se añadió DMAP (34 mg, 0.278 mmol) en un lote, seguido por la adición de anhídrido trifluoroacético (3.6 ml, 25.5 mmol) durante 15 min, manteniendo mientras la temperatura entre -50°C y -45°C. El baño se eliminó 10 min más tarde y la mezcla de reacción se agitó durante 14 h permitiéndola mientras subir a temperatura ambiente. La mezcla de reacción se diluyó con tolueno (15 ml), se enfrió con un baño de agua helada y se trató

lentamente con agua (55 ml) durante 5 min. Las fases se separaron y la fase orgánica se lavó con agua (50 ml, 2x) y se concentró en el vacío. La materia prima se purificó por cromatografía instantánea (gel de sílice; EtOAc al 5%/hexanos) proporcionando 2-((*terc*-butildifenilsililoxi)metil)-2,3-dihidro-1H-pirrol-1-carboxilato de (S)-*terc*-butilo (7.947 g, rendimiento del 82%) en forma de un aceite viscoso incoloro.

CL-EM $[M+Na]^+$ = 460.19, Tr = 2.41 min según las siguientes condiciones de HPLC: gradiente de solvente a partir de A al 100%: B al 0% a A al 0%: B al 100% (A = TFA al 0.1% en MeOH/agua 1:9; B = TFA al 0.1% en MeOH/agua 9:1) durante 2 min y se mantuvo durante 1 min; detección @ 220 nm; columna PHENOMENEX® Luna 3.0 X 50 mm S10, RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (s ancho, 1H), 5.07/5.01 (d ancho traslapado, 1H), 4.18 (s ancho, 1H), 3.89 (s ancho, 0.5H), 3.69 (s ancho, 1.5H), 2.90-2.58 (m ancho, 2H), 1.40/1.26 (s ancho traslapado, 9H), 0.98 (s, 9H).



Intermediario 22

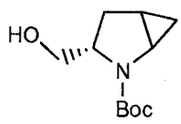
3-((terc-butildifenilsililoxi)metil)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (3S)-terc-butilo

Se añadió gota a gota dietilzinc (19 ml de ~1.1 M

en tolueno, 21 mmol) durante 15 min a una solución de tolueno (27 ml) enfriada (-30 °C) de 2-((*terc*-butildifenilsililoxi)metil)-2,3-dihidro-1H-pirrol-1-carboxilato de (S)-*terc*-butilo (3.94 g, 9.0 mmol). Se añadió gota a gota cloroyodometano (estabilizado sobre cobre; 3.0 ml, 41 mmol) durante 10 y se agitó manteniendo mientras la temperatura del baño a -25°C durante 1 hora y entre -25°C y -21°C durante 18.5 h. La mezcla de reacción se abrió al aire y se desactivó por la adición lenta de solución de $NaHCO_3$ saturada al 50% (40 ml) y después se retiró del baño de enfriamiento y se agitó a temperatura ambiente durante 20 min. La mezcla de reacción se filtró a través de un papel de filtro y la torta blanca se lavó con 50 ml de tolueno. La fase orgánica del filtrado se separó y se lavó con agua (40 ml, 2x), se secó ($MgSO_4$) y se concentró en el vacío. La materia prima se purificó usando cromatografía en gel de sílice (350 g de gel de sílice; la muestra se cargó con EtOAc al 7%/hexanos; eluyó con EtOAc al 7-20%//hexanos) proporcionando 3-((*terc*-butildifenilsililoxi)metil)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (3S)-*terc*-butilo (3.69 g, al 90.7%) en forma de una mezcla de isómeros *cis/trans*. [Nota: en esta fase no se determinó la proporción exacta entre isómeros cis/trans].

CL-EM $[M+Na]^+$ = 474.14, Tr = 2.39 min según las siguientes condiciones de HPLC: gradiente de solvente a

partir de A al 100%: B al 0% a A al 0%: B al 100% (A = TFA al 0.1% en MeOH/agua 1:9; B = TFA al 0.1% en MeOH/agua 9:1) durante 2 min y se mantuvo durante 1 min; detección @ 220 nm; columna PHENOMENEX® Luna 3.0 X 50 mm S10, RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.77/3.67 (s ancho traslapado, 3H), 3.11-3.07 (m, 1H), 2.23 (s ancho aparente, 1H), 2.05-2.00 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (s muy ancho, 9H), 1.00 (s, 9H), 0.80 (m, 1H), 0.30 (m, 1H).



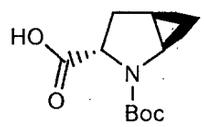
Intermediario 23

3-(hidroximetil)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (3S)-terc-butilo

Se añadió gota a gota TBAF (7.27 ml de 1.0 M en THF, 7.27 mmol) durante 5 min a una solución de THF (30 ml) de 3-((*terc*-butildifenilsililoxi)metil)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (3S)-*terc*-butilo (mezcla de isómeros *cis/trans*) (3.13 g, 6.93 mmol) y la mezcla se agitó a temperatura ambiente durante 4.75 horas. Después de la adición de solución de NH_4Cl saturada (5 ml), la mayoría del material volátil se retiró en el vacío y el residuo se fraccionó entre CH_2Cl_2 (70 ml) y solución de NH_4Cl saturada al 50% (30 ml). La fase acuosa se extrajo con CH_2Cl_2

(30 ml) y la fase orgánica combinada se secó ($MgSO_4$), se filtró, se concentró en el vacío y después se expuso a alto vacío durante toda una noche. La materia prima se purificó usando una cromatografía instantánea (gel de sílice; EtOAc al 40-50%/hexanos) proporcionando 3-(hidroximetil)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (3S)-*terc*-butilo (1.39 g, rendimiento al 94%) en forma de una mezcla de isómeros *cis/trans* y un aceite incoloro. [Nota: en esta fase no se determinó la proporción exacta entre isómeros cis/trans].

CL/EM $(M+H)^+$ = 236.20, RMN de ^1H (400 MHz, DMSO-d_6, δ = 2.5 ppm) δ 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).



Intermediario 24

Ácido (1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico

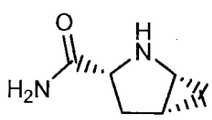
Una semi-solución de $NaIO_4$ (6.46 g, 30.2 mmol) en agua (31 ml) se añadió a una solución de 3-(hidroximetil)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (3S)-*terc*-butilo (mezcla de isómeros *cis/trans*) (2.15 g, 10.08 mmol) en CH_3CN

(20 ml) y CCl_4 (20 ml). Se añadió $RuCl_3$ (0.044 g, 0.212 mmol) inmediatamente 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 CH_2Cl_2 (50 ml, 3x). Las fases orgánicas combinadas se trataron con 1 ml de MeOH, se dejaron reposar durante aproximadamente 5 min y después se filtraron a través de una almohadilla corto de tierra de diatomeas (CELITE®). La almohadilla corto se lavó con CH_2Cl_2 (50 ml) y el filtrado se concentró en el vacío proporcionando un sólido de color gris marengo claro. La materia prima se disolvió en EtOAc (~10 ml) con calor y se dejó reposar a temperatura ambiente con siembra. Aproximadamente 15 min después de empezar la fase de enfriamiento, se observó una rápida formación de cristales. Aproximadamente 1 h después, se añadieron hexanos (~6 ml) y la mezcla se refrigeró toda la noche (no pareció que precipitara material adicional). La mezcla se filtró y se lavó con hexanos refrigerados con agua helada/EtOAc (proporción 2:1; 20 ml) y se secó en vacío elevado proporcionando la primera cosecha del ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico (cristales blanquecinos, 1.222 g). Las aguas madres se concentraron en el vacío y el residuo se disolvió en ~3 ml de EtOAc con calentamiento, se dejó permanecer a temperatura ambiente durante 1 h y después se añadieron 3 ml de hexanos y se almacenaron en un refrigerador durante ~15 h.

Una segunda cosecha de ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico se recuperó de forma similar (cristales grises, 0.133 g), para un rendimiento combinado del 59%.

CL/EM (M+H)+ = 250.22, Tr = 1.48 min según las siguientes condiciones de HPLC: gradiente de solvente a partir de A al 100%: B al 0% a A al 0%: B al 100% (A = TFA al 0.1% en metanol/agua 1:9; B = TFA al 0.1% en MeOH/agua 9:1) durante 3 min; detección @ 220 nm; columna PHENOMENEX® Luna 3.0 X 50 mm S10, Punto de fusión (en grados Celsius) a partir de la primera cosecha = 147.5-149.5°C. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 12.46 (s, 1H), 3.88 (s ancho aparente, 1H), 3.27 (s ancho aparente, 1H; traslapado con señal de agua), 2.28 (s ancho, 1H), 2.07 (s ancho aparente, 1H), 1.56 (s aparente, 1H), 1.40/1.34 (dos s aparentes, 9H), 0.71 (m, 1H), 0.45 (m, 1H). RMN de ^{13}C (100.6 MHz, DMSO-d_6) 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, Análisis calculado para $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16, Encontrado (para primera cosecha): C, 58.24; H, 7.84; N, 6.07, Rotación óptica (10 mg/ml en $CHCl_3$): [α] D = -216 y -212 para la primera y segunda cosecha, respectivamente.

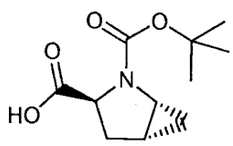
Una síntesis alternativa para el Intermediario 24:



•MSA

Se preparó (1R,3R,5R)-2-azabiciclo[3.1.0]hexano-3-carboxamida (.CH_3SO_3H) según el proceso descrito para la

síntesis de su estereoisómero en la patente WO2004052850.



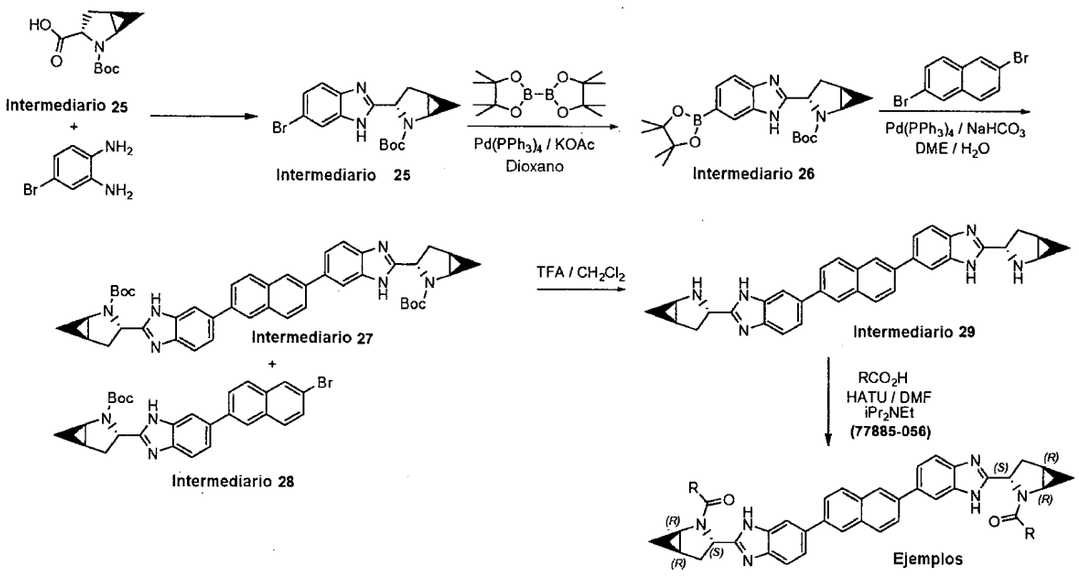
Intermediario 24

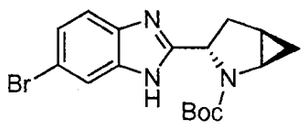
Ácido (1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico

Un matraz de fondo redondo de 1 l equipado con una entrada de nitrógeno, un agitador en la parte alta, termopar y manto calefactor se cargó con 50 g (225 mmol) (1R,3R,5R)-2-azabiciclo[3.1.0]hexano-3-carboxamida ($.CH_3SO_3H$) y 250 ml de isopropanol. La suspensión resultante se cargó después con 252 ml de NaOEl al 23% en peso en EtOH (2.68 M, 675 mmol, 3.0 equiv.) y se agitó a 50°C durante alrededor de 1 hora. La mezcla se cargó con 12.2 ml (675 mmol, 3 equiv.) de agua y se calentó a 60°C. La suspensión resultante se dejó agitar a 60°C durante alrededor de 18 horas. La suspensión se enfrió a ta y se cargó con 250 ml de agua y con 98.2 g (450 mmol, 2.0 equiv.) de di-*t*-butildicarbonato. Se eliminaron etanol e isopropanol por medio de destilación en el vacío y la mezcla acuosa se enfrió a 0°C. La mezcla se neutralizó con 76 ml (456 mmol) de HCl acuoso 6M manteniendo mientras una temperatura interna < 5°C. El producto se extrajo con MTBE 500 ml y la fase orgánica rica se lavó con 100 ml de agua. La solución transparente se concentró hasta 150 ml por medio de destilación en el vacío y la suspensión

resultante se cargó con 600 ml de heptano manteniendo mientras una temperatura interna > 45°C. La suspensión se enfrió a ta durante alrededor de 30 min y se dejó agitar a ta durante alrededor de 2 horas. El producto se filtró, se lavó con 250 ml de heptano:MTBE 4:1 y se secó en agitación a 70°C dando 40.5 g (178 mmol, rendimiento del 79%, 99.8 AP @ 205 nm) de ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico: RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 4.02-3.80 (m, 1H), 3.45-3.15 (m, 1H), 2.40-2.19 (m, 1H), 2.19-2.0 (m, 1H), 1.70-1.50 (m, 1H), 1.50-1.20 (m, 9H), 0.83-0.60 (m, 1H), 0.33-0.55 (m, 1H); RMN de ^{13}C (100 MHz, DMSO-d_6) δ 173.7, 173.2, 155.0, 154.3, 79.4, 60.5, 60.2, 37.6, 32.6, 31.8, 28.4, 28.2, 15.6, 15.2, 14.4; HRMS calculado para $C_{11}H_{18}NO_4$ (M + H; IEP$^+$): 228.1236, Encontrada: 228.1234.

Esquema de reacción 6





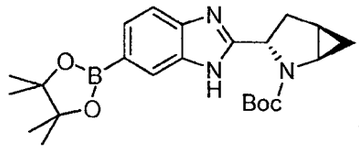
Intermediario 25

3-(6-bromo-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo

Se añadió EDCI·HCl (2.65 g, 13.8 mmol) a una mezcla de 4-bromobenceno-1,2-diamina (2.35 g, 12.6 mmol), (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico (3.00 g, 13.2 mmol) y 1-hidroxibenzotriazol (1.93 g, 12.6 mmol) en CH_2Cl_2 (80 ml) y se agitó en condiciones ambientales durante 16 horas. La mezcla se diluyó después con CH_2Cl_2, se lavó con agua, se secó (salmuera; $MgSO_4$), se filtró y se concentró en el vacío proporcionando una espuma marrón. Se añadió ácido acético (80 ml) a la espuma y la mezcla se calentó a 75°C (temperatura del baño) durante 5 horas. El componente volátil se eliminó en el vacío y el residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ saturado y la fase orgánica se secó (salmuera, $MgSO_4$), se filtró y se concentró en el vacío. La materia prima resultante se sometió a cromatografía instantánea (gel de sílice, EtOAc al 50-100%/hexanos) proporcionando 3-(6-bromo-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-*terc*-butilo (3.01 g, 7.96 mmol,

rendimiento del 63.3%) en forma de una espuma naranja claro, que se usó sin purificación adicional. La reacción también proporcionó 847 mg del mismo producto con pureza más baja. Una alícuota del material recogido se purificó adicionalmente por HPLC preparativa (C-18/CH_3CN-agua al 30-100% + NH_4OAc al 0.1%) logrando una muestra analítica.

Tiempo de retención de CL-EM 1.248 min; calculado para $C_{17}H_{21}BrN_3O_2$: 378.08 encontrado m/z 380.05 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 7.67 (s ancho, 1H), 7.43 (s ancho, 1H), 7.34 (d, J=8.6 Hz, 1H), 4.75 (s ancho, 1H), 3.62 (s ancho, 1H), 2.50 - 2.57 - 2.31 (m, 1H), 2.31 (dt, J=13.2, 6.7 Hz, 1H), 1.66 - 1.85 (m, 1H), 1.45 (s ancho, 3H), 1.11 (s ancho, 6H), 0.87 (dt, J=8.6, 5.8 Hz, 1H), 0.66 (s ancho, 1H).



Intermediario 26

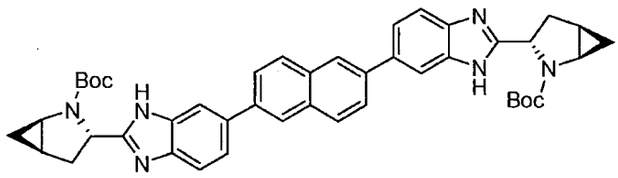
3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo

A un matraz que contiene una mezcla de 3-(6-bromo-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-*terc*-butilo (2.0 g, 5.3 mmol) y bis(pinacolato)diboro (2.69 g, 10.6 mmol) en 1,4-dioxano (50 ml) se añadió acetato de potasio (0.78 g, 7.9 mmol). El matraz de reacción se desgasificó en el vacío durante 10 min y se purgó con nitrógeno. Se añadió $Pd(Ph_3P)_4$ (305 mg, 0.264 mmol) a la mezcla de reacción y el matraz a presión se tapó y se calentó con un baño de aceite a 85°C (temperatura del baño) durante 16 horas. La mezcla de reacción se concentró en el vacío y la materia prima se fraccionó entre CH_2Cl_2 (150 ml) y un medio acuoso (50 ml de agua + 10 ml de solución de $NaHCO_3$ saturada). La fase acuosa se extrajo con CH_2Cl_2 y la fase orgánica combinada se secó (Na_2SO_4), se filtró y se concentró en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel de sílice y se eluyó con acetato de etilo al 20-100%/hexanos) proporcionando 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-

il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-*terc*-butilo (1.74 g, rendimiento del 77%) en forma de espuma blanca. Una alícuota del material recogido se purificó adicionalmente por HPLC preparativa (C-18/CH_3CN-agua al 30-100% + NH_4OAc al 0.1%).

Tiempo de retención de CL-EM 1.78 min; calculado para $C_{23}H_{32}BN_{32}$ 425.25 encontrado m/z 426.21 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX®-Luna 10 u C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Visible con una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio a 10 mmol y el solvente B fue acetonitrilo al 95%/agua al 5%/acetato de amonio a 10 mmol. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 7.94 (s, 1H), 7.61 (d, J=7.9 Hz, 1H), 7.41 - 7.56 (m, 1H), 4.83 (s ancho, 1H), 3.64 (d, J=1.2 Hz, 1H), 2.51 - 2.70 (m, 1H), 2.33 (dt, J=13.4, 6.6 Hz, 1H), 1.67 - 1.84 (m, J=8.5, 6.10, 5.8, 5.8 Hz, 1H), 1.39 - 1.59 (s ancho, 3H), 1.37 (s, 12H), 1.10 (s ancho, 6H), 0.88 (dt, J=8.2, 5.8

Hz, 1H), 0.66 (s ancho, 1H).



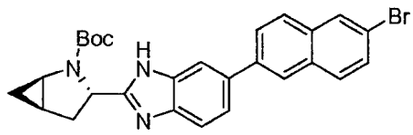
Intermediario 27

3,3'-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexano-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-terc-butilo

A una mezcla de 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-2-carboxilato de (1R,3S,5R)-*terc*-butilo (1.50 g, 3.53 mmol) y 2,6-dibromonaftaleno (403 mg, 1.41 mmol) en 1,2-dimetoxietano (21.7 ml) y agua (6.50 ml) se añadió $NaHCO_3$ (356 mg, 4.23 mmol). La mezcla de reacción se desgasificó en el vacío durante 10 minutos y se purgó con flujo de nitrógeno. Se añadió $Pd(Ph_3P)_4$ (82 mg, 0.071 mmol) y la mezcla de reacción se calentó con un baño de aceite a 100°C durante 16 horas y después el componente volátil se eliminó en el vacío. El residuo se fraccionó entre CH_2Cl_2 y agua (30 ml) y la fase acuosa se extrajo varias veces con CH_2Cl_2, Las fases orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel

de sílice y se eluyó con acetato de etilo al 0-70%/CH_2Cl_2) proporcionando 3,3-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexano-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-*terc*-butilo (377 mg) en forma de sólido amarillo.

Tiempo de retención de CL-EM 1.49 min; calculado para $C_{44}H_{46}N_6O_4$: 722.36 encontrado m/z 723.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.26 (s, 2H), 8.12 (d, *J*=8.5 Hz, 2H), 8.09 (s, 2H), 8.00 (m, *J*=8.6 Hz, 2H), 7.93 (m, *J*=8.6 Hz, 2H), 7.86 (d, *J*=8.6 Hz, 2H), 5.01 (s ancho, 2H), 3.68 (s ancho, 2H), 2.76 (dd, *J*=13.3, 9.3 Hz, 2H), 2.42 - 2.54 (m, 2H), 1.87 (s ancho, 2H), 1.49 (s ancho, 9H), 1.19 (s ancho, 9H), 0.94 (dt, *J*=8.3, 6.1 Hz, 2H), 0.79 (s ancho, 2H).



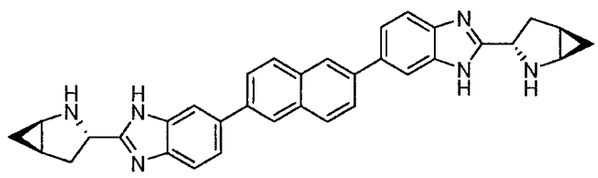
Intermediario 28

3-(6-(6-bromonaftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo

La reacción anterior también proporcionó 3-(6-(6-bromonaftalen-2-il)-1H-benzo[d]imidazol-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-*terc*-butilo (418 mg) en forma de sólido amarillo.

Tiempo de retención de CL-EM 1.90 min; calculado para $C_{27}H_{26}BrN_3O_2$: 503.12 encontrado m/z 506.05 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una

Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.93 - 8.00 (m, 2H), 7.86 - 7.93 (m, 2H), 7.84 (d, *J*=8.6 Hz, 1H), 7.63 (dd, *J*=8.6, 1.8 Hz, 1H), 5.00 (s ancho, 1H), 3.68 (s ancho, 1H), 2.75 (dd, *J*=13.4, 9.2 Hz, 1H), 2.41 - 2.54 (m, 1H), 1.87 (s ancho, 1H), 1.49 (s ancho, 5H), 1.17 (s ancho, 4H), 0.87 - 0.98 (m, 1H), 0.79 (s ancho, 1H).



Intermediario 29

2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0}hexan-3-il)-1H-benzo[d]imidazol-6-il)naftaleno

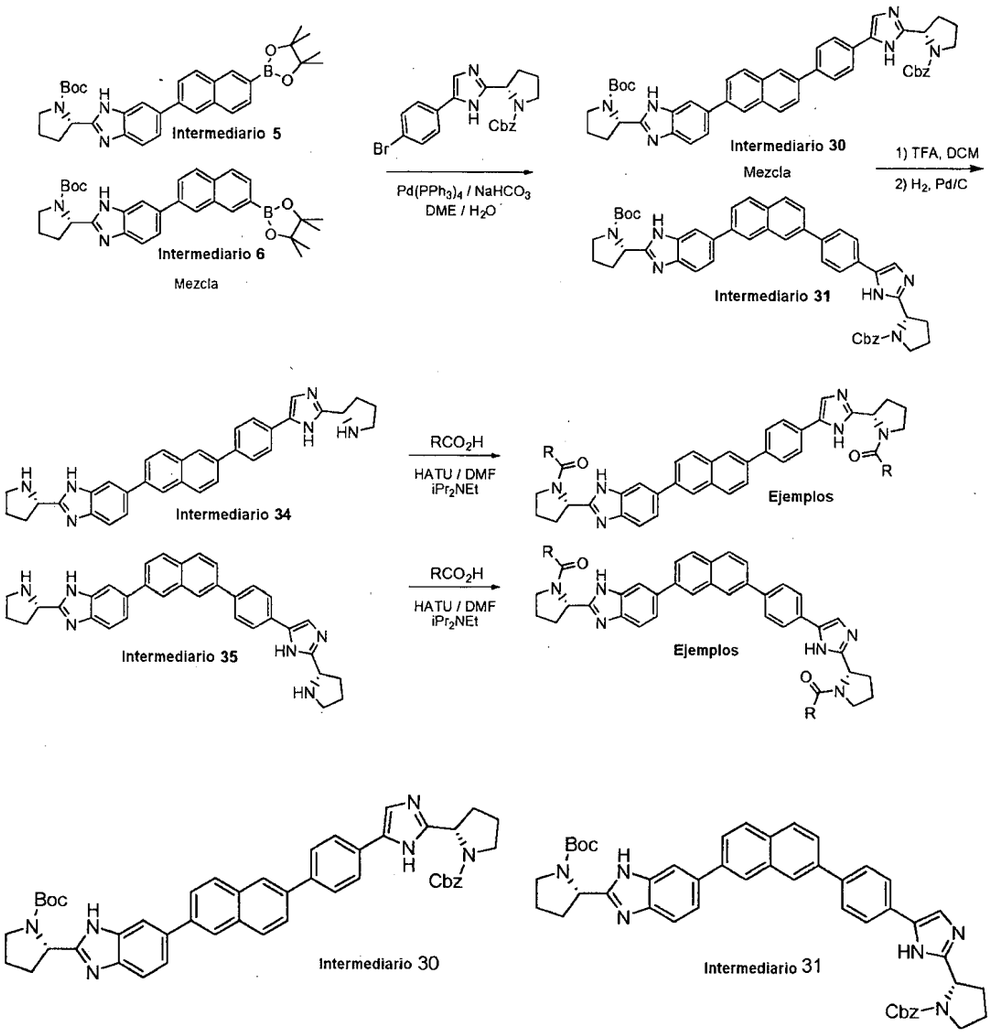
Una mezcla de 3,3'-(6,6'-(naftaleno-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexano-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-*terc*-butilo (360 mg, 0.498 mmol) y TFA (2 ml) en CH_2Cl_2 (10 ml) se agitó en condiciones ambientales durante 3 horas. El componente volátil se eliminó en el vacío y el material resultante se cargó sobre una columna MCX, se purgó con flujo de metanol, se eluyó con NH_3 2.0

M/metanol y se concentró proporcionando 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftaleno en forma de sólido amarillo (253 mg).

Tiempo de retención de CL-EM 1.07 min; calculado para $C_{34}H_{30}N_6$: 522.25 encontrado m/z 523.19 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.17 (s, 2H), 8.06 (d, J=8.2 Hz, 2H), 8.00 (s, 2H), 7.88 (d, J=8.6 Hz, 2H), 7.71 - 7.81 (m, 4H), 4.84 (dd, J=10.8, 7.5 Hz, 2H), 3.47 - 3.53 (m, 2H), 2.80 (dd, J=12.8, 7.6 Hz, 2H), 2.54 - 2.63 (m, 2H), 2.04 - 2.11

(m, 2H), 1.20 - 1.27 (m, 2H), 1.02 (c, *J*=7.7 Hz, 2H).

Esquema de reacción 7



Mezcla de Intermediario 30

2-(5-(4-(6-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato bistrifluoroacetato de (S)-bencilo

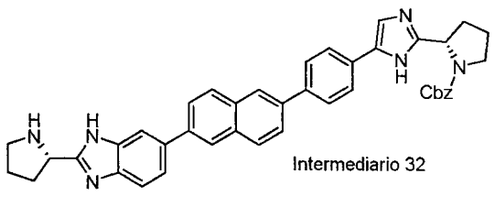
e Intermediario 31

2-(5-(4-(7-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato bistrifluoroacetato de (S)-bencilo

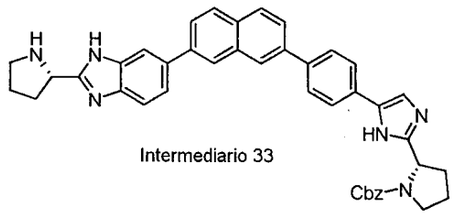
A una mezcla de una sal de TFA de 2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo y una sal de TFA de 2-(6-(7-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (190 mg), 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo (Solicitudes de Patente: WO 2008021928, WO 2008021936 y WO 2008021927) (213 mg, 0.499 mmol), en 1,2-dimetoxietano (10.0 ml) y agua (2.0 ml) se añadió $NaHCO_3$ (140 mg, 1.663 mmol). La mezcla de reacción se desgasificó en el vacío durante 5 minutos y se purgó con flujo de nitrógeno. Se añadió $Pd(Ph_3P)_4$ (19 mg, 0.017 mmol) y el matraz a presión se tapó y se calentó con un baño de aceite a 85°C durante 16 horas. El componente volátil se eliminó en el vacío y el residuo se fraccionó entre acetato de etilo y agua. Se separaron las fases y se extrajo la fase acuosa varias veces con acetato de etilo. Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron en el vacío. El material resultante se purificó con cromatografía instantánea (la muestra se cargó en seco en gel de sílice y

se eluyó con metanol al 0-5%/CH_2Cl_2) proporcionando productos parcialmente purificados. El residuo se purificó adicionalmente por una HPLC en fase reversa (agua/acetonitrilo/TFA) proporcionando una mezcla de sal TFA de 2-(5-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo y una sal de TFA de 2-(5-(4-(7-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo (381 mg) que se usó sin purificación adicional.

Tiempo de retención de CL-EM 1.54 min; calculado para $C_{47}H_{46}N_6O_4$ 758.36 encontrado m/z 759.37 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%.



Intermediario 32



Intermediario 33

Mezcla de Intermediario 32

2-(5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo

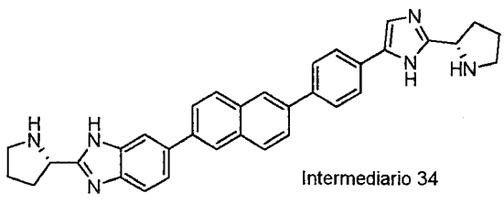
e Intermediario 33

2-(5-(4-(7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo

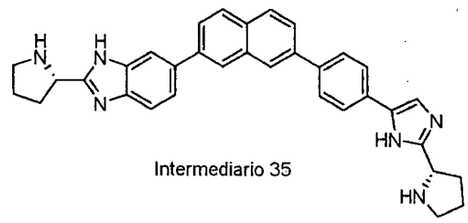
Una mezcla de una sal TFA de 2-(5-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo y una sal de TFA de 2-(5-(4-(7-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (381 mg) y TFA (2 ml) en CH_2Cl_2 (10 ml) se agitó en condiciones ambientales durante 4 horas. El componente volátil se eliminó en el vacío y la materia prima se purificó por una HPLC en fase reversa (agua al 0 a 50%/acetonitrilo/NH_4OAc) proporcionando una mezcla de 2-(5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-

imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo y 2-(5-(4-(7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo (70 mg, rendimiento del 21%) en forma de aceite amarillo.

Tiempo de retención de CL-EM 2.87 min; calculado para $C_{42}H_{38}N_6O_2$ 658.31 encontrado m/z 659.47 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo líquido Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 3.0 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 80%/solvente B al 20% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de retención de 1 min y un tiempo de análisis de 5 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/NH_4OAc a 10 mmol y el solvente B fue acetonitrilo al 95%/agua al 5%/NH_4OAc a 10 mmol. RMN de ^1H (Mezcla de compuestos, 500 MHz, MeOD) δ ppm 8.07 - 8.24 (m, 4H), 7.91 - 8.03 (m, 6H), 7.73 - 7.89 (m, 12H), 7.66 - 7.73 (m, 4H), 7.27 - 7.46 (m, 6H), 7.09 - 7.18 (m, 4H), 6.97 - 7.04 (m, 2H), 5.01 - 5.21 (m, 5H), 4.83 - 5.01 (m, 2H), 3.72 - 3.82 (m, 2H), 3.53 - 3.65 (m, 2H), 3.42 - 3.52 (m, 2H), 3.35 - 3.42 (m, 4H), 2.48 - 2.62 (m, 2H), 2.28 - 2.47 (m, 4H), 2.04 - 2.24 (m, 8H).



Intermediario 34



Intermediario 35

Intermediario 34

Tetratrifluoroacetato de 2-((S)-pirrolidin-2-il)-6-(6-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol

e Intermediario 35

Tetratrifluoroacetato de 2-((S)-pirrolidin-2-il)-6-(7-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol

A una solución de una mezcla de 2-(5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo y 2-(5-(4-(7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-bencilo (70 mg, 0.057 mmol) y carbonato de potasio (K_2CO_3) en metanol (5 ml) se añadió una suspensión de paladio en carbono (al 10%, 11 mg) en metanol (2 ml) a temperatura ambiente. El reactor se purgó en el vacío y se volvió a llenar con hidrógeno. La reacción se agitó durante 16 horas bajo un balón de hidrógeno. La mezcla se filtró a través de una almohadilla corto de tierra

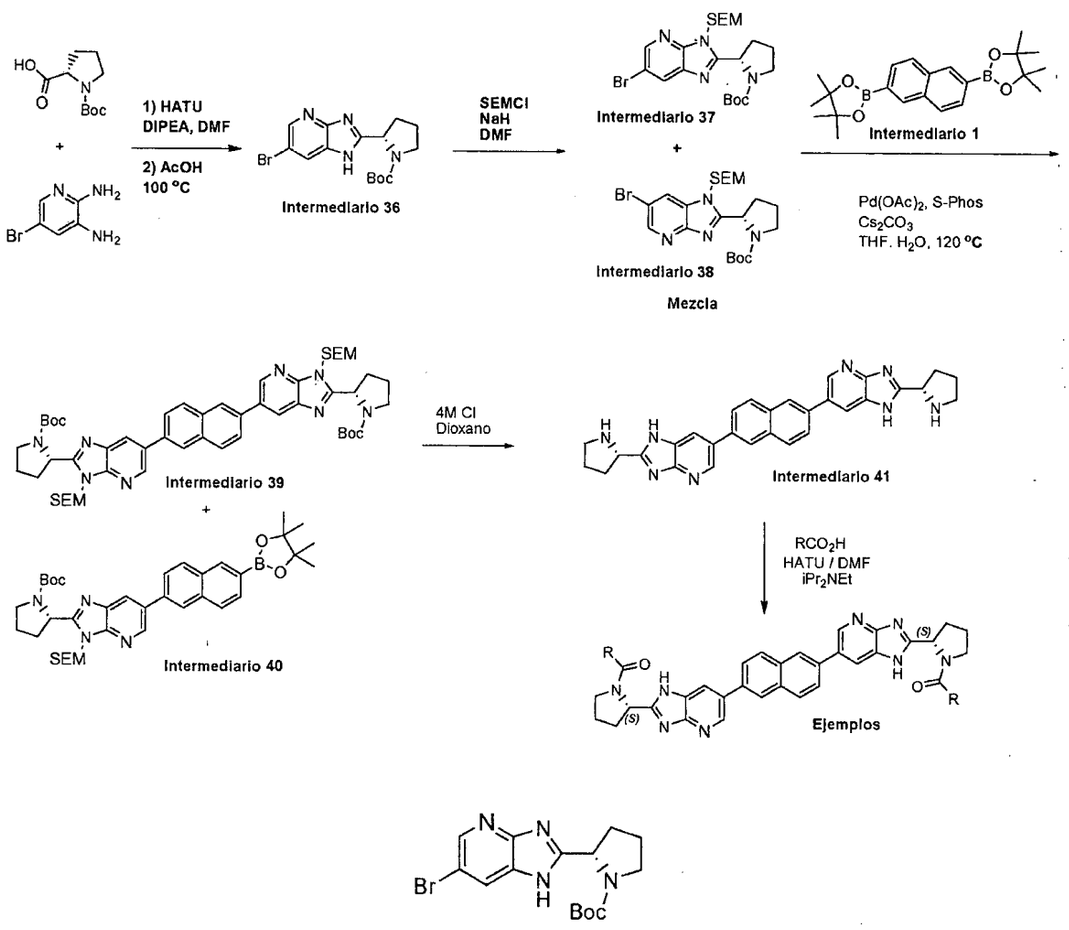
de diatomeas (CELITE®) en el vacío y el filtrado se evaporó en el vacío. La materia prima se purificó por una HPLC de fase reversa (agua al 0 a 50%/acetonitrilo/TFA) proporcionando una sal de TFA de 2-((S)-pirrolidin-2-il)-6-(6-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol (50 mg) en forma de aceite amarillo y una sal de TFA de 2-((S)-pirrolidin-2-il)-6-(7-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-benzo[d]imidazol (24 mg) en forma de sólido blanco.

Datos analíticos para el Intermediario 34: tiempo de retención de CL-EM 1.06 min; calculado para $C_{34}H_{32}N_6$ 524.27 encontrado m/z 525.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 80%/solvente B al 20% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (sal de TFA, 500

MHz, MeOD) δ ppm 8.19 (d, *J*=10.4 Hz, 2H), 8.02 - 8.10 (m, 3H), 7.84 - 7.96 (m, 7H), 7.77 - 7.83 (m, 2H), 5.14 (t, *J*=7.8 Hz, 1H), 5.06 - 5.11 (m, 1H), 3.52 - 3.67 (m, 4H), 2.61 - 2.74 (m, 2H), 2.43 - 2.56 (m, 2H), 2.30 - 2.42 (m, 2H), 2.18 - 2.30 (m, 2H).

Datos analíticos para el Intermediario 35: Tiempo de retención de CL-EM 1.13 min; calculado para $C_{34}H_{32}N_6$ 524.27 encontrado m/z 525.24 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire 5u C18 de 4.6 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente de solvente A al 80%/solvente B al 20% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (sal de TFA, 500 MHz, MeOD) δ ppm 8.27 (d, *J*=7.0 Hz, 2H), 7.99 - 8.06 (m, 3H), 7.90 - 7.96 (m, 4H), 7.87 (td, *J*=8.2, 1.7 Hz, 2H), 7.76 - 7.85 (m, 3H), 5.13 (t, *J*=7.8 Hz, 1H), 5.03 - 5.08 (m, 1H), 3.51 - 3.67 (m, 4H), 2.61 - 2.74 (m, 2H), 2.42 - 2.54 (m, 2H), 2.20 - 2.40 (m, 4H).

Esquema de reacción 8



Intermediario 36

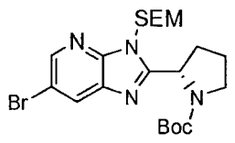
2-(6-bromo-1H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

Se añadió HATU (3.64 g, 9.57 mmol) a una solución agitada de 5-bromopiridina-2,3-diamina (1.64 g, 8.70 mmol) y ácido (S)-1-(*terc*-butoxicarbonil)pirrolidina-2-carboxílico (1.87 g, 8.70 mmol) en DMF (50 ml) y DIPEA (3.19 ml, 18.3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 días, se diluyó con agua (400 ml) y se extrajo con

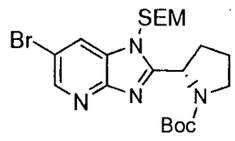
EtOAc (150 ml). La fase orgánica se lavó con salmuera (50 ml), se seco ($MgSO_4$), se filtró y se concentró. La materia prima se purificó parcialmente por cromatografía instantánea (110 g de SiO_2, MeOH al 1-4%/DCM) proporcionando 3.36 g de espuma solidificada. El material se disolvió en AcOH (35.0 ml) y se calentó a 100°C durante 8 h. La reacción se enfrió a temperatura ambiente, se concentró y se purificó por cromatografía instantánea (se cargó con DCM, 80 g de SiO_2, EtOAc al 20-40%/Hexanos) proporcionando 2-(6-bromo-1H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (1.73 g) en forma de sólido amarillo.

Tiempo de retención en la CL-EM 1.33 min; m/z 365, 367 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo líquido Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 3.0 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron una velocidad de flujo de 5 ml/minuto, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min, y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN

de ^{1}H (400 MHz, MeOD) δ ppm 8.40 (s ancho, 1H), 8.09 (s ancho, 1H), 5.12 - 4.96 (m, 1H), 3.77 - 3.67 (m, 1H), 3.62 - 3.51 (m, 1H), 2.56 - 2.38 (m, 1H), 2.15 - 1.90 (m, 3H), 1.46 (s, 3.5H), 1.16 (s, 5.5H).



Intermediario 37



Intermediario 38

Mezcla de Intermediario 37

2-(6-bromo-3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

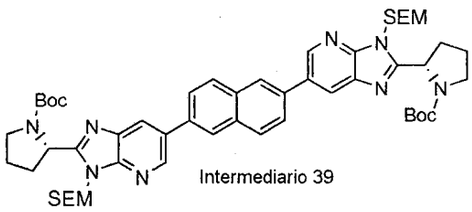
e Intermediario 38

2-(6-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

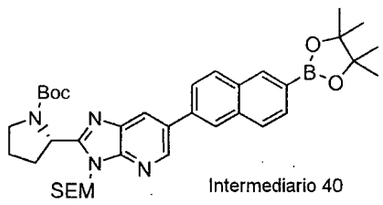
Una dispersión del 60% de NaH (0.120 g, 3.00 mmol) se añadió a una solución agitada de 2-(6-bromo-1H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (1.0 g, 2.7 mmol) en DMF (25 ml) y la reacción se agitó durante 1.5 horas a temperatura ambiente. Después se añadió SEM-Cl (0.483 ml, 2.72 mmol) y la reacción se agitó 16 horas. La reacción se diluyó con agua (~ 30 ml) y EtOAc (~35 ml), las fases se separaron y la fase orgánica se lavó con salmuera (30 ml), se secó ($MgSO_4$), se filtró y se concentró. El

aceite amarillo en bruto residual se purificó por cromatografía instantánea (80 g SiO_2, EtOAc al 20-30%/hexanos) proporcionando una mezcla de 2-(6-bromo-3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo y 2-(6-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (838 mg) en forma de un aceite amarillo. La mezcla se usó sin purificación adicional.

Tiempo de retención en la CL-EM 2.54 min; m/z 497.499 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo líquido Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 3.0 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron una velocidad de flujo de 5 ml/minuto, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min, y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 39



Intermediario 40

Intermediario 39

2,2'-(6,6'-(naftaleno-2,6-diil)bis(3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridina-2,6-diil))dipirrolidina-1-carboxilato de (2S,2'S)-terc-butilo

e Intermediario 40

2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-terc-butilo

En un vial de microondas, 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (57 mg, 0.150 mmol), una mezcla de 2-(6-bromo-3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo y 2-(6-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (112 mg), carbonato de cesio (147 mg, 0.450 mmol) y diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (12.3 mg, 0.030 mmol) se disolvieron en THF (3 ml) y agua (0.3 ml). Se añadieron 1.5 ml adicionales de THF y la reacción se roció con nitrógeno burbujeante hasta que se hubieron evaporado aparte ~2 ml. A la solución transparente se añadió acetato de paladio (II)

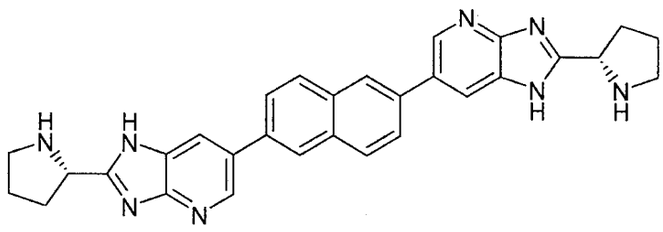
(3.37 mg, 0.015 mmol). El vial se purgó con flujo de nitrógeno, se selló y después se calentó con irradiación de microondas a 120°C durante 30 min. La reacción se diluyó con EtOAc (~ 3 ml) y se lavó con agua (2 ml) y salmuera (2 ml). La reacción se secó ($MgSO_4$), se filtró y se concentró a un sólido amarillo que se purificó por cromatografía instantánea (12 g de SiO_2, EtOAc al 25-75%/hexanos) proporcionando 2,2'-(6,6'-(naftaleno-2,6-diil)bis(3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridina-6,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-*terc*-butilo (74 mg) en forma de un aceite incoloro transparente (mezcla de regioisómeros de SEM) y 2-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-2-il)pirrolidina-1-carboxilato de (S)-*terc*-butilo (32 mg) en forma de un sólido incoloro (mezcla de regioisómeros de SEM). Se usó cada uno sin purificación adicional.

Datos analíticos para el Intermediario 39: Tiempo de retención en la CL-EM 3.42 minutos; m/z 961.9 (MH+). Los datos de CL se registraron en un cromatógrafo líquido Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 3.0 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron una velocidad de flujo de 5 ml/minuto, un gradiente de solvente A al 100%/solvente B al 0% a solvente A

al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min, y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, MeOD) (mezcla de regioisómeros de SEM) δ ppm 8.84 - 8.75 (m, 2H), 8.39 - 8.31 (m, 2H), 8.26 - 8.18 (m, 2H), 8.11 (s ancho, 2H), 7.92 - 7.84 (m, 2H), 5.94 - 5.83 (m, 3H), 5.79 (d, J = 11.0 Hz, 1H), 5.34 - 5.25 (m, 2H), 3.86 - 3.57 (m, 8H), 2.61 - 2.39 (m, 2H), 2.34 - 1.99 (m, 6H), 1.45 (s, 8H), 1.17 (s, 10H), 1.10 - 0.87 (m, 4H), -0.02 (s, 18H).

Datos analíticos para el Intermediario 40: Tiempo de retención en la CL-EM 3.15 minutos; m/z 671.5 (MH+). Los datos de CL se registraron en un cromatógrafo líquido Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 3.0 x 50 mm usando un detector SPD-10AV UV-Visible a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron una velocidad de flujo de 5 ml/minuto, un gradiente de solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de retención de 1 min, y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al

5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo de electrorrocío. (Mezcla de regioisómeros de SEM) δ ppm 8.82 - 8.75 (m, 1H), 8.39 - 8.29 (m, 2H), 8.21 - 8.15 (m, 1H), 8.07 - 8.01 (m, 1H), 8.11 (s ancho, 2H), 7.98 - 7.93 (m, 1H), 7.89- 7.80 (m, 2H), 5.94 - 5.85 (m, 1.5H), 5.79 (d, *J* = 11.3 Hz, 0.5H), 5.33 - 5.24 (m, 1H), 3.85 - 3.56 (m, 4H), 2.62 - 2.39 (m, 1H), 2.33 - 1.99 (m, 1H), 1.49 - 0.87 (m, 23H), -0.02 (s, 9H).



Intermediario 41

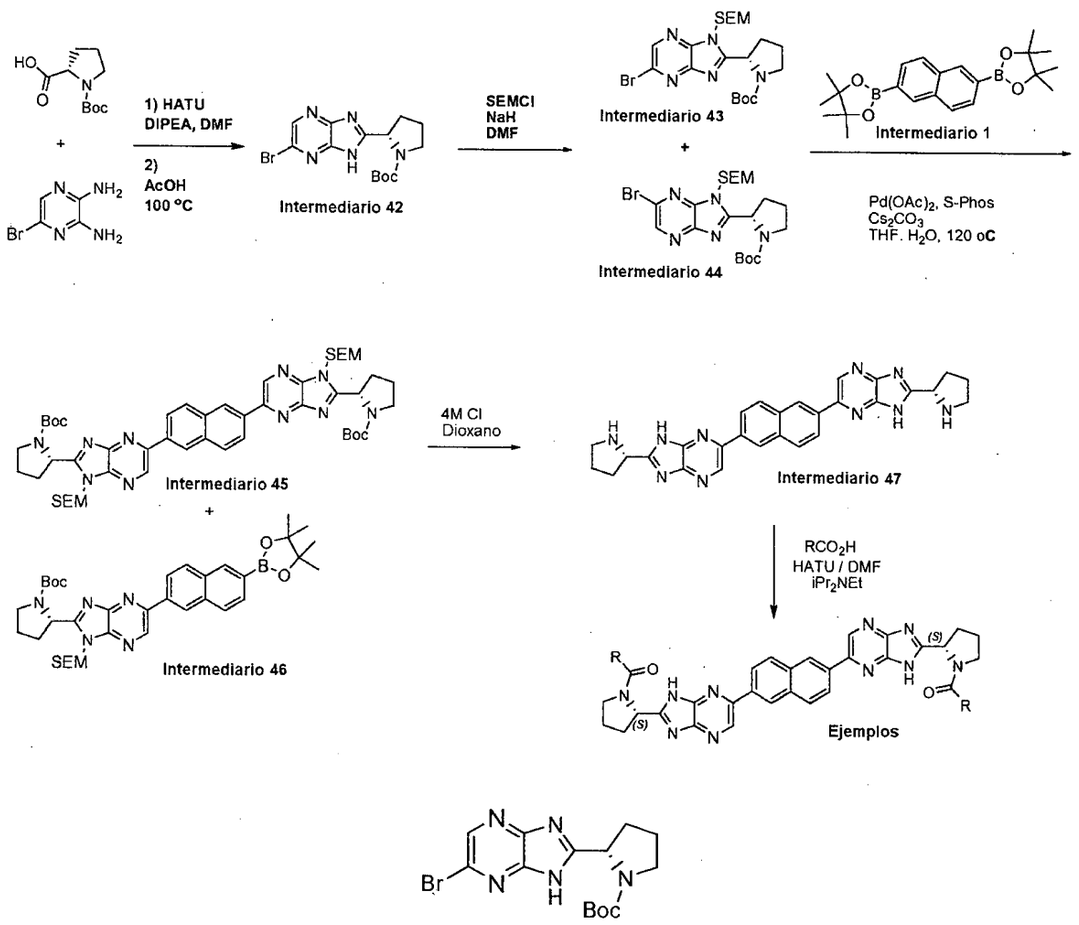
2,6-bis(2-((S)-pirrolidin-2-il)-3H-imidazo[4,5-b]piridin-6-il)naftaleno

A una solución agitada de 2,2'-(6,6'-(naftalen-2,6-diil)bis(3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-6,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-butilo (74 mg, 0.077 mmol) (mezcla de regioisómeros SEM) en metanol (1 ml) se añade cloruro de hidrógeno 4M (2.0 ml, 8.0 mmol) en dioxano. La reacción se agitó a temperatura ambiente durante 16

horas y, después, se concentró hasta sequedad para dar una sal clorhidrato de 2,6-bis(2-((S)-pirrolidin-2-il)-3H-imidazo[4,5-b]piridin-6-il)naftaleno (51.1 mg) en forma de un sólido amarillo que se usó sin más purificación.

Tiempo de retención en la CL-EM 0.83 min; m/z 501.13 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 5 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min en el que el solvente A fue 10% de acetonitrilo/90% de agua/0.1% de ácido trifluoroacético y el solvente B fue 10% de agua/90% de acetonitrilo/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma Micromass® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, D_2O) δ ppm 8.76 (s, 2H), 8.54 (s, 2H), 8.07 - 7.97 (m, 4H), 7.86- 7.78 (m, 2H), 5.26 - 5.16 (m, 2H), 3.98 - 3.65 (m, 8H), 2.79 - 2.63 (m, 2H), 2.46 - 2.25 (m, 6H).

Esquema de reacción 9



Intermediario 42

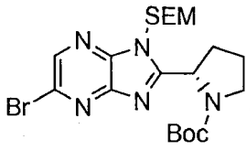
2-(6-bromo-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

A una solución agitada de 5-bromopirazin-2,3-diamina (2.28 g, 12.1 mmol) y ácido (S)-1-(*terc*-butoxicarbonil)pirrolidina-2-carboxílico (2.60 g, 12.0 mmol) en DMF (50 ml) y DIPEA (4.42 ml, 25.3 mmol) se añadió HATU (5.05 g, 13.3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 días y después a90°C durante 1

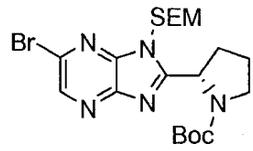
día. La mezcla de reacción se diluyó con agua (350 ml) y se extrajo con EtOAc (200 ml). La capa orgánica se lavó con salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró. El material bruto se purificó parcialmente mediante cromatográfica instantánea (110 g de SiO_2, 1-4% MeOH/DCM) para dar 1.9 g de espuma solidificada. El material s disolvió en AcOH (35.0 ml) y se calentó a 95 °C durante 8 horas. La reacción se enfrió hasta la temperatura ambiente, se concentró y se purificó mediante cromatográfica instantánea (se cargó con DCM, 80 g de SiO_2, 20-30% EtOAc/Hexanos) para dar 2-(6-bromo-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (760 mg, 2.06 mmol, rendimiento del 17%) en forma de una espuma solidificada amarilla.

Tiempo de retención en la CL-EM 1.28 min; m/z 366, 368 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Phenomenex-Luna de 10u C18, de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y

el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass® para CL en modo de electrorrocío. RMN de ^{1}H NMR (400 MHz, MeOD) δ ppm 8.50 - 8.43 (m, 1H), 5.11 - 4.99 (m, 1H), 3.77 - 3.68 (m, 1H), 3.62 - 3.51 (m, 1H), 2.57 - 2.40 (m, 1H), 2.19 - 1.95 (m, 3H), 1.46 (s, 3.5H), 1.17 (s, 5.5H).



Intermediario 43



Intermediario 44

Intermediario 43

2-(5-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

e Intermediario 44

2-(6-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

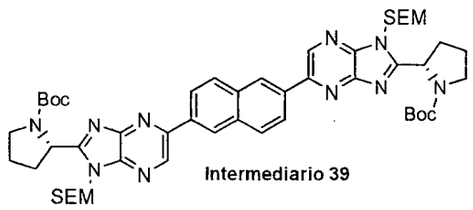
Una dispersión al 60% de NaH (75 mg, 1.9 mmol) se añadió una solución agitada de 2-(6-bromo-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (627 mg, 1.70 mmol) en DMF (15 ml) y la reacción se agitó durante 1.5 horas a temperatura ambiente. Después se añadió SEM-Cl (0.30 ml, 1.7 mmol) y la reacción se agitó durante la noche. La reacción se diluyó con agua (~ 30 ml) y EtOAc (~35 ml), se separaron las capas y la capa orgánica se lavó con

salmuera (30 ml), se secó ($MgSO_4$), se filtró y se concentró. El aceite Amarillo bruto se purificó mediante cromatográfica instantánea (40 g de SiO_2, 20-30% EtOAc/hexanos) para dar 2-(5-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (421 mg) en forma de un aceite incoloro transparente y 2-(6-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (345 mg) forma de un aceite incoloro transparente. La regioquímica absoluta del grupo SEM no se estableció de forma no ambigua, los nombres (y estructuras) se pueden intercambiar en estos intermediarios.

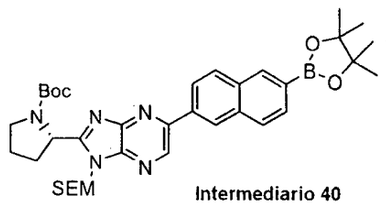
Datos analíticos del Intermediario 43: Tiempo de retención en la CL-EM 2.43 min; m/z 496, 498 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de

EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H NMR (400 MHz, MeOD) δ ppm 8.52 (s, 0.5H), 8.49 (s, 0.5H), 5.90 - 5.72 (m, 2H), 5.32 - 5.25 (m, 1H), 3.82 - 3.54 (m 4H), 2.59 - 2.41 (m, 1H), 2.32 - 1.98 (m, 3H), 1.43 (s, 4.5H), 1.15 (s, 4.5H), 1.07 - 0.85 (m, 2H), -0.02 (s, 9H).

Datos analíticos del Intermediario 44: Tiempo de retención en la CL-EM 2.41 min; m/z 496, 498 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H NMR (400 MHz, MeOD) δ ppm 8.61 (s, 0.5H), 8.58 (s, 0.5H), 5.88 - 5.71 (m, 2H), 5.28 (dd, J= 8.5, 4.5 Hz, 1H), 3.82 - 3.54 (m 4H), 2.59 - 2.41 (m, 1H), 2.32 - 1.98 (m, 3H), 1.43 (s, 4.5H), 1.15 (s, 4.5H), 1.09 - 0.85 (m, 2H), -0.02 (s, 9H).



Intermediario 39



Intermediario 40

Intermediario 45

2,2'-(5,5'-(naftalen-2,6-diil)bis(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-5,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-terc-butilo

e Intermediario 46

2-(5-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

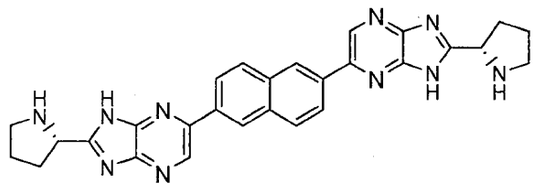
En un vial de microondas, 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (149 mg, 0.393 mmol), 2-(5-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (294 mg, 0.590 mmol) (o un regioisómero SEM), carbonato de cesio (384 mg, 1.18 mmol) y diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (32.3 mg, 0.079 mmol) se disolvieron en THF (4 ml) y agua (0.4 ml). Se añadió 1.5 ml adicionales de THF y la reacción se roció con nitrógeno en burbujas hasta que el 1.5 se hubo evaporado. A la solución transparente se añadió acetato de paladio (II) (8.83 mg, 0.039 mmol). El vial se aclaró con nitrógeno, se selló y después se calentó con irradiación de microondas a 120 °C

durante 30 min. La reacción se diluyó con EtOAc (~ 3 ml) y se lavó con agua (2 ml) y salmuera (2 ml). La reacción se secó ($MgSO_4$), se filtró y se concentró hasta un aceite Amarillo que se purificó mediante cromatográfica instantánea(12 g de SiO_2, 25-75% EtOAc/hexanos) para dar 2,2'-(5,5'-(naftalen-2,6-diil)bis(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-5,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-butilo (o un regioisómero SEM) (210 mg) en forma de una espuma solidificada amarilla y 2-(5-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (o un regioisómero SEM) (53.5 mg) en forma de un aceite incoloro.

Datos analíticos del Intermediario 45: Tiempo de retención en la CL-EM 3.27 min; m/z 963.89 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al

5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, MeOD) (mezcla de regioisómeros SEM) δ ppm 9.29 - 9.15 (m 2H), 8.79 - 8.66 (m, 2H), 8.43 - 8.29 (m, 2H), 8.20 - 7.98 (m, 2H), 6.03 - 5.84 (m, 4H), 5.34 (dd, *J* = 8.3, 4.3 Hz, 2H), 3.87 - 3.70 (m, 6H), 3.68 - 3.58 (m, 2H), 2.63 - 2.43 (m, 2H), 2.36 - 1.14 (m, 4H), 2.14 - 1.99 (m, 2H), 1.46 (s, 8H), 1.17 (s, 10H), 1.35- 0.85 (m, 4H), -0.02 (s, 18H).

Datos analíticos del Intermediario 46: Tiempo de retención en la CL-EM 3.07 min; m/z 672.52 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



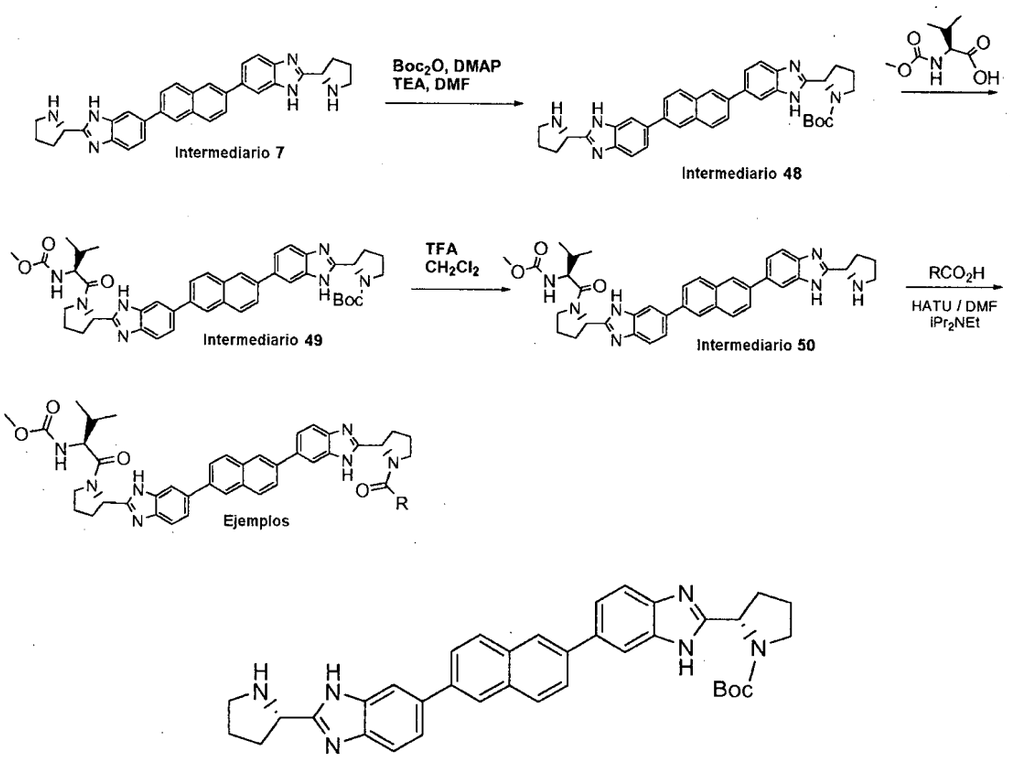
2,6-bis(2-((S)-pirrolidin-2-il)-1H-imidazo[4,5-b]pirazin-5-il)naftaleno

A una solución agitada de 2,2'-(5,5'-(naftalen-2,6-diil)bis(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazo[4,5-b]pirazin-5,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-butilo (210 mg, 0.218 mmol) (no se estableció la regioquímica absoluta del SEM) en metanol (3 ml) se añadió cloruro de hidrógeno 4M (6.0 ml, 24 mmol) en dioxano. La reacción se agitó a temperatura ambiente durante 16 horas y, después, se concentró hasta sequedad para dar una sal clorhidrato de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-imidazo[4,5-b]pirazin-5-il)naftaleno (143 mg) en forma de un sólido naranja que se usó sin purificación adicional.

Tiempo de retención en la CL-EM 0.90 min; m/z 503.21 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 5 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B,

un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min en el que el solvente A fue 10% de acetonitrilo/90% de agua/0.1% de ácido trifluoroacético y el solvente B fue 10% de agua/90% de acetonitrilo/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, D_2O) δ ppm 8.59 (s, 2H), 7.94 (s, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 5.23 - 5.16 (m, 2H), 3.98 - 3.66 (m, 8H), 2.78 - 2.64 (m, 2H), 2.47- 2.28 (m, 6H).

Esquema de reacción 10



Intermediario 48

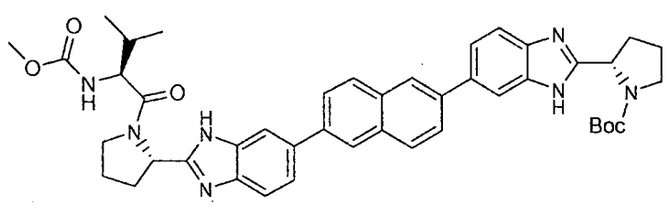
(2S)-2-(5-(6-(2-((2S)-2-pirrolidinil)-1H-benzimidazol-5-il)-

2-naftil)-1H-bencimidazol-2-il)-1-pirrolidincarboxilato de terc-butilo

A una solución de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (885 mg, 1.78 mmol), DMAP (10.8 mg, 0.089 mmol) y trietilamina (1.2 ml, 8.9 mmol) en DMF (30 ml) a temperatura ambiente se añadió, en una porción, dicarbonato de di-*terc*-butilo (387 mg, 1.78 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente y se purificó en un BIOTAGE® (cargado en seco a un cartucho de gel de sílice de 80 g y eluido con un gradiente de 0 a 50 % de DCM en MeOH), para dar (2S)-2-(5-(6-(2-((2S)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidincarboxilato de *terc*-butilo (500 mg, 0.835 mmol, rendimiento de 47.1 %) en forma de un sólido naranja.

Tiempo de retención en la CL-EM 1.207 min; m/z 599.25 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A

fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.27 (d, *J*=3.1 Hz, 1H), 8.23 (s, 1H), 8.04 - 8.17 (m, 4H), 8.03 (s, 1H), 7.88 - 7.97 (m, 3H), 7.75 - 7.83 (m, 2H), 5.28 - 5.35 (m, 1H), 5.11 (t, *J*=7.8 Hz, 1H), 3.75 - 3.83 (m, 1H), 3.60 - 3.72 (m, 2H), 3.51 - 3.59 (m, 1H), 2.60 - 2.74 (m, 2H), 2.40 - 2.50 (m, 1H), 2.21 - 2.38 (m, 3H), 2.10 - 2.20 (m, 2H), 1.52 (s, 4H), 1.25 (s, 4H).



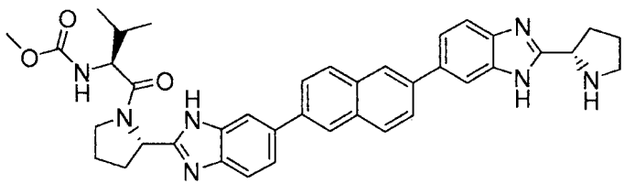
Intermediario 49

(2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidincarboxilato de terc-butilo

A una solución de (2S)-2-(5-(6-(2-((2S)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidincarboxilato de *terc*-butilo (400 mg, 0.668 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (176 mg, 1.00 mmol) y DIEA (0.583 ml, 3.34 mmol) en DMF (10 ml) se añadió HATU (381 mg, 1.00 mmol). La mezcla de

reacción se agitó 2 h a temperatura ambiente y después se purificó mediante HPLC prep (usando una columna Waters Sunfire de C18 de 30 X 150 mm de 5u, eluida con un gradiente de 0 a 50 % de ACN -Water + 0.1 % en TFA) para dar una sal en TFA de (2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidincarboxilato de *terc*-butilo (445 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.317 min; m/z 756.28 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



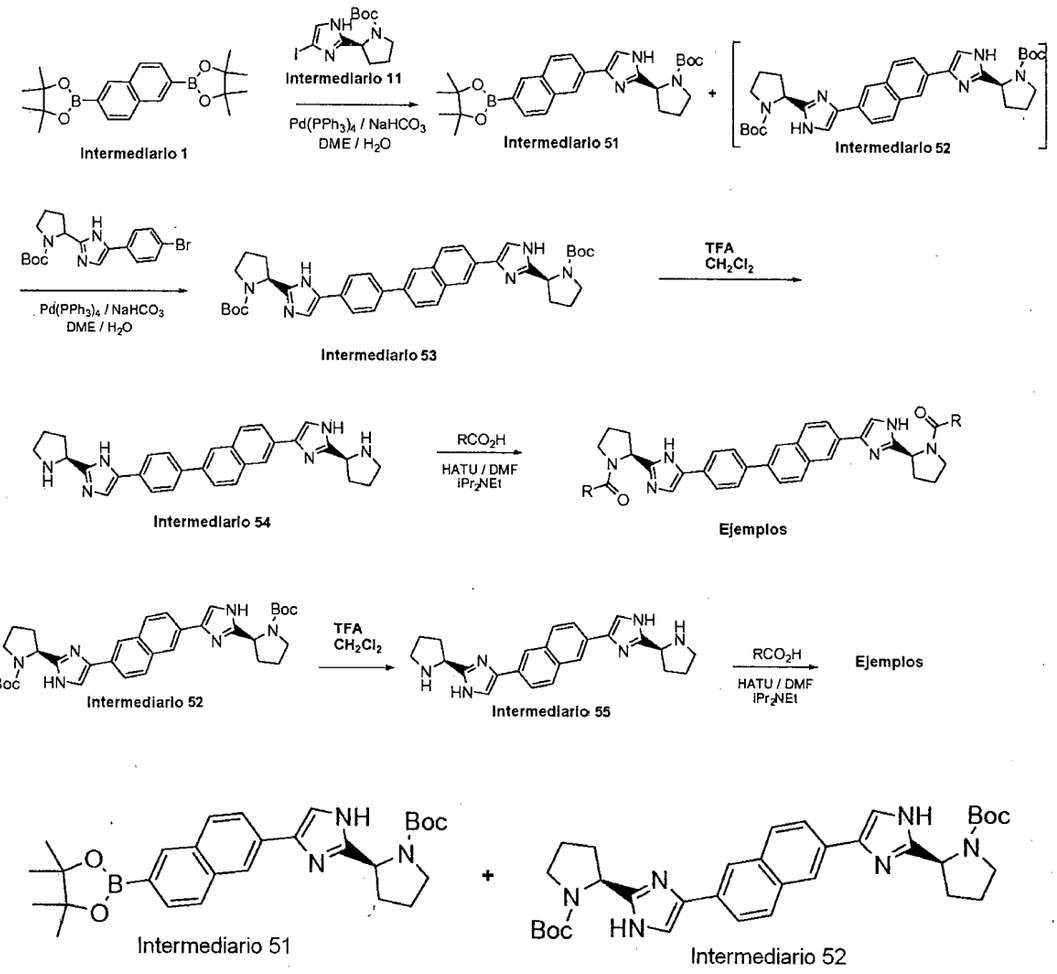
Intermediario 50

((1S)-2-metil-1-(((2S)-2-(5-(6-(2-((2S)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo

A una solución de sal en TFA de (2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidincarboxilato de *terc*-butilo (445 mg) en DCM (10 ml) a temperatura ambiente se añadió TFA (1 ml, 13 mmol). La mezcla se agitó a temperatura ambiente durante 3 horas, se concentró y el residuo se diluyó en MeOH, se cargó en un cartucho Strata XC MCX y se lavó con metanol. El compuesto se liberó del cartucho eluyendo con una solución de amoniaco 2M en metanol y después se evaporó a presión reducida para dar ((1S)-2-metil-1-(((2S)-2-(5-(6-(2-((2S)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo (275 mg) en forma de un sólido naranja.

Tiempo de retención en la CL-EM 1.120 min; m/z 656.27 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.26 (s ancho, 1H), 8.22 (s ancho, 1H), 8.08 - 8.16 (m, 3H), 8.04 - 8.08 (m, 1H), 8.03 (s, 1H), 7.86 - 7.96 (m, 3H), 7.73 - 7.82 (m, 2H), 5.88 - 5.93 (m, 0.1H), 5.37 - 5.44 (m, 0.9H), 5.07 - 5.15 (m, 1H), 4.28 - 4.33 (m, 1H), 4.12 - 4.19 (m, 0.8H), 4.06 - 4.10 (m, 0.2H), 3.94 - 4.02 (m, 1H), 3.59 - 3.75 (m, 4H), 3.50 - 3.59 (m, 1H), 2.63 - 2.74 (m, 2H), 2.41 - 2.47 (m, 1H), 2.23 - 2.40 (m, 5H), 2.06 - 2.16 (m, 1H), 1.00 - 1.04 (m, 0.4H), 0.94 - 1.00 (m, 3H), 0.88 - 0.93 (m, 2.6H).

Esquema de reacción 11



Intermediario 51

2-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

e

Intermediario 52

2,2'-(4,4'-(naftalen-2,6-diil)bis-(1H-imidazol-4,2-

diil))dipirrolidin-1-carboxilato de (2S,2'S)-terc-butilo

Un recipiente de presión de 100 ml equipado con una barra de agitación magnética con 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (2.00 g, 5.26 mmol), 2-(5-yodo-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (2.10 g, 5.79 mmol) y $Pd(Ph_3P)_4$ (0.058 g, 0.05 mmol) en DME (47.8 ml) y agua (4.8 ml). La solución se desgasificó a vacío durante 5 minutos y el reactor se cargó de Nuevo con nitrógeno. El vaso se selló y la mezcla de reacción se calentó durante la noche a 120° C. La reacción se enfrió hasta la temperatura ambiente y los volátiles se eliminaron al vacío El residuo se repartió entre agua y EtOAc y la capa de agua se extrajo con EtOAc adicional. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El producto bruto se purificó con un BIOTAGE® (cargado en seco sobre un cartucho de gel de sílice de 90 g y eluyó con un gradiente de 0 a 30 % de EtOAc en DCM) y se volvió a purificar con un BIOTAGE® (cargado en seco sobre un cartucho de gel de sílice de 80 g y eluyó con un gradiente de 0 a 50 % de EtOAc en DCM) para dar 2-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (949 mg) en forma de un sólido amarillo. El material (contaminado con 2,2'-(4,4'-(naftalen-2,6-diil)bis-(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-

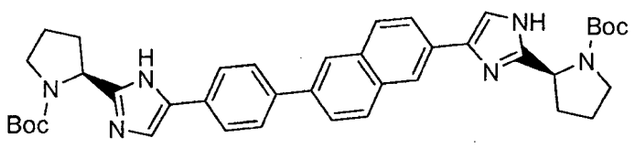
terc-butilo) se usó en la siguiente etapa sin purificación adicional.

Tiempo de retención en la CL-EM 1.760 min; m/z 490.21 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

La HPLC preparativa de la reacción siguiente dio 2,2'-(4,4'-(naftalen-2,6-diil)bis-(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-butilo (92 mg, 0.111 mmol, rendimiento del 11%) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.113 min; m/z 599.24 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un

detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.35 (s ancho, 2H), 8.13 (s ancho, 2H), 8.08 (s ancho, 1H), 8.00 (s ancho, 1H), 7.95 (m, 2H), 5.18 (s ancho, 2H), 3.68 - 3.78 (m, 2H), 3.62 (s ancho, 2H), 2.51 - 2.68 (m, 2H), 2.21 (s ancho, 2H), 2.06 - 2.15 (m, 4H), 1.50 (s ancho, 9H), 1.31 s ancho, 9H).



Intermediario 53

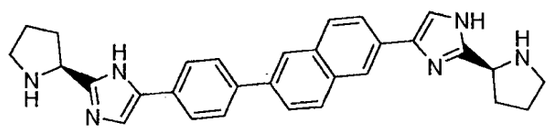
2-(5-(4-(6-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

Un recipiente de presión de 100 ml equipado con una barra de agitación magnética se cargó con 2-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-

imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (500 mg, 1.02 mmol), 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (601 mg, 1.53 mmol) y $Pd(Ph_3P)_4$ (58 mg, 0.05 mmol) en DME (10 ml) y agua (1.0 ml). La solución se desgasificó a vacío durante 5 minutos y el reactor se cargó de Nuevo con nitrógeno. La mezcla se calentó durante 8 horas a 120 °C, se añadió $Pd(Ph_3P)_4$ adicional (57.8 mg, 0.05 mmol) y la mezcla se desgasificó y agitó durante la noche a 130°C. La reacción se enfrió hasta la temperatura ambiente y los volátiles se eliminaron al vacío. El residuo se repartió entre agua y EtOAc y la capa de agua se extrajo con EtOAc adicional. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El producto bruto se purificó en un BIOTAGE® (cargado en seco en un cartucho de gel de sílice de 90 g y eluido con un gradiente de 5 a 100 % de EtOAc en DCM) y, después, se volvió a purificar mediante HPLC prep (usando una columna Waters Sunfire de C18 de 30 X 100 mm de 5u eluyó con MeOH -Aguar + 0.1 % TFA) para dar una sal TFA de 2-(5-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (50 mg).

Tiempo de retención en la CL-EM 1.278 min; m/z 675.70 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una

columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.31 (d, *J*=15.9 Hz, 2H), 8.14 - 8.18 (m, 1H), 8.10 (d, *J*=8.85 Hz, 1H), 8.05 (s, 0.6H), 7.96 - 8.03 (m, 4H), 7.85 - 7.94 (m, 3.4H), 5.11 - 5.23 (m, 2H), 3.69 - 3.77 (m, 2H), 3.62 (s ancho, 2H), 2.51 - 2.67 (m, 2H), 2.16 - 2.26 (m, 2H), 2.05 - 2.16 (m, 4H), 1.51 (s, 9H), 1.32 (s, 9H).



Intermediario 54

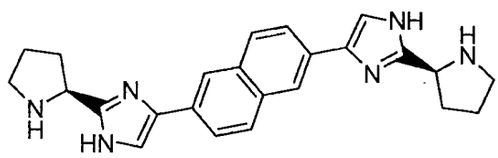
2-((2S)-2-pirrolidinil)-4-(4-(6-(2-((2S)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol

A una solución de sal en TFA de 2-(5-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-

il)pirrolidin-1-carboxilato de (S)-*terc*-butilo en DCM (10 ml) se añadió TFA (2.0 ml, 26 mmol) en una porción. La mezcla se agitó a temperatura ambiente durante 2 h. La reacción se concentró al vacío para dar una sal en TFA de 2-((S)-pirrolidin-2-il)-5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol (51.5 mg) en forma de un sólido naranja, que se usó sin purificación adicional.

Tiempo de retención en la CL-EM 0.978 min; m/z 475.19 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La HPLC-EM (TFA) 78457-087

usando una columna Waters Sunfire de C18 de 4.6 X 50 mm de 5u mostró que la reacción estaba completa, pico encontrado a temperatura ambiente = 0.978 min. MH+ = 475.19, RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.34 (s, 1H), 8.20 (s, 1H), 8.03 (dd, *J*=14.2, 8.7 Hz, 2H), 7.84 - 7.96 (m, 7H), 7.79 - 7.84 (m, 1 H,) 4.99 - 5.11 (m, 2H), 3.48 - 3.63 (m, 4H), 2.57 - 2.70 (m, 2H), 2.41 - 2.55 (m, 2H), 2.29 - 2.41 (m, 2H), 2.15 - 2.29 (m, 2H).



Intermediario 55

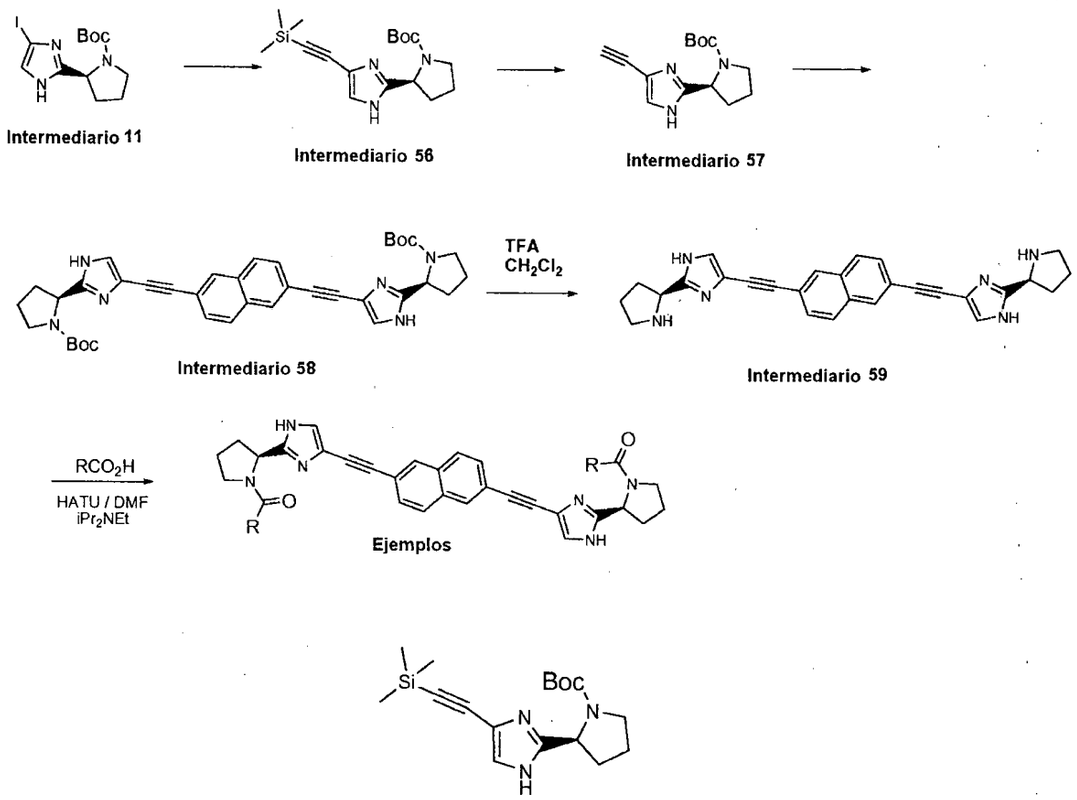
4,4'-(2,6-naftalendiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol)

A una solución de sal en TFA de 2,2'-(4,4'-(naftalen-2,6-diil)bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-butilo (82 mg) en DCM (2 ml) a temperatura ambiente se añadió TFA (2.0 ml, 26 mmol) en una porción. La mezcla se agitó durante 3 horas a temperatura ambiente, se purificó mediante HPLC prep (columna Waters Sunfire de C18 de 30 X 100 mm de 5u eluyó con un gradiente de 5 a 90 % MeOH -Agua + 0.1 % de TFA) y se volvió a purificar mediante HPLC prep (columna

PHENOMENEX® Luna C18 de 30 X 100 mm de 10u eluida con un gradiente de 10 a 90 % de metanol -Agua + 0.1 % de TFA) para dar una sal TFA de 4,4'-(2,6-naftalendiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol) (68 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 0.978 min; m/z 399.18 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90% /agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.31 (s, 2H), 7.95 - 8.00 (m, 2H), 7.91 - 7.95 (m, 2H), 7.85 (s, 2H), 5.03 (t, J=8.2 Hz, 2H), 3.49 - 3.62 (m, 4H), 2.59 - 2.67 (m, 2H), 2.42 - 2.52 (m, 2H), 2.31 - 2.40 (m, 2H), 2.17 - 2.28 (m, 2H).

Esquema de reacción 12



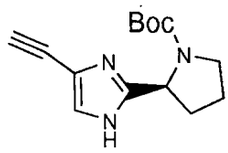
Intermediario 56

2-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

2-(5-yodo-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (750 mg, 2.07 mmol) y yoduro de cobre (I) (79 mg, 0.41 mmol) se disolvieron en DMF (20 ml) y trietilamina (1.439 ml, 10.33 mmol). La solución de reacción se aclaró al vacío durante 10 minutos (aspirador de vacío, se aclaró con nitrógeno) y después se añadieron etiniltrimetilsilano (1.2 ml, 8.3 mmol) y, por último, $Pd(PPh_3)_4$ (119 mg, 0.103 mmol). El matraz se aclaró con

nitrógeno, se selló y se calentó a 50 °C durante la noche. La reacción se concentró hasta un alquitrán negro bruto, se disolvió en DCM y se purificó mediante BIOTAGE® Horizon (80 g de SiO_2, 20-40% de EtOAc/hexanos) para dar 2-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (546 mg, 1.64 mmol, rendimiento del 79 %) en forma de un sólido amarillo. Este material se usó sin purificación adicional.

Tiempo de retención en la CL-EM 1.393 min; m/z 332.33 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 - 7.13 (m, 1H), 4.92 - 4.85 (m, 1H), 3.43 - 3.31 (m, 2H), 3.04 - 2.83 (m, 1H), 2.20 - 1.88 (m, 3H), 1.51 (s, 3H), 1.49 (s, 6H), 0.25 (s, 3H), 0.23 (s, 6H).



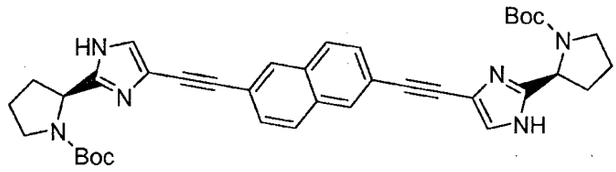
Intermediario 57

2-(5-etinil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

El 2-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (537 mg, 1.61 mmol) se disolvió en MeOH (20 ml) y después se añadió carbonato potásico (22 mg, 0.16 mmol) y la reacción se agitó a temperatura ambiente durante 3 horas. La reacción se concentró, se disolvió en diclorometano, se cargó en una columna de SiO_2 y se purificó mediante BIOTAGE® Horizon (30-40% de EtOAc/hexanos) para dar 2-(5-etinil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (s)-*terc*-butilo (346 mg, 1.32 mmol, rendimiento del 82 %) en forma de un sólido blancuzco.

Tiempo de retención en la CL-EM 0.878 min; m/z 260.35 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de

1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.21 - 7.17 (m, 1H), 4.92 - 4.87 (m, 1H), 3.43 - 3.30 (m, 2H), 3.05 (s, 1H), 3.03 - 2.85 (m, 1H), 2.20 - 1.88 (m, 3H), 1.60 -1.45 (m, 9H).



Intermediario 58

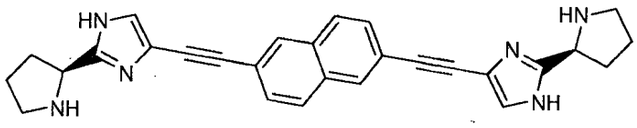
(2S)-2-(4-((6-((2-((2S)-1-(terc-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)etinil)-2-naftil)etinil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de terc-butilo

Los compuestos 2-(5-etinil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (340 mg, 1.30 mmol), 2,6-dibromonaftaleno (744 mg, 2.60 mmol) y yoduro de cobre (I) (12.39 mg, 0.065 mmol) se suspendieron en DMF (10 ml) y trietilamina (0.54 ml, 3.9 mmol). La solución se aclaró al vacío con nitrógeno (5X), se trató con $Pd(PPh_3)_4$ (75 mg, 0.065 mmol)y después se aclaró al vacío con nitrógeno (2X). La solución amarillo turbia se agitó en nitrógeno a temperatura ambiente durante 3 horas. La reacción se concentró hasta un semisólido de color Amarillo-naranja, se

suspendió en DMF/MeOH (~1:1), se filtró y se purificó en cinco inyecciones mediante HPLC prep (acetonitrilo/agua con acetato amónico 10 mM, 15-100%). Las fracciones que contienen el producto deseado se combinaron y se concentraron para dar (2S)-2-(4-((6-((2-((2S)-1-(*terc*-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)etinil)-2-naftil)etinil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de *terc*-butilo (70 mg, 0.11 mmol, rendimiento del 18%) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.448 min; m/z 647.45 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 10.70 (s ancho, 2H),

7.98 (s, 2H), 7.74 (d, *J* = 8.3 Hz , 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.30 - 7.25 (m, 2H, bajo el pico del solvente), 4.95 (dd, *J* = 7.3, 3.3 Hz , 2H), 3.46 - 3.37 (m, 4H), 3.08 - 2.91 (m, 2H), 2.24 - 2.08 (m, 4H), 2.03 - 1.92 (m, 2H), 1.51 (s, 18H).



Intermediario 59

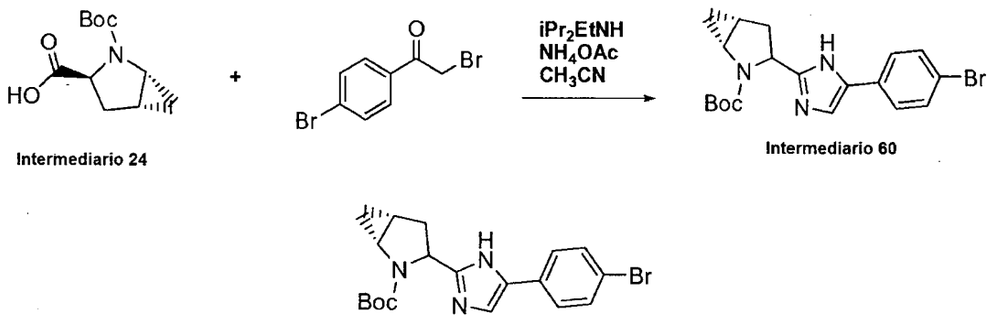
4,4'-(2,6-naftalendiildiil-2,1-etindiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol)

El 2,2'-(5,5'-(naftalen-2,6-diilbis(etin-2,1-diil))bis(1H-imidazol-5,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-butilo (32 mg, 0.049 mmol) se disolvió en diclorometano (2 ml) y, después, se añadió TFA (1 ml, 13 mmol). La solución se agitó a temperatura ambiente durante 1 hora. La reacción se concentró hasta sequedad para dar una sal en TFA de 4,4'-(2,6-naftalendiildi-2,1-etindiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol) (41.6 mg) en forma de un sólido pardo.

RMN de ^{1}H (500 MHz, CD_3OD) δ ppm 8.05 (s, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.52 (s, 2H), 4.89 - 4.84 (m, 2H), 3.56 - 3.44 (m, 4H), 2.59 - 2.50 (m, 2H), 2.42 - 2.24 (m, 4H), 2.26 - 2.14 (m,

2H).

Esquema de reacción 13



Intermediario 60

3-(5-(4-bromofenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,5R)-terc-butilo

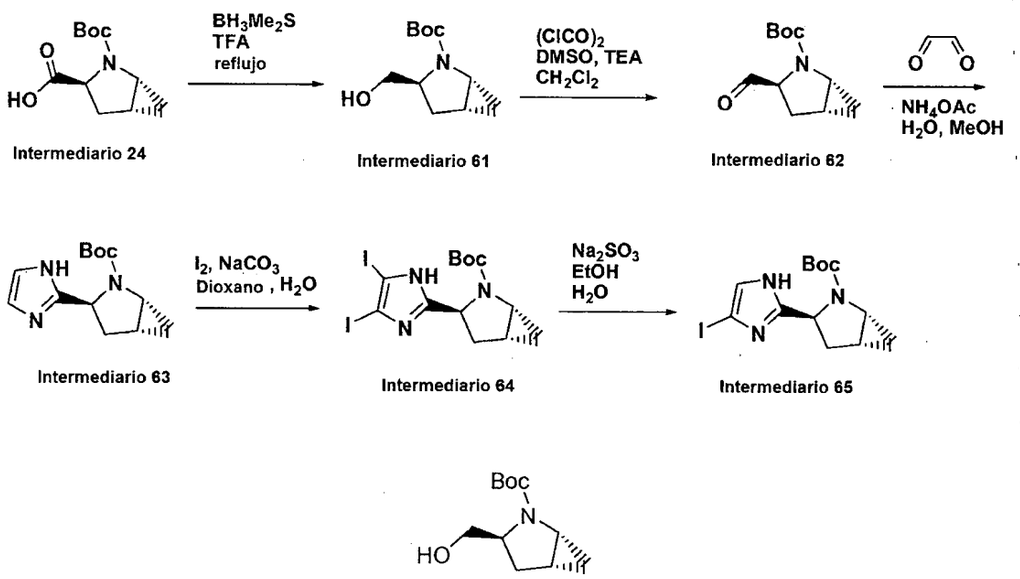
A una solución agitada de ácido 2-bromo-1-(4-bromofenil)etanona (12.23 g, 44.0 mmol) y (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico (10 g, 44 mmol) en MeCN seco (400 ml) se añadió Base de Hunig (7.69 ml, 44.0 mmol). La mezcla se agitó a temperatura ambiente durante 16 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato sódico saturada y salmuera, se secó (sulfato sódico), se filtró y se concentró. En un recipiente de presión, el residuo se suspendió en xileno (400 ml) y se añadió acetato amónico (33.9 g, 440 mmol). El vaso se selló y se calentó a 140ºC durante 2 horas El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato sódico saturada (pH= 9),

salmuera, se secó sobre sulfato sódico, se filtró y se concentró. El producto bruto, en forma de una espuma naranja rojiza, se disolvió en cloruro de metileno y se introdujo en un cartucho de gel de sílice Thompson de 300 g (eluido con 20% de B a 100% de B para 4000 ml, donde el solvente B = acetato de etilo y el solvente A = hexanos) para dar 3-(5-(4-bromofenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (16.67 g, 39.1 mmol, rendimiento del 88.8 %) en forma de una espuma de color marrón dorado.

Tiempo de retención en la CL-EM 1.762 min; m/z 403.94 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna S10 de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 7.62 (d ancho, J = 8.6 Hz, 2H), 7.50 (d ancho, J = 8.6 Hz, 2H), 7.37

(s, 1H), 4.66 (s ancho, 1H), 3.58 (s ancho, 1H), 2.56 - 2.47 (m, 1H), 2.36 - 2.27 (m, 1H), 1.75 - 1.67 (m, 1H), 0.97 (s ancho, 9H), 0.88 - 0.81 (m, 1H), 0.64 - 0.57 (m, 1H).

Esquema de reacción 14



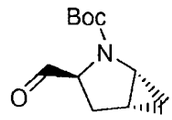
Intermediario 61

3-(hidroximetil)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución de ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (9.85 g, 43.3 mmol) en THF (200 ml) a 0 °C se añadió, gota a gota, el complejo borano-sulfuro de metilo (282 ml, 563 mmol) durante 30 min. Se eliminó el baño de hielo, la mezcla se agitó durante 1 hora y después se calentó a reflujo durante 2 horas. La mezcla se enfrió hasta 0°C, lentamente se inactivó con metanol (~200 ml) y se concentró al vacío. El residuo se

disolvió en DCM y se lavó con agua (emulsión), HCl 1N, $NaHCO_3$ ac. sat, y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para dar 3-(hidroximetil)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (8.43 g, 39.5 mmol, rendimiento del 91 %) para dar un aceite incoloro.

Tiempo de retención en la CL-EM 1.398 min; m/z 236.20 $[M+Na]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue metanol al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 3.72 - 3.79 (m, 1H), 3.52 - 3.64 (m, 3H), 3.15 - 3.24 (m, 1H), 2.00 - 2.08 (m, 1H), 1.62 - 1.72 (m, 1H), 1.54 - 1.62 (m, 1H), 1.45 - 1.51 (m, 9H), 0.84 (s ancho, 1H), 0.36 (td, *J*=5.0, 2.4 Hz, 1H).



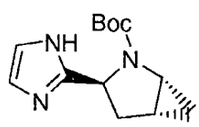
Intermediario 62

. *3-formil-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo*

A una solución de 3-(hidroximetil)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (4.85 g, 22.74 mmol) en DCM (125 ml) a 0 °C se añadió periodinano de Dess-Martin (11.57 g, 27.3 mmol). La reacción se calentó hasta la temperatura ambiente y se agitó durante 3 horas. La reacción se vertió en una solución acuosa saturada de $NaHCO_3$, después se añadieron aproximadamente ~20g de $Na_2S_2O_3$ y se agitó durante 1 hora. Se separaron las capas y la capa acuosa se extrajo varias veces con DCM. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se evaporaron *al vacío*. El residuo se purificó mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 40% de EtOAc/hexanos, para dar 3-formil-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (4.47 g, 21.2 mmol, rendimiento del 93 %) en forma de un aceite incoloro.

Tiempo de retención en la CL-EM 0.813 min; m/z sin ionización (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una

columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 9.48 (s ancho, 1H), 3.67 - 3.97 (m, 1H), 3.33 - 3.59 (m, 1H), 2.10 - 2.31 (m, 2H), 1.56 - 1.67 (m, 1H), 1.47 (s ancho, 9H), 0.80 (s ancho, 1H), 0.55 (s ancho, 1H).



Intermediario 63

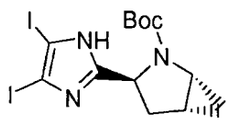
3-(1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución agitada de 3-formil-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (4.4 g) en metanol (15 ml) se añadió gota a gota hidróxido amónico (16.40 ml, 421 mmol)a 0°C. La reacción se dejó calentar hasta la temperatura ambiente y se agitó

durante 45 minutos. Después, gota a gota se añadió oxalaldehído H_2O al 40% (5.32 ml, 46.3 mmol) y la mezcla de reacción se agitó durante la noche. Con el tiempo, el color de la reacción pasó a marrón. La reacción se diluyó con salmuera y se concentró para eliminar el solvente volátil. La capa acuosa restante se extrajo varias veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se evaporaron al vacío. El residuo se purificó mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 70% de EtOAc/hexanos, para dar 3-(1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (3.71 g, 14.9 mmol, rendimiento del 71 %) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 0.772 min; m/z 250.20 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se

determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 10.43 (s ancho, 1H), 6.99 (s, 2H), 4.86 (dd, *J*=9.0, 5.0 Hz, 1H), 3.35 (s ancho, 1H), 3.20 (s ancho, 1H), 2.28 - 2.38 (m, 1H), 1.71 - 1.80 (m, 1H), 1.49 (s, 9H), 0.83 - 0.90 (m, 1H), 0.45 (s ancho, 1H).



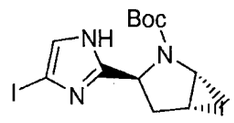
Intermediario 64

3-(4,5-diyodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución de 3-(1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato (5.55 g, 22.3 mmol) y carbonato sódico (7.08 g, 66.8 mmol) en dioxano (56 ml) y agua (56 ml) se añadió yodo (I_2, 12.43 g, 49.0 mmol) y la mezcla de reacción se agitó en oscuridad durante 16 horas a temperatura ambiente La mezcla de reacción se diluyó con EtOAc y se lavó con solución acuosa saturada de tiosulfato sódico. Las capas se separaron y la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se evaporaron al vacío. El residuo se purificó mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 100% de EtOAc/hexanos, para dar 3-(4,5-diyodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-

2-carboxilato de (1R,3S,5R)-*terc*-butilo (8.3 g, 16 mmol, rendimiento del 71 %) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.455 min; m/z 502.07 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 4.51 (s ancho, 1H), 3.56 (s ancho, 1H), 2.40 - 2.54 (m, 1H), 2.18 - 2.27 (m, 1H), 1.65 - 1.73 (m, 1H), 1.20 - 1.40 (s ancho, 9H), 0.82 (dt, *J*=8.6, 5.8 Hz, 1H), 0.58 (s ancho, 1H).



Intermediario 65

3-(4-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-

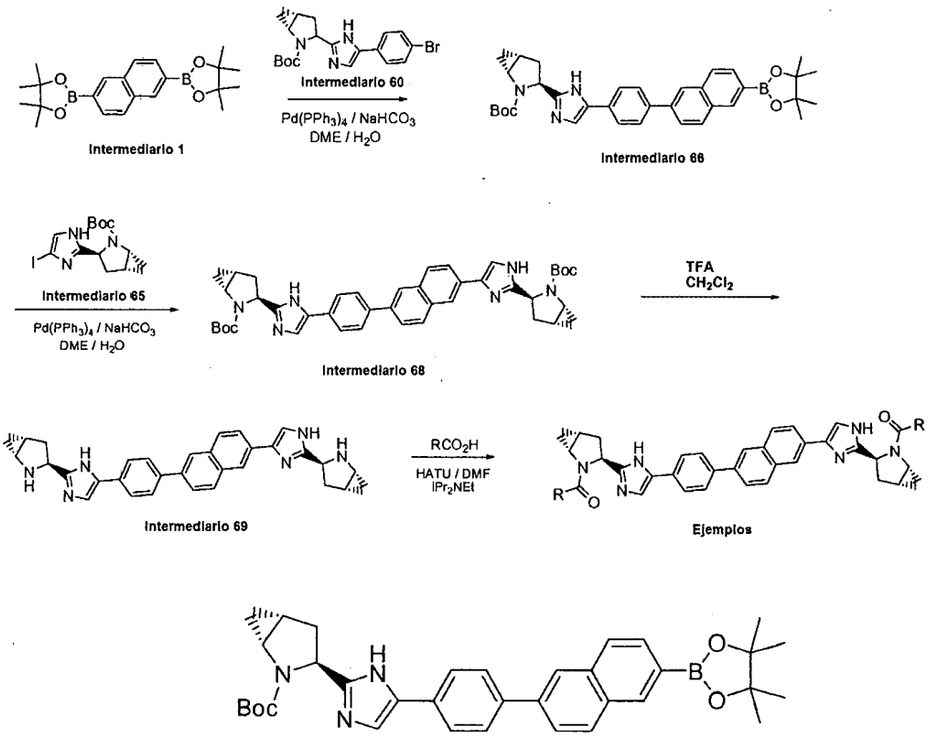
carboxilato de (1R,3S,5R)-terc-butilo

Un matraz de presión de 250 ml equipado con una barra de agitación se cargó con una solución de 3-(4,5-diyodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (8.3 g, 17 mmol) en EtOH (83 ml) y agua (83 ml). Después, se añadió sulfito sódico (20.88 g, 166 mmol) y la mezcla se calentó a 90°C durante 16 horas. La mezcla de reacción se extrajo con EtOAc y las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se evaporaron al vacío. El residuo se purificó mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 15% de EtOAc/DCM, para dar 3-(4-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (3.84 g, 10.2 mmol, rendimiento del 62 %) en forma de un sólido amarillo junto con el producto completamente reducido 3-(1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (550 mg, 2.21 mmol, rendimiento del 13%).

Tiempo de retención en la CL-EM 0.932 min; m/z 376.22 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de

100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 7.12 (s ancho, 1H), 4.59 (s ancho, 1H), 3.44 - 3.64 (s ancho, 1H), 2.40 - 2.52 (m, 1H), 2.17 - 2.30 (m, 1H), 1.65 - 1.73 (m, 1H), 1.27 (s ancho, 9H), 0.84 (dt, J=8.5, 5.7 Hz, 1H), 0.58 (s ancho, 1H).

Esquema de reacción 15



Intermediario 66

(1R,3S,5R)-terc-butil 3-(5-(4-(6-(4,4,5,5-tetrametil-

1,3,2-dioxaborolan-2-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

e

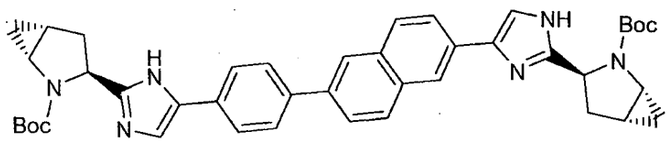
Intermediario 67

3,3'-(5,5'-(4,4'-(naftalen-2,6-diil)bis(4.1-fenilen))bis(1H-imidazol-5,2-diil))bis(2-azabiciclo[3.1.0]hexan-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-terc-butilo

Una solución de 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (1.0 g, 2.6 mmol), 3-(5-(4-bromofenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (1.06 g, 2.63 mmol), Na_2CO_3 (0.837 g, 7.89 mmol) en DME (20 ml) y agua (2 ml) se desgasificó al vacío durante 10 minutos. La mezcla se calentó a 80°C y, después, se añadió $Pd(Ph_3P)_4$ (0.152 g, 0.132 mmol) bajo una corriente de de nitrógeno. Se selló el reactor y se prosiguió el calentamiento adicionalmente 1 20°C durante 16 horas. El DME se eliminó *al vacío* y el material bruto se repartió entre EtOAc/H_2O. Se separaron las capas y la capa acuosa se extrajo varias veces con EtOAc. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se evaporaron *al vacío*. El residuo se purificó mediante cromatográfica instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 5% de MeOH/DCM para dar el producto diana parcialmente puro

contaminado con productos secundarios de la reacción. El producto impuro se purificó de nuevo mediante cromatográfica instantánea (BIOTAGE®), eluyendo con un gradiente de 50 a 100% de EtOAc/hexanos, después, la columna se aclaró con 10% de MeOH/DCM para dar 3-(5-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (606 mg) en forma de una espuma amarilla.

Tiempo de retención en la CL-EM 1.608 min; m/z 578.4 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, CLOROFORMO-*d*, RMN parcial) δ ppm 4.89 (s ancho, 1H), 3.20 - 3.66 (m, 1H), 2.33 - 2.50 (m, 1H), 1.76 - 1.86 (m, 1H), 1.52 (s ancho, 9H), 1.24 - 1.32 (m, 12H), 0.87 - 0.93 (m, 1H), 0.51 (s ancho, 1H).



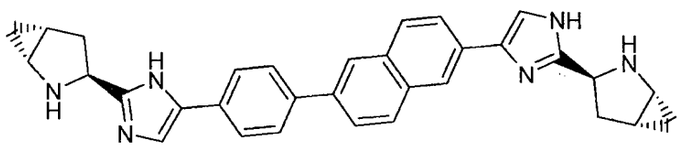
Intermediario 68

3-(5-(4-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Una solución de 3-(5-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (568 mg), 3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato (369 mg, 0.983 mmol) de (1R, 3S, 5R)-*terc*-butilo (369 mg, 0.983 mmol), Na_2CO_3 (313 mg, 2.95 mmol) en DME (10 ml) y agua (2 ml) se desgasificó al vacío durante 10 minutos. La mezcla se calentó a 80°C y, después, se añadió $Pd(Ph_3P)_4$ (114 mg, 0.098 mmol) bajo una corriente de de nitrógeno. Se selló el reactor y se prosiguió el calentamiento adicionalmente 130°C durante la noche. El DME se eliminó *al vacío* y el material bruto se repartió entre EtOAc/H_2O. Se separaron las capas y la capa acuosa se extrajo varias veces con EtOAc. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se evaporaron *al vacío*. El residuo se purificó mediante cromatografía en columna instantánea

((BIOTAGE®), eluyendo con un gradiente de 20 a 100% de EtOAc/hexanos, después 5% de MeOG/DCM, para dar el compuesto3-(5-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (277 mg) parcialmente puro.

Tiempo de retención en la CL-EM 1.578 min; m/z 699.56 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 7.62 - 7.69 (m, 6H), 7.53 - 7.59 (m, 4H), 6.95 (s, 2H), 4.67 (s ancho, 2H), 3.46 - 3.56(m, 2H), 2.50 - 2.59 (m, 0.5H), 2.32 - 2.49 (m, 2H), 2.27 (s ancho, 1.5H), 1.65 - 1.78 (m, 2H), 1.28 (s ancho, 18H), 0.80 - 0.88 (m, 2H), 0.53 - 0.66 (m, 2H).



Intermediario 69

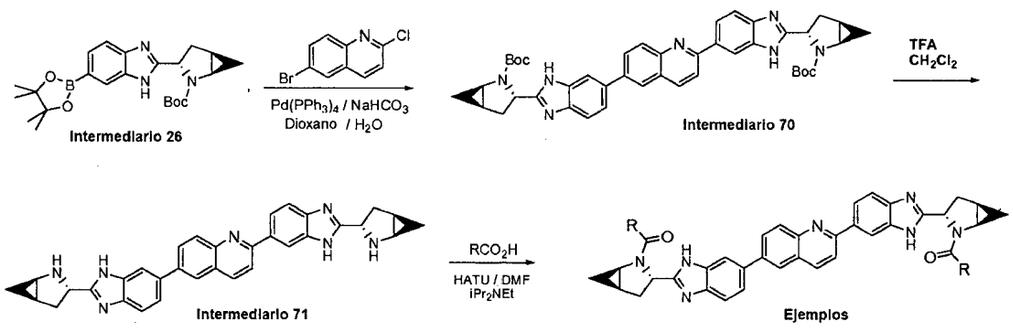
(1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

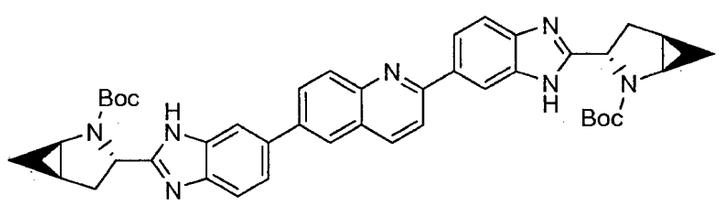
A una solución de 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (275 mg) en DCM (10 ml) se añadió TFA (2 ml, 26.0 mmol). La mezcla se agitó a temperatura ambiente durante 2 h. Los volátiles se eliminaron al vacío y el residuo bruto se purificó mediante HPL de fase inversa (agua/MeOH/TFA) para dar una sal en TFA de (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (106 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.153 min; m/z 499.36 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un

velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.19 (s, 1H), 7.99 - 8.05 (m, 2H), 7.85 - 7.95 (m, 6H), 7.83 (s, 1H), 7.76 (s, 1H), 4.78 (c, *J*=9.4 Hz, 2H), 3.47 - 3.54 (m, 2H), 2.65 - 2.74 (m, 4H), 2.02 - 2.12 (m, 2H), 1.18 - 1.25 (m, 2H), 0.97 - 1.05 (m, 2H).

Esquema de reacción 16





Intermediario 70

(1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(terc-

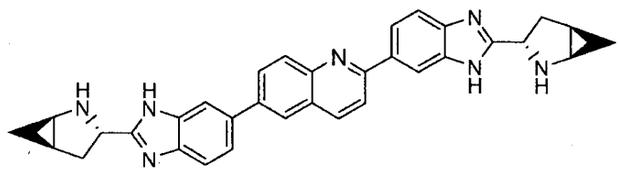
butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-6-quinolinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución desgasificada de 6-bromo-2-cloroquinolina (30 mg, 0.12 mmol), Na_2CO_3 (39.3 mg, 0.371 mmol) y 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (116 mg, 0.272 mmol) en dioxano (1 ml) y H_2O (0.2 ml) se añadió $Pd(Ph_3P)_4$ (14.3 mg, 0.012 mmol) y la mezcla se agitó a 110 °C durante 2 h. La mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador de TFA 0.1%) para dar una sal TFA de (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-6-quinolinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (60.6 mg, 0.057 mmol, rendimiento 46.3%) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 2.05 min; m/z 724 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).

RMN de ^1H (400 MHz, MeOD) δ ppm 8.68 (1H, d, *J*=8.5 Hz), 8.60 (1H, s), 8.44 (1H, dd, *J*=8.5, 1.5 Hz), 8.39 (1H, d,

J=1.3 Hz), 8.33 (1H, d, *J*=8.8 Hz), 8.23 - 8.29 (1H, m), 8.25 (1H, d, *J*=8.5 Hz), 8.19 (1H, s), 8.08 (1H, d, *J*=9.0 Hz), 7.96 (1H, d, *J*=9.0 Hz), 7.93 (1H, d, *J*=9.5 Hz), 5.02 - 5.12 (2H, m), 3.70 (2H, s ancho), 2.74 - 2.85 (2H, m), 2.45 - 2.57 (2H, m), 1.84 - 1.96 (2H, m), 1.05 - 1.68 (18H, m), 0.89 - 1.01 (2H, m), 0.77 - 0.86 (2H, m).



Intermediario 71

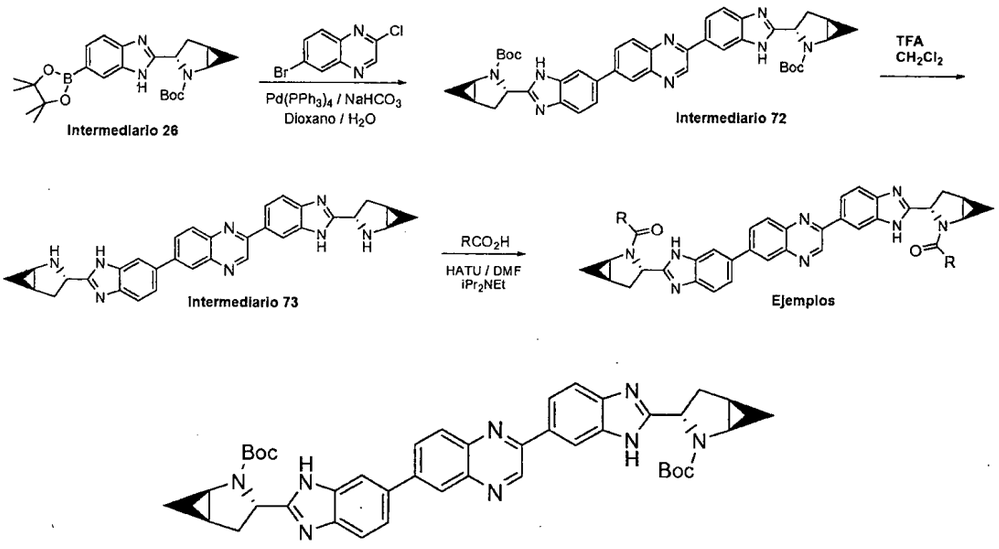
2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinolina

Una sal en TFA de (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-benzimidazol-6-il)-6-quinolinil)-1H-benzimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (51 mg, 0.054 mmol) se mezcló con una solución en dioxano de HCl (0.5 ml, 2.00 mmol) y se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron para dar una sal HCl de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinolina (53 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.20 min; m/z 524 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10,

solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).

Esquema de reacción 17



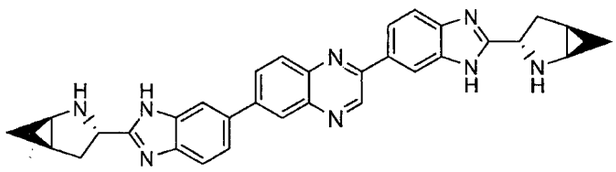
Intermediario 72

(1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-6-quinoxalinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución desgasificada de 6-bromo-2-cloroquinoxalina (30 mg, 0.123 mmol), $NaHCO_3$ (31.1 mg, 0.370 mmol) y 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-

azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (131 mg, 0.308 mmol) en dioxano (1.0 ml) y H_2O (0.2 ml) se añadió $Pd(Ph_3P)_4$ (14.24 mg, 0.012 mmol) y la mezcla se agitó a 100 °C durante 2 h, después a 110°C durante 2 horas. La reacción se diluyó con MeOH, se filtró y el filtrado se purificó mediante HPLC prep (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-6-quinoxalinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (67.6 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 2.13 min; m/z 725 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, MeOD) δ ppm 9.60 (1H, s), 8.71 (1H, s), 8.56 (1H, dd, *J*=8.8, 1.5 Hz), 8.45 (1H, d, *J*=1.5 Hz), 8.26 - 8.35 (2H, m), 8.21 (1H, s), 8.06 - 8.11 (1H, m), 7.91 - 7.99 (2H, m), 5.02 - 5.13 (2H, m), 3.70 (2H, s ancho), 2.79 (2H, dd, *J*=13.4, 9.2 Hz), 2.43 - 2.57 (2H, m), 1.83 - 1.96 (2H, m), 1.07 - 1.65 (18H, m), 0.95 (2H, m), 0.77 - 0.85 (2H, m).



Intermediario 73

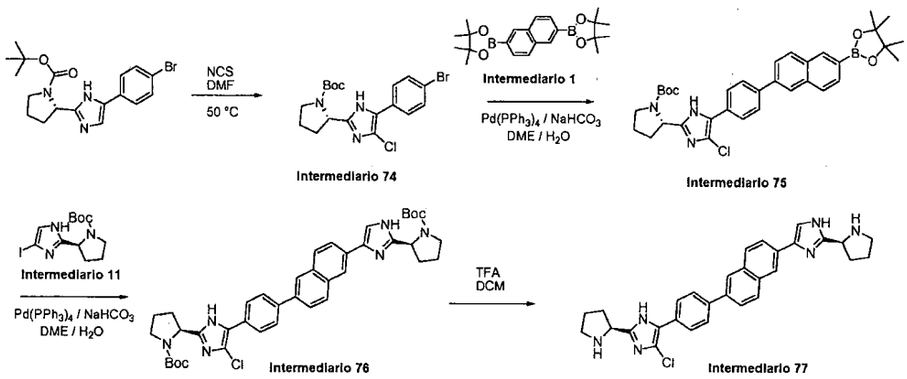
2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalina

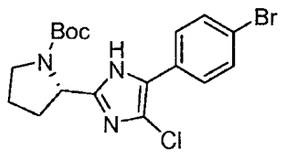
A una solución de sal en TFA de (1R,3S,5R)-3-(5-(2-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-6-quinoxalinil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (65 mg) en DCM (0.5 mL) se añadió TFA (0.25 ml, 3.24 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. Los volátiles se eliminaron y el residuo se trituró con Et_2O. El sólido resultante se recogió mediante embudo de filtración y se aclaró con Et_2O · para dar una sal en TFA de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalina (60 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.51 min; m/z 525 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).

RMN de ^{1}H (400 MHz, MeOD) δ ppm 9.52 (1H, s), 8.58 (1H, s), 8.36 (1H, s), 8.22 - 8.33 (2H, m), 8.30 (1H, d, *J*=9.5 Hz), 8.08 (1H, s), 7.76 - 7.94 (2H, m), 7.83 (1H, d, *J*=9.5 Hz), 4.80 - 5.05 (2H, m), 3.45 - 3.61 (2H, m), 2.70 - 2.92 (2H, m), 2.50 - 2.67 (2H, m), 2.00 - 2.18 (2H, m), 1.26 (2H, s ancho), 1.04 (2H, s ancho).

Esquema de reacción 18





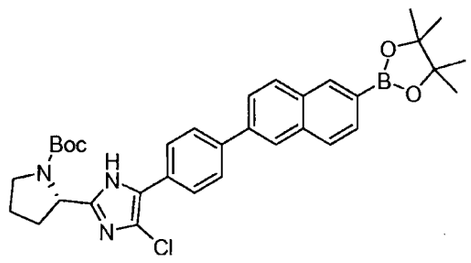
Intermediario 74

2-(5-(4-bromofenil)-4-cloro-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

A una solución de 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de *terc*-butilo (1.0 g, 2.55 mmol) en DMF (25 ML) se añadió NCS (0.51 g, 3.82 mmol) y la mezcla se calentó a 50°C durante la noche. Los filtrados se evaporaron al vacío. El residuo se purificó mediante

cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 10 % de EtOAc/DCM, para dar el compuesto 2-(5-(4-bromofenil)-4-cloro-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (1.04 g) parcialmente puro en forma de una espuma amarilla.

Tiempo de retención en la CL-EM 1.99 min; m/z 427.12 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 7.63 (s, 4H), 4.74 - 4.81 (m, 1H), 3.64 - 3.72 (m, 1H), 3.45 - 3.55 (m, 1H), 2.27 - 2.42 (m, 1H), 2.00 - 2.15 (m, 2H), 1.90 - 2.00 (m, 1H), 1.48 (m, 3H), 1.27 (m, 6H).



Intermediario 75

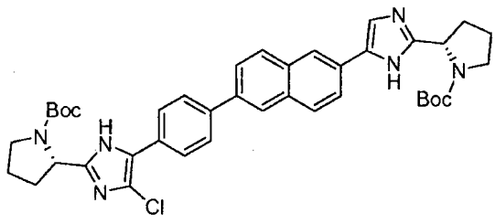
2-(4-cloro-5-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)fenil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

Una solución de 2-(5-(4-bromofenil)-4-cloro-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (1.0 g, 2.44 mmol) y 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (0.926 g, 2.44 mmol) en DME (10 ml) y agua (2 ml) se desgasificó al vacío durante 10 minutos. La mezcla se calentó a aproximadamente ~80°C, se añadió $Pd(Ph_3P)_4$ (0.282 g, 0.244 mmol) bajo una corriente de de nitrógeno y se selló el reactor. El calentamiento prosiguió adicionalmente hasta 130°C durante 8 h. Se añadió $Pd(PPh_3)_4$ adicional (100 mg) y el calentamiento prosiguió durante la noche. El DME se eliminó *al vacío* y el material bruto se repartió entre EtOAc/H_2O. Se separaron las capas y la capa acuosa se extrajo varias veces con EtOAc. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se evaporaron *al vacío*. El residuo se purificó mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de

0 a 100 % de EtOAc/hexanos, para dar el compuesto 2-(4-cloro-5-(4-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (292 mg) parcialmente puro contaminado con trifenilfosfina (292 mg). Una alícuota pequeña se purificó de forma adicional mediante HPLC en fase inversa (agua/acetonitrilo/TFA) para dar el material del título puro. El material restante se usó en la etapa posterior sin purificación adicional.

Tiempo de retención de CL-EM 2.227 min; m/z 598.46 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 10%/H_2O al 90%/acetato de amonio 10 mM y el solvente B fue H_2O al 10%/MeOH al 90%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD, sal en TFA, RMN parcial) δ ppm 3.71 (s ancho, 2H), 3.55 (s ancho, 2H), 2.45 (s ancho, 1H), 2.07 - 2.17 (m, 2H),

1.97 - 2.06 (m, 1H), 1.50 (s, 3H), 1.43 (m, 6H), 1.31 (s ancho, 6H).



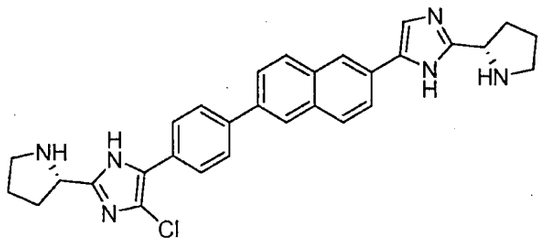
Intermediario 76

2-(5-(4-(6-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-4-cloro-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

Una solución de 2-(5-yodo-1H-imidazol-2-il)pirrolidin-1-carboxilato (163 mg, 0.450 mmol) de (S)-*terc*-butilo, 2-(5-yodo-1H-imidazol-2-il)pirrolidin-1-carboxilato (S)-*terc*-butilo (163 mg, 0.450 mmol) de (S)-*terc*-butilo, bicarbonato sódico (113 mg, 1.350 mmol) en una mezcla de solvente de DME (10 ml) y agua (2 ml) se desgasificó al vacío durante 10 min. La mezcla se calentó a 80°C, después se añadió $Pd(Ph_3P)_4$ (52.0 mg, 0.045 mmol) y el reactor se aclaró con nitrógeno y se selló. El calentamiento se prosiguió adicionalmente hasta 120°C durante 16 horas. El matraz se enfrió hasta la temperatura ambiente, el DME se eliminó *al vacío* y el material bruto se repartió entre DCM/H_2O. Se separaron las capas y la capa acuosa se extrajo varias veces con DCM. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se evaporaron *al vacío*. El residuo se purificó

mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 0 a 100 % de EtOAc/hexanos, para dar el compuesto 2-(5-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-4-cloro-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo parcialmente puro contaminado con trifenilfosfina (77 mg).

Tiempo de retención en la CL-EM 1.830 min; m/z 709.43 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, CLOROFORMO-*d* RMN Parcial) δ ppm 5.00 (d, *J*=4.5 Hz, 2H), 3.38 - 3.52 (m, 4H), 3.10 (s ancho, 1H), 2.91 (s ancho, 1H), 2.09 - 2.33 (m, 4H), 1.93 - 2.05 (m, 2H), 1.54 (s, 18H).



Intermediario 77

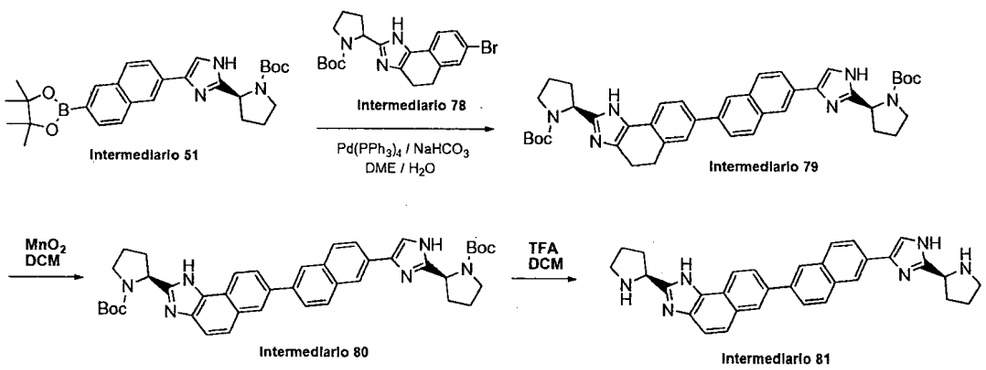
4-cloro-2-((S)-pirrolidin-2-il)-5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol

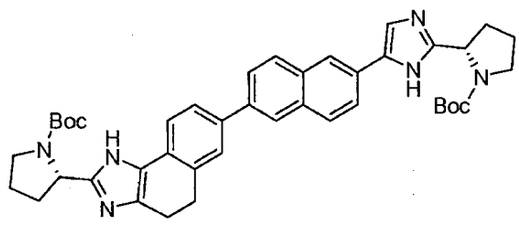
Se añadió TFA (2 ml) a una solución de 2-(5-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-4-cloro-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo en DCM (10 ml) y la mezcla se agitó durante 2 horas a temperatura ambiente. Los solventes se eliminaron al vacío y el residuo se suspendió en una mezcla de solventes de 1:1 de metanol/CH_2Cl_2 y se filtraron a través de un cartucho de MCX (Strata XC). El cartucho se lavó con metanol y el compuesto se eluyó con una solución de NH_3 en metanol (2M). Las fracciones se concentraron al vacío para dar 4-cloro-2-((S)-pirrolidin-2-il)-5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol (40 mg, 0.079 mmol) en forma de sólido amarillo.

Tiempo de retención en la CL-EM 1.353 min; m/z 509.32 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una

columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD, sólo parcialmente soluble) δ ppm 8.20 (s, 1H), 8.09 (s, 1H), 7.88 - 7.96 (m, 2H), 7.76 - 7.88 (m, 6H), 7.51 (s, 1H), 4.50 (t, *J*=7.28 Hz, 1H), 4.35 (t, *J*=7.15 Hz, 1H), 3.03 - 3.31 (parcialmente enmascarado por metanol, m, 4H), 2.24 - 2.42 (m, 2H), 1.88 - 2.21 (m, 6H).

Esquema de reacción 19





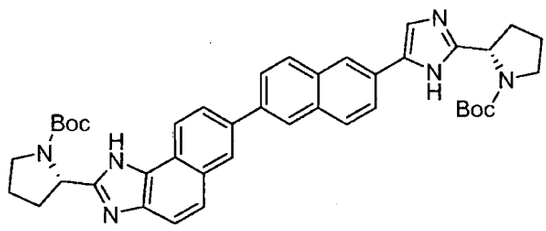
Intermediario 79

2-(7-(4-(6-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-4,5-dihidro-1H-naftol[1,2-d]-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

Una solución de 2-(5-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (402 mg, 0.821 mmol), 2-(7-bromo-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (344 mg, 0.821 mmol) y bicarbonato sódico (207 mg, 2.46 mmol) en DME (14 ml) y agua (1.8 ml) se desgasificó al vacío durante 10 minutos. La mezcla se calentó a 80°C, momento en el cual el matraz se abrió y se añadió $Pd(Ph_3P)_4$ (76 mg, 0.066 mmol). El matraz se aclaró con nitrógeno, se selló y se calentó a 120°C durante 16 horas. El matraz se enfrió hasta la temperatura ambiente, el DME se eliminó *al vacío* y el material bruto se repartió entre DCM y H_2O. Se separaron las capas y la capa acuosa se extrajo varias veces con DCM. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se evaporaron *al vacío*. El residuo se purificó mediante cromatografía en columna instantánea (BIOTAGE®), eluyendo con un gradiente de 20 a

100% de EtOAc/hexanos y después de 0 a 10% de metanol/DCM, para dar el compuesto 2-(7-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-4,5-dihidro-1H-naftol[1,2-d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (183 mg).

Tiempo de retención en la CL-EM 1.543 min; m/z 701.47 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 80

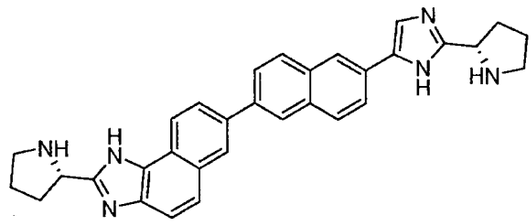
2-(7-(4-(6-(2-((S)-1-(terc-butoxicarbonil)pirrolidin-2-

il)-1H-imidazol-5-il)naftalen-2-il)-1H-naftol[1,2-d]-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo

A una solución de 2-(7-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-4,5-dihidro-1H-nafto[1,2-d]-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (183 mg, 0.196 mmol) en DCM (5 ml) se añadió óxido de manganeso (IV) (1.53 g, 17.6 mmol) y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró a través de una lámina de tierra de diatomeas (CELITE®) y se lavó con una solución de metanol/DCM a 1:1, Los volátiles se eliminaron al vacío usando un rotavap para dar el compuesto 2-(7-(4-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-nafto[1,2-d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (163 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.523 min; m/z 699.53 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de

1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 81

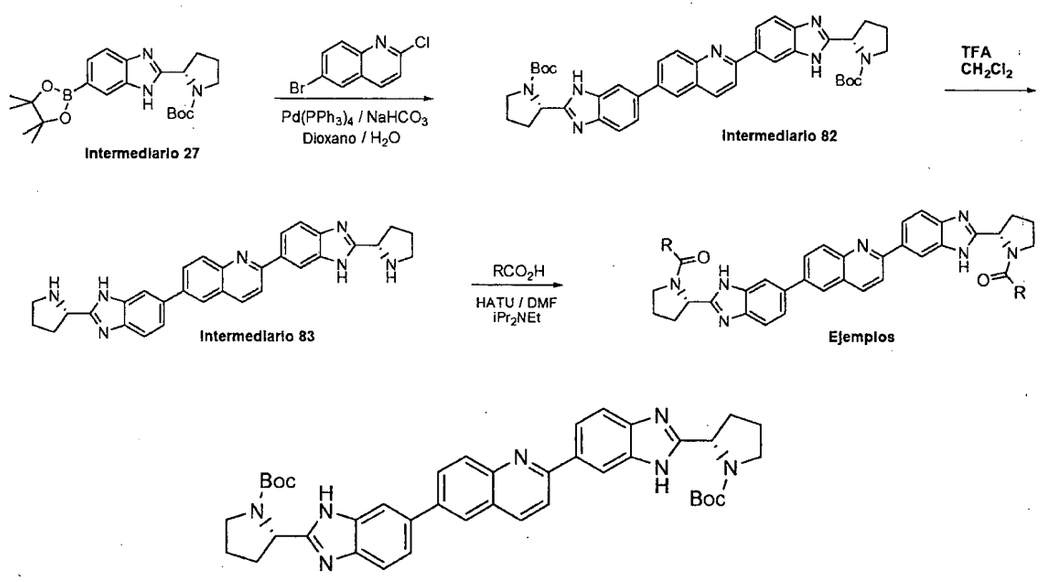
2-((S)-pirrolidin-2-il)-7-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-nafto[1,2-d]imidazol

A una solución agitada de 2-(7-(6-(2-((S)-1-(*terc*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-nafto[1,2-d]-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (137 mg) en CH_2Cl_2 (10 ml) se añadió en una porción TFA (2 ml, 26.0 mmol) a temperatura ambiente. La mezcla se agitó durante 2 horas a temperatura ambiente y, después, los solventes se eliminaron *al vacío*. El residuo se suspendió en 50% de metanol/CH_2Cl_2 y se filtró a través de un cartucho de MCX (Strata XC). El cartucho se lavó con metanol y el compuesto se eluyó con una solución de NH_3 en metanol (2M). Las fracciones adecuadas se concentraron *al vacío* para dar 2-((S)-pirrolidin-2-il)-

7-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)-1H-nafto[1,2-d]imidazol (98 mg, 0.20 mmol) en forma de un sólido naranja.

Tiempo de retención en la CL-EM 1.245 min; m/z 499.30 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN d ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.59 (d, *J*=8.5 Hz, 1H), 8.43 (d, *J*=1.5 Hz, 1H), 8.36 (s, 1H), 8.31 (s, 1H), 8.13 (dd, *J*=8.6, 1.8 Hz, 1H), 8.01 - 8.10 (m, 3H), 7.90 - 7.98 (m, 2H), 7.87 (s, 1H), 7.80 (d, *J*=8.6 Hz, 1H), 5.18 (t, *J*=7.9 Hz, 1H), 5.05 (t, *J*=8.1 Hz, 1H), 3.63 - 3.72 (m, 1H), 3.52 - 3.63 (m, 3H), 2.61 - 2.77 (m, 2H), 2.45 - 2.58 (m, 2H), 2.33 - 2.43 (m, 2H), 2.20 - 2.33 (m, 2H).

Esquema de reacción 20



Intermediario 82

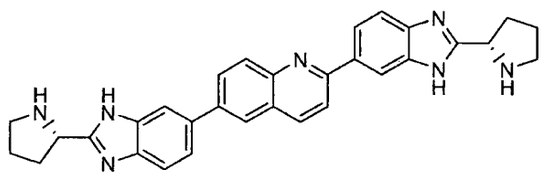
2,2'-(6,6'-(quinolin-2,6-diil)bis-(1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-terc-butilo

A una solución agitada y desgasificada de 6-bromo-2-cloroquinolina (40 mg, 0.165 mmol), 2-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de (S)-*terc*-butilo (150 mg, 0.363 mmol) y $NaHCO_3$ (41.6 mg, 0.495 mmol) en dioxano (1 ml) y H_2O (0.2 ml) se añadió $Pd(Ph_3P)_4$ (19.06 mg, 0.016 mmol). Después, la mezcla de reacción se calentó a 110 °C durante 2 horas, se enfrió hasta la temperatura ambiente, se diluyó con MeOH y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de 2,2'-(6,6'-(quinolin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-

carboxilato de (2S,2'S)-*terc*-butilo (73 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 2.02 min; m/z 700 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).

RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.63 - 8.74 (1H, m), 8.60 (1H, s), 8.44 (1H, dd, *J*=8.7, 1.6 Hz), 8.38 (1H, s ancho), 8.32 (1H, d, *J*=8.8 Hz), 8.25 (2H, d, *J*=8.8 Hz), 8.14 - 8.21 (1H, m), 8.04 - 8.12 (1H, m), 7.90 - 8.00 (2H, m), 5.24 - 5.36 (2H, m), 3.73 - 3.83 (2H, m), 3.59 - 3.72 (2H, m), 2.57 - 2.74 (2H, m), 2.20 - 2.33 (2H, m), 2.09 - 2.20 (4H, m), 1.50 (9H, s ancho), 1.23 (9H, s ancho).



Intermediario 83

2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo-[d]imidazo-6-il)quinolina

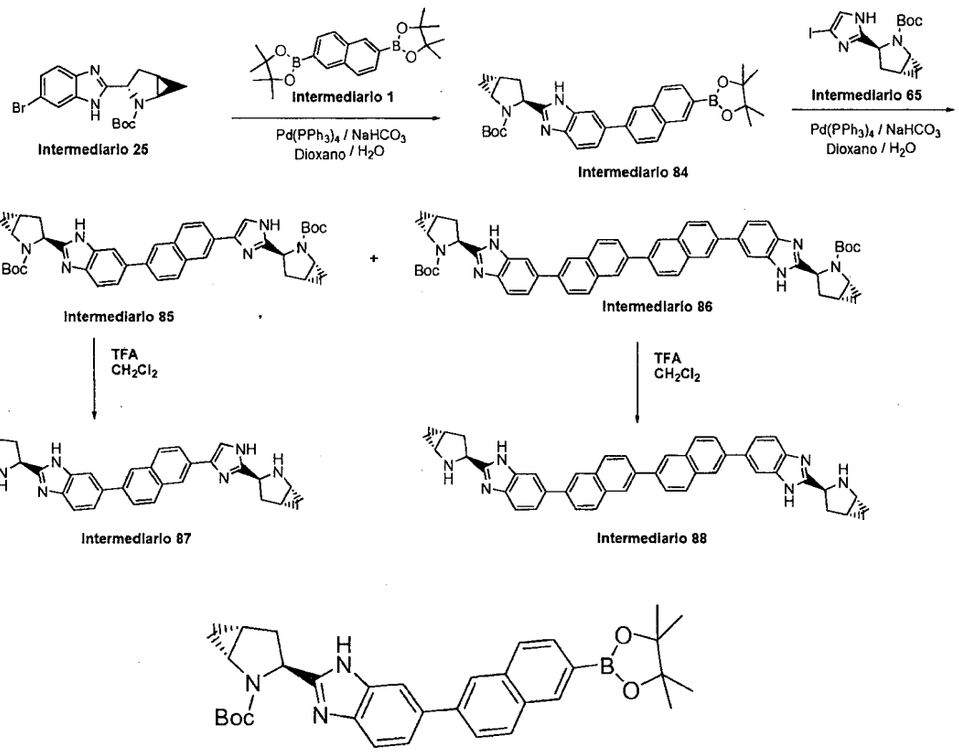
A una solución de sal en TFA de 2,2'-(6,6'-(quinolin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*terc*-

butilo (65 mg) en DCM (0.5 ml) se añadió TFA (0.25 ml, 3.24 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron al vacío y el residuo se trituró con Et_2O. El sólido resultante se recogió mediante embudo de filtración y se aclaró con Et_2O para dar una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)quinolina (61 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.12 min; m/z 500 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).

RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.89 (1H, d, *J*=8.8 Hz), 8.48 (1H, d, *J*=1.3 Hz), 8.45 (1H, s), 8.34 - 8.41 (2H, m), 8.31 (1H, d, *J*=8.8 Hz), 8.12 (1H, dd, *J*=8.5, 1.8 Hz), 8.09 (1H, s), 7.89 (1H, d, *J*=8.5 Hz), 7.77 - 7.85 (2H, m), 5.05 - 5.19 (2H, m), 3.44 - 3.72 (4H, m), 2.61 - 2.75 (2H, m), 2.19 - 2.49 (6H, m).

Esquema de reacción 21



Intermediario 84

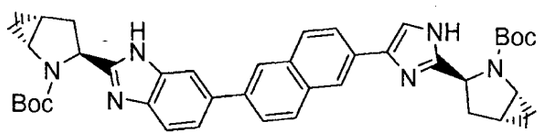
3-(6-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución desgasificada de 2,6-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftaleno (2.51 g, 6.61 mmol), 3-(5-bromo-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (2.5 g, 6.6 mmol) y carbonato sódico (2.78 g, 33.0 mmol) en DME (52.9 ml) y agua (13.2 mL) a 80°C se añadió

$Pd(Ph_3P)_4$ (0.382 g, 0.330 mmol). La reacción se llenó con nitrógeno, se selló y se calentó a 100°C durante la noche. Los volátiles se eliminaron al vacío y el residuo se suspendió en EtOAc, se lavó con agua y la capa de agua se extrajo con EtOAc. Las capas orgánicas combinadas se filtraron a través de una lámina de tierra de diatomeas (CELITE®) y se secaron sobre Na_2SO_4, se concentraron y se purificaron en una BIOTAGE® (cargada en seco en gel de sílice, se cargó un cartucho de gel de sílice de 90 g y eluyó con un gradiente 0 a 70 % de acetato de etilo en hexanos, después se aclaró con 10% de MeOH/ DCM), para dar 3-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (1.8 g, 3.3 mmol, rendimiento del 49 %) en forma de un sólido amarillento.

Tiempo de retención en la CL-EM 1.905 min; m/z 552.47 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A

fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 85

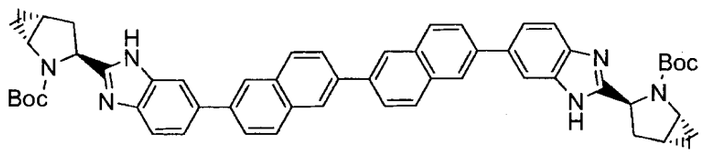
(1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

Un matraz de presión de fondo redondo de 200 ml equipado con una barra de agitación magnética se cargó con 3-(5-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (795 mg, 1.44 mmol), 3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (538 mg, 1.43 mmol) y bicarbonato sódico (502 mg, 5.97 mmol) en DME (9.5 ml) y agua (2.4 ml). La solución se desgasificó a vacío durante 5 minutos y el reactor se cargó de nuevo con N_2, Después se añadió $Pd(Ph_3P)_4$ (110 mg, 0.096 mmol) en una corriente de N_2 y el reactor se selló y se calentó durante la noche a 120°C. La reacción se enfrió hasta la temperatura ambiente y los

volátiles se eliminaron al vacío. El residuo se repartió entre agua y EtOAc y la capa acuoso se extrajo con EtOAc. Las fases orgánicas combinadas se filtraron a través de un lámina de tierra de diatomeas (CELITE®), se secaron Na_2SO_4 y los volátiles se eliminaron al vacío. El residuo se purificó mediante cromatográfica instantánea (BIOTAGE®), eluyendo con un gradiente de 50 a 100% de EtOAc/Hexanos y después 10% de metanol/DCM para dar el producto diana parcialmente puro contaminado con el material de partida, material de partida reducida y otros productos secundarios de la reacción. El residuo se purificó adicionalmente mediante HPLC prep (ACN/agua, TFA al 0.1%), para dar la sal en CFA de (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (200.5 mg). A partir del mismo mezcla de reacción también se recogió un producto secundario, que se identificó como una sal en TFA de (1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-2,2'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato (108 mg)

Tiempo de retención en la CL-EM 1.497 min; m/z 673.52 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un

detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.31 (s, 1H), 8.09 - 8.20 (m, 3H), 7.96 - 8.08 (m, 2H), 7.87 - 7.94 (m, 2H), 5.07 (t, *J*=8.2 Hz, 1H), 4.91 (m, 1H), 3.69 (s ancho, 2H), 2.70 - 2.84 (m, 2H), 2.48 (s ancho, 2H), 1.81 - 1.94 (m, 2H), 1.51 (s ancho, 1H), 1.51 (s ancho, 9H), 1.31 (s ancho, 5H), 1.21 (s ancho, 4H), 0.89 - 0.99 (m, 2H), 0.82 (s ancho, 1H), 0.77 (s ancho, 1H).



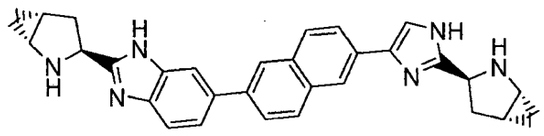
Intermediario 86

(1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-2,2'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato

El producto secundario se obtuvo en forma de una

sal en TFA (108 mg) después de la purificación de la mezcla de reacción de la síntesis del intermediario 85.

Tiempo de retención en la CL-EM 1.882 min; m/z 849.84 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.36 (s, 2H), 8.28 (s, 2H), 8.11 - 8.19 (m, 6H), 8.03 - 8.09 (m, 4H), 7.87 - 7.96 (m, 4H), 5.07 (t, J=8.2 Hz, 2H), 3.71 (s ancho, 2H), 2.75 - 2.85 (m, 2H), 2.51 (s ancho, 2H), 1.86 - 1.94 (m, 2H), 1.52 (m, 10H), 1.22 (s ancho, 8H), 0.97 (ddd, J=8.4, 6.0, 5.8 Hz, 2H), 0.83 (s ancho, 2H).



Intermediario 87

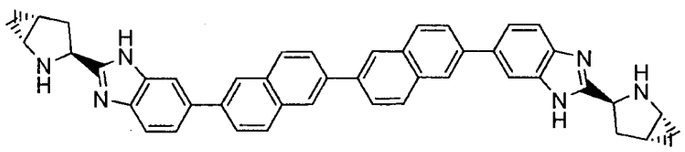
6-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-

imidazol-4-il)naftalen-2-il)-2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol

A una solución agitada de una sal en TFA de 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]sean-3-il)-1H-benzo-[d]imidazol-5-il)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (151 mg) en DCM (3 ml) se añadió HCl 4M en dioxano (10 ml, 40.0 mmol). Inmediatamente se formó un precipitado. La suspensión se agitó durante 30 minutos. Los componentes volátiles se evaporaron al vacío. El residuo bruto se suspendió en DCM (3 ml) y se añadió TFA (2 ml). La solución se agitó durante 1 hora. Los componentes volátiles se evaporaron a presión reducida. El residuo se suspendió en MeOH y se filtró a través de un cartucho Strata XC MCX. El cartucho se lavó con metanol y el compuesto se liberó del cartucho eluyendo con una solución de 2M de amoniaco/metanol. El filtrado de amoniaco/metanol se evaporó a presión reducida para dar 6-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)-2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol (79 mg, 0.17 mmol) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.130 min; m/z 473.35 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una

columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.19 (s, 1H), 8.07 (s, 1H), 7.92 (dd, *J*=8.6, 5.8 Hz, 2H), 7.88 (s, 1H), 7.82 (dd, *J*=5.8, 1.5 Hz, 2H), 7.61 - 7.66 (m, 2H), 7.51 (s, 1H), 4.24 - 4.35 (m, 2H), 3.11 (td, *J*=6.1, 2.4 Hz, 1H), 3.06 (td, *J*=6.0, 2.6 Hz, 1H), 2.40 - 2.53 (m, 2H), 2.18 - 2.33 (m, 2H), 1.69 - 1.76 (m, 1H), 1.62 - 1.69 (m, 1H), 0.88 (ddd, *J*=6.6, 4.3, 2.6 Hz, 1H), 0.79 - 0.84 (m, 1H), 0.61 - 0.68 (m, 1H), 0.55 - 0.60 (m, 1H).



Intermediario 88

6,6'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-5-il)-2,2'-binaftilo

A una solución de una sal en TFA de (1R,3S,5R)-3-

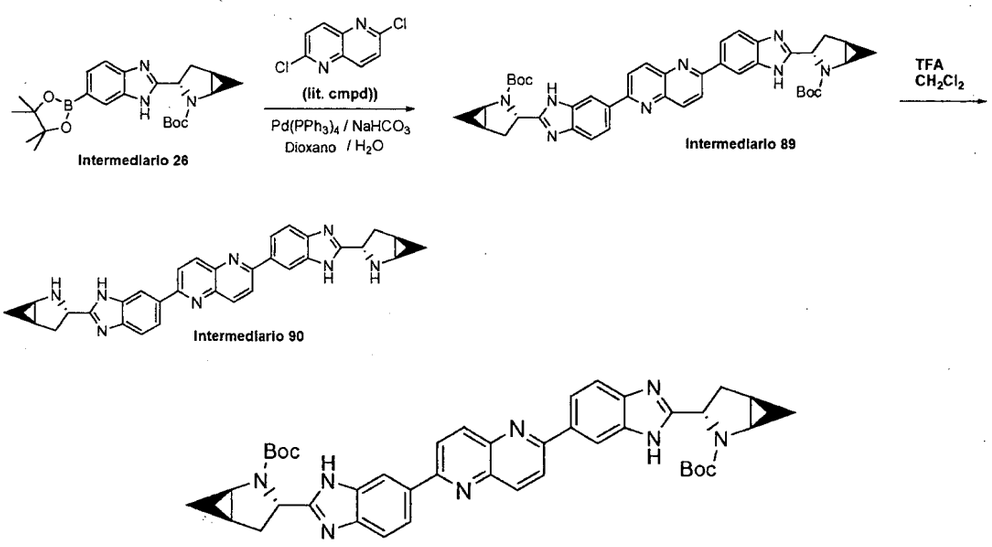
(5-(6'-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-2,2'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato (108 mg) en DCM (5 ml) se añadió TFA (2.0 ml, 26 mmol) y la mezcla de reacción se agitó durante 2 horas a temperatura ambiente. Después, la mezcla de reacción se concentró para dar una sal en TFA de 6,6'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-5-il)-2,2'-binaftilo (22 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.722 min; m/z 649.54 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

RMN de ^1H (500 MHz, MeOD) δ ppm 8.33 (s ancho, 2H),

8.22 (s ancho, 2H), 8.09 - 8.15 (m, 4H), 8.01 - 8.07 (m, 4H), 7.89 - 7.95 (m, 2H), 7.77 - 7.87 (m, 4H), 4.85 - 4.98 (m, 2H), 3.51 - 3.57 (m, 2H), 2.79 - 2.87 (m, 2H), 2.59 - 2.68 (m, 2H), 2.07 - 2.14 (m, 2H), 1.23 - 1.30 (m, 2H), 1.01 - 1.09 (m, 2H).

Esquema de reacción 22



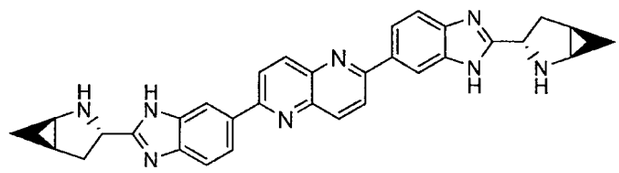
Intermediario 89

(1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-1,5-naftiridin-2-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución de 2,6-dicloro-1,5-naftiridina (30 mg, 0.151 mmol), bicarbonato sódico (38.0 mg, 0.452 mmol) y 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (141 mg, 0.332 mmol) en dioxano

(1.0 ml) y H_2O (0.2 ml) se añadió tetrakis(trifenilfosfina)paladio (0) (17.4 mg, 0.015 mmol) y la mezcla se calentó y se agitó a 110 °C durante 2 h. La reacción se diluyó con MeOH, se filtró y se concentró y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador de NH_4OAc 10 mM) para dar (1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-1,5-naftiridin-2-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (22.3 mg, 0.030 mmol) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 2.11 min; m/z 725 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



Intermediario 90

2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-1,5-naftiridina

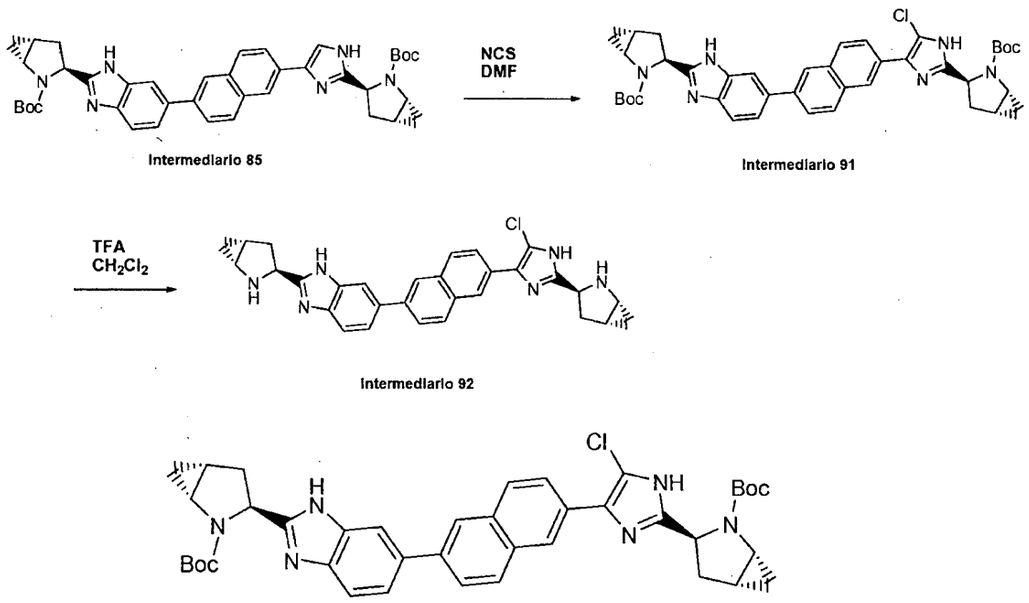
A una solución de (1R,3S,5R)-3-(0.5-(6'-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-

1,5'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (20 mg, 0.028 mmol) en DCM (0.5 ml) se añadió TFA (0.25 ml, 3.2 mmol) y la mezcla se agitó durante 16 horas a temperatura ambiente. Los volátiles se eliminaron al vacío y el residuo se trituró con Et_2O. El sólido resultante se recogió mediante embudo de filtración y se aclaró con Et_2O para dar una sal en TFA de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-1,5-naftiridina (26 mg, 0.022 mmol, rendimiento del 78%) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.41 min; m/z 525 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).

RMN de ^1H (400 MHz, MeOD) δ ppm 8.61 (2H, d, *J*=8.8 Hz), 8.51 (2H, s), 8.40 (2H, d, *J*=9.0 Hz), 8.23 (2H, dd, *J*=8.5, 1.5 Hz), 7.81 (2H, d, *J*=8.5 Hz), 4.74 - 4.97 (2H, m), 3.47 - 3.57 (2H, m), 2.78 - 2.88 (2H, m), 2.52 - 2.65 (2H, m), 2.04 - 2.15 (2H, m), 1.22 - 1.33 (2H, m), 0.99 - 1.11 (2H, m).

Esquema de reacción 23



Intermediario 91

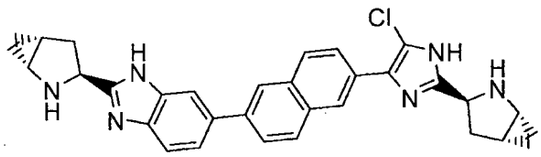
(1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil-5-cloro-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución en agitación de (1R,3S,5R)-3-(4-(6'-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (183 mg, 0.272 mmol) en DMF (5 ml) se añadió en porciones NCS (20 mg, 0.15 mmol) a temperatura ambiente. La mezcla de reacción se calentó a 50°C durante 3 horas. La reacción se enfrió hasta 0° C, se añadió NCS (15 mg, 0.112 mmol) adicional y la mezcla se agitó durante 2 horas a 50

°C. La reacción se diluyó con agua (2 ml) y metanol (2 ml), los volátiles se eliminaron y el producto bruto se purificó mediante HPLC prep (TFA) para dar una sal en TFA de (1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-benzimidazol-5-il)-2-naftil)-5-cloro-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (140.4 mg) en forma de un sólido naranja.

Tiempo de retención en la CL-EM 1.822 min; m/z 707.54 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 µm, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.27 (d, *J*=2.8 Hz, 2H), 8.03 - 8.18 (m, 4H), 7.87 - 7.98 (m, 3H), 5.04 - 5.10 (m, 1H), 4.63 (d, *J*=7.6 Hz, 1H), 3.71 (s ancho, 1H), 3.63 (s ancho, 1H), 2.74 - 2.87 (m, 1H), 2.59 (dd,

J=13.3, 8.7 Hz, 1H), 2.51 (s ancho, 1H), 2.41 (ddd, *J*=13.6, 6.7, 6.6 Hz, 1H), 1.86 - 1.95 (m, 1H), 1.78 (s ancho, 1H), 1.12 - 1.63 (m, 18H), 0.97 (ddd, *J*=8.7, 6.0, 5.8 Hz, 1H), 0.79 - 0.91 (m, 2H), 0.66 (s ancho, 1H).



Intermediario 92

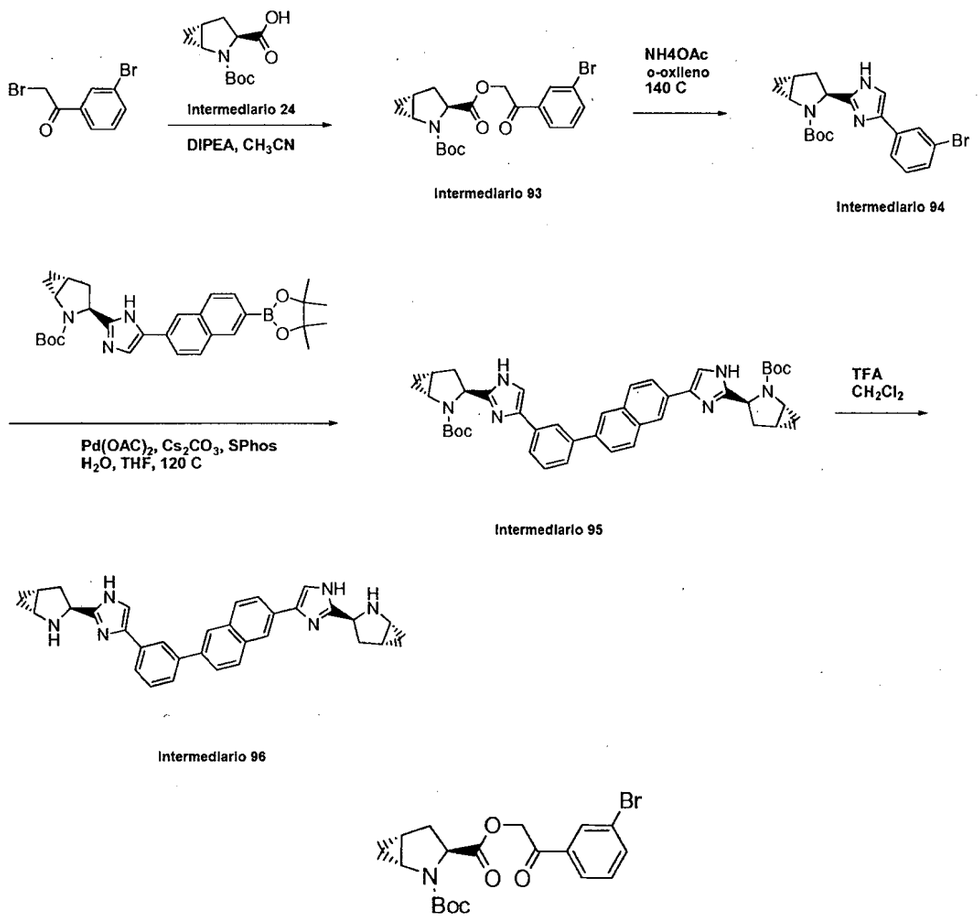
2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-5-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-4-cloro-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol

A una solución de sal en TFA DE (1R,3S,5R)-3-(10-(6'-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-5'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (131 mg, 0.140 mmol) en DCM (10 ml) se añadió TFA (2 ml, 26.0 mmol) y la mezcla se agitó durante 3 horas a temperatura ambiente. Los volátiles se eliminaron al vacío y el residuo se suspendió en MeOH y se filtró a través de un cartucho Strata XC MCX. El cartucho se lavó con metanol y el compuesto se liberó del cartucho eluyendo con una solución de 2M de amoniaco/metanol. El filtrado de amoniaco/metanol se evaporó a presión reducida para dar 2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-5-(6-(2-((1R,3S,5R)-2-

azabiciclo[3.1.0]hex-3-il)-4-cloro-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol (55 mg, 0.11 mmol) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.375 min; m/z 507.33 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 µm, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.26 (s, 1H), 8.19 (s, 1H), 8.00 - 8.09 (m, 3H), 7.92 (ddd, *J*=12.1, 8.6, 1.8 Hz, 2H), 7.85 (dd, *J*=8.6, 1.5 Hz, 1H), 7.81 (d, *J*=8.6 Hz, 1H), 4.96 (dd, *J*=11.0, 7.6 Hz, 1H), 4.64 (app t, *J*=9.3 Hz, 1H), 3.53 - 3.59 (m, 1H), 3.44 - 3.50 (m, 1H), 2.82 (dd, *J*=13.0, 7.5 Hz, 1H), 2.61 - 2.74 (m, 3H), 2.03 - 2.15 (m, 2H), 1.24 - 1.30 (m, 1H), 1.18 - 1.24 (m, 1H), 0.96 - 1.09 (m, 2H).

Esquema de reacción 24



Intermediario 93

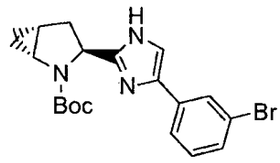
(1R,3S,5R)-3-(2-(3-bromofenil)-2-oxoetil) 2-terc-butil 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato

A una suspensión espesa en agitación de ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (2.00 g, 8.80 mmol) y 2-bromo-1-(3-bromofenil)etanona (2.22 g, 8.00 mmol) en acetonitrilo (25 ml) se añadió DIPEA (2.79 ml, 16.0 mmol) (la solución se convirtió en transparente y de color ámbar) y la mezcla de

reacción se agitó durante la noche. La reacción se concentró y se purificó en BIOTAGE® (80 g de SiO_2, 10-25% de EtOAc/hexanos) para dar 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(3-bromofenil)-2-oxoetil) 2-*terc*-butilo (3.37 g, 7.94 mmol) en forma de un aceite amarillo claro viscoso.

Tiempo de retención en la CL-EM 1.853 min; m/z 423 y 425.98 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna waters XTERRA® M de 7u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 8.04 (d, J = 1.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.0, 7.8 Hz, 1H), 5.58 - 5.10 (m, 2H), 4.23 (s ancho, 1H), 3.62 - 3.39 (m, 1H), 2.58 (dt, J = 13.3, 6.5 Hz, 1H), 2.46 (dd, J = 13.3, 9.5 Hz, 1H), 1.73 - 1.51 (m, 1H), 1.47 (s, 9H), 0.85 (s ancho,

1H), 0.51 (s, 1H).



Intermediario 94

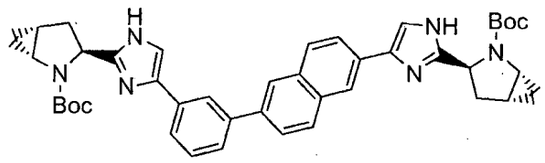
3-(4-(3-bromofenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

En un recipiente de presión alta de 350 ml se añadió acetato amónico (5.94 g, 77 mmol) a una solución de 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(3-bromofenil)-2-oxoetil)2-*terc*-butilo (3.33 g, 7.85 mmol) en xileno (75 ml) y se agitó en nitrógeno durante 5 minutos. El vaso se selló y después se introdujo en un baño de aceite, que se había calentado hasta 140°C (la reacción pasó a ser marrón oscura) y la reacción se mantuvo a 140°C durante 11 horas. Se añadió acetato amónico adicional (3.0 g) y la reacción se agitó a 145°C durante 8 horas, se enfrió hasta la temperatura ambiente y se agitó (conversión >90% mediante CLEM). La reacción se concentró en alto vacío hasta un aceite marrón que se repartió entre DCM (~ 200 ml) y 1/2 de bicarbonato sódico sat. (~200 ml). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró. La espuma bruta solidificada naranja se

purificó en un BIOTAGE® Horizon (20-50% de EtOAc/hexanos, 160 g de SiO_2) para dar 3-(4-(3-bromofenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (2.03 g, 5.02 mmol) en forma de una espuma solidificada amarilla.

Tiempo de retención en la CL-EM 2.450 min; m/z 404 y 406.06 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7.89 (s, 1H), 7.65 (d, J = 6.5 Hz, 1H), 7.42 - 7.32 (m 2H), 7.26 (t, J = 7.8 Hz, 1H), 4.72 - 4.61 (m, 1H), 3.62 - 3.53 (m, 1H), 2.51 (dd, J = 13.0, 7.8 Hz, 1H), 2.36 - 2.26 (m, 1H), 1.75 - 1.66 (m, 1H), 1.29 (s ancho, 9H), 0.84

(dt, J = 8.0, 5.7 Hz, 1H), 0.63 - 0.57 (m, 1H).



Intermediario 95

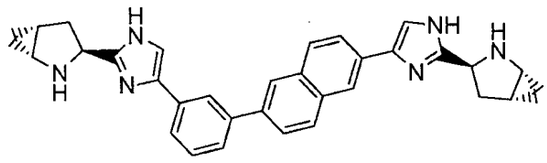
(1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

Una solución de 3-(5-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (220 mg, 0.395 mmol) (preparada del mismo modo que el intermediario 51 a partir del intermediario 55), 3-(4-bromofenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (192 mg, 0.474 mmol) y carbonato de cesio (386 mg, 1.185 mmol) en THF (4 ml) en un matraz de presión de 100 ml se desgasificó a vacío durante 5 minutos y, después, se llenó con nitrógeno. Se añadió acetato de paladio (II) (8.9 mg, 0.039 mmol) y la mezcla se calentó durante 4 horas a 120 °C. La mezcla de reacción se enfrió hasta la temperatura ambiente, se diluyó con agua y se extrajo con EtOAC y DCM. Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se

concentraron. El residuo bruto se purificó en un sistema BIOTAGE® (cartucho de 90 g de gel de sílice, eluido con un gradiente de 0 a 100 % de EtOAc en hexanos), para dar (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (142 mg, 0.203 mmol) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.585 min; m/z 699.57 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.33 (d, *J*=1.2 Hz, 1H), 8.31 (s, 1H), 8.20 - 8.24 (m, 1H), 8.14 - 8.20 (m, 1H), 8.10 - 8.14 (m, 1H), 7.97 - 8.07 (m, 3H), 7.94 (d, *J*=7.9 Hz, 1H), 7.87 - 7.92 (m, 1H), 7.77 - 7.82 (m, 1H),

7.67 - 7.74 (m, 1H), 4.84 - 4.96 (m, 2H), 3.67 (s ancho, 2H), 2.69 - 2.80 (m, 2H), 2.47 (s ancho, 2H), 1.82 - 1.91 (m, 2H), 1.19 - 1.63 (m, 18H), 0.89 - 0.97 (m, 2H), 0.77 (s ancho, 2H).



Intermediario 96

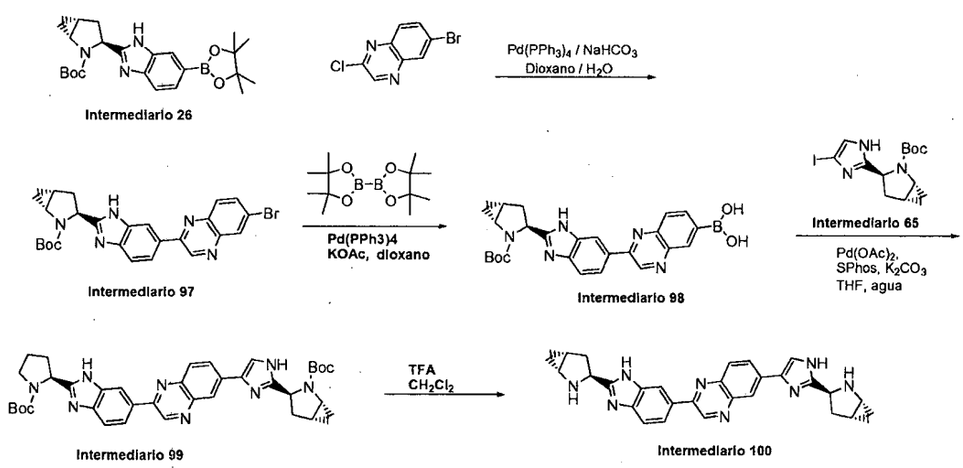
(1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

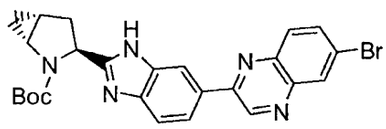
A una solución de (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (130 mg, 0.20 mmol) en DCM (2 ml) se añadió TFA (2 ml, 26.0 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. Los volátiles se eliminaron al vacío y el producto bruto se purificó mediante HPLC prep (metanol/agua/TFA al 0.1%) para dar una sal en TFA de (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (103 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.303 min; m/z 499.13 (MH+). Los datos de CL se registraron en un

cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 µm, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.22 (d, *J*=12.5 Hz, 2H), 8.02 (dd, *J*=8.6, 5.8 Hz, 2H), 7.90 - 7.97 (m, 2H), 7.75 - 7.82 (m, 4H), 7.58 (t, *J*=7.8 Hz, 1H), 4.74 - 4.78 (m, 2H), 3.46 - 3.53 (m, 2H), 2.64 - 2.74 (m, 4H), 2.04 - 2.12 (m, 2H), 1.19 - 1.26 (m, 2H), 1.02 (ddd, *J*=14.2, 7.3, 7.2 Hz, 2H).

Esquema de reacción 25





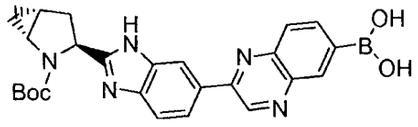
Intermediario 97

3-(6-(6-bromoquinoxalin-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución desgasificada de 6-bromo-2-cloroquinoxalina (60 mg, 0.246 mmol), 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (115 mg, 0.271 mmol) y bicarbonato sódico (62.1 mg, 0.739 mmol) en dioxano (1 ml) y H_2O (0.2 ml) se añadió $Pd(Ph_3P)_4$ (28.5 mg, 0.025 mmol) y la mezcla se agitó a 110 °C durante 2 h, después a 120°C durante 2 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador de NH_4OAc 10 mM) para dar 3-(6-(6-bromoquinoxalin-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo o de *terc*-butilo (102.2 mg, 0.202 mmol, rendimiento del 82%) en forma de un sólido amarillo brillante.

Tiempo de retención en la CL-EM 2.31 min; m/z 506 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo

= 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



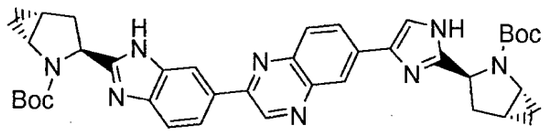
Intermediario 98

Ácido 2-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalin-6-ilborónico

A una solución desgasificada de 3-(6-(6-bromoquinoxalin-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (102 mg, 0.201 mmol), KOAc (49.4 mg, 0.504 mmol) y bis(pinacolato)diboro (113 mg, 0.443 mmol) en dioxano (2 ml) se añadió $Pd(Ph_3P)_4$ (23.28 mg, 0.020 mmol) y la reacción se agitó a 83 °C durante 16 h. La mezcla de reacción se repartió entre EtOAc (20 ml) y NH_4Cl (ac.) sat. (5 ml). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró hasta obtener un aceite naranja, que se purificó mediante HPLC prep (H_2O-MeOH con amortiguador del TFA al 0.1%) para dar ácido 2-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalin-6-ilborónico (57 mg, 0.121 mmol, rendimiento del 60.0 %) en forma de un sólido naranja.

Tiempo de retención en la CL-EM 1.94 min; m/z 472

$[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



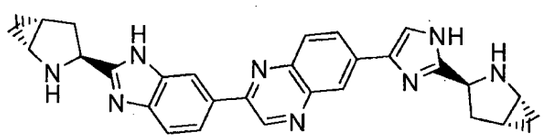
Intermediario 99

(1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-6-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución desgasificada de ácido 2-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalin-6-ilborónico (56 mg, 0.119 mmol), 3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (66.9 mg, 0.178 mmol), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (9.76 mg, 0.024 mmol) y K_2CO_3 (49.3 mg, 0.356 mmol) en THF (1 ml) y agua (0.25 ml) se añadió $Pd(OAc)_2$ (2.67 mg, 0.012 mmol) y la mezcla se agitó a 120 °C durante 2 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador de NH_4OAc 10mM), para dar 3-(5-(2-(2-

((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalin-6-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (32 mg, 0.047 mmol) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.89 min; m/z 675 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 95%/metanol al 5%/acetato amónico 10 mM. solvente B = agua al 5%/metanol al 95%/acetato amónico 10 mM. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 2 min. Longitud de onda = 220). RMN de ^1H (400 MHz, MeOD) δ ppm 9.44 (s, 1H), 8.45 (s ancho, 1H), 8.39 (s, 1H), 8.23 (d, *J*=8.8 Hz, 1H), 8.18 (d, *J*=8.5 Hz, 1H), 8.13 (d, *J*=8.8 Hz, 1H), 7.69 - 7.76 (m, 1H), 7.64 (s, 1H), 4.69 - 4.78 (m, 1H), 4.49 - 4.57 (m, 1H), 3.56 - 3.70 (m, 2H), 2.50 - 2.73 (m, 2H), 2.31 - 2.47 (m, 2H), 1.67 - 1.86 (m, 2H), 1.31 (s ancho, 18H), 0.82 - 0.95 (m, 2H), 0.54 - 0.75 (m, 2H).



Intermediario 100

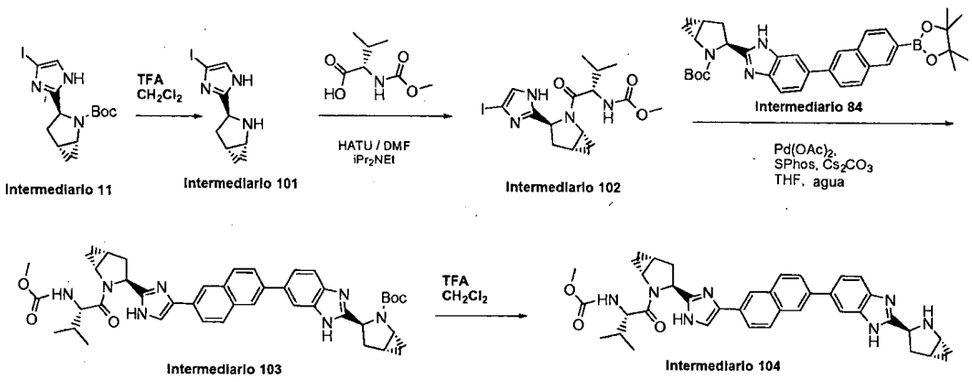
2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)quinoxalina

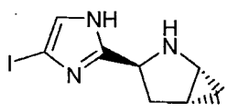
A una solución de 3-(5-(2-(2-((1R,3S,5R)-2-(*terc*-

butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalin-6-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (30 mg, 0.044 mmol) en DCM (0.5 ml) se añadió TFA (0.25 ml, 3.24 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. Los volátiles se eliminaron al vacío y el residuo se trituró con Et_2O, para dar una sal en TFA de 2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)quinoxalina (32.7 mg) en forma de sólido amarillo.

Tiempo de retención en la CL-EM 1.33 min; m/z 475 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, MeOD) δ ppm 9.47 (s, 1H), 8.54 (s, 1H), 8.50 (s, 1H), 8.31 (dd, *J*=8.8, 1.8 Hz, 1H), 8.26 (dd, *J*=8.5, 1.3 Hz, 1H), 8.15 (d, *J*=8.8 Hz, 1H), 7.83 (s, 1H), 7.82 (d, *J*=8.8 Hz, 1H), 4.85 - 4.97 (m, 1H), 4.67 (dd, *J*=10.8, 7.5 Hz, 1H), 3.45 - 3.57 (m, 2H), 2.77 - 2.86 (m, 1H), 2.65 - 2.74 (m, 1H), 2.52 - 2.65 (m, 2H), 2.02 - 2.15 (m, 2H), 1.18 - 1.30 (m, 2H), 0.95 - 1.09 (m, 2H).

Esquema de reacción 26





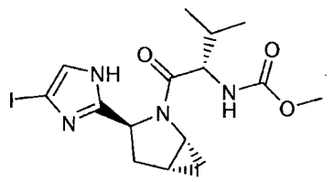
Intermediario 101

(1R,3S,5R)-3-(4-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

A una solución 3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (450 mg, 1.20 mmol) en DCM (5 ml) se añadió, gota a gota, TFA (1 ml, 12.98 mmol) a temperatura ambiente. La mezcla se agitó durante 2 horas a temperatura ambiente, después se eliminaron los volátiles y el residuo se suspendió en MeOH (5 ml) y se filtró a través de un cartucho de Strata XC MCX. El cartucho se lavó con metanol (30 ml) y el compuesto se liberó del cartucho eluyendo con una solución 2M de amoniaco/metanol (40 ml) y se concentró para dar (1R,3S,5R)-3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (283 mg, 1.03 mmol, rendimiento del

86 %) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 0.448 min; m/z 275.94 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7.17 (s, 1H), 4.20 (dd, *J*=10.4, 7.3 Hz, 1H), 3.08 (td, *J*=6.2, 2.6 Hz, 1H), 2.38 (dd, *J*=12.5, 7.3 Hz, 1H), 2.19 (ddd, *J*=12.7, 10.5, 4.9 Hz, 1H), 1.68 - 1.74 (m, 1H), 0.85 (ddd, *J*=6.6, 4.4, 2.8 Hz, 1H), 0.61 - 0.67 (m, 1H).



Intermediario 102

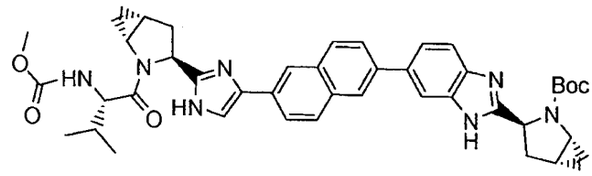
(S)-1-((1R,3S,5R)-3-(4-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato

de metilo

A una solución de (1R,3S,5R)-3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (280 mg, 1.02 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (214 mg, 1.22 mmol) y DIEA (1.8 ml, 10 mmol) en DMF (3 ml) se añadió HATU (464 mg, 1.22 mmol). La mezcla de reacción se agitó 2 horas a temperatura ambiente y después se diluyó con MeOH (5 ml) y agua (5 ml). Los volátiles se eliminaron al vacío y el residuo se purificó con cromatografía instantánea (la muestra se cargó en seco sobre gel de sílice y se eluyó con 0-100 de acetato de etilo/ hexanos), para dar (S)-1-((1R,3S,5R)-3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (500 mg, 0.925 mmol, rendimiento del 91 %) en forma de un aceite amarillento.

Tiempo de retención en la CL-EM 0.850 min; m/z 432.97 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B

fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7.09 (s, 1H), 5.09 (dd, *J*=8.9, 4.6 Hz, 1H), 4.47 - 4.60 (m, 1H), 3.67 (s, 3H), 3.59 -3.62 (m, 1H), 2.39 - 2.49 (m, 1H), 2.29 - 2.39 (m, 1H), 2.12 (dc, *J*=13.6, 6.8 Hz, 1H), 1.95 - 2.06 (m, 1H), 1.11 (dt, *J*=8.6, 5.5 Hz, 1H), 0.94 - 1.02 (m, 3H), 0.91 (d, *J*=6.7 Hz, 3H), 0.76 (s ancho, 1H).



Intermediario 103

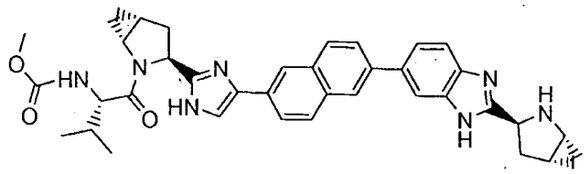
3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Una solución de 3-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (573 mg, 1.04 mmol), (S)-1-((1R,3S,5R)-3-(5-iodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (374 mg, 0.87 mmol), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (SPHOS, 71.0 mg, 0.173 mmol) y carbonato de cesio (846 mg, 2.60 mmol) en

THF (7.9 ml) y agua (0.8 ml) se desgasificó a 0°C al vacío durante 5 minutos y, después, el reactor se llenó con nitrógeno. Se añadió acetato de paladio(II) (19.4 mg, 0.087 mmol) y la mezcla de reacción se calentó a 100 °C durante 3 horas. A la solución enfriada se añadió agua y la reacción se diluyó adicionalmente con EtOAc (15 ml). Las fases se separaron, y la capa acuosa se extrajo con EtOAc (15 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron a través de un lámina de tierra de diatomeas (CELITE®) y los volátiles se eliminaron a presión reducida. El residuo se purificó mediante cromatografía instantánea (la muestra se cargó en seco sobre gel de sílice y eluyó con 20-100% de acetato de etilo/hexanos, después con 5% de MeOH/DCM), para dar 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (246 mg, 0.337 mmol, rendimiento del 39.0%).

Tiempo de retención de CL-EM 1.448 min; m/z 730.21 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire de C18 de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4

ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.32 (s ancho, 1H), 8.30 (s, 1H), 8.03 - 8.19 (m, 4H), 7.96 - 8.03 (m, 1H), 8.01 (s, 1H), 7.85 - 7.96 (m, 2H), 5.18 (dd, *J*=9.0, 7.0 Hz, 1H), 5.09 (dd, *J*=8.9, 7.6 Hz, 1H), 4.58 (d, *J*=6.5 Hz, 1H), 3.81 - 3.89 (m, 1H), 3.65 - 3.75 (m, 1H), 3.69 (s, 3H), 2.68 - 2.86 (m, 2H), 2.52 (dt, *J*=13.6, 6.8 Hz, 2H), 2.15 - 2.29 (m, 1H), 2.06 - 2.15 (m, 1H), 1.85 - 1.95 (m, 1H), 1.51 (s ancho, 4H), 1.41 (d, *J*=16.3 Hz, 1H), 1.27 (s, 1H), 1.20 (s ancho, 3H), 1.12 (ddd, *J*=8.7, 6.0, 5.9 Hz, 1H), 1.04 (d, *J*=6.8 Hz, 3H), 0.87 - 1.00 (m, 5H), 0.83 (s ancho, 1H).



Intermediario 104

(S)-1-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

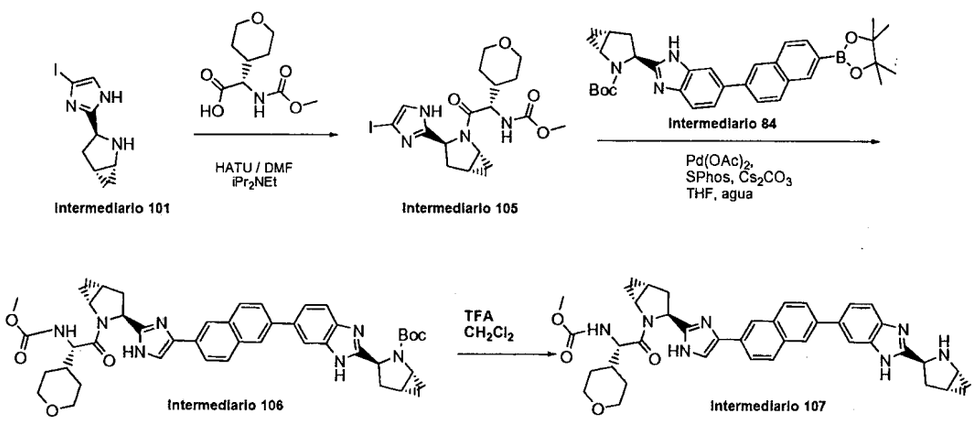
A una solución de 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-

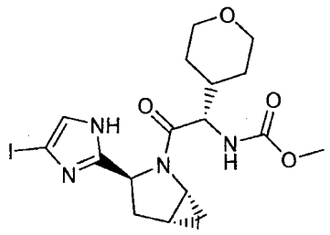
(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)-naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (226 mg, 0.310 mmol) en DCM (5 ml) se añadió TFA (2 ml) y la reacción se agitó durante 2 horas a temperatura ambiente. La solución se concentró al vacío y el residuo se suspendió en MeOH (10 ml) y se filtró a través de un cartucho de Strata XC MCX y se lavó con metanol (25 ml). El compuesto se liberó del cartucho lavando la columna con una solución 2M de amoniaco/metanol (10 ml) y se concentró a presión reducida para dar (S)-1-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (131 mg, 0.208 mmol) en forma de un sólido pardo.

Tiempo de retención de CL-EM 1.235 min; m/z 630.17 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire de C18 de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de

análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.16 (s, 1H), 8.07 (s, 1H), 7.92 (dd, *J*=8.3, 6.3 Hz, 2H), 7.87 (s, 1H), 7.78 - 7.85 (m, 2H), 7.60 - 7.69 (m, 2H), 7.44 (s, 1H), 5.20 (dd, *J*=8.8, 4.8 Hz, 1H), 4.62 (d, *J*=6.8 Hz, 1H), 4.28 (dd, *J*=9.8, 7.8 Hz, 1H), 3.66 - 3.76 (m, 4H), 3.35 - 3.41 (m, 2H), 3.03 (td, *J*=6.0, 2.5 Hz, 1H), 2.40 - 2.59 (m, 3H), 2.12 - 2.25 (m, 2H), 1.99 - 2.09 (m, 1H), 1.59 - 1.68 (m, 1H), 1.10 - 1.18 (m, 1H), 1.00 - 1.08 (m, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 - 1.04 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.76 - 0.84 (m, 2H), 0.50 - 0.59 (m, 1H).

Esquema de reacción 27





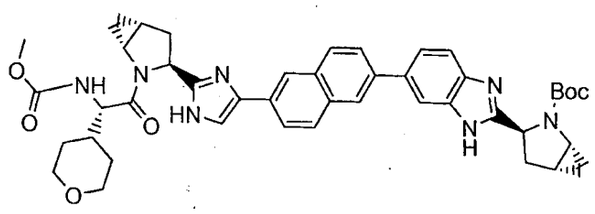
Intermediario 105

(S)-2-((1R,3S,5R)-3-(4-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo

A una solución de (1R,3S,5R)-2-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (510 mg, 1.85 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (483 mg, 2.23 mmol) y DIEA (3.24 ml, 18.5 mmol) en DMF (5 ml) se añadió HATU (846 mg, 2.23 mmol) y la reacción se agitó 2 horas a temperatura ambiente. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (5 ml). Los volátiles se eliminaron al vacío y el residuo se purificó con cromatografía instantánea (la muestra se cargó en seco sobre gel de sílice y se eluyó con 0-100% de acetato de etilo/hexanos, después 10% de MeOH/DCM), para dar (S)-2-((1R,3S,5R)-3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-OXO-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo (370 mg, 0.780 mmol, rendimiento del 42.1 %) en forma de una espuma blanca. El material impuro se purificó adicionalmente sobre HPLC de fase inversa (agua/metanol, TFA al 0.1%), para dar la sal en TFA de (S)-2-

((1R,3S,5R)-3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo, (387 mg) en forma de un aceite incoloro.

Tiempo de retención en la CL-EM 0.690 min; m/z 474.95 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 7.58 (s, 1H), 5.04 (dd, J=9.2, 6.7 Hz, 1H), 4.56 (d, J=7.8 Hz, 1H), 3.96 (td, J=11.7, 3.1 Hz, 2H), 3.74 - 3.81 (m, 1H), 3.65 - 3.73 (m, 3H), 3.35 - 3.44 (m, 2H), 2.61 (dd, J=13.6, 9.3 Hz, 1H), 2.37 (ddd, J=13.6, 6.7, 6.5 Hz, 1H), 1.96 - 2.09 (m, 2H), 1.37 - 1.62 (m, 4H), 1.06 (dt, J=8.8, 5.9 Hz, 1H), 0.84 (td, J=5.6, 2.4 Hz, 1H).



Intermediario 106

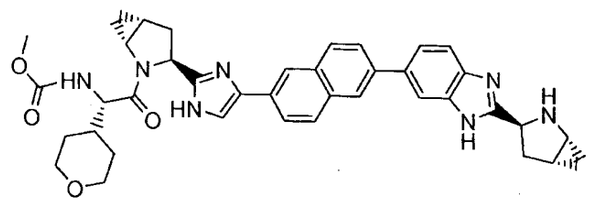
3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Una suspensión espesa de 3-(6-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (407 mg, 0.738 mmol), una sal en TFA de (S)-2-((1R,3S,5R)-3-(5-yodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo (350 mg), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (60.6 mg, 0.148 mmol) y carbonato de cesio (721 mg, 2.21 mmol) en THF (6.7 ml) y agua (0.7 ml) se desgasificó a 0 °C al vacío durante 5 minutos y, después, el reactor se llenó con nitrógeno. Se añadió acetato de paladio (II) (16.6 mg, 0.074 mmol) y la mezcla se calentó a 100°C durante 3 horas. Los volátiles se eliminaron al vacío y la mezcla se diluyó con agua (20 ml) y EtOAc (20 ml). Las fases se separaron, y la capa acuosa se extrajo con EtOAc (20

ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron y se evaporaron al vacío. El residuo se purificó mediante cromatografía instantánea (la muestra se cargó en seco en gel de sílice y eluyó con 20-100% de acetato de etilo/ hexanos, después con 10% de MeOH/DCM). El residuo se purificó de nuevo mediante HPLC de fase inversa (agua/metanol, TFA al 0.1%), para dar la sal en TFA de 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (231 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.395 min; m/z 772.31 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en

modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.09 - 8.18 (m, 3H), 8.05 (dd, *J*=8.7, 1.7 Hz, 1H), 7.97 - 8.02 (m, 2H), 7.91 (d, *J*=8.6 Hz, 1H), 7.88 (dd, *J*=8.7, 1.7 Hz, 1H), 5.16 (dd, *J*=9.2, 7.0 Hz, 1H), 5.01 - 5.09 (m, 1H), 4.62 (d, *J*=7.6 Hz, 1H), 3.91 - 4.02 (m, 3H), 3.83 - 3.89 (m, 1H), 3.70 (s ancho, 4H), 3.35 - 3.45 (m, 2H), 2.68 - 2.83 (m, 2H), 2.45 - 2.57 (m, 2H), 2.04 - 2.16 (m, 2H), 1.90 (s ancho, 1H), 1.43 - 1.61 (m, 8H), 1.14 - 1.31 (m, 4H), 1.07 - 1.13 (m, 1H), 0.97 (dt, *J*=8.8, 5.8 Hz, 1H), 0.91 (s ancho, 1H), 0.82 (s ancho, 1H).



Intermediario 107

(S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo

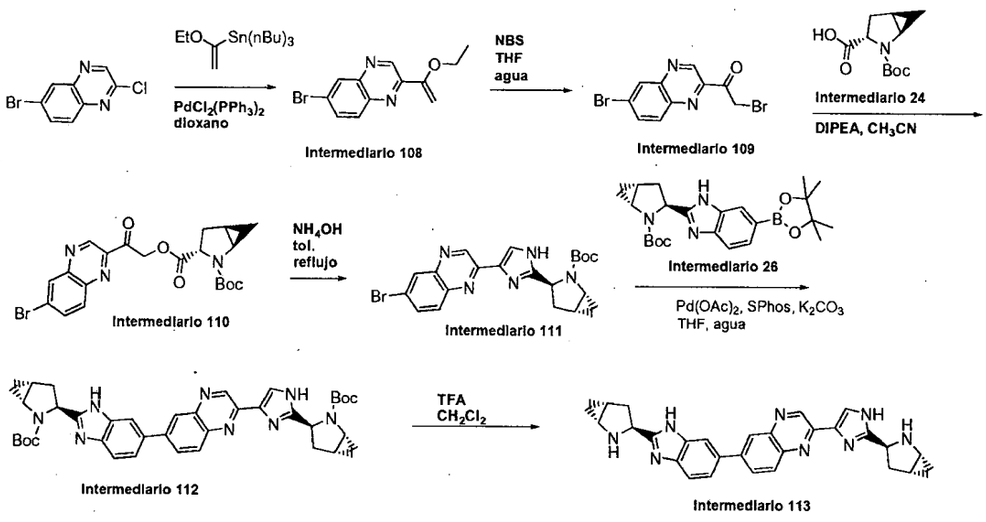
A una solución de una sal en TFA de 3-(6-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (150 mg) en DCM se añadió TFA (2 ml, 26.0 mmol) y la

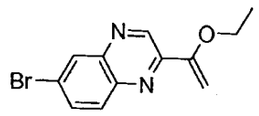
mezcla se agitó durante 2 horas a temperatura ambiente. Los volátiles se eliminaron al vacío y el residuo se suspendió en MeOH (15 ml) y se filtró a través de un cartucho de Strata XC MCX (1 g) y se lavó con metanol. El compuesto se liberó del cartucho lavando la columna con una solución 2M de amoniaco/metanol (20 ml) y se concentró para dar (S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo (100 mg, 0.149 mmol) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.772 min; m/z 670.36 (M-H+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/acetato de amonio 10 mM y el solvente B fue agua al 10%/metanol al 90%/acetato de amonio 10 mM y solvente. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en

modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.28 (s, 1H), 8.24 (s, 1H), 8.13 (d, *J*=8.9 Hz, 1H), 8.05 - 8.10 (m, 1H), 8.03 (s, 1H), 7.96 - 8.00 (m, 2H), 7.84 (dd, *J*=8.7, 1.7 Hz, 1H), 7.75 - 7.82 (m, 2H), 5.16 (dd, *J*=9.2, 7.3 Hz, 1H), 4.84 - 4.88 (parcialmente matizado por MeOD, m, 1H), 4.62 (d, *J*=7.6 Hz, 1H), 3.91 - 4.01 (m, 2H), 3.84 - 3.89 (m, 1H), 3.66 - 3.76 (m, 3H), 3.51 - 3.56 (m, 1H), 3.35 - 3.46 (m, 2H), 2.82 (dd, *J*=12.8, 7.3 Hz, 1H), 2.73 (dd, *J*=13.7, 9.2 Hz, 1H), 2.61 (td, *J*=12.0, 4.7 Hz, 1H), 2.53 (ddd, *J*=13.8, 6.8, 6.6 Hz, 1H), 2.06 - 2.16 (m, 3H), 1.58 - 1.64 (m, 1H), 1.44 - 1.57 (m, 3H), 1.23 - 1.30 (m, 1H), 1.08 - 1.16 (m, 1H), 1.05 (c, *J*=7.8 Hz, 1H), 0.88 - 0.93 (m, 1H).

Esquema de reacción 28



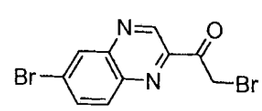


Intermediario 108

6-bromo-2-(1-etoxivinil)quinoxalina

A una solución de 6-bromo-2-cloroquinoxalina (60 mg, 0.246 mmol) y tributil(1-etoxivinil)estanano (107 mg, 0.296 mmol) en dioxano (1.5 ml) se añadió diclorobis(trifenilfosfina)-paladio (II) (17.30 mg, 0.025 mmol) y la mezcla se agitó a 110 °C durante 2 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador 10mM de NH_4OAc), para dar 6-bromo-2-(1-etoxivinil)quinoxalina (36 mg, 0.129 mmol, rendimiento del 52.3 %) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 2.76 min; m/z 279 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90% : metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



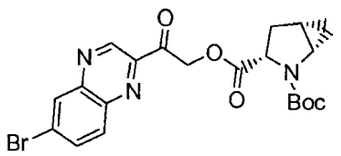
Intermediario 109

2-bromo-1-(6-bromoquinoxalin-2-il)etanona

A una solución de 6-bromo-2-(1-

etoxivinil)quinoxalina (72 mg, 0.26 mmol) en THF (2 ml) y agua (0.500 ml) se añadió NBS (55.1 mg, 0.310 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador 10mM de NH_4OAc), para dar 2-bromo-1-(6-bromoquinoxalin-2-il)etanona (50 mg, 0.15 mmol, rendimiento del 59 %) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 2.40 min; m/z 329 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = 90% water:10% metanol: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



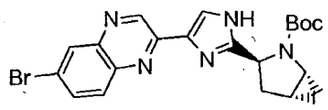
Intermediario 110

2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromoquinoxalin-2-il)-2-oxoetil) 2-terc-butilo

A una solución de 2-bromo-1-(6-bromoquinoxalin-2-il)etanona (50 mg, 0.152 mmol) y ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (37.9 mg, 0.167 mmol) en acetonitrilo (1.5 ml) se añadió DIPEA (0.040 ml, 0.227 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. El solvente se evaporó y el

residuo se repartió entre EtOAc (20 ml)/ $NaHCO_3$ ac. sat. (5 ml). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró, para dar 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromoquinoxalin-2-il)-2-oxoetil) 2-*terc*-butilo (63 mg) bruto en forma de un sólido naranja.

Tiempo de retención en la CL-EM 2.74 min; m/z 476 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



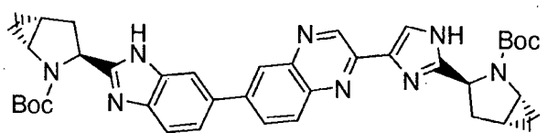
Intermediario 111

3-(4-(6-bromoquinoxalin-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución de 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromoquinoxalin-2-il)-2-oxoetil) 2-*terc*-butilo (63 mg, 0.13 mmol) en tolueno (3 ml) se añadió NH_4OAc (102 mg, 1.323 mmol) y la mezcla se agitó a 120 °C durante 4 horas. Se añadió NH_4OAc adicional (102 mg, 1.323 mmol) y la reacción se calentó adicionalmente a 120 °C durante 4 horas. La reacción se diluyó con EtOAc (20 ml) y

$NaHCO_3$ ac. sat. (5 ml). La capa orgánica se secó ($MgSO_4$), se filtró, se concentró y se purificó mediante cromatografía instantánea (eluido con 1:2 de EtOAc/hexano), para dar 3-(4-(6-bromoquinoxalin-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (25 mg, 0.055 mmol) en forma de un sólido naranja rojizo.

Tiempo de retención en la CL-EM 2.07 min; m/z 456 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



Intermediario 112

(1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinoxalinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato

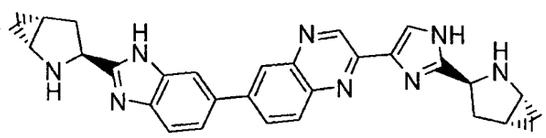
A una suspensión desgasificada de 3-(4-(6-bromoquinoxalin-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (25 mg, 0.055 mmol), K_2CO_3 (22.71 mg, 0.164 mmol),

diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (4.50 mg, 10.96 µmol) y 3-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-benzo[d]imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (30.3 mg, 0.071 mmol) en THF (1 ml) y agua (0.250 ml) se añadió $Pd(OAc)_2$ (1.230 mg, 5.48 µmol) y la mezcla se agitó a 110 °C durante 2 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC prep (H_2O-MeOH con amortiguador 10mM de NH_4OAc), para dar 3-(5-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalin-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (12 mg, 0.018 mmol, rendimiento del 33 %) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.90 min; m/z 675 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 95%/metanol al 5%/acetato amónico 10 mM. solvente B = agua al 5%/metanol al 95%/acetato amónico 10 mM. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 2 min. Longitud de onda = 220).

RMN de ^1H (400 MHz, MeOD) δ ppm 9.38 (s, 1H), 8.28 (d, *J*=2.0 Hz, 1H), 8.16 - 8.22 (m, 1H), 8.10 - 8.15 (m, 1H), 7.95 (s, 2H), 7.66 - 7.76 (m, 2H), 3.54 - 3.73 (m, 2H), 2.52 - 2.69 (m, 2H), 2.33 - 2.47 (m, 2H), 1.71 - 1.84 (m, 2H), 1.08 - 1.57 (m, 20H), 0.83 - 0.95 (m, 2H), 0.60 - 0.74 (m,

2H).



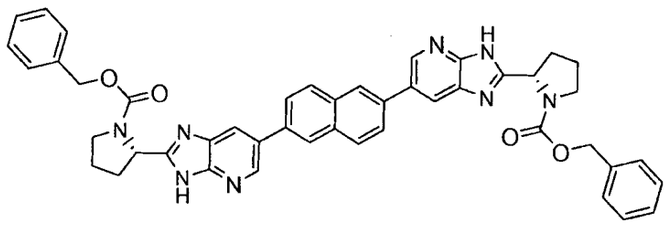
Intermediario 113

6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)quinoxalina

A una solución de 3-(5-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-quinoxalin-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (10 mg, 0.015 mmol) en DCM (0.5 ml) se añadió TFA (0.25 ml, 3.24 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. Los volátiles se eliminaron al vacío y el residuo se trituró con Et_2O. El sólido resultante se aclaró con Et_2O para dar la sal en TFA de 6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)quinoxalina (10.5 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.32 min; m/z 475 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo

= 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220).



Intermediario 114

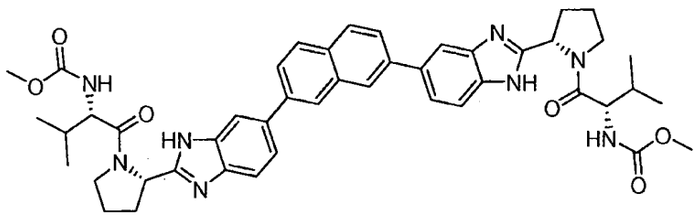
(2S)-2-(6-(6-(2-((2S)-1-((benciloxi)carbonil)-2-pirrolidinil)-1H-imidazo[4,5-b]piridin-6-il)-2-naftil)-3H-imidazo[4,5-b]piridin-2-il)-1-pirrolidincarboxilato de bencilo

Se preparó de forma similar al Intermediario 39 usando ácido (S)-1-(benciloxicarbonil)pirrolidin-2-carboxílico como material de partida en lugar de ácido (S)-1-(*terc*-butoxicarbonil)pirrolidin-2-carboxílico y los intermediarios no se protegieron con SEM. Se preparó (2S)-2-(6-(6-(2-((2S)-1-((benciloxi)carbonil)-2-pirrolidinil)-1H-imidazo[4,5-b]piridin-6-il)-2-naftil)-3H-imidazo[4,5-b]piridin-2-il)-1-pirrolidincarboxilato de bencilo (20.8 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.742 min; m/z 769.41 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector

de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

EJEMPLOS



Ejemplo 1

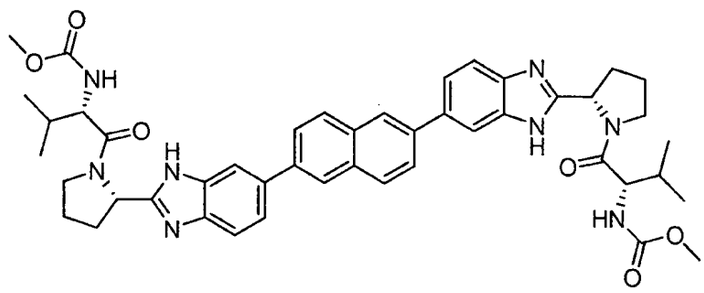
((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de una sal en TFA de 2,7-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (37 mg), diisopropiletilamina (68 µl, 0.40 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (27 mg, 0.15 mmol) en DMF (2 ml) se añadió HATU (59 mg, 0.15 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2.5

horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml) y se agitó durante 15 min. El componente volátil se eliminó *al vacío* y el residuo se purificó dos veces mediante HPLC de fase inversa (agua/acetonitrilo/TFA) y HPLC de fase inversa (agua/acetonitrilo/NH_4OAc) para proporcionar el producto deseado, que se suspendió en metanol y TFA. Los volátiles se eliminaron *al vacío* para dar una sal en TFA de ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (11.3 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.34 min; Análisis calculado para $C_{46}H_{52}N_8O_6$ 812.4 Encontrado m/z 813.42 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (sal en TFA, 500

MHz, MeOD) δ ppm 8.31 (s, 2H), 8.03 - 8.10 (m, 4H), 7.96 - 8.02 (m, Hz, 2H), 7.89 (dd, *J*=8.6, 1.5 Hz, 2H), 7.85 (m, 2H), 5.36 (t, *J*=7.0 Hz, 2H), 4.22 - 4.32 (m, 2H), 4.09 - 4.19 (m, 2H), 3.89 - 4.00 (m, 2H), 3.63 - 3.74 (m, 6H), 2.56 - 2.70 (m, 2H), 2.31 - 2.40 (m, 2H), 2.19 - 2.31 (m, 4H), 2.08 (dd, *J*=13.6, 6.9 Hz, 2H), 0.95 (d, *J*=7.0 Hz, 6H), 0.89 (d, *J*=6.7 Hz, 6H).



Ejemplo 2

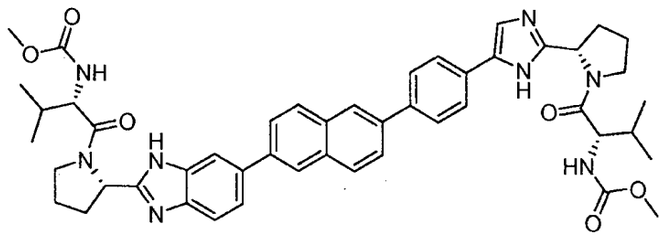
((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (69 mg), diisopropiletilamina (126 µl, 0.723 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (51 mg, 0.29 mmol) en DMF (2 ml) se añadió HATU (82 mg, 0.217 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2.5 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al*

vacío y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA) para proporcionar una sal en TFA de ((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (47 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.30 min; Calculado para $C_{46}H_{52}N_8O_6$: 812.40 Encontrado m/z 813.42 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.25 (s, 2H), 8.07 - 8.16 (m, 4H), 8.02 (m, J=8.6 Hz, 2H), 7.91 (m, J=8.6 Hz, 2H), 7.87 (d, J=8.6 Hz, 2H), 5.37 (t, J=7.2 Hz, 2H), 4.28 (d, J=7.0 Hz, 2H), 4.09 - 4.18 (m, 2H), 3.90 - 4.01 (m, 2H), 3.63 - 3.73 (m, 6H), 2.57 - 2.70 (m, 2H), 2.32 - 2.45 (m, 2H), 2.19 - 2.32 (m, 4H), 2.09 (dc,

J=13.6, 6.9 Hz, 2H), 0.95 (d, *J*=6.7 Hz, 6H), 0.89 (d, *J*=6.7 Hz, 6H).



Ejemplo 3

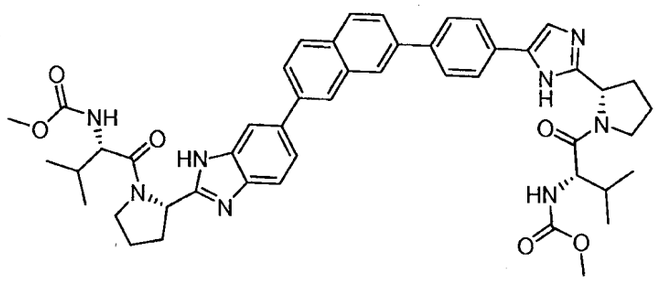
((1S)-1-(((2S)-2-(4-(4-(6-(2-(1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de una sal en TFA de 2-((S)-pirrolidin-2-il)-6-(6-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol (50 mg), diisopropiletilamina (89 µl, 0.51 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (27 mg, 0.15 mmol) en DMF (2 ml) se añadió HATU (39 mg, 0.10 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2.5 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). El componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA) para proporcionar una sal en TFA de ((1S)-1-(((2S)-2-(4-

(4-(6-(2-(1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-piyrrolidinil)carbonil)-2-metilpropil)carbamato de metilo (31.4 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.37 min; Análisis calculado para $C_{48}H_{54}N_8O_6$ 838.42 Encontrado m/z 839.36 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.23 - 8.28 (m, 2H), 8.08 - 8.15 (m, 3H), 8.02 (d, J=8.6 Hz, 1H), 7.95 - 8.00 (m, 2H), 7.85 - 7.95 (m, 6H), 5.40 (t, J=7.2 Hz, 1H), 5.29 (t, J=7.5 Hz, 1H), 4.29 (dd, J=19.4, 7.2 Hz, 2H), 4.10 - 4.19 (m, 2H), 3.96 - 4.03 (m, 1H), 3.87 - 3.96 (m, 1H),

3.69 (m, 6H), 2.55 - 2.73 (m, 2H), 2.04 - 2.42 (m, 8H), 0.89 - 1.05 (m, 12H).



Ejemplo 4

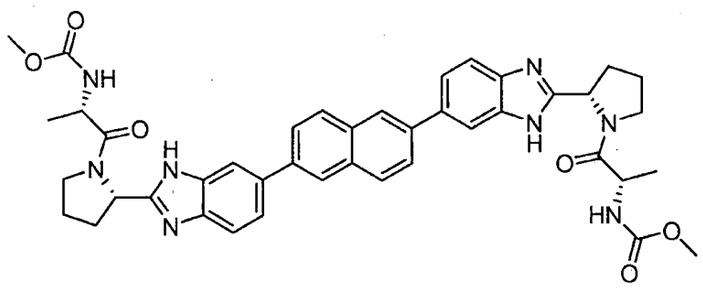
((1S)-1-(((2S)-2-(4-(4-(7-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de una sal en TFA de 2-((S)-pirrolidin-2-il)-6-(7-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol (25 mg), diisopropiletilamina (45 µl, 0.26 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (13 mg, 0.76 mmol) en DMF (2 ml) se añadió HATU (29 mg, 0.076 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2.5 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). El componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA) para proporcionar una sal en TFA de ((1S)-1-(((2S)-2-(4-(4-(7-(2-((2S)-1-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (14.2 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.40 min; Análisis calculado para $C_{48}H_{54}N_8O_6$ 838.42 Encontrado m/z 839.36 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.33 (s ancho, 2H), 8.13 (s, 1H), 8.03 - 8.10 (m, 3H), 8.00 (d, J=8.2 Hz, 2H), 7.86 - 7.94 (m, 6H), 5.40 (t, J=7.2 Hz, 1H), 5.29 (t, J=7.6 Hz, 1H), 4.31 (d, J=7.3 Hz, 1H), 4.27 (d, J=7.3 Hz, 1H), 4.10 - 4.20 (m, 2H), 3.85 - 4.10 (m, 2H), 3.69 (s, 6H), 2.55 - 2.74 (m, 2H), 2.03

- 2.37 (m, 8H), 0.85 - 1.05 (m, 12H).

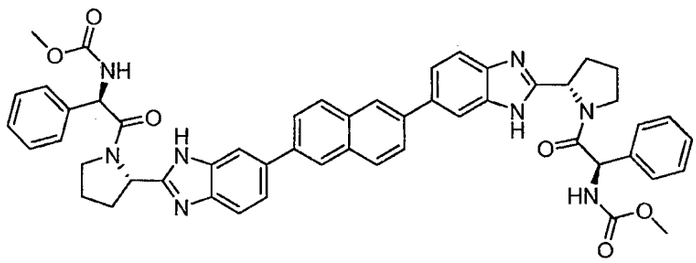


Ejemplo 5

((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg), ácido (S)-2-(metoxicarbonilamino)propanoico (28.8 mg, 0.196 mmol) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%), para dar una sal en TFA de ((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-nafil)-1H-bencimidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo (35.9 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.12 min; Calculado para $C_{42}H_{44}N_8O_6$ 756.34 Encontrado m/z 757.20 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.22 - 8.30 (m, 2H), 8.08 - 8.18 (m, 4H), 7.99 - 8.07 (m, 2H), 7.83 - 7.96 (m, 4H), 5.44 (dd, *J*=8.6, 5.2 Hz, 2H), 4.56 (c, *J*=6.9 Hz, 2H), 4.0 - 4.09 (m, 2H), 3.94 - 4.02 (m, 2H), 3.61 - 3.75 (m, 6H), 2.58 - 2.72 (m, 2H), 2.21 - 2.38 (m, 6H), 1.32 - 1.45 (m, 6H).



Ejemplo 6

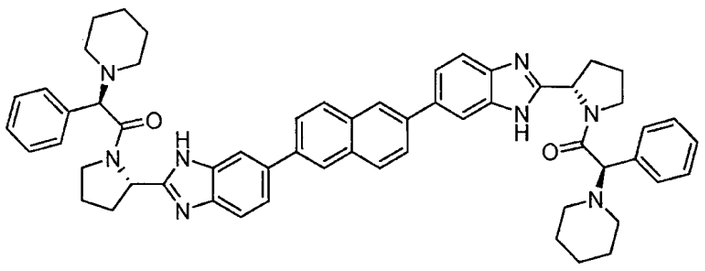
(2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-

etanodiil)))biscarbamato de dimetilo

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg), ácido (R)-2-(metoxicarbonilamino)-2-fenilacético (41.0 mg, 0.196 mmol) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar (2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etanodiil)))biscarbamato de dimetilo (32.3 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.43 min; Análisis calculado para $C_{52}H_{48}N_8O_6$ 880.37 Encontrado m/z 881.23 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de

análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.25 - 8.35 (m, 2H), 8.12 - 8.21 (m, 4H), 8.05 - 8.12 (m, 2H), 7.90 - 8.00 (m, 4H), 7.38 - 7.54 (m, 10H), 5.62 (s, 2H), 5.38 - 5.53 (m, 2H), 4.04 - 4.18 (m, 2H), 3.67 (s, 6H), 2.34 - 2.41 (m, 2H), 2.46 - 2.58 (m, 2H), 2.15 - 2.35 (m, 4H), 2.02 - 2.13 (m, 2H).



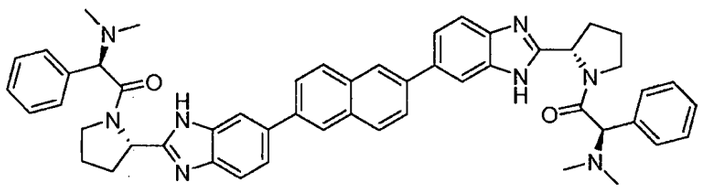
Ejemplo 7

5,5'-(2,6-naftalendiil)bis(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-benzimidazol)

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg), ácido (R)-2-fenil-2-(piperidin-1-il)acético (43.0 mg, 0.196 mmol) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC

preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar 5,5'-(2,6-naftalendiil)bis(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-benzimidazol) (44.3 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.18 min; Calculado para $[M+H]^+$ $C_{58}H_{50}N_8O_2$ 900.48 Encontrado m/z 451.33 [½ M+H]$^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%.



Ejemplo 8

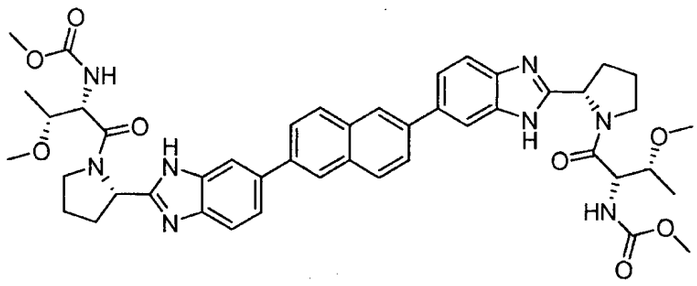
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-6-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-

feniletanamina;

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg, 0.065 mmol), ácido (R)-2-(dimetilamino)-2-fenilacético (35.1 mg) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar (1R)-2-((2S)-2-(5-(6-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-bencimidazol-6-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina (44.3 mg) en forma de un sólido blancuzco.

Tiempo de retención en la CL-EM 1.07 min; Análisis calculado para $C_{52}H_{52}N_8O_2$ 820.42 Encontrado m/z 821.29 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de

análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN DE ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.20 - 8.24 (m, 2H), 8.13 - 8.20 (m, 2H), 8.07 - 8.13 (m, 2H), 7.89 - 8.05 (m, 4H), 7.60 - 7.70 (m, 10H), 5.55 - 5.59 (m, 2H), 5.52 (dd, *J*=8.7, 3.8 Hz, 2H), 4.11 - 4.19 (m, 2H), 2.42 - 3.18 (m, 13H), 2.17 - 2.36 (m, 5H), 1.98 - 2.08 (m, 4H).



Ejemplo 9

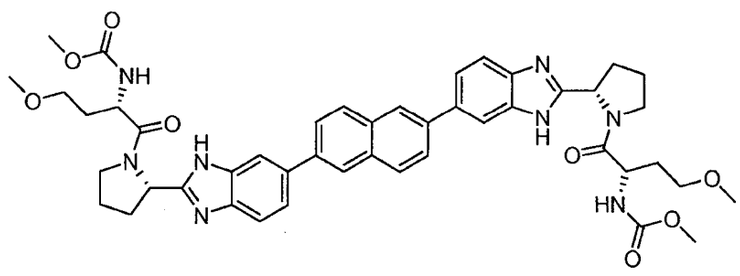
((1S,2R)-2-metoxi-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg), ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico (37.4 mg, 0.196 mmol) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se

concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar ((1S,2R)-2-metoxi-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo (9.3 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.22 min; Calculado para $[M+H]^+$ $C_{46}H_{52}N_8O_8$ 844.39 Encontrado m/z 845.25 [½ M+H]$^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.10 - 8.21 (m, 2H), 7.99 - 8.08 (m, 2H), 7.83 - 7.96 (m, 4H), 7.58 - 7.77 (m, 4H), 5.70 - 5.75 (m, 0.4H), 5.35 (dd, *J*=7.9, 4.9 Hz, 1.6H), 4.58 - 4.61 (m, 0.2H), 4.51 (d, *J*=4.9 Hz, 1.5H), 4.37 - 4.43 (m, 0.3H), 3.89 - 4.08 (m, 3H), 3.61 -

3.78 (m, 7H), 3.38 - 3.45 (m, 2H), 3.23 - 3.31 (m, 5H), 1.93 - 2.57 (m, 9H), 1.10 - 1.28 (m, 6H).

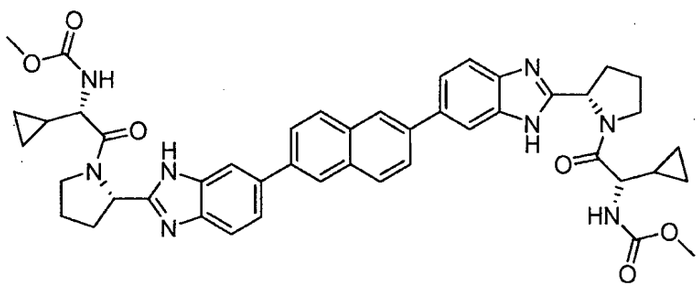


Ejemplo 10

((1S)-3-metoxi-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-homoseril)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg), ácido (S)-4-metoxi-2-(metoxicarbonilamino)butanoico (37.4 mg, 0.196 mmol) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%), para dar una sal en TFA de ((1S)-3-metoxi-1-(((2S)-2-(5-(6-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-homoseril)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo (28.6 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.18 min; Calculado para $[M+H]^+$ $C_{46}H_{52}N_8O_8$ 844.39 Encontrado m/z 845.22 $[½ M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.23 - 8.30 (m, 2H), 8.09 - 8.18 (m, 4H), 8.00 - 8.09 (m, 2H), 7.84 - 7.97 (m, 4H), 5.84 -5.90 (m, 0.2H), 5.44 (dd, J=8.2, 4.9 Hz, 1.8H), 4.65 (dd, J=9.2, 4.0 Hz, 1.8H), 4.38 - 4.45 (m, 0.2H), 3.91 - 4.11 (m, 4H), 3.66 - 3.78 (m, 6H), 3.39 - 3.55 (m, 4H), 3.27 - 3.38 (m, 7H), 2.59 - 2.75 (m, 2H), 2.25 - 2.40 (m, 5H), 2.16 (dddd, J=14.3, 7.0, 6.8, 4.3 Hz, 2H), 1.74 - 1.93 (m, 2H).



Ejemplo 11

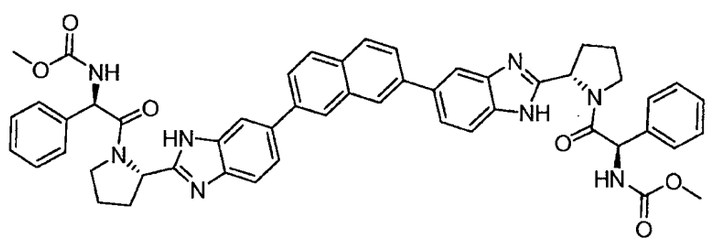
(2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(2S)-2,1-

pirrolidindiil((1S)-1-ciclopropil-2-oxo-2,1-etanodiil))biscarbamato de dimetilo

A una solución en agitación de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (40 mg, 0.065 mmol), ácido (S)-2-ciclopropil-2-(metoxicarbonilamino)acético (33.9 mg, 0.196 mmol) y DIEA (0.114 ml, 0.653 mmol) en DMF (2 ml) se añadió HATU (74.5 mg, 0.196 mmol). La reacción se agitó 9 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) para dar una sal en TFA de (1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(naftalen-2,6-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(1-ciclopropil-2-oxoetano-2,1-diil)dicarbamato de dimetilo (34.9 mg, 0.038 mmol, rendimiento del 58 %) en forma de sólido blanco.

Tiempo de retención en la CL-EM 1.23 min; Calculado para $C_{46}H_{48}N_8O_6$ 808.37 Encontrado m/z 809.22 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3

min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.20 - 8.29 (m, 2H), 8.07 - 8.16 (m, 4H), 7.98 - 8.07 (m, 2H), 7.84 - 7.95 (m, 4H), 5.37 - 5.48 (m, 2H), 4.03 - 4.13 (m, 2H), 3.87 - 4.03 (m, 4H), 3.64 - 3.74 (m, 6H), 2.65 - 2.74 (m, 2H), 2.20 - 2.40 (m, 6H), 1.09 - 1.22 (m, 2H), 0.47 - 0.67 (m, 6H), 0.30 - 0.46 (m, 2H).



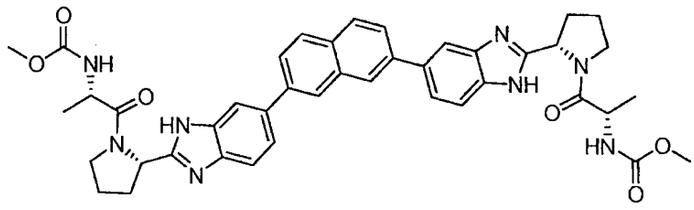
Ejemplo 12

(2,7-naftalendiilbis(1H-bencimidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etanodiil)))biscarbamato de dimetilo

A una solución agitada de una sal en TFA de 2-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)-7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (47 mg), ácido (R)-2-(metoxicarbonilamino)-2-fenilacético (30.9 mg, 0.148 mmol) y DIEA (0.086 ml, 0.49 mmol) en DMF (2 ml) se añadió HATU (56.2 mg, 0.148 mmol). La reacción se agitó 4 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se

purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) para dar una sal en TFA de (1R,1'R)-2,2'-((2S,2'S)-2,2'-(5,5'-(naftalen-2,7-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(2-oxo-1-feniletano-2,1-diil)dicarbamato de dimetilo (38 mg) en forma de sólido amarillo claro.

Tiempo de retención en la CL-EM 1.45 min; Análisis calculado para $C_{52}H_{48}N_8O_6$ 880.37 Encontrado m/z 881.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.31 - 8.39 (m, 2H), 8.03 - 8.17 (m, 6H), 7.84 - 8.00 (m, 4H), 7.33 - 7.53 (m, 10H), 5.55 - 5.63 (m, 2H), 5.40 - 5.54 (m, 2H), 4.01 - 4.17 (m, 2H), 3.67 (s, 6H), 3.27 - 4.41 (m, 2H), 2.44 - 2.75 (m, 2H), 2.01 - 2.33 (m, 6H).



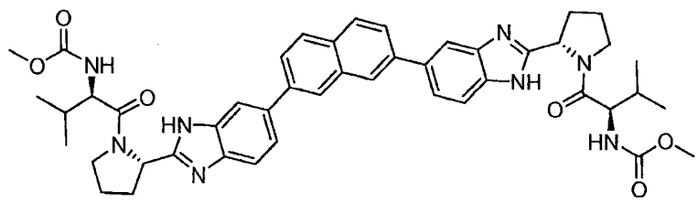
Ejemplo 13

((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)-7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (47 mg), ácido (S)-2-(metoxicarbonilamino)propanoico (21.7mg, 0.148 mmol) y DIEA (0.086 ml, 0.49 mmol) en DMF (2 ml) se añadió HATU (56.2 mg, 0.148 mmol). La reacción se agitó 5 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo (20.9 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.16 min; Calculado

para $C_{42}H_{44}N_8O_6$ 756.34 Encontrado m/z 757.27 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.16 - 8.24 (m, 2H), 7.87 - 8.02 (m, 4H), 7.80 - 7.87 (m, 2H), 7.60 - 7.75 (m, 4H), 5.42 - 5.46 (m, 0.3H), 5.34 (dd, *J*=7.9, 4.0 Hz, 1.7H), 4.55 (c, *J*=7.0 Hz, 1.7H), 4.31 - 4.37 (m, 0.3H), 3.80 - 3.98 (m, 4H), 3.67 (s, 5H), 3.47 (s, 1H), 2.39 - 2.55 (m, 2H), 2.04 - 2.36 (m, 4H), 1.92 - 2.01 (m, 2H), 1.31 - 1.42 (m, 6H).



Ejemplo 14

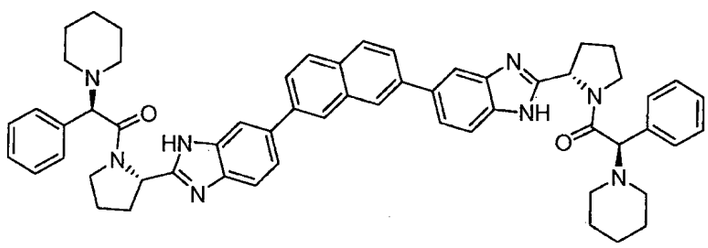
((1R)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-

bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)-7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (47 mg), ácido (R)-2-(metoxicarbonilamino)-3-metilbutanoico (25.9 mg, 0.148 mmol) y DIEA (0.086 ml, 0.49 mmol) en DMF (2 ml) se añadió HATU (56.2 mg, 0.148 mmol). La reacción se agitó 5 horas a temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar una sal en TFA d ((1R)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2R)-2-(metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (25 mg) en forma de un sólido beige.

Tiempo de retención en la CL-EM 1.36 min; Análisis calculado para $C_{46}H_{52}N_8O_6$ 812.40 Encontrado m/z 813.36 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4

ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.33 (s, 2H), 8.07 - 8.13 (m, 4H), 8.05 (dd, *J*=8.5, 1.2 Hz, 2H), 7.84 - 7.96 (m, 4H), 5.49 (dd, *J*=8.6, 3.7 Hz, 2H), 4.36 (d, *J*=7.3 Hz, 2H), 4.15 - 4.23 (m, 2H), 3.83 - 3.97 (m, 2H), 3.72 (s, 6H), 2.58 - 2.71 (m, 2H), 2.21 - 2.38 (m, 6H), 2.05 - 2.18 (m, 2H), 1.07 (d, *J*=6.7 Hz, 6H), 1.04 (d, *J*=6.7 Hz, 6H).



Ejemplo 15

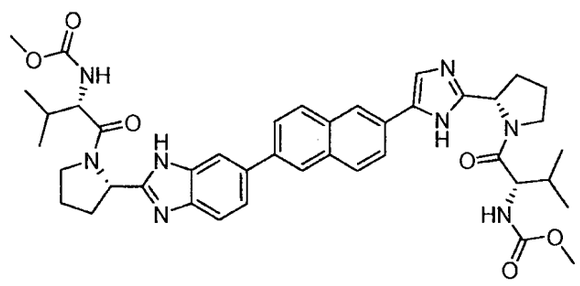
5,5'-(2,7-naftalendiil)bis(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-benzimidazol)

A una solución agitada de una sal en TFA de 2-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)-7-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (47 mg), ácido (R)-2-fenil-2-(piperidin-1-il)acético (32.4 mg, 0.148 mmol) y DIEA (0.086 ml, 0.49 mmol) en DMF (2 ml) se añadió HATU (56.2 mg, 0.148 mmol). La reacción se agitó 5 horas a

temperatura ambiente, se diluyó con MeOH (2 ml) y agua (2 ml), se concentró para eliminar los volátiles y se purificó mediante HPLC preparativa (acetonitrilo/agua con TFA al 0.1%) y, después, mediante HPLC preparativa (acetonitrilo/agua con acetato amónico 10 mM) para dar 5,5'-(2,7-naftalendiil)bis(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-benzimidazol) (16.4 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.21 min; Calculado para $[M+H]^+$ $C_{58}H_{60}N_8O_6$ 900.48 Encontrado m/z 451.43 ½ $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (400 MHz, MeOD) δ ppm 8.18 - 8.28 (m, 2H), 7.96 - 8.05 (m, 2.2H), 7.92 (d, *J*=1.0 Hz, 1.5H), 7.80 - 7.90 (m, 2.2H), 7.65 - 7.76 (m, 3.8H), 7.55 - 7.64 (m, 3.2H), 7.46 - 7.55 (m, 4.5H), 6.85 - 6.97 (m, 1.6H), 6.76-6.83 (m, 1H), 5.65 - 5.70 (m, 0.5H),

5.28 (dd, *J*=7.5, 3.3 Hz, 1.5H), 4.48 (s ancho, 0.5H), 4.02 - 4.12 (m, 1.5H), 3.90 - 3.98 (m, 0.5H), 3.74 - 3.84 (m, 0.5H), 3.25 - 3.40 (m, 3H), 2.51 - 2.93 (m, 8H), 1.89 - 2.33 (m, 8H), 1.62 - 1.75 (m, 8H), 1.47 - 1.59 (m 4H).



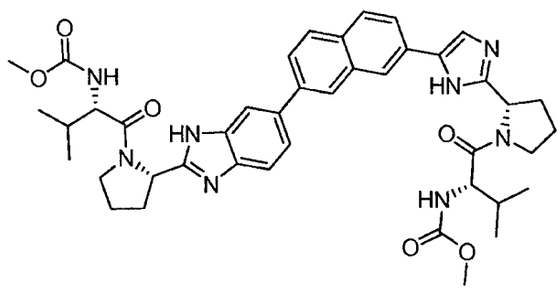
Ejemplo 16

((1S)-1-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de una sal en TFA de 2-((S)-pirrolidin-2-il)-6-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol (32 mg), diisopropiletilamina (62 µl, 0.35 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (19 mg, 0.106 mmol) en DMF (2 ml) se añadió HATU (40 mg, 0.11 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 9 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). El componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (una vez con agua/acetonitrilo/acetato amónico 10 Mm y dos veces con

agua/acetonitrilo/TFA al 0.1%) para proporcionar una sal en TFA de ((1S)-1-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (21 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.17 min; Calculado para $C_{42}H_{50}N_8O_6$ 762.39 Encontrado m/z 763.34 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.27 (s, 1H), 8.15 (d, J=8.9 Hz, 1H), 8.10 (d, J=8.9 Hz, 1H), 8.07 (s, 1H), 7.94 - 8.01 (m, 3H), 7.82 - 7.89 (m, 2H), 5.38 (t, J=7.2 Hz, 1H), 5.31 (t, J=7.6 Hz, 1H), 4.28 (dd, J=14.5, 7.2 Hz, 2H), 4.15 (s ancho, 2H), 3.86 - 4.01 (m, 2H), 3.69 (s, 6H), 2.55 - 2.69 (m, 2H), 2.19 - 2.39 (m, 6H), 2.04 - 2.15 (m, 2H), 0.86 - 1.05 (m, 12H).



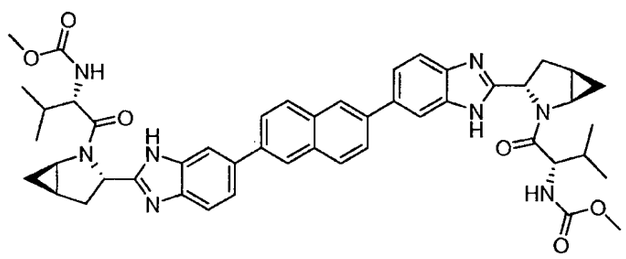
Ejemplo 17

((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de una sal en TFA de 2-((S)-pirrolidin-2-il)-6-(7-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol (16 mg), diisopropiletilamina (31 µl, 0.18 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (9.3 mg, 0.053 mmol) en DMF (2 ml) se añadió HATU (20 mg, 0.053 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 9 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). El componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA al 0.1%) para proporcionar una sal en TFA de ((1S)-1-(((2S)-2-(4-(7-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (7.9

mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.20 min; Calculado para $C_{42}H_{50}N_8O_6$ 762.39 Encontrado m/z 763.35 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. RMN de ^1H (500 MHz, MeOD) δ ppm 8.35 (s, 1H), 8.25 (s, 1H), 8.09 (dd, J=8.4, 3.2 Hz, 2H), 8.04 (s, 1H), 7.89 - 8.00 (m, 3H), 7.77 - 7.87 (m, 2H), 5.37 (t, J=7.0 Hz, 1H), 5.30 (t, J= 7.3 Hz, 1H), 4.28 (dd, J=15.4, 7.2 Hz, 2H), 4.08 - 4.20 (m, 2H), 3.86 - 4.01 (m, 2H), 3.69 (s, 6H), 2.56-2.68 (m, 3H), 2.39 - 2.02 (m, 7H), 0.87 - 1.04 (m, 12H).



Ejemplo 18

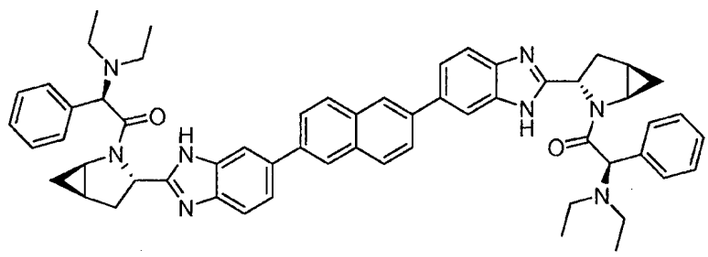
((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftaleno (100 mg), diisopropiletilamina (334 µl, 1.91 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (101 mg, 0.574 mmol) en DMF (2 ml) se añadió HATU (218 mg, 0.574 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 4 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA al 0.1%) para proporcionar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (85 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.33 min; Calculado para $C_{48}H_{52}N_8O_6$: 836.4 Encontrado m/z 837.32 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una

longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.22 (s, 2H), 8.05 - 8.13 (m, 4H), 7.96 - 8.02 (m, 2H), 7.82 - 7.92 (m, 4H), 5.22 - 5.32 (m, 2H), 4.59 (d, *J*=6.4 Hz, 2H), 3.86 (t, *J*=6.0 Hz, 2H), 3.60 - 3.75 (m, 6H), 2.66 - 2.79 (m, 2H), 2.54 (m, 2H), 2.16 - 2.26 (m, 2H), 2.02 - 2.16 (m, 2H), 1.10 - 1.16 (m, 2H), 0.98 - 1.05 (m, 6H), 0.94 - 0.97 (m, 2H), 0.91 (d, *J*=6.7 Hz, 6H).



Ejemplo 19

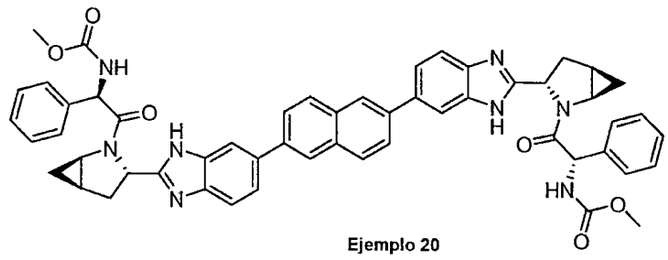
(1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2R)-2-(dimetilamino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-N,N-dietil-2-oxo-1-feniletanamina

A una mezcla de 2,6-bis(2-((1R,3S,5R)-2-

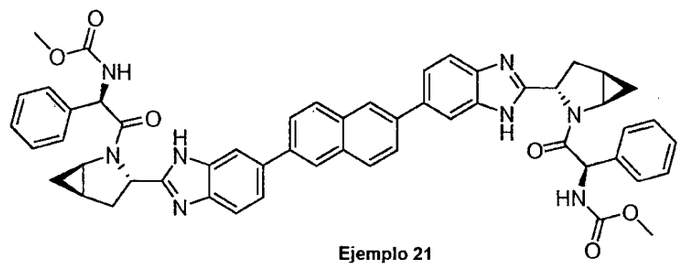
azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftaleno (50 mg), diisopropiletilamina (0.167 ml, 0.957 mmol) y ácido (R)-2-(dietilamino)-2-fenilacético, HCl (70.0 mg, 0.287 mmol) en DMF (2 ml) se añadió HATU (109 mg, 0.287 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 5 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA al 0.1%), después mediante HPLC de fase inversa (agua/acetonitrilo acetato amónico 10 mM) y, por último, mediante HPLC de fase inversa (agua/acetonitrilo, TFA al 0.1%) para proporcionar una sal en TFA de (1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2R)-2-(dietilamino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-6-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-N,N-dietil-2-oxo-1-feniletanamina (25.2 mg) en forma de un polvo blanco.

Tiempo de retención en la CL-EM 1.15 min; Calculado para $M+H]^+$ $C_{58}H_{60}N_8O_2$: 900.48 Encontrado m/z 451.46 $[½M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a

0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.27 (s, 2H), 8.08 - 8.17 (m, 4H), 7.96 (td, *J*=8.7, 1.5 Hz, 4H), 7.87 (d, *J*=8.6 Hz, 2H), 7.68 - 7.72 (m, 4H), 7.57 - 7.68 (m, 6H), 5.79 (s, 2H), 5.23 (dd, *J*=9.0, 6.3 Hz, 2H), 3.95 - 4.05 (m, 2H), 3.25 - 3.48 (m, 4H), 3.06 (s ancho, 4H), 2.43 - 2.61 (m, 4H), 2.01 - 2.11 (m, 2H), 1.31 (t, *J*=6.9 Hz, 12H), 0.62 (ddd, *J*=8.7, 6.0, 5.8 Hz, 2H), -0.21 (td, *J*=5.7, 2.4 Hz, 2H).



Ejemplo 20



Ejemplo 21

Ejemplo 20

(1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-

(metoxicarbonil)amino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-feniletil)carbamato de metilo

y

Ejemplo 21

(2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1R)-2-oxo-1-fenil-2,1-etanodiil)))biscarbamato de dimetilo

A una mezcla de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftaleno (50 mg), diisopropiletilamina (0.167 ml, 0.957 mmol) y ácido (R)-2-(metoxicarbonilamino)-2-fenilacético (60 mg, 0.287 mmol) en DMF (2 ml) se añadió HATU (109 mg, 0.287 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 5 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA al 0.1%), después mediante HPLC de fase inversa (agua/acetonitrilo acetato amónico 10 mM) y, por último, mediante HPLC de fase inversa (agua/acetonitrilo, TFA al 0.1%) para proporcionar una sal en TFA de (1R)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-(metoxicarbonil)amino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil)-

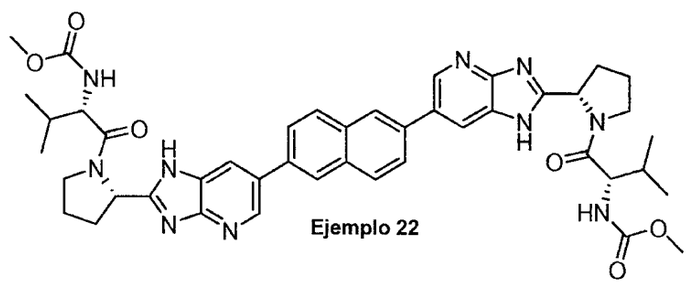
1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-feniletil)carbamato de metilo (6.9 mg) en forma de un sólido blanco y una sal en TFA de (2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1R)-2-oxo-1-fenil-2,1-etanodiil)))biscarbamato de dimetilo (12.5 mg) en forma de un sólido blanco.

Datos analíticos del Ejemplo 20: Tiempo de retención en la CL-EM 1.46 min; Calculado para $C_{46}H_{52}N_8O_6$: 904.37 Encontrado m/z 453.35 $[½M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.28 (d, J=4.6 Hz, 2H), 8.15 (d, J=8.6 Hz, 2H), 8.12 (s, 1H), 8.07 (s, 1H), 8.03 (t, J=8.9 Hz, 2H), 7.92 - 7.98 (m, 2H), 7.90 (d, J=8.6 Hz, 1H), 7.85 (d, J=8.6 Hz, 1H), 7.48 - 7.54 (m, 2H), 7.37 - 7.48 (m, 8H), 5.85

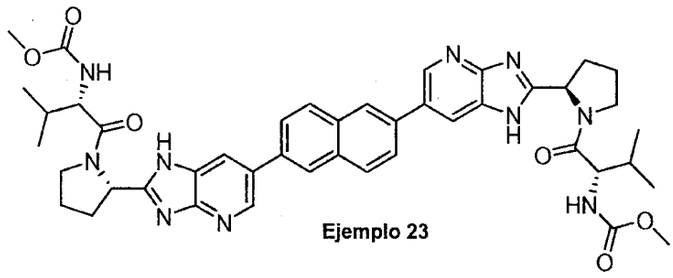
(s, 1H), 5.78 (s, 1H), 5.39 (dd, *J*=9.0, 6.3 Hz, 1H), 5.29 (dd, *J*=9.2, 5.8 Hz, 1H), 3.91 - 3.97 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.52 - 3.61 (m, 1H), 2.73 (dd, *J*=13.7, 9.2 Hz, 1H), 2.46 - 2.65 (m, 3H), 2.06 - 2.14 (m, 1H), 1.98 - 2.06 (m, 1H), 1.23 - 1.30 (m, 1H), 1.10 (s ancho, 1H), 0.66 - 0.72 (m, 1H), 0.01 - 0.10 (m, 1H).

Datos analíticos del Ejemplo 21: Tiempo de retención en la CL-EM 1.48 min; Calculado para $[M+H]^+$ $C_{54}H_{48}N_8O_6$: 904.37 Encontrado m/z 453.35 $[½M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (s, 2H), 8.16 (d, *J*=8.6 Hz, 2H), 8.11 (s, 2H), 8.01 - 8.06 (m, 2H), 7.95 (d, *J*=8.6 Hz, 2H), 7.90 (m, *J*=8.6 Hz, 2H), 7.48 - 7.55 (m, 4H), 7.36 - 7.48 (m, 6H), 5.85 (s, 2H),

5.29 (dd, *J*=9.2, 5.8 Hz, 2H), 3.92 - 3.97 (m, 2H), 3.66 (s, 6H), 2.55 - 2.66 (m, 2H), 2.51 (ddd, *J*=13.3, 6.6, 6.4 Hz, 2H), 1.97 - 2.07 (m, 2H), 0.63 - 0.74 (m, 2H), -0.02 - 0.10 (m, 2H).



Ejemplo 22



Ejemplo 23

Ejemplo 22

((1S)-1-(((2S)-2-(6-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piridin-6-il)-2-naftil-1H-imidazo[4,5-b]piridin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

y

Ejemplo 23

((1S)-1-(((2S)-2-(6-(6-(2-((2R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piridin-6-il)-2-naftil-1H-imidazo[4,5-

b]piridin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

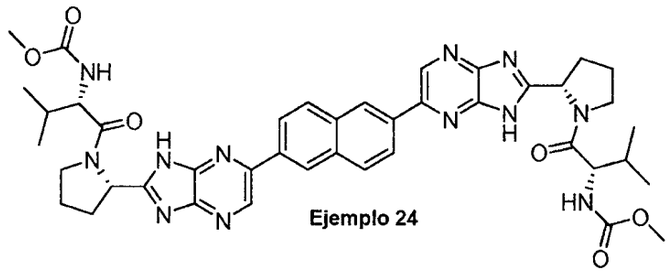
A una suspensión espesa agitada de una sal clorhidrato de 2,6-bis(2-((S)-pirrolidin-2-il)-3H-imidazo[4,5-b]piridin-6-il)naftaleno (45 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (29.3 mg, 0.167 mmol) en DMF (1 ml) y DIPEA (0.122 ml, 0.696 mmol) se añadió HATU (63.5 mg, 0.167 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (acetonitrilo/agua cono acetato amónico 10 mM) para proporcionar ((1S)-1-(((2S)-2-(6-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piridin-6-il)-2-naftil)-1H-imidazo[4,5-b]piridin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (19.2 mg) en forma de un sólido blanco y ((1S)-1-(((2R)-2-(6-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piridin-6-il)-2-naftil)-1H-imidazo[4,5-b]piridin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (16.5 mg) en forma de un sólido blanco (incierto si el estereocentro de la pirrolidina se

racemizó durante esta etapa o en una etapa previa). La resolución de 2,6-bis(2-((S)-pirrolidin-2-il)-3H-imidazo[4,5-b]piridin-6-il)naftaleno mediante HPLC quiral mostró un pico ancho, pero los diaestereómeros individuales no se pudieron resolver en las condiciones en las que se intentó.

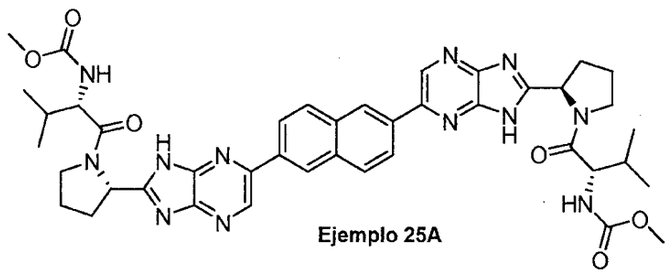
Datos analíticos del Ejemplo 22: Tiempo de retención en la CL-EM 1.407 min; m/z 815.60 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.82 - 8.71 (m, 2H), 8.32 - 8.18 (m, 4H), 8.14 - 8.07 (m, 2H), 7.92 - 7.84 (m, 2H), 5.37 - 5.29 (m,

2H), 4.30 (d, J = 7.3 Hz, 2H), 4.13 - 4.04 (m, 2H), 4.02 - 3.92 (m, 2H), 3.68 (s, 6H), 2.54 - 1.98 (m, 10H), 1.03 - 0.89 (m, 12H).

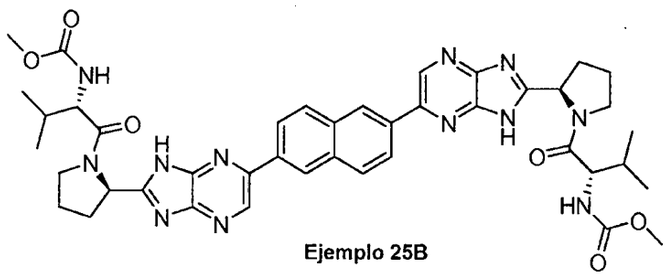
Datos analíticos del Ejemplo 23: Tiempo de retención en la CL-EM 1.442 min; m/z 815.59 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min dónde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.89 - 8.66 (m, 2H), 8.36 - 8.20 (m, 4H), 8.15 - 8.10 (m, 2H), 7.94 - 7.86 (m, 2H), 5.44 - 5.29 (m, 2H), 4.34 (d, J = 7.6 Hz, 1H), 4.30 (d, J = 7.6 Hz, 1H), 4.21 - 3.80 (m, 4H), 3.74 (s, 3H), 3.68 (s, 3H), 2.69 - 1.95 (m, 10H), 1.09 - 0.41 (m, 12H). .



Ejemplo 24



Ejemplo 25A



Ejemplo 25B

Ejemplo 24

((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piracin-5-il)-2-naftil-1H-imidazo[4,5-b]piracin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

y

Ejemplo 25A

((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-

imidazo[4,5-b]piracin-5-il)-2-naftil-1H-imidazo[4,5-b]piracin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

y Ejemplo 25B

((1S)-1-(((2R)-2-(5-(6-(2-((2R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piracin-5-il)-2-naftil-1H-imidazo[4,5-b]piracin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una suspensión espesa agitada de una sal HCl de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-imidazo[4,5-b]piracin-5-il)naftaleno (45 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (29 mg, 0.17 mmol) en DMF (1 ml) y DIPEA (0.12 ml, 0.69 mmol) se añadió HATU (63 mg, 0.17 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (acetonitrilo/agua cono acetato amónico 10 mM) para dar ((1S)-1-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piracin-5-il)-2-naftil)-1H-imidazo[4,5-b]piracin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (11.2 mg) en forma de un sólido amarillo y ((1S)-1-(((2R)-2-(5-(6-(2-((2R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piracin-5-il)-2-naftil)-1H-imidazo[4,5-

b]piracin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (17.3 mg) y ((1S)-1-(((2R)-2-(5-(6-(2-((2R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazo[4,5-b]piracin-5-il)-2-naftil)-1H-imidazo[4,5-b]piracin-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (6.7 mg) en forma de un sólido amarillo (se desconoce su el estereocentro de la pirrolidina racemizó durante esta etapa o en una etapa previa). La resolución de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-imidazo[4,5-b]piracin-5-il)naftaleno mediante HPLC quiral mostró un pico ancho, pero los diaestereómeros individuales no se pudieron resolver en las condiciones en las que se intentó.

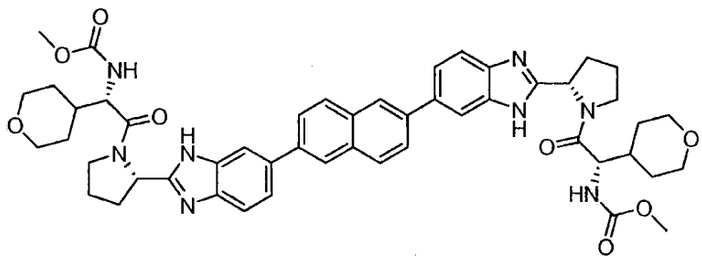
Datos analíticos del Ejemplo 24: Tiempo de retención en la CL-EM 1.420 min; m/z 817.59 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al

5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 9.14 - 9.06 (m, 2H), 8.71 - 8.64 (m, 2H), 8.37 - 8.29 (m, 2H), 8.18 - 8.11 (m, 2H), 5.59 - 5.30 (m, 2H), 4.30 (d, *J* = 7.3 Hz, 2H), 4.13 - 3.96 (m, 4H), 3.78 - 3.64 (m, 6H), 2.57 - 2.01 (m, 10H), 1.07 - 0.92 (m, 12H).

Datos analíticos del Ejemplo 25A: Tiempo de retención en la CL-EM 1.507 min; m/z 817.56 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 9.14 - 9.02 (m, 2H), 8.69 - 8.60 (m, 2H), 8.36 - 8.27 (m, 2H), 8.15 - 8.08 (m, 2H), 5.41 - 5.36 (m, 1H), 5.34 - 5.29 (m, 1H), 4.35 (d, *J* = 7.9 Hz, 1H), 4.31 (d, *J* = 7.3 Hz, 1H),

4.24 - 3.81 (m, 4H), 3.78 (s, 3H), 3.68 (s, 3H), 2.62 - 1.97 (m, 10H), 1.09 - 0.46 (m, 12H).

Datos analíticos del Ejemplo 25B: Tiempo de retención en la CL-EM 1.562 min; m/z 817.58 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 5 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 5%/agua al 95%/acetato de amonio 10 mM y el solvente B fue agua al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Ejemplo 26

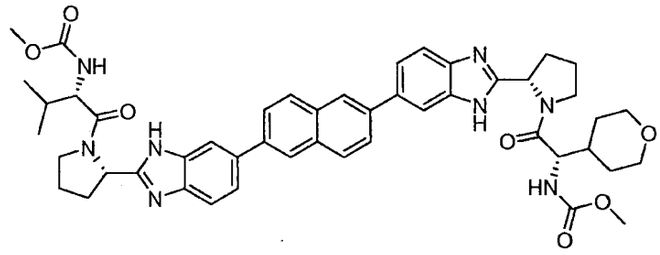
(2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(2S)-2,1-pirrolidindiil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo

A una solución agitada de 2,6-bis(2-((S)-

pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)naftaleno (50 mg), diisopropiletilamina (175 µl, 1.0 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (65 mg, 0.30 mmol) en DMF (5 ml) se añadió HATU (114 mg, 0.301 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA) para proporcionar una sal en TFA de (2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(2S)-2,1-pirrolidindiil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo (51.5 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.117 min; m/z 897.31 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%.

Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA 500 MHz, MeOD) δ ppm 8.27 (s ancho, 2H), 8.10 , 8.18 (m, 4H), 8.01 , 8.07 (m, 2H), 7.86 , 7.96 (m, 4H), 5.88 , 5.93 (m, 0.2H), 5.39 (t, *J*=7.0 Hz, 1.8H), 4.33 , 4.38 (m, 2H), 4.12 , 4.22 (m, 2H), 3.89 , 4.05 (m, 7H), 3.70 (s, 6H), 3.35 , 3.45 (m, 2H), 2.60 , 2.75 (m, 2H), 2.14 , 2.47 (m, 6.5H), 1.94 , 2.12 (m, 2.5H), 1.32 , 1.69 (m, 8H).



Ejemplo 27

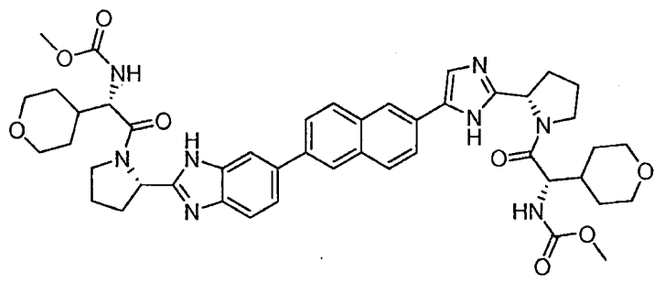
((1S)-2-(((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de ((1S)-2-metil-1-(((2S)-2-(5-(6-(2-((2S)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo (50 mg), diisopropiletilamina (133 µl, 0.76 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (50 mg, 0.23 mmol) en DMF (3 ml) se añadió HATU (87 mg, 0.23

mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA) para proporcionar una sal en TFA de ((1S)-2-((2S)-2-(5-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (36 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.177 min; m/z 855.30 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal

en TFA, 500 MHz, MeOD) δ ppm 8.22 - 8.30 (m, 1.8H), 8.20 (s ancho, 0.2H), 8.07 - 8.17 (m, 4H), 8.00 - 8.06 (m, 1.8H), 7.98 (s ancho, 0.2H), 7.85 - 7.95 (m, 4H), 5.86 (m, 0.1H), 5.35 - 5.44 (m, 1.8H), 5.25 - 5.31 (m, 0.1H), 4.36 (d, *J*=7.6 Hz, 0.5H), 4.31 (d, *J*=6.7 Hz, 1H), 4.15 (s ancho, 1.5H), 3.87 - 4.05 (m, 4H), 3.69 (s ancho, 6H), 3.34 - 3.47 (m, 1H), 2.96 - 3.23 (m, 2H), 2.61 - 2.77 (m, 2.5H), 2.21 - 2.47 (m, 6H), 1.95 - 2.16 (m, 2H), 1.33 - 1.69 (m, 3.5H), 1.00 - 1.05 (m, 0.3H), 0.94 - 0.99 (m, 3H), 0.91 (d, *J*=6.7 Hz, 2.7H).



Ejemplo 28

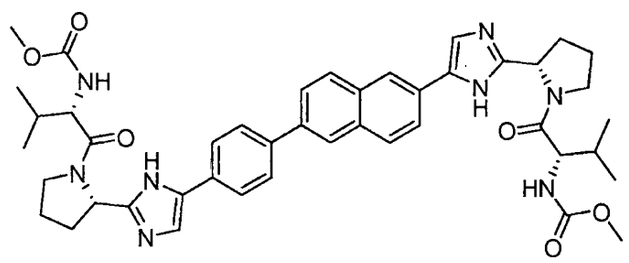
((1S)-2-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil-1H-bencimidazol-5-il)-2-naftil)-1H-imidazo-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((S)-pirrolidin-2-il)-6-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-benzo[d]imidazol (29 mg), diisopropiletilamina (56 µl, 0.32 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (21

mg, 0.10 mmol) en DMF (2 ml) se añadió HATU (36.6 mg, 0.096 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). Después, el componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo/TFA) para proporcionar una sal en TFA de ((1S)-2-((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-bencimidazol-5-il)-2-naftil)-1H-imidazol-2-il)1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (16.3 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.023 min; m/z 847.31 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma

MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=12.5 Hz, 2H), 8.15 (d, *J*=8.6 Hz, 1H), 8.10 (d, *J*=8.5 Hz, 1H), 8.07 (s, 1H), 7.92 - 8.01 (m, 3H), 7.81 - 7.90 (m, 2H), 5.37 (dd, *J*=7.9, 6.1 Hz, 1H), 5.30 (t, *J*=7.5 Hz, 1H), 4.28 - 4.39 (m, 2H), 4.12 - 4.22 (m, 2H), 3.88 - 4.04 (m, 7H), 3.65 - 3.77 (m, 6H), 3.38 - 3.45 (m, 1H), 2.56 - 2.69 (m, 2H), 2.20 - 2.40 (m, 6.5H), 2.01 (s ancho, 2.5H), 1.57 - 1.69 (m, 2.5H), 1.35 - 1.53 (m, 6.5H).



Ejemplo 29

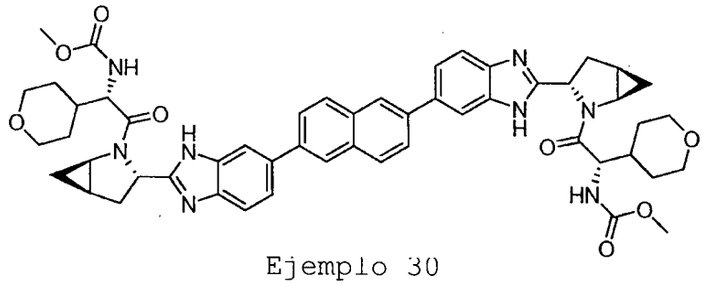
((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((S)-pirrolidin-2-il)-5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil-1H-imidazol (47 mg), diisopropiletilamina (88 µl, 0.51 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (26.5 mg, 0.152 mmol) en DMF (4 ml) se añadió HATU (57.6 mg, 0.152 mmol) y la

mezcla resultante se agitó en condiciones ambientales durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). El componente volátil se eliminó *al vacío* y el residuo se purificó mediante HPLC de fase inversa (agua/metanol/TFA), se volvió a purificar mediante HPLC de fase inversa (agua/acetonitrilo/acetato amónico) y, por último, se volvió a purificar mediante HPLC de fase inversa (agua/metanol/TFA) para proporcionar una sal en TFA de ((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (33.3 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.237 min; m/z 789.29 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%.

Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=8.9 Hz, 2H), 8.15 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.9 Hz, 1H), 7.95 - 8.03 (m, 4H), 7.93 (s, 1H), 7.84 - 7.91 (m, 3H), 5.69 - 5.72 (m, 0.2H), 5.24 - 5.35 (m, 1.8H), 4.27 (dd, *J*=7.2, 2.6 Hz, 2H), 4.09 - 4.19 (m, 2H), 3.85 - 3.97 (m, 2H), 3.67 - 3.76 (m, 6H), 2.55 - 2.68 (m, 2H), 2.27 - 2.38 (m, 2H), 2.14 - 2.27 (m, 4H), 2.02 - 2.14 (m, 2H), 0.86 - 1.06 (m, 12H).



Ejemplo 30

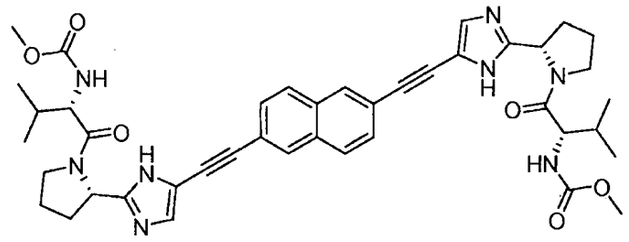
(2,6-naftalendiilbis(1H-bencimidazol-5,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo

A una solución agitada de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftaleno (25 mg), diisopropiletilamina (84 µl, 0.48 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (31.2 mg, 0.144 mmol) en DMF (5 ml) se añadió HATU (54.6 mg, 0.144 mmol) y la mezcla resultante se agitó en condiciones ambientales durante 4 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml). El

componente volátil se eliminó al vacío y el residuo se purificó mediante HPLC de fase inversa (agua/metanol/TFA), se volvió a purificar mediante HPLC de fase inversa (agua/acetonitrilo/acetato amónico) y, por último, se volvió a purificar mediante HPLC de fase inversa (agua/metanol/TFA) para proporcionar una sal en TFA de (2,6-naftalendiilbis(1H-bencimidazol-5,2-diyl(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo (8.2 mg) en forma de un sólido blancuzco.

Tiempo de retención en la CL-EM 1.220 min; m/z 461.3 $[1/2M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue acetonitrilo al 10%/agua al 90%/TFA al 0.1% y el solvente B fue acetonitrilo al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.28 (s ancho, 2H), 8.07 - 8.18

(m, 4H), 8.00 - 8.07 (m, 2H), 7.84 - 7.96 (m, 4H), 5.23 - 5.31 (m, 2H), 4.59 - 4.67 (m, 2H), 3.85 - 4.01 (m, 6H), 3.70 (s, 6H), 3.28 - 3.44 (m, 4H), 2.71 - 2.80 (m, 2H), 2.58 (ddd, *J*=13.2, 6.5, 6.3 Hz, 2H), 2.03 - 2.20 (m, 4H), 1.41 - 1.65 (m, 8H), 1.13 (s ancho, 2H), 0.97 (s ancho, 2H).



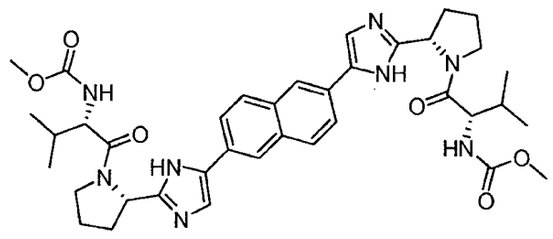
Ejemplo 31

((1S)-1-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)etinil--2-naftil)etinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una sal en TFA de 2,6-bis((2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)etinil)naftaleno (38 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (22 mg, 0.13 mmol) en DMF (0.7 ml) y TEA (0.047 ml, 0.33 mmol) se añadió HATU (47.6 mg, 0.125 mmol) y la solución amarilla transparente a temperatura ambiente. La reacción se diluyó con MeOH (1 ml), se filtró y se purificó mediante HPLC preparativa 15-100% de MeOH/agua/amortiguador TFA, para dar una sal en TFA de ((1S)-1-(((2S)-2-(4-((6-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)etinil)-1H-imidazol-2-il)-1-

pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (37.1 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 2.530 min; m/z 759.61 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Ejemplo 32

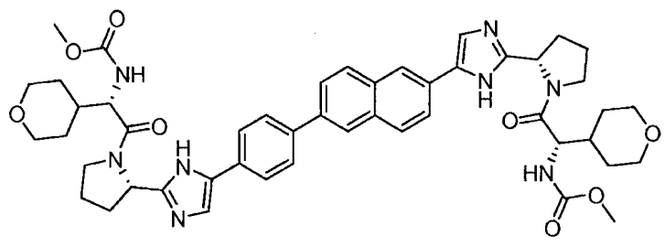
((1S)-1-(((2S)-2-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)etinil--2-naftil)etinil)-1H-imidazol-2-il)-1-

pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

Una sal en TFA de 4,4'-(2,6-naftalendiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol) (21 mg, 0.025 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (12.9 mg) se disolvieron en DMF (3 ml) y DIEA (0.043 ml, 0.246 mmol). Después se añadió HATU (28.0 mg, 0.074 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron *al vacío* y el producto bruto se purificó mediante HPLC preparativa (columna Waters Sunfire de C18 de 30 X 100 mm de 5u eluida con un gradiente de 0 a 90 % de MeOH -Aguar + TFA al 0.1 % TFA) para dar una sal en TFA de ((1S)-1-(((2S)-2-(4-((6-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)etinil)-2-naftil)etinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (10.4 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.158 min; m/z 713.60 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 5 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de

1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.31 (s, 2H), 8.11 (d, *J*=8.6 Hz, 2H), 7.94 - 8.03 (m, 2H), 7.84 - 7.94 (m, 2H), 5.29 (t, *J*=7.3 Hz, 2H), 4.26 (d, *J*=7.02 Hz, 2H), 4.14 (t, *J*=10.2 Hz, 2H), 3.85 - 3.96 (m, 2H), 3.68 (s, 6H), 2.53 - 2.67 (m, 2H), 2.31 (d, *J*=10.4 Hz, 2H), 2.16 - 2.28 (m, 4H), 2.03 - 2.15 (m, 2H), 0.88 - 1.08 (m, 12H).



Ejemplo 33

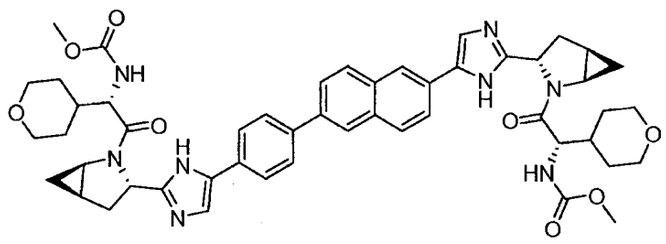
((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((2S)-2-pirrolidinil)-4-(4-(6-(2-((2S)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (50 mg) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (68.7 mg, 0.316 mmol) en DMF (5 ml) y DIEA (0.18

ml, 1.1 mmol) se añadió HATU (120 mg, 0.316 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC prep (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 90 % de MeOH -Aguar + TFA al 0.1 %) y después se volvió a purificar mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de hasta % de ACN - Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (96 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.207 min; m/z 873.63 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 5 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de

1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=7.9 Hz, 2H), 8.14 (d, *J*=8.9 Hz, 1H), 8.06 - 8.11 (m, 1H), 7.94 - 8.03 (m, 4H), 7.90 - 7.94 (m, 1H), 7.80 - 7.90 (m, 3H), 5.74 (s ancho, 0.2H), 5.23 - 5.35 (m, 1.8H), 4.32 (dd, *J*=8.1, 4.7 Hz, 2H), 4.16 (d, *J*=2.8 Hz, 2H), 3.94 (dd, *J*=9.5, 7.3 Hz, 6H), 3.69 (s, 6H), 3.31 - 3.48 (m, 4H), 2.55 - 2.68 (m, 2H), 2.16 - 2.35 (m, 6H), 1.92 - 2.10 (m, 2H), 1.63 (d, *J*=12.8 Hz, 2H), 1.34 - 1.54 (m, 6H).



Ejemplo 34

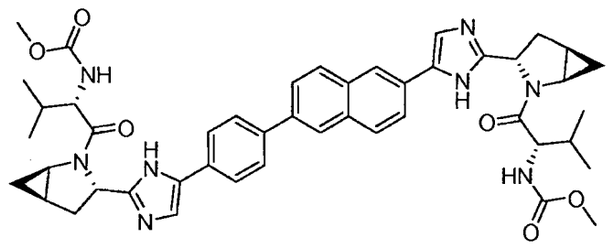
((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hexano (25 mg, 0.050 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (33 mg) en DMF (3 ml) y DIEA (0.078 ml, 0.50 mmol) se añadió HATU (57 mg, 0.150 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 100 % de MeOH -Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (27 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.280 min; m/z 897.65 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de

1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.28 - 8.32 (m, 2H), 8.14 (d, *J*=8.6 Hz, 1H), 8.07 - 8.11 (m, 1H), 7.95 - 8.02 (m, 4H), 7.84 - 7.93 (m, 4H), 5.12 - 5.23 (m, 2H), 4.62 (dd, *J*=7.6, 4.0 Hz, 2H), 3.92 - 4.00 (m, 4H), 3.83 - 3.89 (m, 2H), 3.72 - 3.78 (m, 2H), 3.70 (s, 6H), 3.35 - 3.46 (enmascarado con metanol, m, 4H), 2.68 - 2.77 (m, 2H), 2.47 - 2.57 (m, 2H), 2.00 - 2.15 (m, 4H), 1.42 - 1.65 (m, 6H), 1.06 - 1.17 (m, 2H), 0.84 - 0.93 (m, 2H).



Ejemplo 35

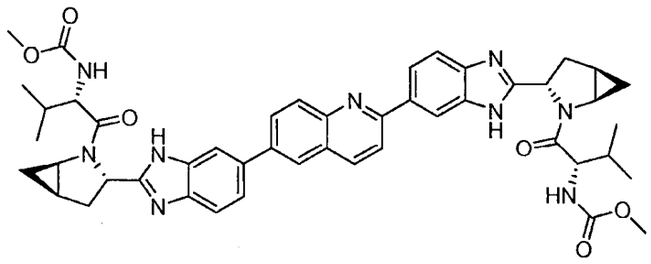
((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil(fenil)--1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hexano (25 mg, 0.050 mmol) y ácido (S)-2-(metoxicarbonilamino)-3metilbutanoico (26 mg, 0.15 mmol) en DMF (3 ml) y DIEA (0.070 ml, 0.40 mmol) se añadió HATU (57 mg, 0.150 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 100 % de MeOH -Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)Carbonil)-2-metilpropil)carbamato de metilo (34.8 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.402 min; m/z 813.69 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A

fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (d, *J*=7.9 Hz, 2H), 8.14 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 7.95 - 8.01 (m, 4H), 7.92 (s, 1H), 7.84 - 7.90 (m, 3H), 5.16 (ddd, *J*=11.6, 9.2, 7.0 Hz, 2H), 4.58 (dd, *J*=6.4, 2.1 Hz, 2H), 3.81 - 3.88 (m, 2H), 3.66 - 3.75 (m, 6H), 2.67 - 2.77 (m, 2H), 2.46 - 2.57 (m, 2H), 2.21 (dc, *J*=12.9, 6.5 Hz, 2H), 2.06 - 2.14 (m, 2H), 1.08 - 1.18 (m, 2H), 1.04 (d, *J*=6.7 Hz, 6H), 0.95 (d, *J*=6.7 Hz, 6H), 0.91 (s ancho, 2H).



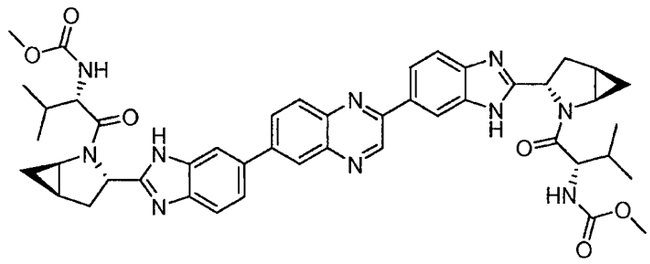
Ejemplo 36

((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinolinil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal clorhidrato de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-

benzo[d]imidazol-6-il)quinolina (25 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (15 mg, 0.086 mmol) en DMF (1 ml) y DIPEA (0.059 ml, 0.34 mmol) se añadió HATU (32.7 mg, 0.086 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (2S,2'S)-1.1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinolin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexan-3,2-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (8.3 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.88 min; m/z 838 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.64 - 8.80 (1H, m), 8.49 - 8.62 (1H, m), 7.45 - 8.48 (9H, m), 5.21 - 5.52 (2H, m), 4.50 - 4.68 (2H, m), 3.82 - 4.13 (2H, m), 3.70 - 3.79 (2H, m), 3.68, 3.66 (6H, s, s), 2.48 - 2.83 (3H, m), 2.02 - 2.28 (3H, m), 1.09 - 1.30 (2H, m), 0.83 - 1.08 (14H, m).

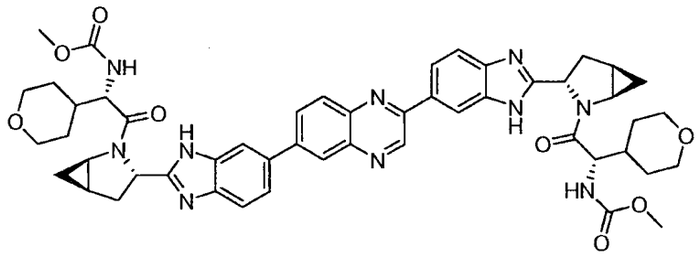


Ejemplo 37

((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinoxalinil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal en TFA de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalina (28 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (11.5 mg, 0.066 mmol) en DMF (0.5 ml) y DIPEA (0.045 ml, 0.26 mmol) se añadió HATU (25 mg, 0.066 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (2S,2'S)-1.1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinoxalin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diyl))bis(2-azabiciclo[3.1.0]hexan-3,2-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (27 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.94 min; m/z 839 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (sal en TFA, 400 MHz, MeOD) δ ppm 9.56 (s, 1H), 8.67 (s, 1H), 8.52 (d, *J*=8.8 Hz, 1H), 8.40 (s, 1H), 8.26 (d, *J*=8.8 Hz, 1H), 8.24 (d, *J*=8.8 Hz, 1H), 8.17 (s, 1H), 8.05 (d, *J*=8.5 Hz, 1H), 7.93 (d, *J*=8.5 Hz, 1H), 7.90 (d, *J*=8.8 Hz, 1H), 5.30 (app dd, *J*=9.0, 6.8 Hz, 2H), 4.60 (app d, *J*=6.0 Hz, 2H), 3.93 - 3.84 (m, 2H), 3.68 (s, 6H), 2.80 - 2.70 (m, 2H), 2.63 - 2.51 (m, 2H), 2.29 - 2.09 (m, 4H), 1.21 - 1.11 (m, 2H), 1.03 (d, *J*=6.8 Hz, 6H), 1.00 - 0.90 (m, 2H), 0.93 (d, *J*=6.5 Hz, 6H).



Ejemplo 38

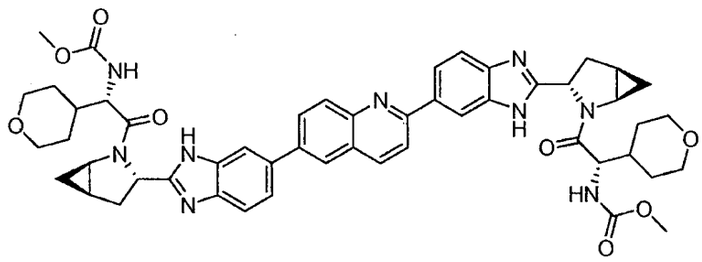
(2,6-quinoxalindiilbis(1H-bencimidazol-5,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo

A una solución de una sal en TFA de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinoxalina (29 mg) y ácido (S)-2-

(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (14.8 mg, 0.068 mmol) en DMF (0.5 ml) y DIPEA (0.046 ml, 0.27 mmol) se añadió HATU (25.9 mg, 0.068 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinoxalin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexan-3,2-diil))bis(2-oxo-1-(tetrahidro-2H-piyran-4-il)etan-2,1-diil)dicarbamato de dimetilo (32.5 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.74 min; m/z 462 $[1/2M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (sal en TFA, 400 MHz, MeOD) δ ppm 9.53 (s, 1H), 8.70 (s, 1H), 8.55 (dd, *J*=8.8, 1.5 Hz, 1H), 8.44 (d, *J*=1.8 Hz, 1H), 8.31 (d, *J*=8.8 Hz, 1H), 8.27 (dd, *J*=8.8, 1.8 Hz, 1H), 8.19 (s ancho, 1H), 8.08 (dd, *J*=8.8, 1.5 Hz, 1H), 7.96 (d, *J*=8.8 Hz, 1H), 7.92 (d, *J*=8.8 Hz, 1H), 5.28 (app dd, *J*=8.8, 6.8 Hz, 2H), 4.63 (app d, *J*=7.3 Hz, 2H), 3.99 - 3.86 (m, 6H), 3.69 (s, 6H), 3.44 - 3.29 (m, 4H), 2.81 - 2.71 (m, 2H), 2.63 - 2.52 (m, 2H), 2.20 - 2.03 (m, 4H), 1.68 - 1.37

(m, 8H), 1.17 - 1.08 (m, 2H), 0.99 - 0.92 (m, 2H).



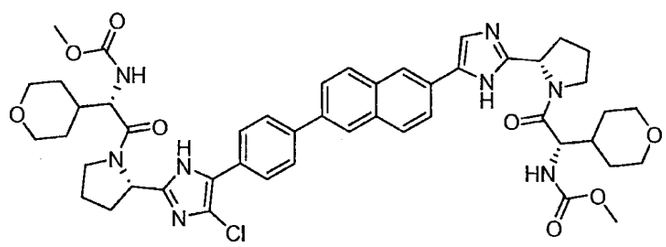
Ejemplo 39

(2,6-quinolindiilbis(1H-bencimidazol-5,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo

A una solución de una sal clorhidrato de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)quinolina (26 mg) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (19.4 mg, 0.089 mmol) en DMF (0.5 ml) y DIPEA (0.061 ml, 0.350 mmol) se añadió HATU (34.0 mg, 0.089 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(quinolin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexan-3,2-diil))bis(2-oxo-1-(tetrahidro-2H-piyran-4-il)etan-2,1-diil)dicarbamato de dimetilo (6.0 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.65 min; m/z 462 $[1/2M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10,

solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 8.70 (1H, d, *J*=8.5 Hz), 8.57 (1H, s), 8.23 - 8.45 (5H, m), 8.17 (1H, s), 8.01 - 8.12 (1H, m), 7.88 - 7.97 (2H, m), 5.27 (2H, t, *J*=7.8 Hz), 4.33 - 4.68 (2H, m), 3.84 - 4.02 (6H, m), 3.69 (6H, s), 3.35 - 3.47 (4H, m), 2.67 - 2.81 (2H, m), 2.49 - 2.64 (2H, m), 1.91 - 2.21 (4H, m), 1.35 - 1.71 (8H, m), 1.07 - 1.17 (2H, m), 0.85 - 1.00 (2H, m).



Ejemplo 40

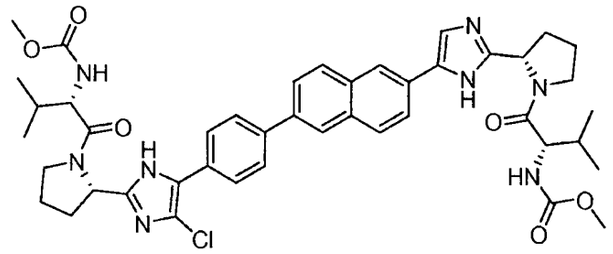
((1S)-2-((2S)-2-(4cloro-5-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de 4-cloro-2-((S)-pirrolidin-2-il)-5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol (20 mg) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético

(25.6 mg, 0.118 mmol) en DMF (3 ml) y DIEA (0.070 ml, 0.40 mmol) se añadió HATU (45 mg, 0.118 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC prep (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 100 % de MeOH -Agua + TFA al 0.1 %) y después se volvió a purificar mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 10 a 100 % de ACN -Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((2S)-2-(4-cloro-5-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (12.9 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.595 min; m/z 907.39 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B,

un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.20 - 8.28 (m, 2H), 8.09 - 8.12 (m, 1H), 8.02 - 8.08 (m, 1H), 7.91 - 8.00 (m, 3H), 7.87 - 7.91 (m, 2H), 7.80 - 7.87 (m, 2H), 5.28 (t, *J*=7.5 Hz, 1H), 5.06 - 5.14 (m, 1H), 4.25 - 4.35 (m, 2H), 4.11 - 4.19 (m, 1H), 4.00 - 4.07 (m, 1H), 3.85 - 4.00 (m, 6H), 3.63 - 3.69 (m, 6H), 3.32 - 3.43 (m, 4H), 2.57- 2.64(m, 1H), 2.34 - 2.40 (m, 1H), 2.26 - 2.32 (m, 2H), 2.12 - 2.25 (m, 4H), 1.95 - 2.09 (m, 2H), 1.34 - 1.64(m, 8H).



Ejemplo 41

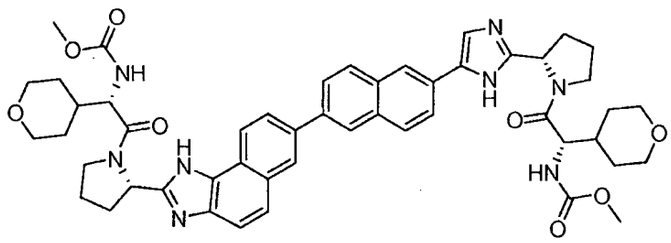
((1S)-1-(((2S)-2-(4-(6-(4-(4-cloro-2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución de 4-cloro-2-((S)-pirrolidin-2-il)-5-(4-(6-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-

il)fenil)-1H-imidazol (20 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (20.7 mg, 0.118 mmol) en DMF (3 ml) y DIEA (0.070 ml, 0.40 mmol) se añadió HATU (45 mg, 0.118 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC prep (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 100 % de MeOH -Agua + TFA al 0.1 %) y después se volvió a purificar mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 10 a 100 % de ACN -Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((2S)-2-(4-(6-(4-(4-cloro-2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-naftil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (3.6 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.715 min; m/z 823.49 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de

100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.24 - 8.29 (m, 1H), 8.22 (s, 1H), 8.08 - 8.15 (m, 1H), 8.03 - 8.08 (m, 1H), 7.81 - 8.01 (m, 7H), 5.31 (t, *J*=7.5 Hz, 1H), 5.12 (app t, *J*=7.5 Hz, 1H), 4.21 - 4.32 (m, 2H), 4.08 - 4.19 (m, 1H), 3.99 - 4.08 (m, 1H), 3.85 - 3.96 (m, 2H), 3.57 - 3.74 (m, 6H), 2.56 - 2.67 (m, 1H), 2.35 - 2.46 (m, 1H), 2.28 - 2.35 (m, 2H), 2.20 - 2.26 (m, 2H), 2.05 - 2.19 (m, 4H), 0.90 - 1.09 (m, 12H).



Ejemplo 42

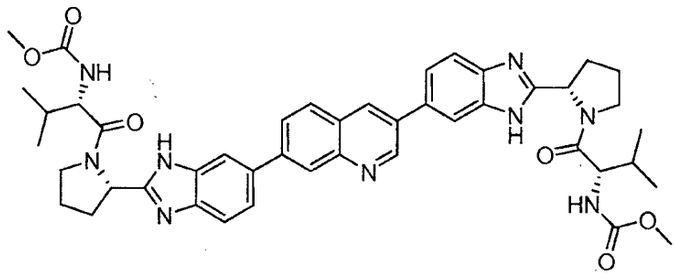
((1S)-2-((1R,3S,5R)-3-(7-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de 2-((S)-pirrolidin-2-il)-7-(6-(2-

((S)-pirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-nafto[1,2-d]imidazol (45 mg) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (58.8 mg, 0.271 mmol) en DMF (3 ml) y DIEA (0.16 ml, 0.90 mmol) se añadió HATU (103 mg, 0.271 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (5 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 100 % de MeOH -Agua + TFA al 0.1%) t, después, se volvió a purificar mediante HPLC (columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 0 a 90 % de ACN -Agua + TFA al 0.1 %) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(7-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (8.7 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 1.307 min; m/z 897.67 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del

detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.51 - 8.57 (m, 2H), 8.40 (s, 1H), 8.30 (s, 1H), 8.23 (d, *J*=10.1 Hz, 1H), 8.18 (d, *J*=8.6 Hz, 1H), 8.05 - 8.15 (m, 3H), 8.00 (s, 1H), 7.87 (dd, *J*=8.6, 1.8 Hz, 1H), 7.79 - 7.85 (m, 1H), 5.43 (t, *J*=7.3 Hz, 1H), 5.30 (t, *J*=7.3 Hz, 1H), 4.28 - 4.40 (m, 2H), 4.19 (s ancho, 2H), 3.88 - 4.07 (m, 6H), 3.70 (d, *J*=1.5 Hz, 6H), 3.26 - 3.45 (traslapado con metanol, m, 4H), 2.57 - 2.71 (m, 2H), 2.30 - 2.42 (m, 3H), 2.20 - 2.29 (m, 3H), 1.93 - 2.10 (m, 2H), 1.58 - 1.68 (m,, 2H), 1.34 - 1.58 (m, 6H).



Ejemplo 43

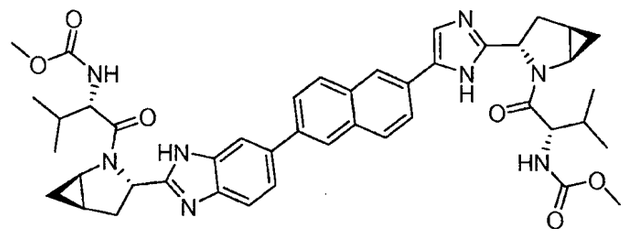
((1S)-2-((1R,3S,5R)-3-(7-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-

2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de una sal en TFA de 2,6-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)quinolina (30 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (11.3 mg, 0.065 mmol) en DMF (1 ml) y DIPEA (0.044 ml, 0.252 mmol) se añadió HATU (24.5 mg, 0.065 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (2S,2'S)-1.1'-((2S,2'S)-2,2'-(6,6'-(quinolin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (34 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.82 min; m/z 814 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.71 (1H, d, *J*=8.8 Hz), 8.57 (1H, s), 8.21 - 8.43 (5H, m), 8.18 (1H, s), 8.04 (1H, dd, *J*=8.5, 1.5 Hz), 7.88 - 7.96 (2H, m), 5.40 (2H, t, *J*=7.03 Hz), 4.31 (2H, d, *J*=6.8 Hz), 4.09 - 4.21 (2H, m), 3.91 - 4.06 (2H, m), 3.68

(6H, s), 2.58 - 2.73 (2H, m), 2.20 - 2.49 (6H, m), 2.02 - 2.19 (2H, m), 0.96 (6H, dd, *J*=6.8, 1.8 Hz), 0.90 (6H, dd, *J*=6.7, 1.6 Hz).



Ejemplo 44

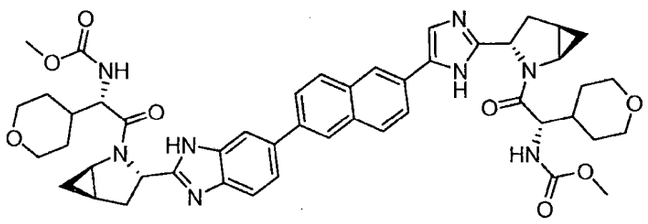
((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de 6-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)-2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol (34 mg) y ácido (S)-2-(metoxicarbonilamino)-3metilbutanoico (37.8 mg, 0.216 mmol) y DIEA (0.13 ml, 0.72 mmol) en DMF (3 ml) se añadió HATU (82 mg, 0.22 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (2 ml) y agua (2 ml). Los volátiles se retiraron a vacío. El residuo se purificó mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 10 a 80 % de ACN - Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-1-

(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (49.8 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.357 min; m/z 787.65 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) □ ppm 8.29 (d, *J*=10.7 Hz, 2H), 8.07 - 8.19 (m, 3H), 7.94 - 8.05 (m, 3H), 7.84 - 7.92 (m, 2H), 5.29 (dd, *J*=9.2, 6.7 Hz, 1H), 5.18 (dd, *J*=9.2, 7.0 Hz, 1H), 4.59 (dd, *J*=12.4, 6.6 Hz, 2H), 3.81 - 3.91 (m, 2H), 3.69 (s, 6H), 2.67 - 2.80 (m, 2H), 2.48 - 2.61 (m, 2H), 2.07 - 2.27 (m, 4H), 1.09 - 1.19 (m, 2H), 0.99

- 1.06 (m, 6H), 0.88 - 1.00 (m, 8H).



Ejemplo 45

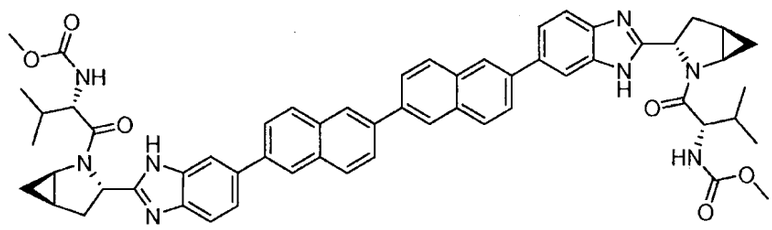
((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de 6-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-2-il)-2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol (34 mg) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (46.9 mg, 0.216 mmol) y DIEA (0.13 ml, 0.72 mmol) en DMF (3 ml) se añadió HATU (82 mg, 0.216 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (2 ml) y agua (2 ml). Los volátiles se retiraron a vacío. El residuo se purificó mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 10 a 80 % de ACN -Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-

2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (38 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.240 min; m/z 871.66 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (sal en TFA, 500 MHz, MeOD) δ ppm 8.30 (d, J=6.1 Hz, 2H), 8.08 - 8.18 (m, 3H), 8.04 (dd, J=8.6, 1.5 Hz, 1H), 7.95 - 8.01 (m, 2H), 7.85 - 7.92 (m, 2H), 5.27 (dd, J=9.2, 6.7 Hz, 1H), 5.16 (dd, J=9.2, 7.0 Hz, 1H), 4.59 - 4.66 (m, 2H), 3.84 - 4.01 (m, 6H), 3.70 (s, 6H), 3.35 - 3.45 (m, 4H), 2.69 - 2.80 (m, 2H), 2.48 - 2.61 (m, 2H), 2.03 - 2.20 (m, 4H), 1.57 - 1.65 (m, 2H), 1.40 - 1.56 (m, 6H), 1.07 - 1.17 (m, 2H), 0.97 (s ancho, 1H), 0.91 (s ancho,

1H).



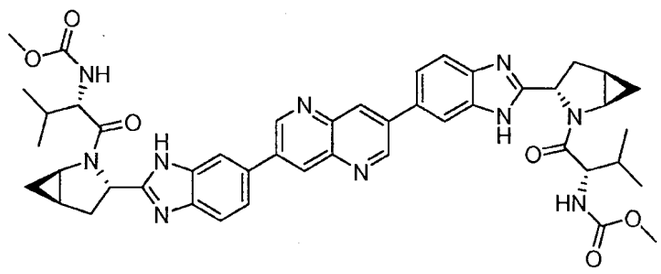
Ejemplo 46

((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2,2'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal en TFA de 6,6'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-5-il)-2,2'-binaftilo (22 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (10.5 mg, 0.060 mmol) y DIEA (0.035 ml, 0.20 mmol) en DMF (3 ml) se añadió HATU (22.7 mg, 0.060 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (2 ml) y agua (2 ml) y los volátiles se eliminaron al vacío. El residuo se purificó mediante HPLC preparativa (columna Waters Sunfire C18 de 30 X 100 mm de 5u eluida con un gradiente de 10 a 80 % de MeOH -Agua + TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(5-(6'-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-

metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2,2'-binaftalen-6-il)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (15.6 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.765 min; m/z 482.68 [1/2M+H+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.36 (s, 2H), 8.27 (s, 2H), 8.12 - 8.18 (m, 4H), 8.11 (s, 2H), 8.05 (app t, *J*=8.6 Hz, 4H), 7.91 - 7.96 (m, 2H), 7.86 - 7.91 (m, 2H), 5.29 (dd, *J*=9.2, 6.7 Hz, 2H), 4.61 (d, *J*=6.4 Hz, 2H), 3.85 - 3.91 (m, 2H), 3.70 (s, 6H), 2.72 - 2.80 (m, 2H), 2.53 - 2.62 (m, 2H), 2.12 - 2.26 (m, 4H), 1.13 - 1.21 (m, 2H), 1.04 (d, *J*=6.7 Hz, 6H), 0.99 (s ancho, 2H), 0.95 (d, *J*=6.7 Hz, 6H).

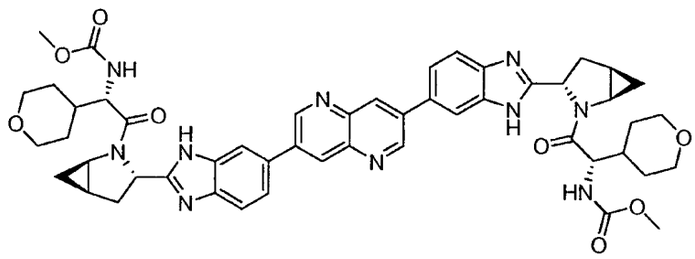


Ejemplo 47

((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-1,5-naftiridin-2-il-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal en TFA de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)1,5-naftiridina (12 mg, 9.93 µmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (4.2 mg) en DMF (0.5 ml) y DIPEA (0.017 ml, 0.099 mmol) se añadió HATU (8.7 mg, 0.023 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (2S,2'S)-1.1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(1,5-naftiridin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diyl))bis(2-azabiciclo[3.1.0]hexan-3,2-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (5.6 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.91 min; m/z 420 $[1/2M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.59 - 8.67 (4H, m), 8.48 (2H, dd, *J*=8.8, 1.3 Hz), 8.44 (2H, d, *J*=8.8 Hz), 7.92 (2H, d, *J*=8.5 Hz), 5.29 (2H, dd, *J*=9.2, 6.7 Hz), 4.60 (2H, d, *J*=6.5 Hz), 3.84 - 3.92 (2H, m), 3.68 (6H, s), 2.69 - 2.80 (2H, m), 2.51 - 2.62 (2H, m), 2.07 - 2.27 (4H, m), 1.10 - 1.21 (2H, m), 1.02 (6H, d, *J*=6.8 Hz), 0.95 - 1.00 (2H, m), 0.93 (6H, d, *J*=6.8 Hz).



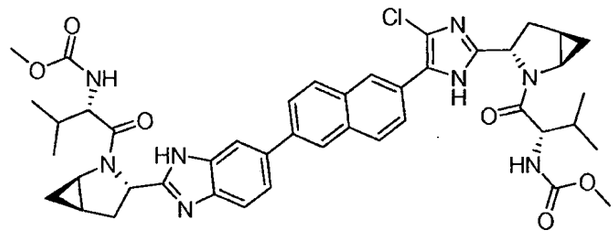
Ejemplo 48

(1,5-naftiridin-2,6-diilbis(1H-bencimidazol-5,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo

A una solución de una sal en TFA de 2,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-1,5-naftiridina (12 mg) y ácido (S)-2-

(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (5.0 mg, 0.023 mmol) en DMF (0.5 ml) y DIPEA (0.016 ml, 0.089 mmol) se añadió HATU (8.68 mg, 0.023 mmol) y la mezcla se agitó a temperatura ambiente durante 3 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(6,6'-(1,5-naftiridin-2,6-diil)bis(1H-benzo[d]imidazol-6,2-diil))bis(2-azabiciclo[3.1.0]hexan-3,2-diil))bis(2-oxo-1-(tetrahidro-2H-piyran-4-il)etan-2,1-diil)dicarbamato de dimetilo (11 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.73 min; m/z 462 $[1/2M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.61 - 8.68 (4H, m), 8.50 (2H, dd, *J*=8.8, 1.51 Hz), 8.45 (2H, d, *J*=8.8 Hz), 7.93 (2H, d, *J*=8.8 Hz), 5.28 (2H, dd, *J*=9.3, 6.8 Hz), 4.64 (2H, d, *J*=7.5 Hz), 3.84 - 4.02 (6H, m), 3.69 (6H, s), 3.35 - 3.46 (4H, m), 2.75 (2H, dd, *J*=13.7, 9.2 Hz), 2.58 (2H, d, *J*=6.8 Hz), 1.99 - 2.22 (4H, m), 1.36 - 1.69 (8H, m), 1.07 - 1.19 (2H, m), 0.96 (2H, m).



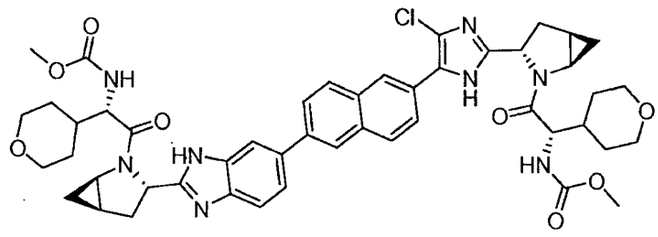
Ejemplo 49

((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de 2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-5-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-4-cloro-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol (34 mg) y ácido (S)-2-(metoxicarbonilamino)-3metilbutanoico (35.2 mg, 0.201 mmol) y DIEA (0.12 ml, 0.67 mmol) en DMF (3 ml) se añadió HATU (76 mg, 0.20 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml) y el componente volátil se retiró *a vacío*. El residuo se purificó mediante HPLC preparativa (agua/metanol/TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-

metilpropil)carbamato de metilo (41.3 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.717 min; m/z 821.58 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.24 (d, J=1.8 Hz, 2H), 8.01 - 8.13 (m, 4H), 7.84 - 7.98 (m, 3H), 5.29 (dd, J=9.2, 6.7 Hz, 1H), 5.09 (t, J=7.2 Hz, 1H), 4.60 (t, J=7.2 Hz, 2H), 3.86 - 3.91 (m, 1H), 3.71 - 3.76 (m, 1H), 3.69 (s, 3H), 3.68 (m, 3H), 2.77 (dd, J=13.6, 9.3 Hz, 1H), 2.57 (ddd, J=13.6, 6.7, 6.6 Hz, 1H), 2.44 - 2.53 (m, 2H), 2.11 - 2.26 (m, 3H), 1.99 - 2.10 (m, 1H), 1.10 - 1.22 (m, 2H), 0.89 - 1.09 (m, 13H), 0.80 - 0.84 (m, 1H).

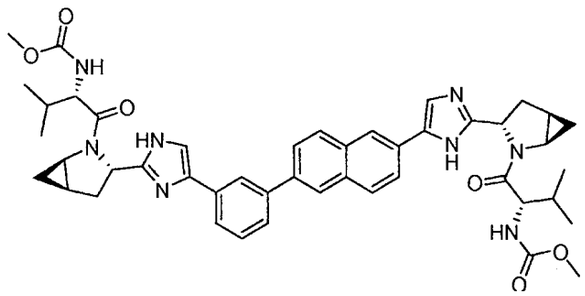


Ejemplo 50

((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de 2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-5-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-4-cloro-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol (20 mg, 0.039 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (25.7 mg) y DIEA (0.069 ml, 0.39 mmol) en DMF (3 ml) se añadió HATU (45.0 mg, 0.118 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml) y el componente volátil se retiró *a vacío*. El residuo se purificó mediante HPLC de fase inversa (agua/metanol, TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-naftil)-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (28.1 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 1.597 min; m/z 905.67 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.24 (s, 2H), 8.02 - 8.13 (m, 4H), 7.86 - 7.97 (m, 3H), 5.27 (dd, *J*=9.2, 7.0 Hz, 1H), 5.08 (t, *J*=7.2 Hz, 1H), 4.65 (t, *J*=7.3 Hz, 2H), 3.88 - 4.02 (m, 5H), 3.75 - 3.83 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.36 - 3.49 (m, 4H), 2.77 (dd, *J*=13.7, 9.5 Hz, 1H), 2.57 (ddd, *J*=13.7, 6.7, 6.4 Hz, 1H), 2.46 - 2.53 (m, 2H), 2.00 - 2.20 (m, 4H), 1.55 - 1.69 (m, 4H), 1.40 - 1.70 (m, 4H), 1.08 - 1.20 (m, 2H), 0.94 - 1.00 (m, 1H), 0.80 - 0.84 (m, 1H).



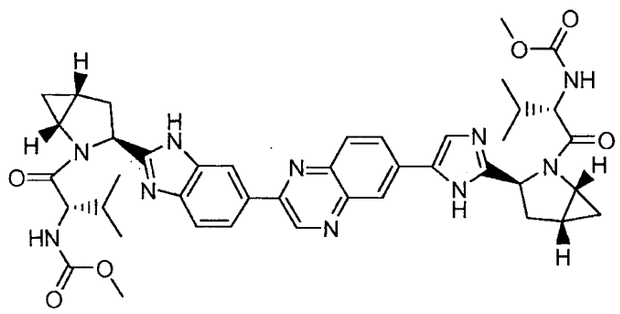
Ejemplo 51

((1S)-1-(((1S,3R,5S)-3-(4-(6-(3-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una mezcla de una sal en TFA de (1R,3S,5R)-3-(4-(3-(6-(2-((1S,3R,5S)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (40 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (22 mg, 0.13 mmol) y DIEA (0.073 ml, 0.42 mmol) en DMF (3 ml) se añadió HATU (47.8 mg, 0.126 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con metanol (2 ml) y agua (2 ml) y el componente volátil se retiró *a vacío*. El residuo se purificó parcialmente mediante HPLC de fase inversa (agua/metanol, TFA al 0.1%) y después se volvió a purificar mediante HPLC de fase inversa (agua/acetonitrilo, TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1S,3R,5S)-3-(4-(6-(3-(2-((1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (45 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 1.458 min; m/z 813.30 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/acetato de amonio 10 mM y el solvente B fue agua al 10%/metanol al 90%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.30 (d, J=4.6 Hz, 2H), 8.18 (s, 1H), 8.14 (d, J=8.9 Hz, 1H), 8.10 (d, J=8.9 Hz, 1H), 7.98 - 8.02 (m, 2H), 7.98 (s, 1H), 7.93 (d, J=8.2 Hz, 1H), 7.88 (dd, J=8.7, 1.7 Hz, 1H), 7.77 (d, J=8.2 Hz, 1H), 7.69 (t, J=7.8 Hz, 1H), 5.13 - 5.20 (m, 2H), 4.57 (t, J=6.1 Hz, 2H), 3.80 - 3.88 (m, 2H), 3.69 (d, J=6.1 Hz, 6H), 2.67 - 2.77 (m, 2H), 2.51 (dc, J=13.7, 6.8 Hz, 2H), 2.15 - 2.25 (m, 2H), 2.10 (dc, J=13.8, 6.8 Hz, 2H), 1.08

- 1.18 (m, 2H), 1.03 (dd, *J*=6.7, 4.6 Hz, 6H), 0.95 (dd, *J*=6.7, 3.4 Hz, 6H), 0.92 (dd, *J*=5.3, 2.0 Hz, 2H).

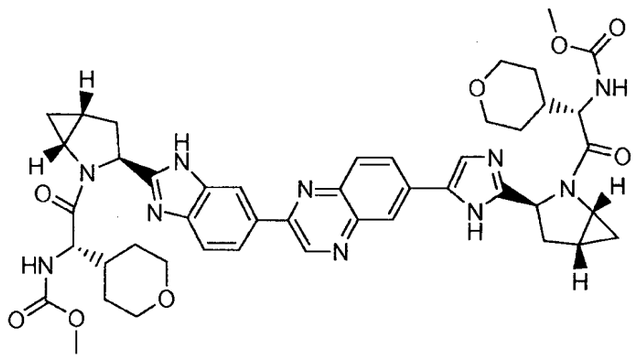


Ejemplo 52

((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinoxalinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-6-metilpropil)carbamato de metilo

A una solución de una sal en TFA de 2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)quinoxalina (14 mg, 0.015 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (6.1 mg) en DMF (0.5 ml) y DIPEA (0.024 ml, 0.135 mmol) se añadió HATU (13.16 mg, 0.035 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-

azabiciclo[3.1.0]hex-3-il)-1H-benzimidazol-5-il)-6-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (11.8 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 1.77 min; m/z 789 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, MeOD) δ ppm 9.59 (s, 1H), 8.67 (s, 1H), 8.51 (d, *J*=8.8 Hz, 1H), 8.46 (d, *J*=1.8 Hz, 1H), 8.27 (d, *J*=8.8 Hz, 1H), 8.19 (dd, *J*=8.8, 2.0 Hz, 1H), 8.11 (s, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 5.29 (dd, *J*=9.2, 6.7 Hz, 1H), 5.17 (dd, *J*=9.2, 7.2 Hz, 1H), 4.58 (dd, *J*=13.2, 6.7 Hz, 2H), 3.78 - 3.92 (m, 2H), 3.68 (s, 6H), 2.67 - 2.79 (m, 2H), 2.45 - 2.62 (m, 2H), 2.03 - 2.27 (m, 4H), 1.07 - 1.21 (m, 2H), 1.03 (d, *J*=6.8 Hz, 6H), 0.93 - 1.00 (m, 2H), 0.93 (dd, *J*=6.3, 5.8 Hz, 6H).



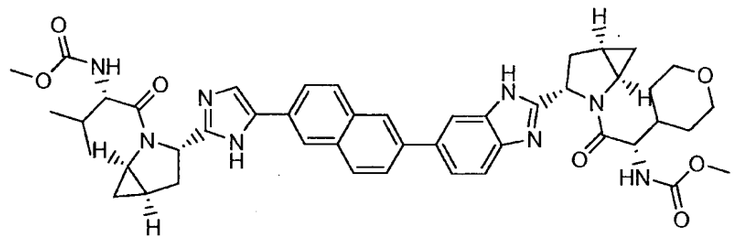
Ejemplo 53

((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-6-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-6-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de una sal en TFA de 2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)quinoxalina (16 mg) y ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético (8.6 mg, 0.040 mmol) en DMF (0.5 ml) y DIPEA (0.027 ml, 0.16 mmol) se añadió HATU (15.0 mg, 0.040 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de NH_4OAc 100 Mm) para dar ((1S)-2-((1R,3S,5R)-3-(4-(2-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-benzimidazol-5-il)-6-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (14.5 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 1.58 min; m/z 873 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3

min. Longitud de onda = 220). RMN de ^{1}H (400 MHz, MeOD) δ ppm 9.34 (s, 1H), 8.36 (s, 1H), 8.28 (d, *J*=1.0 Hz, 1H), 8.08 - 8.19 (m, 2H), 8.03 (d, *J*=8.8 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.54 (s, 1H), 5.27 (t, *J*=6.9 Hz, 1H), 5.18 (dd, *J*=8.9, 4.9 Hz, 1H), 4.69 (d, *J*=5.5 Hz, 2H), 3.87 - 4.03 (m, 4H), 3.73 - 3.85 (m, 2H), 3.68 (s, 6H), 3.32 - 3.47 (m, 4H), 2.50 - 2.61 (m, 3H), 2.40 - 2.49 (m, 1H), 1.99 - 2.16 (m, 4H), 1.51 - 1.72 (m, 6H), 1.38 - 1.51 (m, 2H), 1.09 - 1.22 (m, 2H), 0.76 - 0.92 (m, 2H).



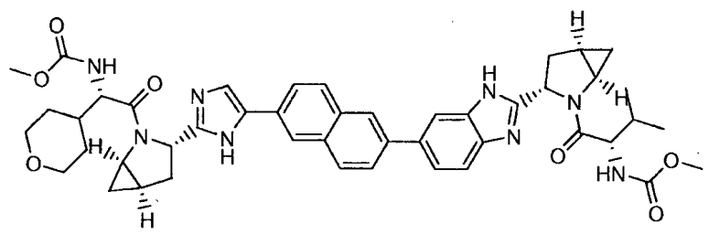
Ejemplo 54

((1S)-2-(((1R,3S,5R)-3-(5-(6-(2-chloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo

A una solución de (S)-1-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naphthalen-2-il)-1H-imidazol-2-il)-2-azabicyclo[3.1.0]hexan-2-il)-3-methyl-1-oxobutan-2-ilcarbamate de metilo (130 mg) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (90

mg, 0.41 mmol) y DIEA (0.36 ml, 2.1 mmol) en DMF (4 ml)se añadió HATU (157 mg, 0.413 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (2 ml) y agua (2 ml). Los volátiles se retiraron a vacío. El material se purificó mediante HPLC en fase inversa (agua/metanol/TFA al 0.1%) para dar una sal en TFA de ((1S)-2-(((1R,3S,5R)-3-(5-(6-(2-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (194 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 1.307 min; m/z 829.27 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal

en TFA, 500 MHz, MeOD) δ ppm 8.31 (s, 1H), 8.29 (s, 1H), 8.16 (d, *J*=8.5 Hz, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 1H), 8.02 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.00 (s, 1H), 7.98 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.27 (dd, *J*=9.2, 6.7 Hz, 1H), 5.18 (dd, *J*=9.2, 7.0 Hz, 1H), 4.62 - 4.67 (m, 1H), 4.58 (d, *J*=6.4 Hz, 1H), 3.87 - 4.01 (m, 3H), 3.82 - 3.87 (m, 1H), 3.70 (m, 6H), 3.36 - 3.44 (m, 2H), 2.74 (td, *J*=13.3, 9.5 Hz, 2H), 2.48 - 2.62 (m, 2H), 2.04 - 2.24 (m, 4H), 1.40 - 1.60 (m, 4H), 1.09 - 1.19 (m, 2H), 1.04 (d, *J*=6.7 Hz, 3H), 0.89 - 0.99 (m, 5H).



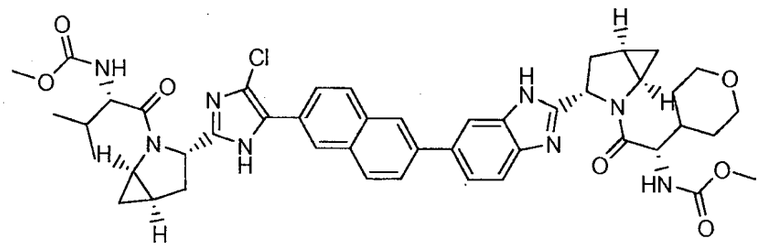
Ejemplo 55

((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de (S)-2-((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-

il)etilcarbamato de metilo (118 mg), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (46.2 mg, 0.263 mmol) y DIEA (0.31 ml, 1.8 mmol) en DMF (4 ml)se añadió HATU (100 mg, 0.263 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH (2 ml) y agua (2 ml). Los volátiles se retiraron a vacío usando un rotavap y el residuo se purificó en HPLC de fase inversa (agua/metanol, TFA al 01.%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (55.3 mg). Tiempo de retención en la CL-EM 1.320 min; m/z 829.42 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando

una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.31 (s, 1H) 8.29 (s, 1H), 8.08 - 8.18 (m, 3H), 8.04 (dd, *J*=8.9, 1.5 Hz, 1H), 7.95 - 8.00 (m, 2H), 7.90 (d, *J*=8.6 Hz, 1H), 7.87 (dd, *J*=8.6, 1.8 Hz, 1H), 5.29 (dd, *J*=9.3, 6.9 Hz, 1H), 5.17 (dd, *J*=9.2, 7.0 Hz, 1H), 4.62 (dd, *J*=9.2, 7.3 Hz, 2H), 3.96 (td, *J*=10.8, 2.9 Hz, 2H), 3.83 - 3.92 (m, 2H), 3.64 - 3.77 (m, 6H), 3.35 - 3.46 (m, 2H), 2.74 (ddd, *J*=19.3, 13.5, 9.3 Hz, 2H), 2.48 - 2.62 (m, 2H), 2.06 - 2.26 (m, 4H), 1.45 - 1.63 (m, 4H), 1.06 - 1.22 (m, 2H), 1.03 (d, *J*=6.7 Hz, 3H), 0.96 - 1.01 (m, 1H), 0.93 (d, *J*=6.7 Hz, 3H), 0.88 - 0.91 (m, 1H).



Ejemplo 56

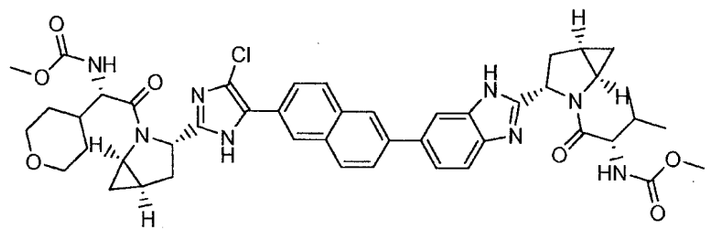
((1S)-2-(((1R,3S,5R)-3-(5-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo

A una solución de ((1S)-2-(((1R,3S,5R)-3-(5-(6-(2-chloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-

il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo (93 mg) en DMF se añadió NCS (14.98 mg, 0.112 mmol) y la mezcla de reacción se calentó a 50°C (temperatura del baño de aceite) durante 2 horas. La mezcla de reacción bruta se purificó mediante HPLC en fase inversa (agua/metanol/TFA al 0.1%) para dar una sal en TFA de ((1S)-2-(((1R,3S,5R)-3-(5-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (102.8 mg).

Tiempo de retención en la CL-EM 1.648 min; m/z 863.32 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en

modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.22 (s ancho, 2H), 8.10 (s, 1H), 8.00 - 8.06 (m, 3H), 7.85 - 7.94 (m, 3H), 5.28 (dd, *J*=9.2, 7.0 Hz, 1H), 5.09 (t, *J*=7.2 Hz, 1H), 4.65 (d, *J*=7.3 Hz, 1H), 4.59 (d, *J*=7.0 Hz, 1H), 3.89 - 3.99 (m, 3H), 3.66 - 3.77 (m, 7H), 3.35 - 3.44 (m, 2H), 2.77 (dd, *J*=13.6, 9.3 Hz, 1H), 2.57 (ddd, *J*=13.8, 6.8, 6.6 Hz, 1H), 2.47 - 2.52 (m, 2H), 2.02 - 2.22 (m, 4H), 1.44 - 1.63 (m, 4H), 1.13 (dt, *J*=8.6, 5.8 Hz, 2H), 1.05 (d, *J*=7.0 Hz, 3H), 0.92 - 1.02 (m, 4H), 0.83 (d, *J*=1.8 Hz, 1H).



Ejemplo 57

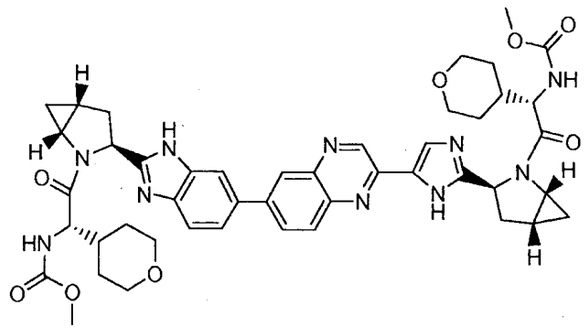
((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de ((1S)-1-(((1R,3S,5R)-3-(5-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)-1H-benzimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (64 mg) en DMF (2 ml) se añadió NCS (10.31 mg,

0.077 mmol) y la mezcla de reacción se calentó a 50°C durante 2 horas. La mezcla de reacción bruta se purificó en HPLC de fase inversa (agua/metanol, TFA al 01.%) y se volvió a purificar en HPLC de fase inversa (agua/ACN/TFA al 0.1%) para dar la sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)-1H-benzimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (44.7 mg) en forma de un sólido pardo.

Tiempo de retención en la CL-EM 1.63 min; m/z 863.39 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue agua al 10%/ metanol al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.24 (s ancho, 2H), 8.02 - 8.12 (m, 4H), 7.86 - 7.95

(m, 3H), 5.28 (dd, *J*=9.2, 6.7 Hz, 1H), 5.08 (t aparente, *J*=7.0 Hz, 1H), 4.65 (d, *J*=7.6 Hz, 1H), 4.60 (d, *J*=6.7 Hz, 1H), 3.93 - 4.01 (m, 2H), 3.86 - 3.91 (m, 1H), 3.75 - 3.81 (m, 1H), 3.65 - 3.74 (m, 6H), 3.36 - 3.46 (m, 2H), 2.77 (dd, *J*=13.7, 9.2 Hz, 1H), 2.57 (ddd, *J*=13.7, 6.7, 6.4 Hz, 1H), 2.49 (dd, *J*=7.8, 3.2 Hz, 2H), 2.12 - 2.25 (m, 2H), 2.00 - 2.12 (m, 2H), 1.54 - 1.67 (m, 3H), 1.41 - 1.51 (m, 1H), 1.09 - 1.19 (m, 2H), 0.97 - 1.06 (m, 4H), 0.94 (d, *J*=6.7 Hz, 3H), 0.82 (s ancho, 1H).



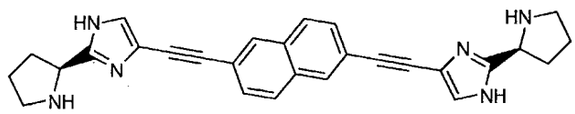
Ejemplo 58

((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-6-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-6-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de una sal en TFA de 6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)quinoxalina (6.0 mg) y ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-

piran-4-il)acético (3.2 mg) en DMF (0.5 ml) y DIPEA (10.13 µl, 0.058 mmol) se añadió HATU (5.64 mg, 0.015 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. El solvente se retiró y el residuo se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (5.5 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 1.60 min; m/z 873 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 95%/metanol al 5%/acetato amónico 10 mM. solvente B = agua al 5%/metanol al 95%/acetato amónico 10 mM. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 2 min. Longitud de onda = 220). RMN de ^1H (400 MHz, MeOD) δ ppm 9.42 (s, 1H), 8.41-8.50 (m, 2H), 8.30 (d, *J*=1.3 Hz, 2H), 8.19 (d, *J*=1.0 Hz, 1H), 8.07 (dd, *J*=8.5, 1.5 Hz, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 5.13-5.33 (m, 3H), 4.57-4.70 (m, 1H), 3.81-4.04 (m, 6H), 3.62-3.77 (m, 6H), 3.34-3.46 (m, 4H), 2.65-2.82 (m, 2H), 2.45-2.61 (m, 2H), 2.01-2.22 (m, 4H), 1.40 - 1.65 (m, 8H), 1.03-1.17 (m, 2H), 0.83-0.98 (m, 2H).

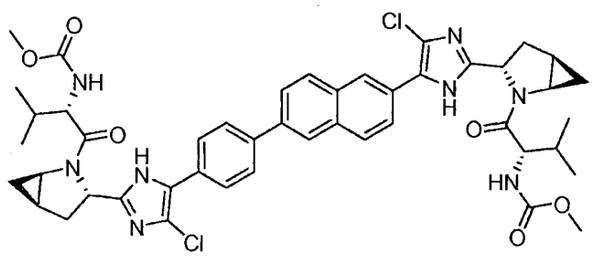


Ejemplo 59

((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal en TFA de 6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-6-il)-2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)quinoxalina (6.0 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (2.60 mg, 0.015 mmol) en DMF (0.5 ml) y DIPEA (10.13 µl, 0.058 mmol) se añadió HATU (5.64 mg, 0.015 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. El solvente se retiró y el residuo se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-bencimidazol-5-il)-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (3.6 mg) en forma de un sólido amarillo.

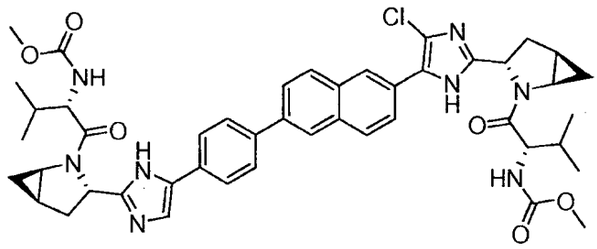
Tiempo de retención en la CL-EM 1.75 min; m/z 789 $[M+H]^+$. (Columna PHENOMENEX® Luna de 3.0 x 50mm S10, solvente A = agua al 90%: metanol al 10%: TFA al 0.1%. solvente B = agua al 10% : metanol al 90%: TFA al 0.1%. Velocidad de flujo = 4 ml/min. % B Inicial = 0, % B Final = 100, Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, MeOD) δ ppm 9.42 (s, 1H), 8.41 - 8.48 (m, 2H), 8.30 (d, *J*=1.3 Hz, 2H), 8.18 (d, *J*=1.0 Hz, 1H), 8.06 (dd, *J*=8.7, 1.6 Hz, 1H), 7.92 (d, *J*=8.5 Hz, 1H), 5.24 - 5.33 (m, 1H), 5.16 - 5.24 (m, 1H), 4.52 - 4.63 (m, 2H), 3.78 - 3.91 (m, 2H), 3.68 (d, *J*=1.0 Hz, 6H), 2.65 - 2.79 (m, 2H), 2.46 - 2.61 (m, 2H), 2.05 - 2.26 (m, 4H), 1.07 - 1.20 (m, 2H), 0.99 - 1.06 (m, 6H), 0.94 - 1.01 (m, 2H), 0.92 (dd, *J*=6.8, 3.3 Hz, 6H).



Ejemplo 60

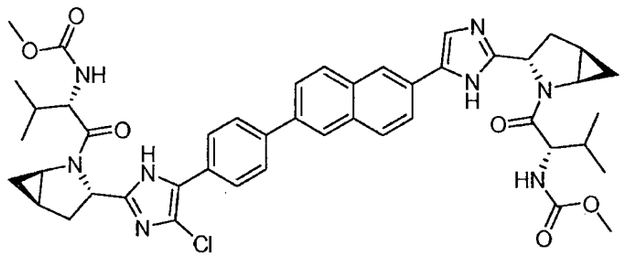
((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-az[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de

metilo;



Ejemplo 62

((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)2-metilpropil)carbamato de metilo



Ejemplo 63

((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-

2-il)carbonil)-2-metilpropil)carbamato *de metilo* (79 mg) en DMF (2 ml) a temperatura ambiente se añadió NCS (13.0 mg, 0.097 mmol) y la mezcla se calentó a 50°C durante 16 horas. El producto bruto se purificó mediante HPLC preparativa (TFA) usando una columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 30 a 90 % de MeOH -agua +TFA al 0.1% para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (20.2 mg) en forma de un sólido amarilla y una mezcla de dos productos monocloruro que se separaron mediante SFC en una columna CHIRALPAK® IB y después se volvió a purificar individualmente mediante HPLC preparativa (TFA) usando una columna Waters Sunfire C18 de 30 X 150 mm de 5u eluida con un gradiente de 25 a 100 % MeOH -Agua + TFA al 0.1% para dar un TFA de ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (11.1 mg) en forma de un sólido amarillo y una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-

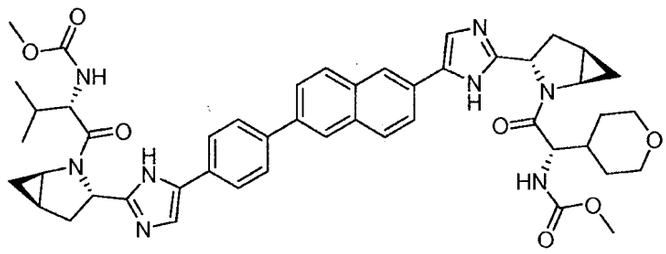
((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (11.4 mg) en forma de un sólido amarillo.

Para el Ejemplo 60: Tiempo de retención en la CL-EM 2.133 min; m/z 883.35 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.22 (s, 2H), 8.07 (d, J=8.5 Hz, 1H), 8.03 (d, J=8.9 Hz, 1H), 7.83 - 7.95 (m, 6H), 5.08 (td, J=9.1, 6.0 Hz, 2H), 4.59 (dd, J=6.7, 1.8 Hz, 2H), 3.71 - 3.79 (m, 2H), 3.68 (s, 6H), 2.44 - 2.57 (m, 4H), 2.13 - 2.25 (m, 2H), 2.00 - 2.10 (m, 2H), 1.09 - 1.16 (m, 2H), 1.05 (dd, J=6.7, 1.5 Hz, 6H), 0.91 - 1.02 (m, 6H), 0.79 - 0.87 (m, 2H).

Para el Ejemplo 62: Tiempo de retención en la CL-EM 1.745 min; m/z 847.33 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.23 (s, 2H), 8.02 - 8.09 (m, 2H), 7.98 (d, *J*=8.2 Hz, 2H), 7.89 - 7.94 (m, 3H), 7.86 (d, *J*=8.6 Hz, 2H), 5.15 (dd, *J*=9.2, 7.0 Hz, 1H), 5.09 (t, *J*=7.0 Hz, 1H), 4.58 (t, *J*=6.7 Hz, 2H), 3.84 (t, *J*=4.7 Hz, 1H), 3.71 - 3.77 (m, 1H), 3.69 (d, *J*=3.1 Hz, 6H), 2.72 (dd, *J*=13.7, 9.5 Hz, 1H), 2.45 - 2.54 (m, 3H), 2.14 - 2.24 (m, 2H), 2.00 - 2.14 (m, 2H), 1.09 - 1.18 (m, 2H), 1.00 - 1.08 (m, 6H), 0.96 (t, *J*=7.6 Hz, 6H), 0.92 (s ancho, 1H), 0.83 (s ancho, 1H).

Para el Ejemplo 63: Tiempo de retención en la CL-EM 1.753 min; m/z 847.32 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS

equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.26 (d, *J*=7.0 Hz, 2H), 8.13 (d, *J*=8.9 Hz, 1H), 8.04 - 8.10 (m, 1H), 7.95 - 8.01 (m, 2H), 7.89 - 7.95 (m, 2H), 7.82 - 7.89 (m, 3H), 5.17 (dd, *J*=9.2, 7.0 Hz, 1H), 5.07 (t, *J*=7.2 Hz, 1H), 4.58 (d, *J*=6.4 Hz, 2H), 3.81 - 3.88 (m, 1H), 3.71 - 3.76 (m, 1H), 3.69 (d, *J*=4.6 Hz, 6H), 2.73 (dd, *J*=13.4, 9.5 Hz, 1H), 2.44 - 2.56 (m, 3H), 2.14 - 2.25 (m, 2H), 2.08 - 2.14 (m, 1H), 1.09 - 1.18 (m, 2H,) 1.00 - 1.08 (m, 6H), 0.96 (t, *J*=6.4 Hz, 6H), 0.92 (s ancho, 1H) 0.78 - 0.85 (m, 1H).



Ejemplo 61

((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-

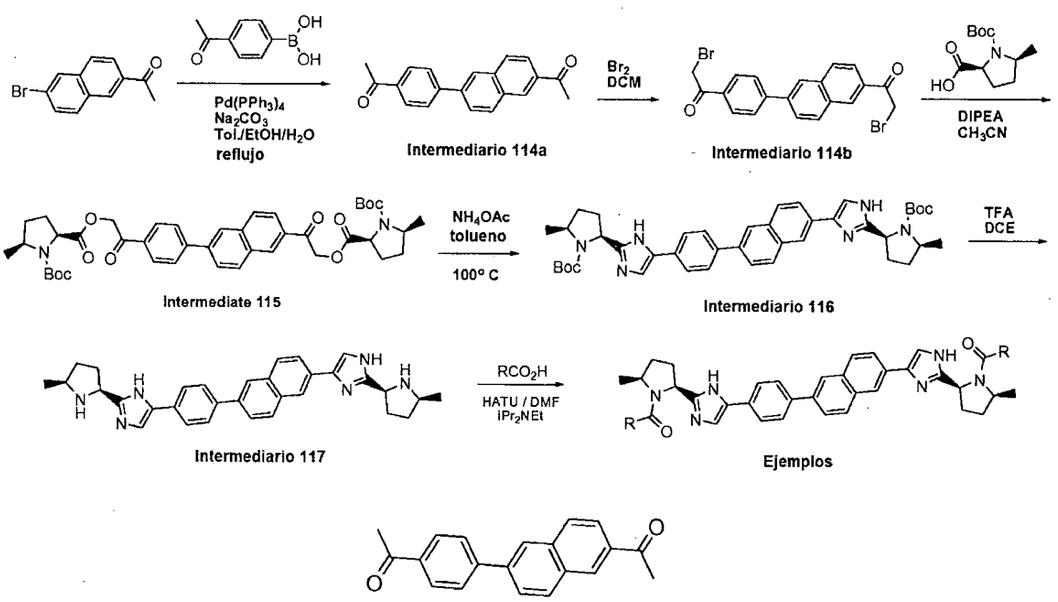
2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

La reacción del intermediario 105 y el adecuado ácido borónico (preparado de forma similar al intermediario 66 usando los materiales de partida adecuados) mediante una reacción de acoplamiento similar a la preparación del intermediario 106 dio una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo(91 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 1.362 min; m/z 855.31 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Waters Sunfire, de 5 u, C18, de 4.6 x 30 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 10%/H_2O al 90%/TFA al 0.1% y el solvente B fue

H_2O al 10%/MeOH al 90%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 8.01 - 7.94 (m, 4H), 7.93 - 7.91 (m, 1H), 7.90 - 7.83 (m, 3H), 5.19 - 5.12 (m, 2H), 4.62 (d, *J*= 7.6 Hz, 1H), 4.58 (d, *J*= 6.4 Hz, 1H), 3.99 - 3.91 (m, 2H), 3.89 - 3.80 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.46 - 3.35 (m, 2H), 2.76 - 2.67 (m, 2H), 2.57 - 2.46 (m, 2H), 2.25 - 2.16 (m, 1H), 2.15 - 2.05 (m, 3H), 1.65 - 1.40 (m, 4H), 1.16 - 1.07 (m, 2H), 1.04 (d, *J*= 6.7 Hz, 3H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.93 - 0.87 (m, 2H).

Esquema de reacción 29



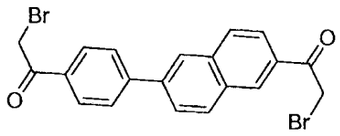
Intermediario 114a

1-(4-(6-acetilnaftalen-2-il)fenil)etanona

Una solución de carbonato sódico (5.43 g, 51.3

mmol) en agua (35 ml) se añadió a una solución agitada de 1-(6-bromonaftalen-2-il)etanona (2.554 g, 10.25 mmol) y ácido 4-acetilfenilborónico (2.017 g, 12.30 mmol) en tolueno (35.0 ml) y etanol (35.0 ml) y se burbujeó nitrógeno a través de la mezcla de reacción durante 15 minutos. Después, se añadió $Pd(PPh_3)_4$ (0.237 g, 0.205 mmol) y la reacción se aclaró con nitrógeno y se calentó a 95°C en nitrógeno durante 8 horas y después se agitó durante la noche a temperatura ambiente. La reacción se concentró hasta sequedad en alto vacío y después se repartió entre DCM (~ 200 ml) y agua (~150 ml). La capa orgánica se lavó después con salmuera (~ 100 ml), se secó ($MgSO_4$), se filtró y se concentró. El residuo se trituró con MeOH (~ 120 ml) y los sólidos restantes se redisolvieron en DCM y se concentraron hasta sequedad (~2.7 g de sólido naranja). Este material se disolvió en EtOAc caliente (80 ml) y se dejó enfriar. Los sólidos resultantes se recogieron mediante filtración y se aclararon con Et_2O para dar 1-(4-(6-acetilnaftalen-2-il)fenil)etanona (1.84 g). Tiempo de retención en la CL-EM 2.443 min; m/z 288.98 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente

A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 8.51 (s, 1 H), 8.05 - 8.16 (m, 5 H), 7.98 (d, *J*=8.8 Hz, 1 H), 7.81 - 7.88 (m, 3 H), 2.76 (s, 3 H), 2.68 (s, 3 H).

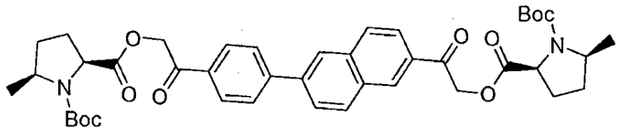


Intermediario 114b

2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona

Una solución de bromo (0.669 ml, 13.0 mmol) en DCM (10 ml) se añadió a una solución agitada de 1-(4-(6-acetilnaftalen-2-il)fenil)etanona (1.827 g, 6.34 mmol) en DCM (30 ml) y la reacción se agitó a temperatura ambiente durante 1 día. La mezcla de reacción se diluyó con DCM (~20 ml) y se concentró hasta sequedad para dar 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (2.83 g) que se usó sin purificación adicional. Tiempo de retención en la CL-EM 2.708 min; m/z 446.71 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm

usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 8.57 (s, 1 H), 8.07 - 8.17 (m, 5 H), 8.02 (d, *J*=8.8 Hz, 1 H), 7.88 (d, *J*=8.8 Hz, 3 H), 4.60 (s, 2 H), 4.51 (s, 2 H).



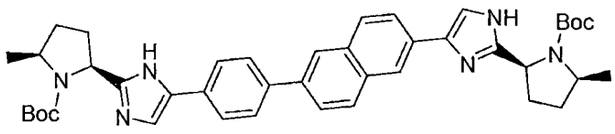
Intermediario 115

5-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(4-(6-(2-((2S,5S)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil) 1-terc-butilo

A una suspensión espesa agitada de 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (1.42 g, 3.17 mmol) y ácido (2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico (1.45 g, 6.34 mmol) en

acetonitrilo (60 ml) se añadió Base de Hunig (1.662 ml, 9.52 mmol). La reacción se agitó a temperatura ambiente durante 1 día (lentamente se convirtió en transparente) y la solución naranja transparente se concentró y se purificó en una columna BIOTAGE® Horizon (160 g de SiO_2, 30 - 40% de EtOAc/hexanos) para dar 5-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(4-(6-(2-((2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil) 1-*terc*-butilo (1.81 g) en forma de una espuma solidificada blancuzca. Tiempo de retención en la CL-EM 3.126 min; m/z 765.87 (M+Na). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 8.48 (s, 1 H), 8.13 (s, 1 H), 7.99 - 8.11 (m, 5 H), 7.86 (d, *J*=8.3 Hz, 3 H), 5.24

- 5.76 (m, 4 H), 4.41 - 4.59 (m, 2 H), 3.93 - 4.11 (m, 2 H), 2.28 - 2.42 (m, 4 H), 2.11 (br, s, 2 H), 1.77 (s ancho, 2 H), 1.49 (s ancho, 9 H), 1.48 (s ancho, 9 H), 1.35 (br, s, 6 H).

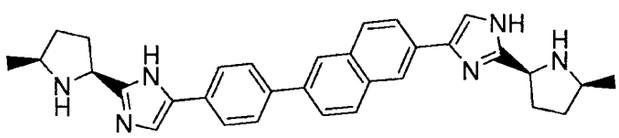


Intermediario 116

(2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(terc-butoxicarbonil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidincarboxilato de terc-butilo

A una solución agitada de 5-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(4-(6-(2-((2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil) 1-*terc*-butilo (1.81 g, 2.437 mmol) en tolueno (40 ml) se añadió acetato amónico (3.76 g, 48.7 mmol) y la suspensión espesa se agitó a temperatura ambiente durante 10 minutos antes de calentar a 100°C durante 12 horas. La reacción se enfrió hasta la temperatura ambiente, se concentró hasta sequedad y el residuo se repartió entre (~150 ml) y 1/2 $NaHCO_3$ sat. (ac) (~150 ml). La capa orgánica se lavó con salmuera (~100 ml), se secó ($MgSO_4$), se filtró y se concentró hasta una espuma marrón solidificada que se purificó en BIOTAGE® Horizon (160 g de SiO_2, 1,5-3% de MeOH/DCM) para dar (2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(tert-butoxicarbonil)-5-metil-2-pirrolidinil)-1H-

imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidincarboxilato de *terc*-butilo (1.46 g) en forma de una espuma solidificada amarillo-naranja. Tiempo de retención en la CL-EM 2.92 min; m/z 703.32 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 117

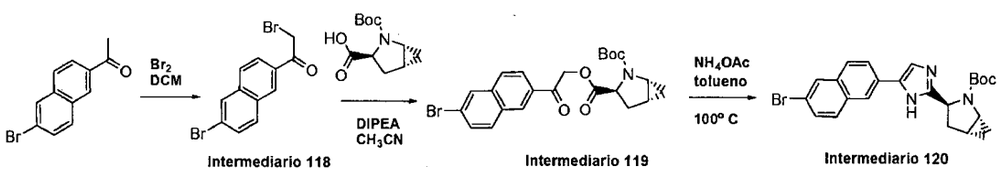
2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol

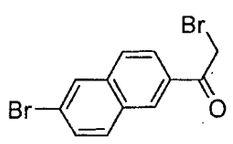
A una solución agitada de (2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(*terc*-butoxicarbonil)-5-metil-2-pirrolidinil)-1H-

imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidincarboxilato de *terc*-butilo (228 mg, 0.324 mmol) en DCE (6 ml) se añadió, gota a gota, TFA (0.500 ml, 6.49 mmol). Durante la adición se formó un precipitado que dificultó la agitación. Se añadió DCM (~ 10 ml) y la suspensión espesa se agitó mientras se añadía el TFA restante. La reacción se agitó a temperatura ambiente durante 30 min, se añadió TFA adicional (~0.5 ml) y la reacción se agitó 3 horas La reacción se concentró para dar una sal en TFA de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (103 mg, 113 mg, 114 mg) en forma de un sólido naranja. Tiempo de retención en la CL-EM 2.756 min; m/z 503.14 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de

electrorrocío. RMN de ^{1}H (400 MHz, MeOD) δ ppm 8.32 (s, 1 H), 8.17 (s, 1 H), 8.01 (app t, *J*=8.2 Hz, 2 H), 7.85 - 7.95 (m, 6 H), 7.80 (s, 1 H), 7.73 (s, 1 H), 5.02 (app q, *J*=8.0 Hz, 2 H), 3.92 (dddd, *J*=8.7, 7.0, 6.9, 4.8 Hz, 2 H), 2.52 - 2.67 (m, 4 H), 2.38 - 2.49 (m, 2 H), 1.95 - 2.07 (m, 2 H), 1.55 (app dd, *J*=6.7, 4.4 Hz, 6 H).

Esquema de reacción 30



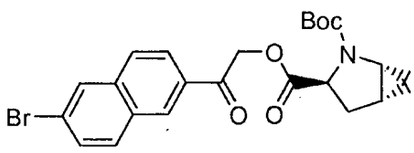


Intermediario 118

2-bromo-1-(6-bromonaftalen-2-il)etanona

Una solución de bromo (0.682 ml, 13.3 mmol) en DCM (20 ml) se añadió a una solución agitada de 1-(6-bromonaftalen-2-il)fenil)etanona (3.30 g, 13.3 mmol) (>90% pureza) en DCM (60 ml) y la reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró para dar 2-bromo-1-(6-bromonaftalen-2-il)etanona (4.35 g) en forma de un sólido blancuzco que se usó sin purificación adicional. Tiempo de retención en la CL-EM 2.177 min; m/z 342.92 (MNa+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una

columna PHENOMENEX® Luna de 10u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 1 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 8.49 (s, 1 H), 8.03 - 8.10 (m, 2 H), 7.86 (d, *J*=8.5 Hz, 1 H), 7.85 (d, *J*=8.8 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.0 Hz, 1 H), 4.56 (s, 2 H).



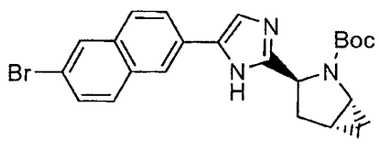
Intermediario 119

2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromonaftalen-2-il)-2-oxoetil) 2-terc-butilo

A una suspensión agitada de 2-bromo-1-(6-2-il)etanona (4.35 g, 13.3 mmol) y ácido (1R,3S,5R)-2-(*terc*-butoxicarbon-bromonaftalenil)-2-azabiciclo[3.1.0]hexan-3-carboxílico bruto (3.01 g, 13.25 mmol) en acetonitrilo (80 ml) se añadió DIPEA (3.47 ml, 19.88 mmol) y la reacción se

agitó a temperatura ambiente durante la noche. La reacción se concentró hasta sequedad y se purificó mediante BIOTAGE® Horizon (160 g de SiO_2, 10-20% de EtOAc/hexanos). Las fracciones que contenían el producto deseado se dejaron reposar durante 3 días. Algunas fracciones tenían cristales grandes (recogieron 240 mg, producto puro deseado mediante RMN de ^1H. Todas las fracciones que contenían el producto deseado se recogieron y se concentraron hasta una espuma solidificada amarilla, que se suspendió con Et_2O (~ 40 ml). El sólido blanco que se formó se recogió mediante filtración y se aclaró con Et_2O para dar 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromonaftalen-2-il)-2-oxoetil) 2-*terc*-butilo (3.24 g). Tiempo de retención en la CL-EM 2.760 min; m/z 472, 474.02 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron

usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 mHz, MeOD) d ppm 8.61 (s ancho, 1H), 8.17 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.71 (dd, J = 8.6, 1.8 Hz, 1H), 5.75 - 5.66 (m, 1H), 5.61 - 5.46 (m, 1H), 4.34 - 4.26 (m, 1H), 3.46 (s ancho, 1H), 2.69 - 2.59 (m, 1H), 2.55 - 2.44 (m, 1H), 1.73 (s ancho, 1H), 1.54 - 1.43 (m, 9H), 0.88 (s ancho, 1H), 0.59 - 0.53 (m, 1H).



Intermediario 120

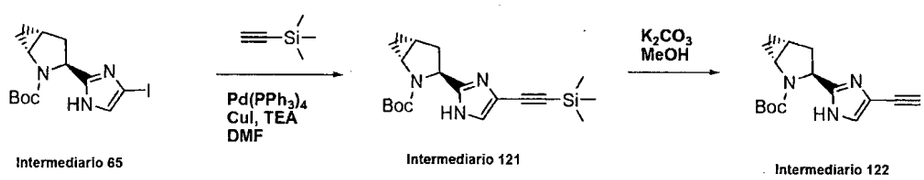
3-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

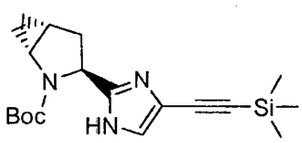
2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromonaftalen-2-il)-2-oxoetil) 2-*terc*-butilo (3.46 g, 7.28 mmol) y acetato amónico (11.2 g, 146 mmol) se disolvieron en tolueno (100 ml) y se agitaron. Después, la reacción se introdujo en un baño de aceite que se había precalentado hasta 100 °C y se agitó a esa temperatura durante 12 horas. La reacción se dejó enfriar hasta la temperatura ambiente, se concentró y se repartió entre (~200 ml) y 1/2 $NaHCO_3$ sat. (ac) (~150 ml). La capa orgánica se lavó con salmuera (~ 100 ml), se secó ($MgSO_4$), se filtró y se

concentró hasta una espuma parda solidificada. Este material se purificó en una BIOTAGE® Horizon (160 g de SiO_2, cargada con DCM, 30-50% de EtOAc/hexanos) para dar (3-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de 1R,3S,5R)-*terc*-butilo (3.05 g) en forma de una espuma amarilla solidificada. Tiempo de retención en la CL-EM 2.238 min; m/z 452.07, 454.02 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 1 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 8.14 (s ancho, 1 H), 7.96 (d, *J*=1.8 Hz, 1 H), 7.79 (d, *J*=9.0 Hz, 1 H), 7.72 (d, *J*=9.8 Hz, 2 H), 7.53 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.38 (s, 1 H), 4.91 (dd, *J*=9.0, 5.3 Hz, 1 H), 3.25 - 3.56 (m, 2 H), 2.40 - 2.51 (m, 1 H), 1.75 - 1.85 (m, 1 H), 1.38 (s ancho, 1 H), 0.86 - 0.93 (m, 1 H), 0.47 - 0.55

(m, 1 H).

Esquema de reacción 31



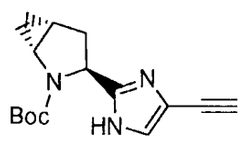


Intermediario 121

3-(4-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Se burbujeó nitrógeno a través de una solución de (3-(5-iodo-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de 1R,3S,5R)-*terc*-butilo (1.65 g, 4.40 mmol) y Cu(I)I (168 mg, 0.880 mmol) en trietilamina (3.07 mL, 22.0 mmol) y DMF (40 ml) durante 20 min. Después se añadieron etiniltrimetilsilano (2.16 g, 22.0 mmol) y $Pd(PPh_3)_4$ (254 mg, 0.220 mmol), la reacción se aclaró con nitrógeno, se selló y se agitó a temperatura ambiente durante 24 horas. La reacción se concentró hasta un aceite marrón y se purificó en una BIOTAGE® Horizon (160 g de SiO_2, 20-40% de EtOAc/hexanos) para dar (3-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de 1R,3S,5R)-*terc*-butilo (980 mg) en forma de un sólido amarillo. Tiempo de retención

en la CL-EM 3.230 min; m/z 346.17 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, CLOROFORMO-*d*) d ppm 7.18 (s, 1 H), 4.77 (dd, *J*=9.2, 5.1 Hz, 1 H), 3.20 (br, s, 1 H), 3.14 - 3.39 (m, 1H), 2.33 (dd, *J*=13.2, 9.4 Hz, 1 H), 1.69 - 1.78 (m, 1 H), 1.34 - 1.56 (m, 1 H), 1.49 (s, 9 H), 0.85 (dt, *J*=8.5, 5.7 Hz, 1 H), 0.41 - 0.47 (m, 1 H), 0.22 - 0.24 (m, 9 H).



Intermediario 122

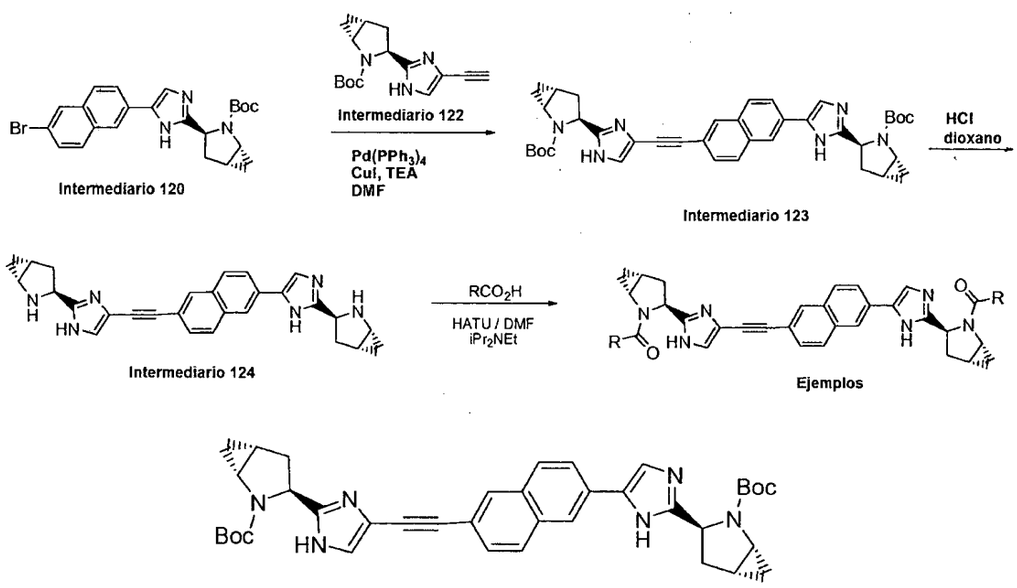
3-(4-etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución de 3-(5-((trimetilsilil)etinil)-1H-

imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (970 mg, 2.81 mmol) en MeOH (30 ml) se añadió carbonato potásico (194 mg, 1.40 mmol) y la reacción se agitó en nitrógeno y después se calentó a 50 °C (temp. del baño) durante 4 horas. La reacción se concentró hasta ~5 ml de volumen, se diluyó con DCM (~ 40 ml) y se lavó con salmuera 1/2 sat. (~20 ml). Los orgánicos se secaron ($MgSO_4$), se filtraron y se concentraron en forma de un sólido pardo. Este material se purificó mediante BIOTAGE® Horizon (40 g de SiO_2, cargada con DCM, 35-45% de EtOAc/hexanos) para dar (3-(5-etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (747 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 2.866 min; m/z 272.12 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma

MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, MeOD) δ ppm 7.18 (s ancho, 1 H), 4.59 (s ancho, 1 H), 3.36 - 3.64 (m, 2 H), 2.46 (dd, *J*=13.2, 8.9 Hz, 1 H), 2.18 - 2.31 (m, 1 H), 1.64 - 1.74 (m, 1 H), 1.18 - 1.45 (m, 9 H), 0.83 (dt, *J*=8.5, 5.8 Hz, 1 H), 0.56 (s ancho, 1 H).

Esquema de reacción 32



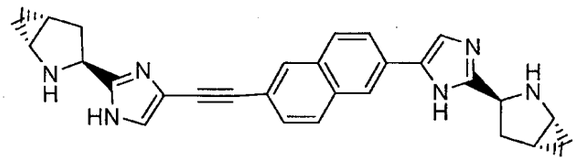
Intermediario 123

(1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

Se burbujeó nitrógeno a través de una solución de 3-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (400 mg, 0.880 mmol), 3-(5-

etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (313 mg, 1.14 mmol) y Cu(I)I (8.4 mg, 0.044 mmol) en trietilamina (0.37 ml, 2.6 mmol) y DMF (8 ml) durante 10 min. Después se añadió $Pd(PPh_3)4$ (50.9 mg, 0.044 mmol), se burbujeó nitrógeno a través de la mezcla de reacción durante 1 min y, después, el matraz se selló y se calentó a 50 °C durante 16 horas. La reacción se concentró a alto vacío y los sólidos residuales se trituraron con EtOAc (~5 ml) y se recogieron mediante filtración (aclarando con EtOAc y hexanos) para dar (1R,3S,5R)-3-(4-(3-(6-((2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (595 mg) en forma de un sólido amarillo claro. El material se usó sin purificación adicional. Tiempo de retención en la CL-EM 3.140 min; m/z 647.35 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente

A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 124

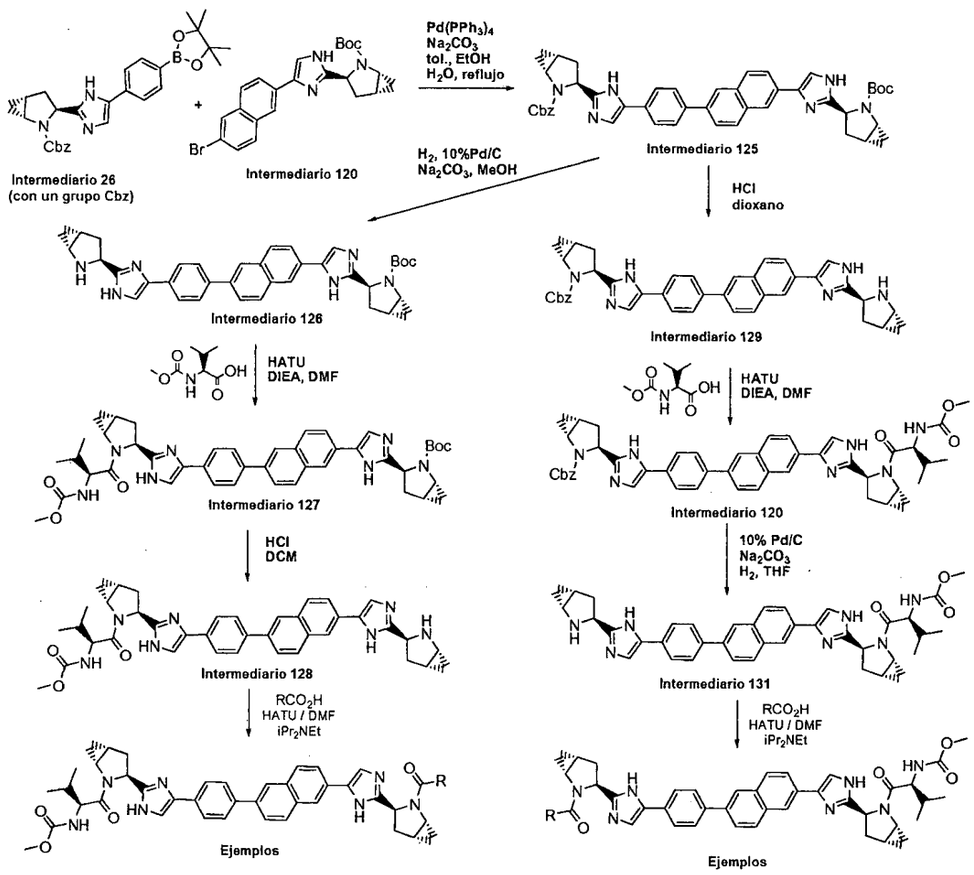
(1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil-naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

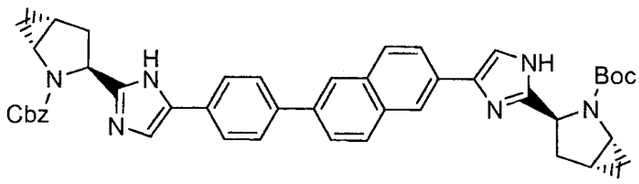
A una solución de (1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (200 mg, 0.309 mmol) en dioxano (3 ml) se añadió HCl 4M (1.546 ml, 6.18 mmol) en dioxano y la reacción se agitó enérgicamente durante 4 horas. La suspensión espesa de la reacción se concentró para dar una sal HCl de (1R,3S,5R)-3-(5-

(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (177 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.403 min; m/z 893.29 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) d ppm 8.42 (s, 1 H), 8.16 (s, 2 H), 8.05 (d, *J*=8.8 Hz, 1 H), 8.03 (d, *J*=8.8 Hz, 1 H), 7.97 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.74 (s, 1 H), 7.66 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.01 (dd, *J*=10.8, 7.8 Hz, 1 H), 4.78 (dd, *J*=10.8, 8.3 Hz, 1 H), 3.57 - 3.77 (m, 2 H), 3.50 - 3.56 (m, 1 H), 2.61 - 2.92 (m, 4 H), 2.13 -

2.21 (m, 1 H), 2.06 - 2.13 (m, 1 H), 1.25 (ddd, *J*=7.8, 5.0, 2.5 Hz, 1 H), 0.99 - 1.14 (m, 2 H).

Esquema de reacción 33





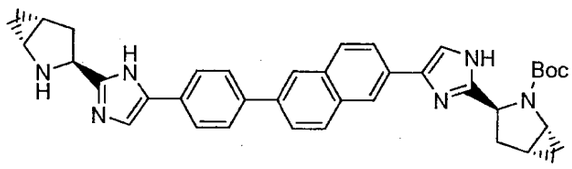
Intermediario 125

3-(5-(4-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-

carboxilato de (1R,3S,5R)-bencilo

Se burbujeó nitrógeno a través de una solución bifásica de 3-(5-(4-(4.4.5.5-tetrametil-1.3.2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-bencilo (preparada de una forma análoga a la del Intermediario 26) (2.0 g, 4.12 mmol), 3-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (1.872 g, 4.12 mmol) y Na_2CO_3 (2.184 g, 20.60 mmol) en una mezcla de EtOH (16.0 ml), tolueno (16.0 ml) y agua (16.0 ml) durante 15 min. Después se añadió $Pd(PPh_3)_4$ (0.143 g, 0.124 mmol), la reacción se aclaró con nitrógeno, se selló, después se calentó a 95 °C durante 10 horas. La suspensión espesa bruta se diluyó con agua (~ 20 ml) y se extrajo con EtOAc (~ 100 ml). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró hasta una espuma amarilla. Este material se disolvió en una cantidad mínima de DCM y se purificó en BIOTAGE® Horizon (110 g de SiO_2, 70-85% de EtOAc/hexanos) para dar 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-bencilo (2.257 g) en forma de una espuma solidificada amarillo claro. Tiempo de retención en la CL-EM 4.158 min; m/z 733.17 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos

Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.17 (s ancho, 1 H), 8.07 (s, 1 H), 7.86 - 7.94 (m, 2 H), 7.71 - 7.86 (m, 6 H), 7.44 (s, 1 H), 7.32 (s, 1 H), 7.20 (s ancho, 5 H), 5.14 (d, *J*=12.3 Hz, 1 H), 4.91 - 5.05 (m, 1 H), 4.63 - 4.77 (m, 1 H), 3.55 - 3.69 (m, 2 H), 3.29 - 3.34 (m, 1 H), 2.46 - 2.59 (m, 2 H), 2.29 - 2.44 (m, 2 H), 1.66 - 1.80 (m, 2 H), 1.30 (s ancho, 9 H), 0.80 - 0.93 (m, 2 H), 0.61 (s ancho, 2 H).



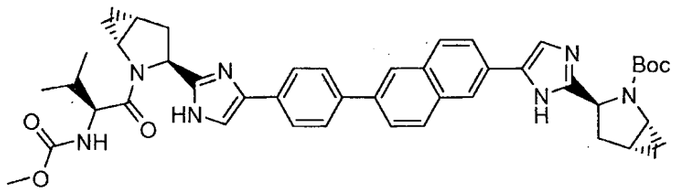
Intermediario 126

3-(5-(6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-4-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-

butilo

Una mezcla de reacción de 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,5R)-*terc*-butilo (0.305 g, 0.416 mmol) y $NaHCO_2$ (0.070 g, 0.832 mmol) en MeOH (15 ml) se cargó con 10% de Pd/C (0.022 g, 0.021 mmol).. La suspensión resultante se aclaró al vacío con N_2 (3X) y se introdujo en 1 atm de H_2 (balón) durante 3 h a temperatura ambiente. Después, la mezcla se filtró a través de una lámina de tierra de diatomeas (CELITE®) y se concentró a vacío. Se recuperó un sólido blancuzco correspondiente a 3-(5-(6-(4-(2-((1R,5R)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (0.235 g) y se usó sin purificación adicional. CL/EM [M+H]+= 599; Tr = 1.96 min es el producto. Columna Luna de 3u C18 de 2x50mm; inicio %B: 0, final %B: 100 solvente A: Acetonitrilo al 10%/H_2O al 90% + TFA al 1%; solvente B: Acetonitrilo al 90%/ H_2O al 10%+ TFA al 1%; velocidad de flujo 4 ml/min. Tiempo de recorrido: 5 min. Pureza = 94 %. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 12.00 (2 H, s ancho,), 8.11 - 8.32 (3 H, m), 7.88 - 8.02 (5 H, m), 7.72 - 7.88 (9 H, m), 7.63 (4 H, s ancho,), 4.64 (2 H, s ancho,), 4.42 (1 H, t, *J*=7.93 Hz), 3.97 - 4.18 (1 H, m), 3.45

(1 H, s ancho,), 3.17 (3 H, s), 2.96 (1 H, dd, *J*=13.43, 6.71 Hz), 2.08 - 2.43 (6 H, m), 1.66 (2 H, s ancho,), 1.07 - 1.50 (20 H, m), 0.81 - 0.89 (3 H, m), 0.77 (1 H, s ancho,), 0.45 - 0.61 (3 H, m), 0.30 (1 H, s ancho.).



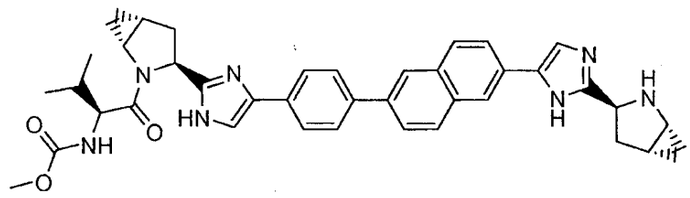
Intermediario 127

3-(5-(6-(4-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-ilfenil))naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

A una solución de 3-(5-(6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (0.235 g, 0.392 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0.069 g, 0.39 mmol) y DIEA (0.137 ml, 0.785 mmol) en DMF (10 ml) se añadió HATU (0.164 g, 0.432 mmol) y la solución amarilla resultante se agitó a temperatura ambiente durante la noche. El solvente se retiró a presión reducida y el residuo se disolvió en metanol, se filtró y se purificó mediante HPLC preparativa (solvente A: MeOH al 10%/agua al 90%/TFA al

0.1% ; solvente B: MeOH al 90%/agua al 10%/TFA al 0.1% ; Columna: Sunfire Prep MS C18 de 30 x 100 mm de 5u; Longitud de onda: 220 nM; Velocidad de flujo: 30 ml/min; gradiente: 0% de B a 100% de B durante 30 min. con un tiempo de conservación de 2 min) para dar una sal en TFA de 3-(5-(6-(4-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-ilfenil))naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (0.10 g) en forma de un sólido blanco. CL/EM [M+H]+= 756; Tr = 2.14 min es el producto. Columna Luna de 3u C18 de 2x50mm; inicio %B: 0, final %B: 100 solvente A: Acetonitrilo al 10%/H_2O al 90% + TFA al 1%; solvente B: Acetonitrilo al 90%/ H_2O al 10%+ TFA al 1%; velocidad de flujo 4 ml/min. Tiempo de recorrido: 5 min. Pureza = 96 %. RMN ^1H (500 MHz, *DMSO-d_6*) δ ppm 14.60 (1 H, br, s,), 8.39 (3 H, d, *J*=4.88 Hz), 8.09 - 8.24 (4 H, m), 7.99 - 8.08 (6 H, m), 7.89 - 7.98 (5 H, m), 7.27 (1 H, d, *J*=8.55 Hz), 4.98 - 5.07 (1 H, m), 4.84 (1 H, br, s,), 4.42 (1 H, t, *J*=7.32 Hz), 3.74 (1 H, br, s,), 3.55 (4 H, s), 2.55 (2 H, d, *J*=9.77 Hz), 2.32 - 2.44 (3 H, m), 2.13 (1 H, dq, *J*=13.43, 6.71 Hz), 1.94 (1 H, dt, *J*=13.28, 6.79 Hz), 1.75 (1 H, dt, *J*=12.89, 6.22 Hz), 1.40 (4 H, d, *J*=10.07 Hz), 1.11 - 1.30 (10 H, m), 0.90 - 1.00 (5 H, m), 0.73 - 0.88

(10 H, m).

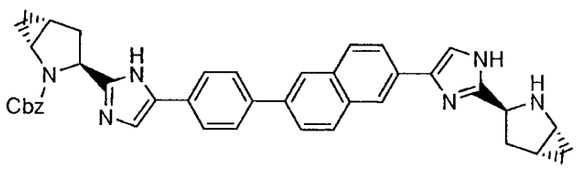


Intermediario 128

(S)-1-((1R,3S,5R)-3-(44-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

A una solución agitada de una sal en TFA de 3-(5-(6-(4-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (0.10 g, 0.12 mmol) en CH_2Cl_2 (20 ml) se añadió HCl 4N en dioxano (2 ml, 8.00 mmol) y la suspensión amarilla resultante se agitó a temperatura ambiente durante 2 horas. La reacción se concentró a vacío y el residuo resultante se trituró con Et_2O para dar una sal HCl de (S)-1-((1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamate de metilo HCl (47 mg) en forma de un sólido amarillo. CL/EM [M+H]+= 656; Tr = 1.73 min es el producto. Columna Luna de 3u

C18 de 2x50mm; inicio %B: 0, final %B: 100 solvente A: Acetonitrilo al 10%/H_2O al 90% + TFA al 1%; solvente B: Acetonitrilo al 90%/ H_2O al 10%+ TFA al 1%; velocidad de flujo 4 ml/min. Tiempo de recorrido: 5 min. Pureza = 95 %. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 14.47 - 15.18 (2 H, m), 9.77 - 10.61 (2 H, m), 8.30 - 8.42 (2 H, m), 8.17 (1 H, s), 7.93 - 8.10 (10 H, m), 7.27 (1 H, d, *J*=8.55 Hz), 5.08 (1 H, t, *J*=7.93 Hz), 4.71 (1 H, t, *J*=8.39 Hz), 4.40 - 4.46 (1 H, m), 3.77 (1 H, br, s,), 3.52 - 3.58 (3 H, m), 3.38 - 3.44 (1 H, m), 2.52 - 2.61 (3 H, m), 2.39 (1 H, dt, *J*=13.58, 6.64 Hz), 2.14 - 2.21 (1 H, m), 1.94 (2 H, dd, *J*=8.24, 4.88 Hz), 1.15 (1 H, d, *J*=5.80 Hz), 0.93 (4 H, d, *J*=6.71 Hz), 0.75 - 0.89 (6 H, m).



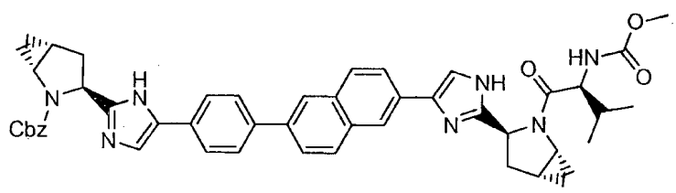
Intermediario 129

3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-4-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-bencilo

A una solución de 3-(5-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-bencilo (228 mg, 0.311 mmol) en dioxano (3 ml) se añadió una solución

de HCl 4.0M (1.167 ml, 4.67 mmol) en dioxano y la reacción se agitó enérgicamente a temperatura ambiente durante 3 horas. La reacción se concentró para dar una sal HCl de 3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-bencilo (233 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.988 min; m/z 633.18 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.44 (s, 1 H), 8.28 (s, 1 H), 8.08 - 8.18 (m, 3 H), 7.92 - 8.02 (m, 4 H), 7.84 (br, s, 3 H), 7.31 (br, s, 5 H), 5.21 (d, J=12.1, 1 H), 4.95 - 5.05 (m, 2 H), 4.80 - 4.91 (m, 1 H), 3.70 - 3.77 (m, 1 H), 3.59 - 3.67 (m, 1 H), 2.77 - 2.93 (m, 2 H), 2.74 (dd, J=13.4, 9.2 Hz, 1

H), 2.46 (dt, *J*=13.5, 6.7 Hz, 1 H), 2.12 - 2.22 (m, 1 H), 1.83 - 1.96 (m, 1 H), 1.27 - 1.35 (m, 1 H), 1.09 (q, *J*=7.9 Hz, 1 H), 0.95 (ddd, *J*=8.7, 5.9, 5.8 Hz, 1 H), 0.75 - 0.83 (m, 1 H).



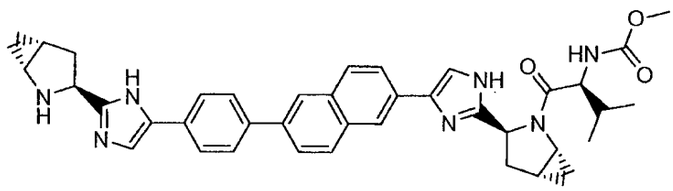
Intermediario 130

3-(5-(4-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il))naftalen-2-il)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-bencilo

A una solución agitada de (3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,5R)-bencilo (225 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (93 mg, 0.53 mmol) en DMF (3 ml) y DIPEA (0.37 ml, 2.1 mmol) se añadió HATU (203 mg, 0.533 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La reacción bruta se concentró bajo corriente de nitrógeno y el residuo se disolvió en MeOH y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de acetato amónico) para dar 3-(5-(4-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-

metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,5R)-bencilo (200 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 4.053 min; m/z 790.25 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.28 (s, 2 H), 8.13 (d, J=8.8 Hz, 1 H), 8.08 (d, J=8.8 Hz, 1 H), 7.94 - 8.02 (m, 4 H), 7.76 - 7.92 (m, 3 H), 7.85 (dd, J=8.7, 1.6 Hz, 1 H), 7.29 (br, s, 5 H), 5.21 (d, J=12.1 Hz 1 H), 5.16 (dd, J=9.2, 6.9 Hz, 1 H), 4.97 (t, J=8.2 Hz, 1 H), 4.57 (d, J=6.5 Hz, 1 H), 3.78 - 3.87 (m, 1 H), 3.68 (s, 3 H), 3.64 - 3.77 (m, 2 H), 2.66 - 2.77 (m, 2 H), 2.40 - 2.56 (m, 2 H), 2.14 - 2.25 (m, 1 H), 2.05 - 2.14 (m, 1 H), 1.87 (d, J=6.5 Hz, 1 H), 1.06 - 1.16 (m, 1 H),

1.02 (d, *J*=6.8 Hz, 3 H), 0.94 (d, *J*=6.8 Hz, 3 H), 0.87 - 0.99 (m, 2 H), 0.74 - 0.82 (m, 1 H).



Intermediario 131

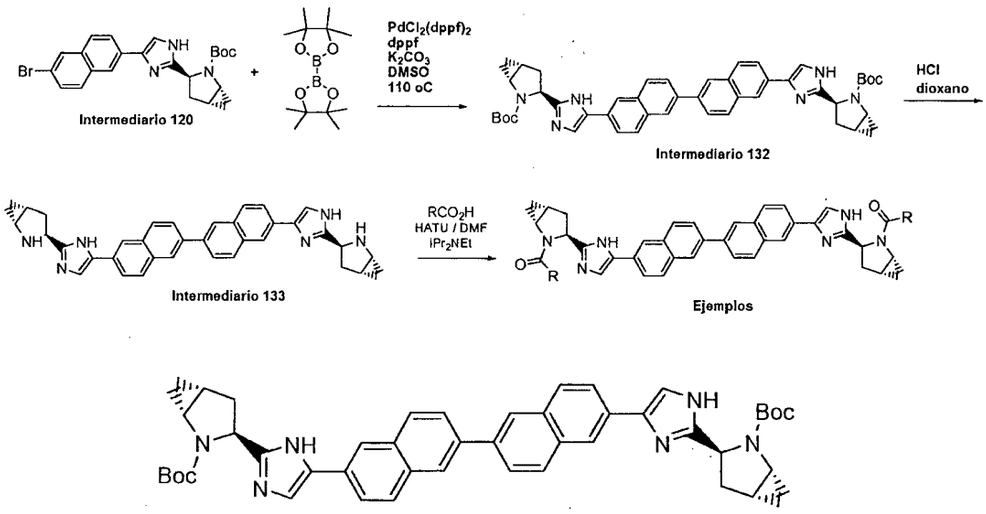
(S)-1-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

A una solución de 3-(5-(4-(6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,5R)-bencilo (190 mg, 0.241 mmol) y Na_2CO_3 (50 mg, 0.472 mmol) en THF (10 ml) se añadió 10% de paladio sobre carbono (100 mg, 0.094 mmol) y la mezcla de reacción se aclaró al vacío con nitrógeno (3X) y después con hidrógeno (5X). La mezcla de reacción se dejó agitar en un balón de hidrógeno durante 2 horas, se filtró a través de tierra de diatomeas (CELITE®) y se concentró. El residuo se volvió a someter a las condiciones de reacción (50 mg de 10% Pd/C usado) durante la noche a temperatura ambiente antes de filtrar a través de tierra de diatomeas (CELITE®) y se concentró. El residuo se disolvió en DMSO/MeOH, se filtró y

se purificó mediante HPLC preparativa (MeOH/H_2O p/ TFA al 0.1%) para dar una sal en TFA de (2S)-1-((R,3S,5R)-3-(5-(6-(4-(2-((1R,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (55 mg). Tiempo de retención en la CL-EM 2.147 min; m/z 656.21 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 1 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.24 (s, 1 H), 8.12 (d, J=8.9 Hz, 1 H), 8.07 (d, J=8.9 Hz, 1 H), 7.91 - 8.01 (m, 4 H), 7.83 - 7.90 (m, 3 H), 7.66 (s, 1 H), 5.17 (dd, J=9.2, 7.0 Hz, 1 H), 4.67 (dd, J=10.7, 7.6 Hz, 1 H), 4.58 (d, J=6.7 Hz, 1 H), 3.82 - 3.87 (m, 1 H), 3.69 (s, 3 H), 3.44 - 3.49 (m, 1 H), 2.59 - 2.77 (m, 3 H), 2.48 - 2.56 (m, 1 H), 2.16 - 2.25 (m, 1

H), 2.03 - 2.15 (m, 2 H), 1.21 (ddd, *J*=7.5, 4.9, 2.6 Hz, 1 H), 1.09 - 1.15 (m, 1 H), 1.04 (d, *J*=6.7 Hz, 3 H), 0.98 - 1.03 (m, 1 H), 0.95 (d, *J*=6.7 Hz, 3 H), 0.89 - 0.95 (m, 1 H).

Esquema de reacción 34



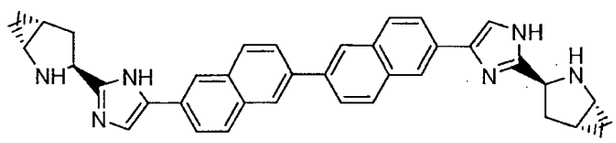
Intermediario 132

3.3'-(4.4'-(2.2'-binaftil-6.6'-diil)bis(1H-imidazol-4.2-diil))bis(2-azabiciclo[3.1.0]hexan-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-terc-butilo

Se burbujeó nitrógeno en una solución de 3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (250 mg, 0.550 mmol), 4.4.4',4',5.5.5',5'-octametil-2.2'-bi(1.3.2-dioxaborolano) (69.9 mg, 0.275 mmol), 1.1'-bis-(difenilfosfino)-ferroceno (15.42 mg, 0.028 mmol) y K_2CO_3 (228 mg, 1.651 mmol) en DMSO (12 ml) durante 10 min. Después se añadió dicloruro de 1.1'-bis-(difenilfosfino)-ferroceno)

paladio (22.63 mg, 0.028 mmol) a la mezcla de reacción y el burbujeo de nitrógeno continuó durante 10 minutos antes de sellar la reacción y después se calentó a 110 °C durante 20 horas. La reacción se repartió entre agua (60 ml) y DCM (60 ml) y los orgánicos se separaron, se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo bruto se purificó mediante BIOTAGE® Horizon (40 g de SiO_2, 70-100% de EtOAc/hexanos) para dar 3.3'-(4.4'-(2.2'-binaftil-6.6'-diil)bis(1H-imidazol-4.2-diil))bis(2-azabiciclo[3.1.0]hexan-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-*terc*-butilo (67 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 4.348 min; m/z 749.29 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.22 (s, 4 H), 7.91 - 8.02 (m, 6

H), 7.87 (d, *J*=8.5 Hz, 2 H), 7.48 (s ancho, 2 H), 4.68 - 4.77 (m, 2 H), 3.61 (s ancho, 2 H), 2.56 (dd, *J*=13.1, 8.8 Hz, 2 H), 2.33 - 2.43 (m, 2 H), 1.70 - 1.79 (m, 2 H), 1.31 (s ancho, 18 H), 0.87 (dt, *J*=8.5, 5.8 Hz, 2 H), 0.63 (s ancho, 2 H).



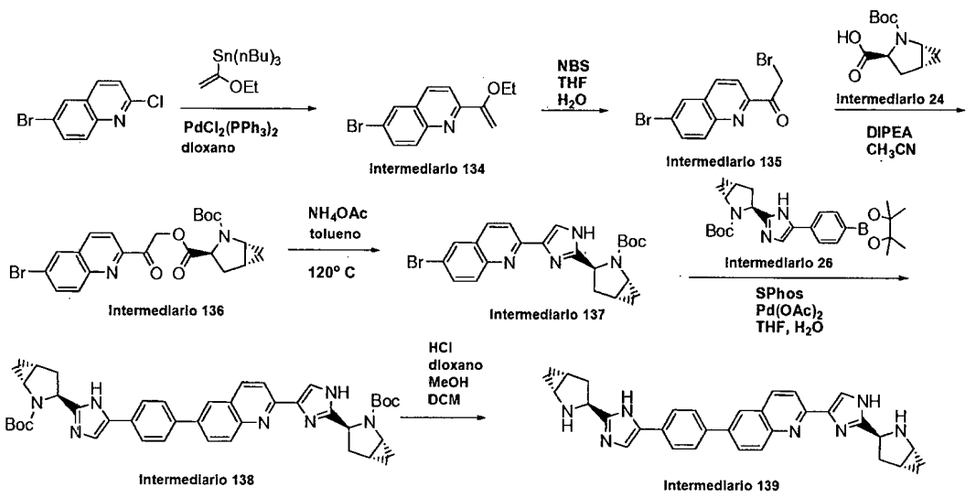
Intermediario 133

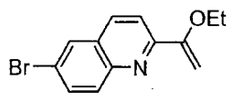
6,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)-2,2-binaftilo

A una solución agitada de 3.3'-(4.4'-(2.2'-binaftil-6.6'-diil)bis(1H-imidazol-4.2-diil))bis(2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,1'R,3S,3'S,5R,5'R)-*terc*-butilo) (62mg, 0.083 mmol) en dioxano (2 ml) se añadió HCl 4.0M (1.0 ml, 4.00 mmol) en dioxano y la suspensión espesa de la reacción se agitó enérgicamente durante 3 horas. La suspensión espesa se diluyó con MEOH y se concentró hasta sequedad para dar una sal HCl de 6.6'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-benzo[d]imidazol-4-il)-2,2'-binaftilo (56 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.971 min; m/z 547.25 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un

detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.44 (s, 2 H), 8.38 (s, 2 H), 8.12 - 8.19 (m, 6 H), 8.09 (dd, 2 H), 7.97 (dd, *J*=8.5, 1.5 Hz, 2 H), 4.97 (dd, *J*=10.5, 8.1 Hz, 2 H), 3.62 - 3.66 (m, 2 H), 2.79 - 2.89 (m, 4 H), 2.15 - 2.22 (m, 2 H), 1.29 - 1.34 (m, 2 H), 1.11 (c, *J*=7.9 Hz, 2 H).

Esquema de reacción 35



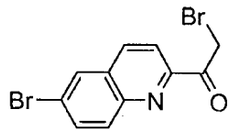


Intermediario 134

6-bromo-2-(1-etoxivinil)quinolina

A una solución de 6-bromo-2-cloroquinolina (1.0 g, 4.1 mmol) y tributil(1-etoxivinil)estanano (1.79 g, 4.95 mmol) en dioxano (8 ml) se añadió diclorobis(trifenilfosfina)-paladio(II) (0.289 g, 0.412 mmol) y la mezcla se agitó a 100 °C durante 5 h, el producto deseado se identificó mediante CLEM. La mezcla de reacción bruta se concentró y se purificó mediante cromatografía instantánea en gel de sílice (eluyó con 1:1 de hexanos/DCM) para dar el producto 6-bromo-2-(1-etoxivinil)quinolina (720 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 4.091 min; m/z 279.84 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de

amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

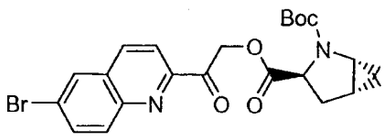


Intermediario 135

2-bromo-1-(6-bromoquinolin-2-il)etanona

A una solución de 6-bromo-2-(1-etoxivinil)quinolina (530 mg, 1.91 mmol) en THF (10 ml) y agua (2.5 ml) se añadió NBS (407 mg, 2.287 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se repartió entre EtOAc y salmuera y la capa orgánica se concentró. El material bruto se purificó mediante cromatografía instantánea en gel de sílice (eluyó con Et2O/hexanos, gradiente de 0 a 5% Et_2O) para dar el 2-bromo-1-(6-bromoquinolin-2-il)etanona (380 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 3.988 min; m/z 329.84 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en

el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 136

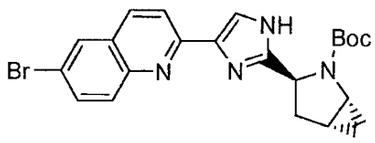
2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromoquinolin-2-il)-2-oxoetil) 2-terc-butilo

2-bromo-1-(6-bromoquinolin-2-il)etanona

A una solución de 2-bromo-1-(6-bromoquinolin-2-il)etanona (268 mg, 0.815 mmol) y ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (204 mg, 0.896 mmol) en acetonitrilo (8 ml) se añadió DIPEA (0.21 ml, 1.2 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con $NaHCO_3$ ac. sat. (5 ml) y se extrajo con EtOAc (2 x 20 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron. El producto bruto se purificó mediante cromatografía instantánea en gel de sílice (usó DCM como solvente de carga, eluyó con Et_2O/hexanos, gradiente de 10% a 30% de Et_2O) para dar 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-

(6-bromoquinolin-2-il)-2-oxoetil) 2-*terc*-butilo (332 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 4.283 min; m/z 476.88 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



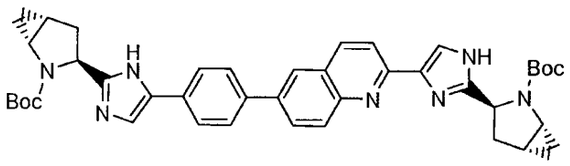
Intermediario 137

(1R,3S,5R)-3-(4-(6-bromo-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución de 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromoquinolin-2-il)-2-

oxoetil) 2-*terc*-butilo (407 mg, 0.856 mmol) en tolueno (10 ml) se añadió acetato amónico (990 mg, 12.8 mmol) y la mezcla se agitó a 120 °C durante 3 horas. La mezcla de reacción se diluyó con $NaHCO_3$ ac, sat. (10 ml) y se extrajo con EtOAc (50 ml). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El material bruto se purificó mediante cromatografía instantánea en gel de sílice (eluyó con 1: 1 EtOAc/hexanos) para dar (1R,3S,5R)-3-(4-(6-bromo-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (272 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.306 min; m/z 456.99 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm

8.08 (d, *J*=8.5 Hz, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.78 (dd, *J*=8.9, 2.2 Hz, 1 H), 7.73 - 8.14 (m, 3 H), 4.86 - 4.98 (m, 1 H), 3.70 - 3.82 (m, 0.5 H), 3.26 - 3.39 (m, 1 H), 2.46 (dd, *J*=13.3, 9.3 Hz, 1 H), 1.84 - 1.91 (m, 0.5 H), 1.74 - 1.84 (m, 1 H), 1.52 (s, 9 H), 0.87 - 0.97 (m, 1 H), 0.48 - 0.61 (m, 1 H).

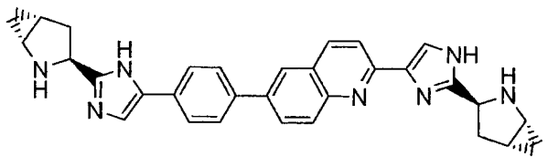


Intermediario 138

(1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución de (1R,3S,5R)-3-(4-(6-bromo-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexane-2-carboxilato de *terc*-butilo (150 mg, 0.329 mmol), 3-(5-(4-(4.4.5.5-tetrametil-1.3.2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo(149 mg, 0.329 mmol), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (27.0 mg, 0.066 mmol) y K_2CO_3 (137 mg, 0.988 mmol) en THF (2 ml) y agua (0.50 ml) se añadió $Pd(OAc)_2$ (7.40 mg, 0.033 mmol) y la mezcla de reacción se agitó a 110 °C durante 2 horas. La mezcla de reacción se diluyó con MeOH, se filtró y se

purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador NH_4OAc 10mM) para dar (1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(tert-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (140 mg) en forma de un sólido amarillo brillante. Tiempo de retención en la CL-EM 3.150 min; m/z 700.36 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 139

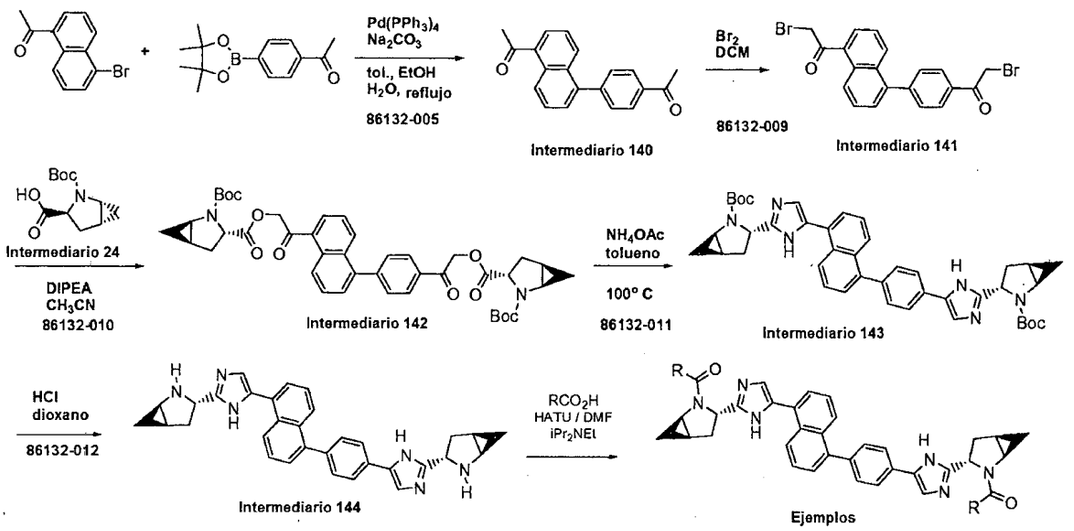
2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-

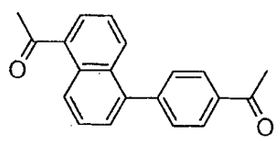
imidazol-4-il)fenil)quinolina

A una suspensión de (1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinolinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (130 mg, 0.186 mmol) en dioxano (3 ml), MeOH (0.5 ml) y DCM (3 ml) se añadió una solución de HCl 4M (1 ml, 400 mmol) en dioxano y la mezcla se agitó durante 2 horas a temperatura ambiente. La reacción se concentró para dar una sal HCl de 2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)quinolina (140 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.063 min; m/z 500.37 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para

CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 9.09 (d, *J*=9.0 Hz, 1 H), 8.66 (s, 1 H), 8.56 - 8.62 (m, 2 H), 8.47 - 8.53 (m, 2 H), 8.07 (s, 1 H), 8.02 - 8.06 (m, 4 H), 4.97 (dd, *J*=10.8, 8.0 Hz, 1 H), 3.65 - 3.71 (m, 1 H), 3.55 - 3.65 (m, 2 H), 2.73 - 2.86 (m, 3 H), 2.61 - 2.72 (m, 1 H), 2.07 - 2.20 (m, 2 H), 1.25 - 1.35 (m, 2 H), 1.07 (t, 2 H).

Esquema de reacción 36





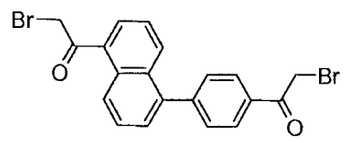
Intermediario 140

1-(4-(5-acetilnaftalen-1-il)fenil)etanona

A una solución de 1-(5-bromonaftalen-1-il)etanona (1.2 g, 4.8 mmol) y ácido 4-acetilfenilborónico (1.03 g, 6.26 mmol) en tolueno (20 ml) y etanol (20 ml) se añadió una solución de carbonato sódico (2.55 g, 24.09 mmol) en agua (20 ml) y la solución heterogénea se agitó enérgicamente con

burbujeo de nitrógeno durante 15 min. Después, se añadió $Pd(PPh_3)_4$ (0.111 g, 0.096 mmol) y el vaso de reacción se selló y se calentó a reflujo durante 6 horas. La reacción se enfrió y se concentró hasta sequedad. El residuo bruto se suspendió en EtOAc (~ 150 ml) y agua (~ 100 ml). Las capas se separaron y la capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró hasta un sólido naranja. El sólido naranja se purificó en BIOTAGE® Horizon (40 g de SiO_2, DCM) para dar 1-(4-(5-acetilnaftalen-1-il)fenil)etanona (1.31 g) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 3.736 min; m/z 289.19 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético.

Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 8.75 (d, *J*=8.8 Hz, 1 H), 8.11 (d, *J*=8.5 Hz, 2 H), 7.99 (d, *J*=8.5 Hz, 1 H), 7.94 (dd, *J*=7.2, 1.1 Hz, 1 H), 7.67 (dd, *J*=8.5, 7.0 Hz, 1 H), 7.58 (d, *J*=8.3 Hz, 2 H), 7.45 - 7.51 (m, 2 H), 2.79 (s, 3 H), 2.70 (s, 3 H).

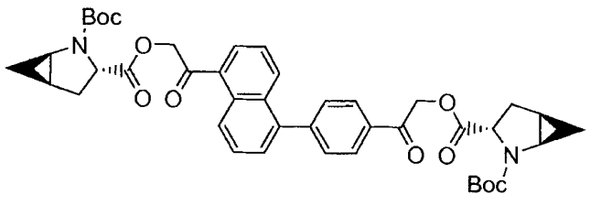


Intermediario 141

2-bromo-1-(4-(5-(2-bromoacetil)naftalen-1-il)fenil)etanona

Una solución de bromo (0.47 ml, 9.1 mmol) en DCM (10 ml) se añadió a una solución de 1-(4-(5-acetilnaftalen-1-il)fenil)etanona (1.285 g, 4.46 mmol) en DCM (20 ml) y la reacción se agitó a temperatura ambiente durante 1 día. La reacción se concentró hasta un aceite naranja claro viscoso (~1.92 g). Mediante RMN de ^{1}H, el producto principal parece ser el producto deseado con picos correspondientes a los dos regioisómeros monobromados (~10%). El material se usó sin purificación. RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 8.64 (d, *J*=8.5 Hz, 1 H), 8.13 - 8.17 (m, 2 H), 8.05 (d, *J*=8.5 Hz, 1 H), 7.94 (dd,

J=7.2, 1.1 Hz, 1 H), 7.71 (dd, *J*=8.8, 7.0 Hz, 1 H), 7.60 - 7.64 (m, 2 H), 7.48 - 7.55 (m, 2 H), 4.60 (s, 2 H), 4.53 (s, 2 H).

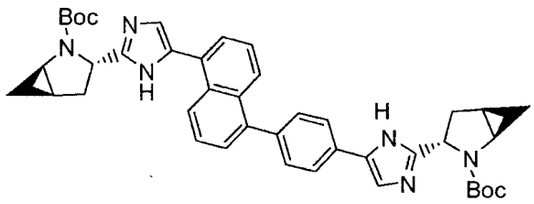


Intermediario 142

2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(4-(5-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboniloxi)acetil)naftalen-1-il)fenil)-2-oxoetil) 2-terc-butilo

A una solución de 2-bromo--(4-(5-(2-bromoacetil)naftalen-1-il)fenil)etanona bruta (1.99 g, 4.46 mmol) y ácido (1R,3S,5R)-2-(tert-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (2.337 ml, 13.38 mmol) en acetonitrilo (50 ml) se añadió DIPEA (2.337 ml, 13.38 mmol) y la solución amarillo transparente se agitó a temperatura ambiente durante la noche. La reacción se concentró hasta una espuma solidificada amarilla que se purificó en BIOTAGE® Horizon (SiO_2, EtOAc/hexanos) para dar 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(4-(5-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboniloxi)acetil)naftalen-1-il)fenil)-2-oxoetil) 2-*terc*-butilo (2.95 g) en forma de un

sólido suave blanco. Tiempo de retención en la CL-EM 4.363 min; m/z 737.38 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 1 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.57 (d, *J*=8.8 Hz, 1 H), 8.14 (d, *J*=8.0 Hz, 2 H), 7.99 - 8.06 (m, 2 H), 7.68 (dd, *J*=8.8, 7.0 Hz, 1 H), 7.64 (d, *J*=8.3 Hz, 2 H), 7.52 - 7.60 (m, 2 H), 5.60 - 5.70 (m, 1 H), 5.32 - 5.56 (m, 3 H), 4.24 - 4.34 (m, 2 H), 3.38 - 3.49 (m, 2 H), 2.59 - 2.69 (m, 1 H), 2.38 - 2.55 (m, 3 H), 1.61 - 1.77 (m, 2 H), 1.47 (s ancho, 18 H), 0.81 - 0.94 (m, 2 H), 0.50 - 0.58 (m, 2 H).



Intermediario 143

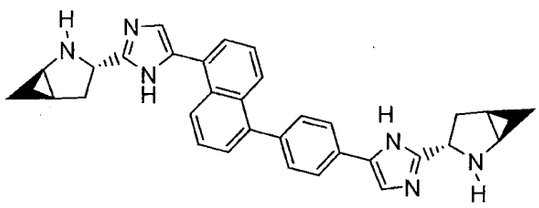
3-(5-(4-(5-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-

azabiciclo[3.1.0]hexn-3-il)-1H-imidazol-5-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Una solución de 2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(4-(5-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboniloxi)acetil)naftalen-1-il)fenil)-2-oxoetil) 2-*terc*-butilo (2.01 g, 2.72 mmol) y acetato amónico (4.19 g, 54.4 mmol) en tolueno (40 ml) se agitó y se calentó a 100°C durante la noche. La reacción se concentró hasta sequedad y los sólidos marrones se repartieron entre DCM (150 ml) y 1/2 $NaHCO_3$ sat. (ac) (100 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron y se concentraron. El material bruto no se purificó fácilmente mediante cromatografía en columna instantánea de modo que se recogieron todas las fracciones que contenían el producto deseado o el material de partida, se concentraron y se volvieron a someter a las condiciones de reacción (ahora 100°C durante la noche). La reacción se concentró y los sólidos marrones se repartieron entre DCM (150 ml) y 1/2 $NaHCO_3$ sat. (100 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron y se concentraron. Aproximadamente ~ 30-35% del material se purificó en HPLC preparativa (disuelta en MeOH, filtrada, 80-100% MeOH/agua, amortiguador de acetato amónico) para dar 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-

3-il)-1H-imidazol-5-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (148 mg) en forma de un sólido amarillo. El material restante se purificó en HPLC preparativa (disuelta en MeOH, filtrada, 60-100% MeOH/agua, amortiguador de TFA) para dar una sal en TFA DE 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (299 mg). Tiempo de retención en la CL-EM 3.100 min; m/z 699.56 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.29 (d, *J*=8.5 Hz, 1 H), 7.90 (d, *J*=8.5 Hz, 1 H), 7.83 (d, *J*=8.3 Hz, 2

H), 7.59 (dd, *J*=7.0, 1.0 Hz, 1 H), 7.53 (dd, *J*=8.5, 7.0 Hz, 1 H), 7.43 - 7.50 (m, 4 H), 7.42 (s, 1 H), 7.23 (s, 1 H), 4.66 - 4.80 (m, 2 H), 3.60 (br, s, 2 H), 2.56 (dt, *J*=13.1, 8.9 Hz, 2 H), 2.32 - 2.46 (m, 2 H), 1.70 - 1.78 (m, 2 H), 1.38 (s ancho, 18 H), 0.82 - 0.90 (m, 2 H), 0.63 (s ancho, 2 H).



Intermediario 144

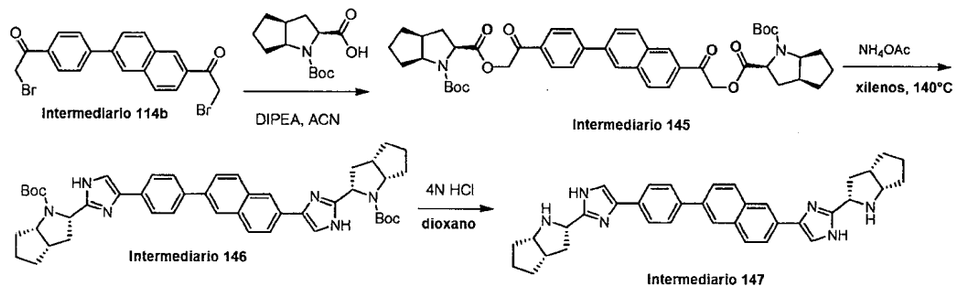
(1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)etinil-naftalen-1-il)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

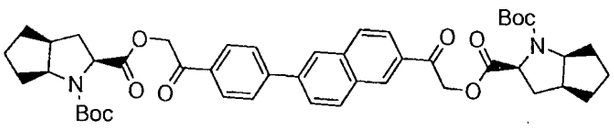
A una solución de 3-(5-(4-(5-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (141 mg, 0.202 mmol) en dioxano (3.0 ml) se añadió HCl 4M (0.757 ml, 3.03 mmol) en dioxano y la reacción se agitó a temperatura ambiente durante 6 horas. Los sólidos se lavaron por los lados del vial con MeOH y la reacción se concentró en corriente de nitrógeno para dar una sal HCl de (1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-

azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (119 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.333 min; m/z 499.57 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.15 (d, J=8.3 Hz, 1 H), 8.03 - 8.08 (m, 2 H), 8.01 (d, J=8.0 Hz, 2 H), 7.95 (s, 1 H), 7.77 (d, J=6.5 Hz, 1 H), 7.68 - 7.74 (m, 1 H), 7.65 (d, J=8.0 Hz, 2 H), 7.57 - 7.64 (m, 2 H), 5.03 (t, J=9.4 Hz, 1 H), 4.97 (dd, J=10.8, 8.0 Hz, 1 H), 3.57 - 3.66 (m, 2 H), 2.76 - 2.89 (m, 4 H), 2.11 - 2.21 (m, 2 H), 1.27 - 1.34 (m, J=7.7, 5.1,

5.1, 2.6 Hz, 2 H), 1.05 - 1.14 (m, 2 H).

Esquema de reacción 37



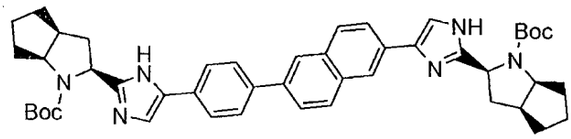


Intermediario 145

Hexahidrociclopenta[b]pirrol-1,2(2H)-dicarboxilato de (2S,3aS,6aS)-2-(2-(4-(6-(2-((2S,3aS,6aS)-1-(terc-butoxicarbonil)- octahidrociclopenta[b]pirrol-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil) 1-terc-butilo

A una suspensión agitada de 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (79 mg, 0.176 mmol) y ácido (2S,3aS,6aS)-1-(*terc*-butoxicarbonil)octahidrociclopenta[b]pirrol-2-carboxílico (90 mg, 0.353 mmol) en acetonitrilo (1.5 ml) y cloroformo (1.5 ml) se añadió DIPEA neta (0.068 ml, 0.388 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se evaporó hasta sequedad y después se purificó mediante gel de sílice FCC (3% de MeOH en DCM) para

dar el intermediario 145 en forma de un sólido pardo. Tiempo de retención en la CL-EM: 2.480 min; m/z 793.7 $(M-H)^-$.

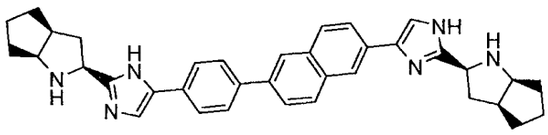


Intermediario 146

2-(4-(4-(6-(2-((2S,3aS,6aS)-1-(terc-butoxicarbonil)-octahidrociclopenta[b]pirrol-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)hexahidrociclopenta[b]pirrol-1(2H)-carboxilato de (2S,3aS,6aS)-terc-butilo

Una suspensión agitada de hexahidrociclopenta[b]pirrol-1,2(2H)-dicarboxilato de (2S,3aS,6aS)-2-(2-(4-(6-(2-((2S,3aS,6aS)-1-(*terc*-butoxicarbonil)octahidrociclopenta[b]pirrol-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil)-1-*terc*-butilo (140 mg, 0.176 mmol) y acetato amónico (272 mg, 3.52 mmol) en xileno (4 ml) se calentó a 140 °C durante 2 h. La mezcla de reacción se enfrió hasta la temperatura ambiente y se diluyó con EtOAc (20 ml) y se lavó con. $NaHCO_3$, agua, salmuera y se secó (Na_2SO_4) para dar un sólido marrón que se purificó mediante FCC en gel de sílice (3-5% de MeOH en DCM) para dar el intermediario 146, Tiempo de retención en la CL-EM: 2.77

min; m/z 755, $(M+H)^+$.

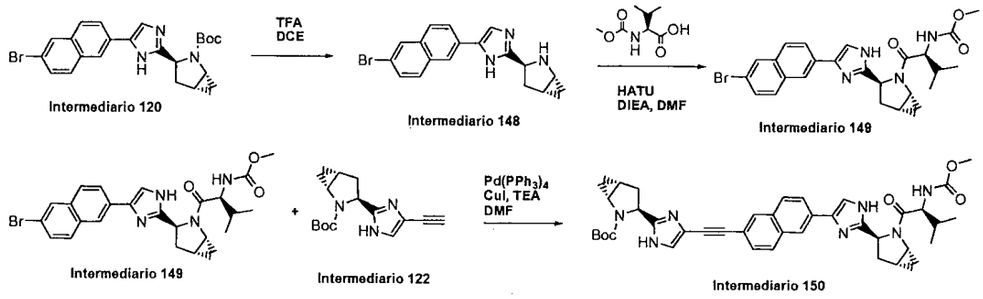


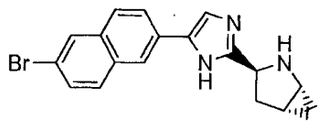
Intermediario 147

(2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-octahirocyclopenta[b]pirol-2-i)-1H-imidazol-4-i)naftalen-2-il)fenil)-1H-imidazol-2-il)octahidrociclopenta[b]pirrol

A una solución del intermediario 146 en DCM se añadió HCl 4N en dioxano (20 equiv) y la mezcla se agitó a temperatura ambiente durante 2-3 horas. Se añadió tolueno anhidro a la suspensión amarilla resultante y después se evaporó hasta sequedad para dar el intermediario 147 en forma de un sólido beige y se aisló en forma de una sal de 4HCl. Tiempo de retención en la CL-EM: 2.43 min; m/z 555 $(M+H)^+$.

Esquema de reacción 38





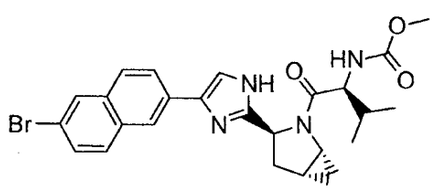
Intermediario 148

(1R,3S,5R)3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hexano

A una solución de 3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (Intermediario 120) (606 mg, 1.334 mmol) en DCE (20 ml) se añadió TFA (1.028 ml, 13.34 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. Después se añadió TFA adicional (1 ml) y la reacción se agitó a temperatura ambiente durante 4 horas. La reacción se concentró hasta sequedad y el aceite marrón bruto se disolvió en éter dietílico y se concentró al vacío (2X) para dar una sal en TFA de (1R,3S,5R)-3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (786 mg) en forma de un sólido amarillo. El material se usó sin purificación adicional. Tiempo de retención en la CL-EM 2.558 min; m/z 352.03, 354.05 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de

amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 10.55 (br, s, 1 H), 8.02 (s, 1 H), 7.93 (d, *J*=1.5 Hz, 1 H), 7.72 (d, *J*=8.5 Hz, 1 H), 7.65 (d ,*J*=8.8 Hz, 1 H), 7.59 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.52 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.44 (s, 1 H), 5.10 (dd, *J*=11.8, 7.3 Hz, 1 H), 3.49 - 3.54 (m, 1 H), 2.94 (td, *J*=12.7, 4.6 Hz, 1 H), 2.68 (dd, *J*=13.2, 7.2 Hz, 1 H), 2.06 - 2.14 (m, 1 H), 1.20 - 1.26 (m, 1 H), 1.00 - 1.09 (m, 1 H).

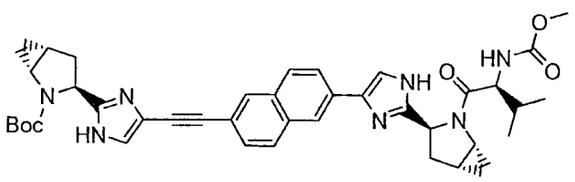


Intermediario 149

(S)-1-((1R,3S,5R)-3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

A una solución de una sal en TFA de (1R,3S,5R)-3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (525 mg, 0.902 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (190 mg, 1.08 mmol) en DMF (10 ml) y DIPEA (0.79 ml, 4.5 mmol) se añadió HATU (411 mg, 1.082 mmol) y la reacción se agitó a temperatura ambiente durante 4 horas. La reacción se diluyó con EtOAc (~80 ml) y se lavó con $NaHCO_3$ ac. sat., agua (30 ml) y salmuera (30 ml). Los orgánicos se secaron ($MgSO_4$), se filtraron y se

concentraron hasta un aceite marrón (625 mg). Este material se purificó en BIOTAGE® Horizon (40 g de SiO_2, 40-80% de EtOAc/hexanos) para dar (S)-1-((1R,3S,5R)-3-(4-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (412 mg) en forma de un cristal amarillo. Tiempo de retención en la CL-EM 1.843 min; m/z 511.24, 513.12 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1.0 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 150

3-(4-((6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-

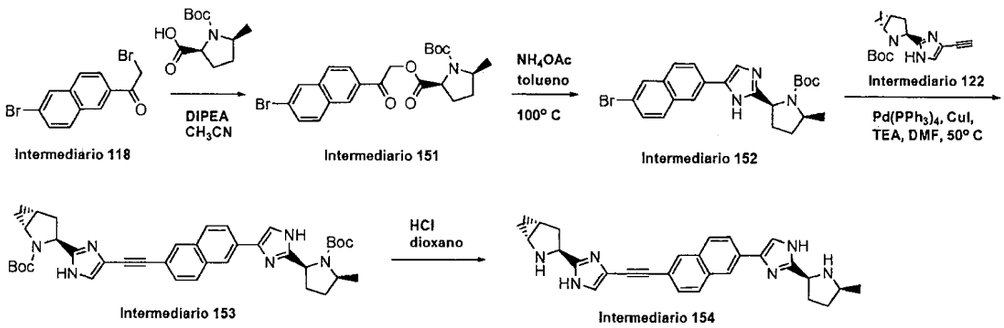
metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il))naftalen-2-il)etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

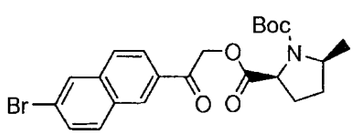
Se burbujeó nitrógeno a través de una mezcla de 3-(5-etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (Intermediario 122) (118 mg, 0.432 mmol), (S)-1-((1R,3S,5R)-3-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (170 mg, 0.332 mmol) y CuI (3.17 mg, 0.017 mmol) en DMF (4 ml) y TEA (0.14 ml, 0.10 mmol) durante 15 min. Después se añadió $Pd(PPh_3)_4$(19.2 mg, 0.017 mmol) y el vaso de reacción se selló y se calentó a 60 °C durante la noche. La reacción se enfrió y se añadieron CuI (5 mg) y TEA (100 ul) adicionales y se burbujeó nitrógeno a través de la reacción durante 15 min. Después se añadió $Pd(PPh_3)_4$ adicional (12 mg) y la reacción se selló y se agitó a 70 °C durante 24 h. La reacción se concentró en alto vacío y el residuo se repartió entre DCM (25 ml) y agua (25 ml). La capa acuosa se extrajo con DCM (2 X 10 ml y las orgánicas combinadas se lavaron con salmuera (~20 ml), se secaron ($MgSO_4$), se filtraron y se concentraron hasta

un aceite oscuro viscoso. El material se disolvió en MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua, amortiguador de acetato amónico) para dar 3-(4-((6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il))naftalen-2-il)etinill-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (187.4 mg) en forma de un sólido amarillo. El material se usó sin purificación adicional. Tiempo de retención en la CL-EM 1.720 min; m/z 704.59 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1.0 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma

MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 39



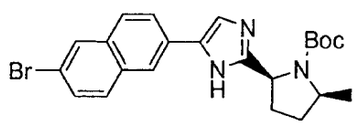


Intermediario 151

5-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(6-bromonaftalen-2-il)-2-oxoetil) 1-terc-butilo

A una suspensión agitada de 2-bromo-1-(6-2-il)etanona (Intermediario 118) (1.03 g, 3.14 mmol) y ácido (2S,5S)-1-(*terc*-butoxicarbonil)metilpirrolidin-2-carboxílico (0.720 g, 3.14 mmol) en acetonitrilo (50 ml) se añadió DIPEA (0.823 ml, 4.71 mmol) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró hasta sequedad y se purificó mediante BIOTAGE® Horizon (40 g de SiO_2, 10-20% de EtOAc/hexanos) para dar 5-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(6-bromonaftalen-2-il)-2-oxoetil) 1-*terc*-butilo (1.09 g) en forma de una espuma solidificada amarilla. Tiempo de retención en la CL-EM 4.413

min; m/z 476, 478.20 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.57 (s ancho, 1 H), 8.14 (d, *J*=1.5 Hz, 1 H), 8.01 (d, *J*=8.5 Hz, 1 H), 7.96 (d, *J*=8.8 Hz, 1 H), 7.91 (d, *J*=8.8 Hz, 1 H), 7.68 (dd, *J*=8.8, 1.8 Hz, 1 H), 5.62 - 5.70 (m, 1 H), 5.47 - 5.60 (m, 1 H), 4.46 (t, *J*=7.3 Hz, 1 H), 3.92 - 4.06 (m, 1 H), 2.26 - 2.37 (m, 2 H), 2.05 - 2.19 (m, 1 H), 1.67 - 1.82 (m, 1 H), 1.46 (d, *J*=6.8 Hz, 9 H), 1.30 (d, *J*=6.5 Hz, 3 H).



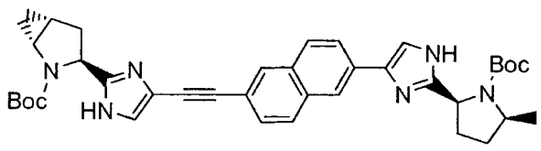
Intermediario 152

2-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-5-

metilpirrolidin-1-carboxilato de (2S,5S)-terc-butilo

A una solución de 5-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(6-bromonaftalen-2-il)-2-oxoetil) 1-*terc*-butilo (1.17 g, 2.47 mmol) en tolueno (30 ml) se añadió acetato amónico (3.79 g, 49.1 mmol) y la reacción se introdujo en un baño de aceite que se había precalentado a 100 °C y se agitó a esa temperatura durante la noche. La reacción se dejó enfriar hasta la temperatura ambiente, se concentró y se repartió entre (100 ml) y 1/2 $NaHCO_3$ sat. (ac.) (75 ml). La capa orgánica se lavó con salmuera (~ 50 ml), se secó ($MgSO_4$), se filtró y se concentró hasta una espuma parda solidificada. Este material se purificó en una BIOTAGE® Horizon (160 g de SiO_2, cargada con DCM, 20-35% de EtOAc/hexanos) para dar (2-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-5-metilpirrolidin-1-carboxilato de (2S,5S)-*terc*-butilo (893 mg) en forma de una espuma parda solidificada. Tiempo de retención en la CL-EM 3.410 min; m/z 456, 458.22 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1

min y un tiempo de análisis de 4 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.19 (s ancho, 1 H), 8.01 (s, 1 H), 7.83 - 7.93 (m, 1 H), 7.76 - 7.83 (m, 2 H), 7.55 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.47 (s ancho, 1 H), 4.94 (s ancho, 1 H), 3.99 - 4.09 (m, 1 H), 2.22 - 2.36 (m, 2 H), 2.09 - 2.21 (m, 1 H), 1.72 (s ancho, 1 H), 1.42 (d, *J*=6.0 Hz, 3 H), 1.34 (s ancho, 9 H).



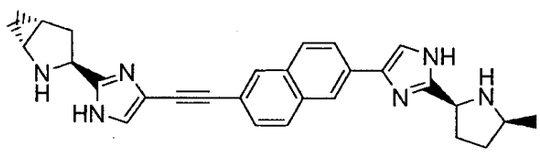
Intermediario 153

3-(4-((6-(2-((2S,5S)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Se burbujeó nitrógeno a través de una solución de 2-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-5-metilpirrolidin-carboxilato de (2S,5S)-*terc*-butilo (127 mg, 0.277 mmol), 3-(5-etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (91 mg, 0.33 mmol) y CuI (2.6 mg, 0.014 mmol) en DMF

(3 ml) y TEA (0.12 ml, 0.83 mmol) durante 15 min. Después se añadió $Pd(PPh_3)4$ (16 mg, 0.014 mmol) y el vaso de reacción se aclaró con nitrógeno, se selló y se calentó a 50 °C durante la noche. La reacción se enfrió hasta la temperatura ambiente, se burbujeó nitrógeno a través de la mezcla de reacción durante 20 minutos y después, se añadieron CuI (~4 mg) y $Pd(PPh_3)_4$ (15 mg) adicionales. La reacción se lavó con nitrógeno durante 5 min, se selló y se calentó a 60 °C durante 1 día. La reacción se enfrió hasta la temperatura ambiente, se diluyó con metanol y se purificó en HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de 3-(5-((6-(2-((2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (56.7 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.161 min; m/z 649.62 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el

solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.31 (s, 1 H), 8.21 (s, 1 H), 8.07 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.04 (m, 2 H), 7.91 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.77 - 7.87 (m, 1 H), 7.69 (dd, *J*=8.7, 1.4 Hz, 1 H), 5.13 (t, *J*=7.5 Hz, 1 H), 4.12 (s ancho, 1 H), 3.61 (s ancho, 1 H), 2.66 (s ancho, 1 H), 2.45 - 2.54 (m, 1 H), 2.33 - 2.42 (m, 1 H), 2.22 - 2.32 (m, 2 H), 1.75 - 1.86 (m, 2 H), 1.25 - 1.59 (m, 21 H), 1.06 (ninguno, 1 H), 0.90 (dt, *J*=8.5, 5.8 Hz, 1 H), 0.71 (s ancho, 1 H).



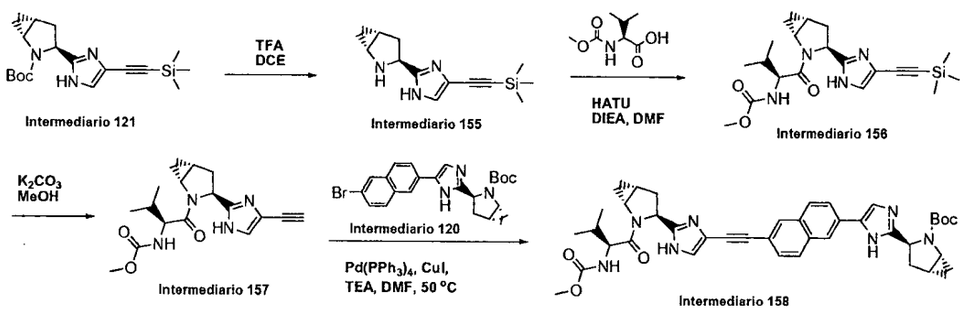
Intermediario 154

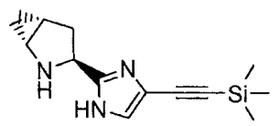
(1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

A una mezcla de una sal en TFA de 3-(5-((6-(2-((2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (53.6 mg, 0.061 mmol) en dioxano (1.5 ml) se añadió HCl 4M (0.611 ml, 2.445 mmol) en dioxano y la reacción se agitó enérgicamente durante 2 horas. La reacción se

concentró bajo vapor de nitrógeno durante la noche para dar una sal HCl de (1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (37 mg), que se usó sin purificación adicional. Tiempo de retención en la CL-EM 2.302 min; m/z 449.40 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 40



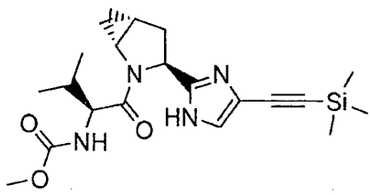


Intermediario 155

(1R,3S,5R)-3-(4-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

A una solución de 3-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (299 mg, 0.865 mmol) en DCE (5 ml) se añadió TFA (500 µl, 6.49 mmol) y la reacción se agitó a temperatura ambiente durante 30 min. La reacción se concentró hasta sequedad y después se volvió a someter a las condiciones de reacción durante 5 horas. La reacción se concentró para dar una sal en TFA de (1R,3S,5R)-3-(4-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano en forma de un aceite marrón viscoso que se usó sin purificación adicional. Tiempo de retención en la CL-EM 2.755 min; m/z 246.25 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de

conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

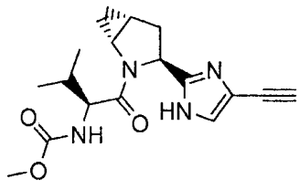


Intermediario 156

(S)-3-metil-1-oxo-1-((1R,3S,5R)-3-(4-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)butan-2-ilcarbamato de metilo

A una solución agitada de (1R,3S,5R)-3-(5-trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (212 mg, 0.865 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (197 mg, 1.125 mmol) en DMF (3 ml) y DIPEA (1.2 ml, 6.9 mmol) se añadió HATU (428 mg, 1.125 mmol) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró hasta sequedad y después se purificó en una BIOTAGE® Horizon (25g de SiO_2, 40-60% de EtOAc/hexanos) para dar (S)-3-metil-1-oxo-1-((1R,3S,5R)-3-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)butan-2-ilcarbamato de metilo

(203 mg) en forma de un cristal amarillo. Tiempo de retención en la CL-EM 3.095 min; m/z 403.29 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 7.17 (s ancho, 1 H), 5.04 - 5.11 (m, 1 H), 4.54 (d, J=6.8 Hz, 1 H), 3.65 (s, 3 H), 3.54 - 3.61 (m, 1 H), 2.82 (s, 1 H), 2.39 - 2.50 (m, 1 H), 2.27 - 2.36 (m, 1 H), 2.04 - 2.15 (m, 1 H), 1.94 - 2.04 (m, 1 H), 1.11 (dt, J=8.7, 5.6 Hz, 1 H), 0.95 (d, J=6.8 Hz, 3 H), 0.90 (d, J=6.8 Hz, 3 H), 0.73 - 0.79 (m, 1 H), 0.21 (s, 9 H).



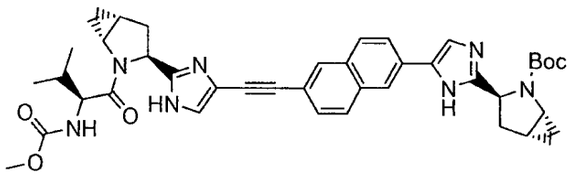
Intermediario 157

(S)-1-((1R,3S,5R)-3-(4-etinil-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

A una solución de (S)-3-metil-1-oxo-1-((1R,3S,5R)-3-(5-((trimetilsilil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)butan-2-ilcarbamato de metilo (200 mg, 0.497 mmol) en metanol (5 ml) se añadió carbonato potásico (34.3 mg, 0.248 mmol) y la reacción se lavó con nitrógeno, se selló y después se calentó a 50 °C durante 4h y después se agitó a temperatura ambiente durante la noche. La reacción se concentró hasta sequedad y después se purificó en una BIOTAGE® Horizon (12g de SiO_2, 70-90% de EtOAc/hexanos) para dar (S)-1-((1R,3S,5R)-3-(5-etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (151 mg) en forma de un cristal amarillo. Tiempo de retención en la CL-EM 1.788 min; m/z 331.32 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10%

de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Intermediario 158

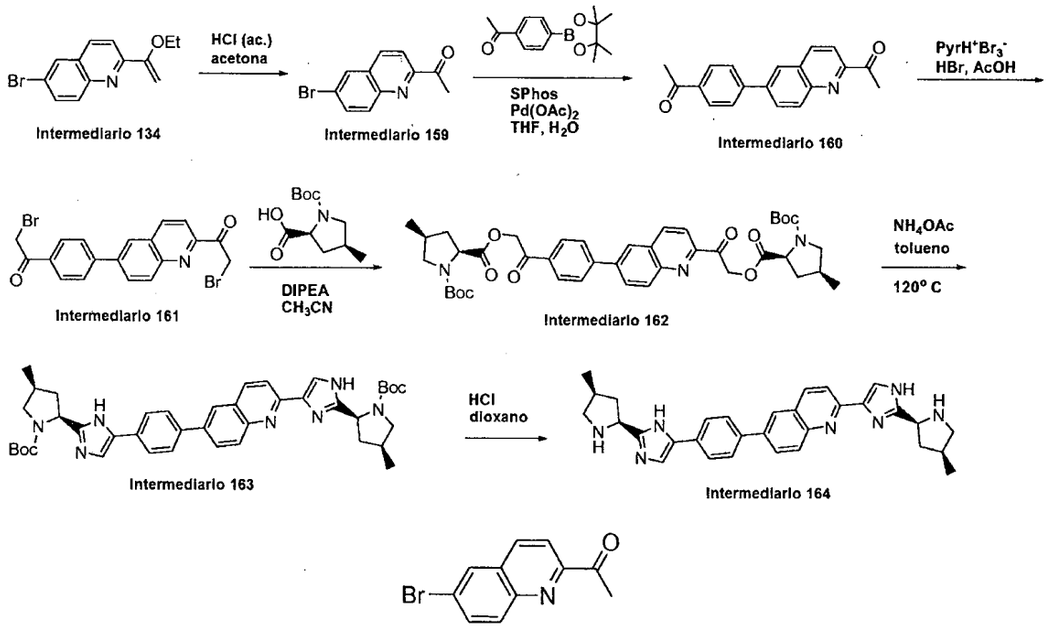
3-(5-(6-((2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il))naftalen-2-il)etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

Una mezcla de 3-(5-(6-bromonaftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (208 mg, 0.457 mmol), (S)-1-((1R,3S,5R)-3-(5-etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (151 mg, 0.457 mmol) y CuI (8.70 mg, 0.046 mmol) en DMF (4 ml) y TEA (0.19 ml, 1.4 mmol) se lavó al vacío con nitrógeno (6X) en 10 minutos. Después se añadió $Pd(PPh_3)_4$ (53 mg, 0.046 mmol) y la mezcla de reacción se lavó la vacío con nitrógeno (3X), se selló y se calentó a 60 °C durante 20h. La reacción bruta se concentró en vapor de nitrógeno durante la noche y después se purificó mediante HPLC preparativa (40-80% de MeOH/agua con amortiguador TFA) para dar una sal en TFA de

3-(5-(6-((2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de ((1R,3S,5R)-*terc*-butilo (270 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.995 min; m/z 704.70 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.18 (s, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.03 (m, 2 H), 7.89 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.69 - 7.85 (m, 1 H), 7.67 (dd, *J*=8.7, 1.4 Hz, 1 H), 5.11 (s ancho, 1 H), 4.84 - 4.91 (m, 2 H), 4.55 (d, *J*=5.8 Hz, 1 H), 3.70 - 3.77 (m, 1 H), 3.67 (s, 3 H), 2.72 (dd, *J*=13.6, 9.0 Hz, 1 H), 2.55 - 2.63 (m, 1 H), 2.39 - 2.50 (m, 2 H), 2.11 - 2.20 (m, 1 H),

2.02 - 2.11 (m, 1 H), 1.81 - 1.89 (m, 1 H), 1.45 (s ancho, 9 H), 1.07 - 1.14 (m, 1 H), 1.00 (d, *J*=6.8 Hz, 3 H), 0.93 (d, *J*=6.8 Hz, 3 H), 0.84 - 0.93 (m, 2 H), 0.74 (s ancho, 1 H).

Esquema de reacción 41

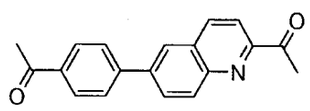


Intermediario 159

1-(6-bromoquinolin-2-il)etanona

Se añadió HCl 3M(ac.) (10 ml, 30.0 mmol) a una suspensión de 6-bromo-2-(1-etoxivinil)quinolina (780 mg, 2.80 mmol) en acetona (20 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 5 horas. La mezcla de reacción se concentró, se disolvió en THF (20 ml) y se trató con HCl 3N (ac.) (5 ml) la solución de reacción transparente se agitó a 60 °C durante 5 horas. La reacción se enfrió, se neutralizó con NaOH ac, y $NaHCO_3$ y se extrajo con EtOAc. La capa orgánica se secó y se concentró para dar 1-(6-bromoquinolin-

2-il)etanona bruta (710 mg) en forma de sólido blanco. Tiempo de retención en la CL-EM 3.703 min; m/z 250, 251.99 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



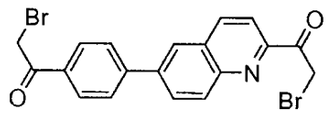
Intermediario 160

1-(6-(4-acetilfenil)quinolin-2-il)etanona

A una solución de ácido 4-acetilfenilborónico (689 mg, 4.20 mmol), 1-(6-bromoquinolin-2-il)etanona (700 mg, 2.8 mmol), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (230 mg, 0.560 mmol) y K_2CO_3 (1.16 g, 8.40 mmol) en dioxano (10 ml) y agua (2.500 ml) se añadió $Pd(OAc)_2$ (62.9 mg, 0.280 mmol) y la mezcla de reacción se sometió a reflujo a 110 °C durante 5

h. La mezcla de reacción se enfrió hasta la temperatura ambiente y se repartió entre NH_4Cl ac. sat, y EtOAc. La capa orgánica se lavó con $NaHCO_3$ y salmuera y después se secó ($MgSO_4$), se filtró, se concentró y se purificó mediante cromatográfica instantánea en gel de sílice (solvente de carga: DCM, eluida con 0 ~ 20 % EtOAc/ hexanos) para dar 1-(6-(4-acetilfenil)quinolin-2-il)etanona (781 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 3.776 min; m/z 290.29 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 8.35 (d, *J*=8.3 Hz, 1 H), 8.34 (d, *J*=8.3 Hz, 1 H), 8.19 (d, *J*=8.5 Hz, 1 H), 8.12 (d, *J*=8.3 Hz, 1 H), 8.08 - 8.16 (m, 3 H), 7.85 (d, *J*=8.3 Hz, 1 H), 7.82 - 7.89 (m, 1 H), 2.91 (s, 3

H), 2.69 (s, 3 H).



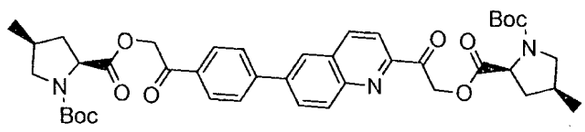
Intermediario 161

2-bromo-1-(6-(4-(2-bromoacetil)fenil)quinolin-2-il)etanona

A una suspensión de 1-(6-(4-acetilfenil)quinolin-2-il)etanona (100 mg, 0.346 mmol) y HBr (0.061 ml, 0.35 mmol) en ácido acético (3 mL) se añadió tribromuro de piridinio (221 mg, 0.691 mmol), la mezcla de reacción se agitó a 70° C) durante 6 h. La reacción se concentró al vacío y el residuo se repartió entre $NaHCO_3$ ac. (15 ml) y EtOAc (30 ml +10 ml + 10 ml). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron, se filtraron y se concentraron, para dar 2-bromo-1-(6-(4-(2-bromoacetil)fenil)quinolin-2-il)etanona bruta (120 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 4.138 min; m/z 448.01 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de

0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

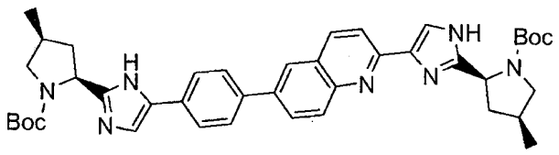


Intermediario 162

4-metilpirrolidin-1,2-dicarboxilato de (2S,4S)-2-(2-(6-(4-(2-((2S,4S)-1-(terc-butoxicarbonil)-4-metilpirrolidin-2-carboniloxi)acetil)fenil)quinolin-2-il)-2-oxoetil) 1-terc-butilo

A una solución de 2-bromo-1-(6-(4-(2-bromoacetil)fenil)quinolin-2-il)etanona (60 mg, 0.134 mmol) y ácido ((2S,4S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-carboxílico (64.6 mg, 0.282 mmol) en acetonitrilo (2 ml) se añadió DIPEA (0.094 ml, 0.537 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se repartió entre EtOAc (20 ml + 20 ml)/ $NaHCO_3$ (5 ml) ac. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ ac., salmuera, se secaron, se filtraron y se concentraron para dar 4-metilpirrolidin-1,2-dicarboxilato de (2S,4S)-2-(2-(6-(4-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-

carboniloxi)acetil)fenil)quinolin-2-il)-2-oxoetil) 1-*terc*-butilo (100 mg) en forma de un sólido naranja. Este material se usó sin purificación adicional. Tiempo de retención en la CL-EM 4.558 min; m/z 742.36 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



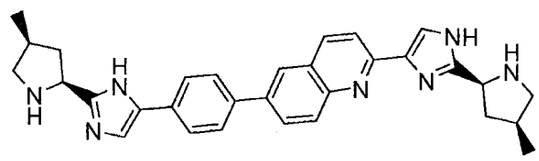
Intermediario 163

2-(5-(4-(2-(2-((2S,4S)-1-(terc-butoxicarbonil)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)quinolin-6-il)fenil)-1H-imidazol-2-il)-4-metilpirrolidin-1-carboxilato de (2S,4S)-terc-butilo

A una solución de (2S,4S)-2-(2-(6-(4-(2-((2S,4S)-1-

(*terc*-butoxicarbonil)-4-metilpirrolidin-2-carboniloxi)acetil)fenil)quinolin-2-il)-2-oxoetil) 1-*terc*-butilo 4-metilpirrolidin-1,2-dicarboxilato (100 mg, 0.134 mmol) en tolueno (3 ml) se añadió acetato amónico (207 mg, 2.69 mmol) y la mezcla de reacción se agitó a 120 °C (reactor de microondas) durante 3 horas. La reacción se repartió entre EtOAc (20 ml + 10 ml + 10 ml) y $NaHCO_3$ ac. (10 ml) y las capas orgánicas combinadas se secaron, se filtraron y se concentraron. Este producto bruto se purificó mediante HPLC preparativa (H_2O-CH_3CN con amortiguador de NH_4OAc 10mM) para dar el producto 2-(5-(6-(4-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolin-2-il)-1H-imidazol-2-il)-4-metilpirrolidin-1-carboxilato de (2S,4S)-*terc*-butilo (16.6 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.270 min; m/z 704.72 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido

trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



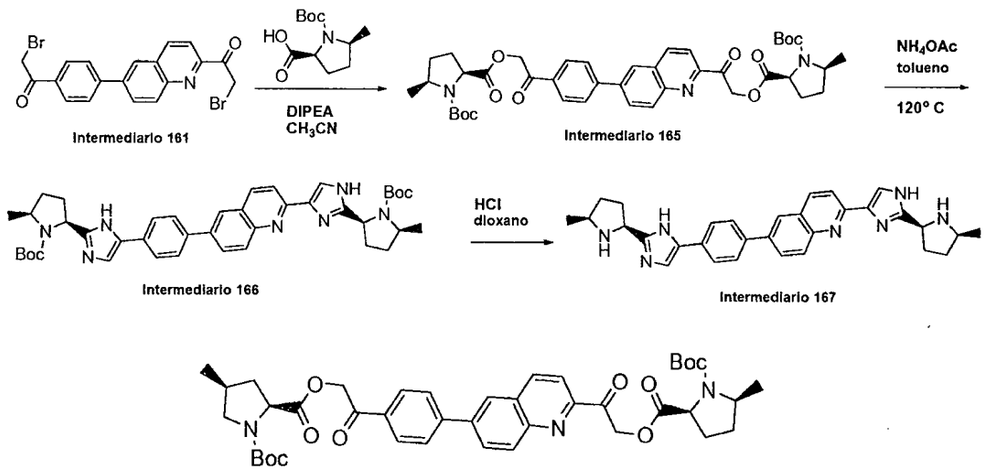
Intermediario 164

2-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)-6-(4-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina

A una solución de 2-(5-(6-(4-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolin-2-il)-1H-imidazol-2-il)-4-metilpirrolidin-1-carboxilato de (2S,4S)-*terc*-butilo (16.6 mg, 0.024 mmol) en dioxano (1 ml) se añadió HCl 4M (0.2 ml, 0.800 mmol) en dioxano y la mezcla de reacción se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se concentró para dar una sal HCL bruta de 2-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)-6-(4-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina (19.1 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.765 min; m/z 504.47 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x

50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 42



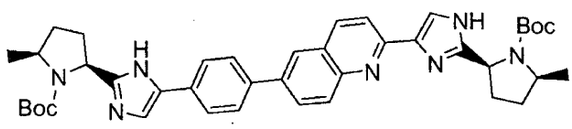
Intermediario 165

4-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(6-(5-(2-((2S,4S)-1-(terc-butoxicarbonil)-4-metilpirrolidin-2-carboniloxi)acetil)fenil)quinolin-2-il)-2-oxoetil) 1-terc-butilo

A una solución de 2-bromo-1-(6-(4-(2-

bromoacetil)fenil)quinolin-2-il)etanona (50 mg, 0.11 mmol) y ácido (2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico (54 mg, 0.24 mmol) en acetonitrilo (2 ml) se añadió DIPEA (0.059 ml, 0.335 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La reacción se repartió entre EtOAc (20 ml + 20 ml)/ $NaHCO_3$ (5 ml) ac. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ ac. sat., salmuera, se secaron, se filtraron y se concentraron para dar 4-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(6-(5-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboniloxi)acetil)fenil)quinolin-2-il)-2-oxoetil) 1-*terc*-butilo (69 mg) en forma de un sólido naranja. Este material se usó sin purificación adicional. Tiempo de retención en la CL-EM 4.483 min; m/z 744.61 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se

determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

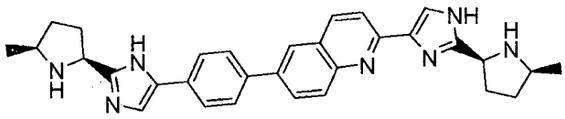


Intermediario 166

2-(5-(4-(2-(2-((2S,5S)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)quinolin-6-il)fenil)-1H-imidazol-2-il)-5-metilpirrolidin-1-carboxilato de (2S,5S)-terc-butilo

Se añadió acetato amónico (107 mg, 1.39 mmol) A una suspensión de 4-metilpirrolidin-1,2-dicarboxilato de (2S,5S)-2-(2-(6-(5-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboniloxi)acetil)fenil)quinolin-2-il)-2-oxoetil) 1-*terc*-butilo (69 mg, 0.093 mmol) en tolueno (volumen: 2 ml) y la mezcla de reacción se agitó a 120°C (reactor de microondas) durante 3 horas. La reacción se repartió entre EtOAc (10 ml + 5 ml + 5 ml) y NaHCO3 ac. (5 ml). Las capas orgánicas combinadas se secaron, se filtraron y se concentraron y el producto bruto se purificó mediante HPLC preparativa (H_2O-CH_3CN con amortiguador de NH_4OAc 10mM) para dar el producto 2-(5-(6-(4-(2-((2S,5S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)fenil)quinolin-2-il)-1H-imidazol-2-il)-5-metilpirrolidin-1-carboxilato de (2S,5S)-*terc*-butilo (13.4 mg) en forma de

un sólido amarillo. Tiempo de retención en la CL-EM 4.350 min; m/z 702.29 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.37 (d, *J*=8.8 Hz, 1 H), 8.16 (s, 1 H), 8.07 - 8.10 (m, 2 H), 8.03 (d, *J*=8.8 Hz, 1 H), 7.79 - 7.88 (m, 5 H), 7.40 (s, 1 H), 4.90 - 5.07 (m, 2 H), 3.99 - 4.13 (m, 2 H), 2.10 - 2.39 (m, 6 H), 1.68 - 1.82 (m, 2 H), 1.43 (d, *J*=6.0 Hz, 6 H), 1.24 - 1.59 (m, 22 H).



Intermediario 167

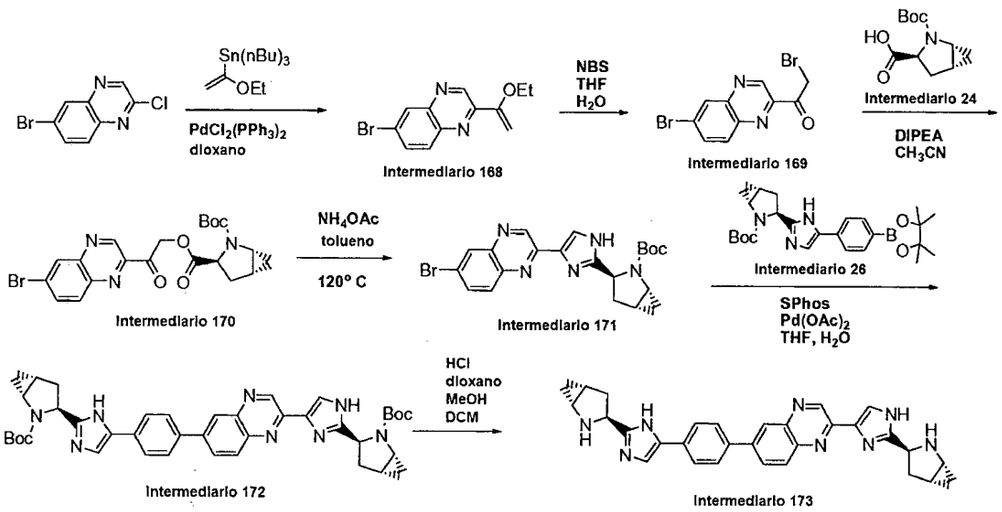
2-(2-((2S,5S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)-6-(4-(2-((2S,5S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina

A una solución de 2-(5-(6-(4-(2-((2S,5S)-1-(*terc*-

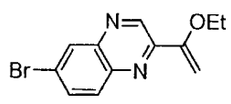
butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolin-2-il)-1H-imidazol-2-il)-5-metilpirrolidin-1-carboxilato de (2S,5S)-*terc*-butilo (12.7 mg, 0.018 mmol) en dioxano (1 ml) se añadió HCl 4M (0.2 ml, 0.8 mmol) en dioxano y la mezcla se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se concentró para dar una sal HCL bruta de 2-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)-6-(4-(2-((2S,5S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina (18.1 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.597 min; m/z 504.46 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 9.09 (d, *J*=9.0 Hz, 1 H), 8.66 (s, 1 H), 8.54 - 8.61 (m, 2 H), 8.51 (d,

J=9.0 Hz, 1 H), 8.50 (d, *J*=8.8 Hz, 1 H), 8.00 - 8.08 (m, 4 H), 7.99 (s, 1 H), 5.14 (t, *J*=8.5 Hz, 1 H), 5.07 (t, *J*=8.0 Hz, 1 H), 3.90 - 4.04 (m, 2 H), 2.52 - 2.75 (m, 4 H), 2.39 - 2.53 (m, 2 H), 1.98 - 2.14 (m, 2 H), 1.59 (dd, *J*=9.7, 6.7 Hz, 6 H).

Esquema de reacción 43



El intermediario 173 se preparó de forma análoga al intermediario 139 del esquema de reacción 35 usando 6-bromo-2-cloroquinoxalina como material de partida en lugar de 6-bromo-2-cloroquinolina. Los datos analíticos se muestran a continuación:



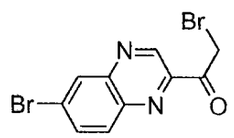
Intermediario 168

6-bromo-2-(1-etoxivinil)quinoxalina

La reacción dio el producto deseado (380 mg) en

forma de un sólido blanco.

Tiempo de retención en la CL-EM 4.178 min; m/z 278.9, 280.98 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

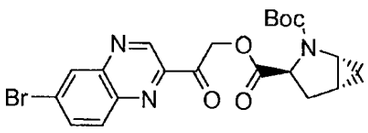


Intermediario 169

2-bromo-1-(6-bromoquinoxalin-2-il)etanona

La reacción dio el producto deseado (390 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 3.743 min; m/z 331.12 (1:2:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS

equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

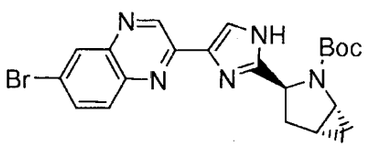


Intermediario 170

2-azabiciclo[3.1.0]hexan-2,3-dicarboxilato de (1R,3S,5R)-3-(2-(6-bromoquinoxalin-2-il)-2-oxoetil) 2-terc-butilo

La reacción dio el producto deseado (270 mg) en forma de un sólido rosa/naranja. Tiempo de retención en la CL-EM 4.115 min; m/z 473, 475.81 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución

usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

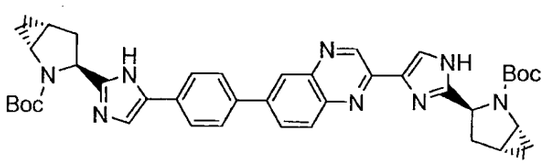


Intermediario 171

(1R,3S,5R)-3-(4-(6-bromo-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

La reacción dio el producto deseado (125 mg) en forma de un sólido rojo/naranja. Tiempo de retención en la CL-EM 3.958 min; m/z 453.90, 455.87 (1:1) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min,

un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 9.40 (s ancho, 1 H), 8.22 (d, *J*=2.0 Hz, 1 H), 7.96 (d, *J*=8.8 Hz, 1 H), 7.93 - 7.99 (m, 1 H), 7.90 (dd, *J*=8.8, 2.0 Hz, 1 H), 4.71 - 4.81 (m, 1 H), 3.59 (s ancho, 1 H), 2.49 - 2.63 (m, 1 H), 2.31 - 2.45 (m, 1 H), 1.68 - 1.82 (m, 1 H), 1.16 - 1.53 (m, 5 H), 0.81 - 0.94 (m, 1 H), 0.64 (s ancho, 1 H).

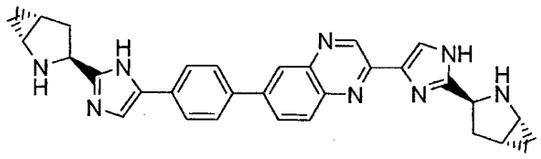


Intermediario 172

(1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

La reacción dio el producto deseado (64.4 mg) en forma de un sólido amarillo brillante. Tiempo de retención en la CL-EM 3.696 min; m/z 699.3 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de

onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *DMSO-d_6*) δ ppm 9.45 (s, 1 H), 8.31 (s, 1 H), 8.19 (d, *J*=8.3 Hz, 1 H), 8.07 (d, *J*=8.8 Hz, 1 H), 7.97 (s, 1 H), 7.81 - 7.95 (m, 4 H), 7.60 (s, 1 H), 4.57 - 4.80 (m, 2 H), 3.23 - 3.60 (m, 2 H), 2.23 - 2.48 (m, 4 H), 1.61 - 1.75 (m, 2 H), 1.28 (s ancho, 18 H), 0.73 - 0.87 (m, 2 H), 0.59 (s ancho, 2 H).



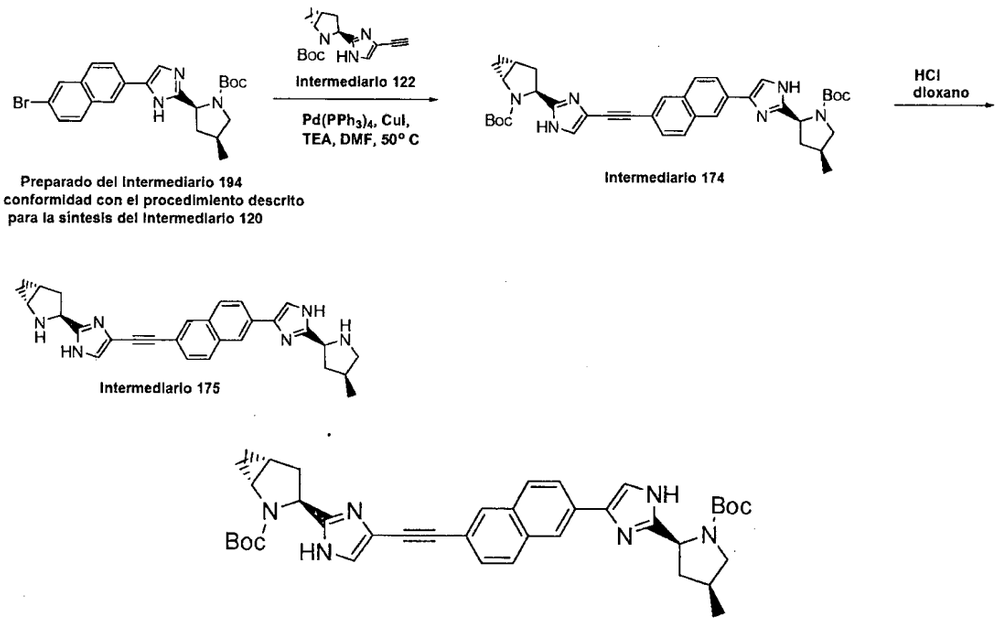
Intermediario 173

((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

La reacción dio una sal HCl del producto

deseado (80 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.915 min; m/z 501.42 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 9.54 (s, 1 H), 8.40 - 8.43 (m, 1 H), 8.34 (s, 1 H), 8.23 - 8.30 (m, 2 H), 8.13 (s, 1 H), 8.00 - 8.08 (m, 4 H), 4.88 - 5.08 (m, 2 H), 3.53 - 3.77 (m, 2 H), 2.64 - 2.90 (m, 4 H), 2.08 - 2.22 (m, 2 H), 1.23 - 1.36 (m, 2 H), 1.02 - 1.14 (m, 2 H).

Esquema de reacción 44

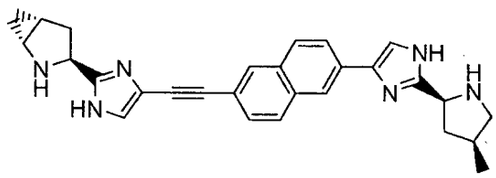


Intermediario 174

3-(4-((6-(2-((2S,4S)-1-(terc-butoxicarbonil)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-terc-butilo

El compuesto se preparó de un modo análogo al del intermediario 153 con los materiales de partida adecuados para dar una sal en TFA del compuesto del título (121 mg) en forma de un cristal amarillo. Tiempo de retención en la CL-EM 4.100 min; m/z 647.37 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un

velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



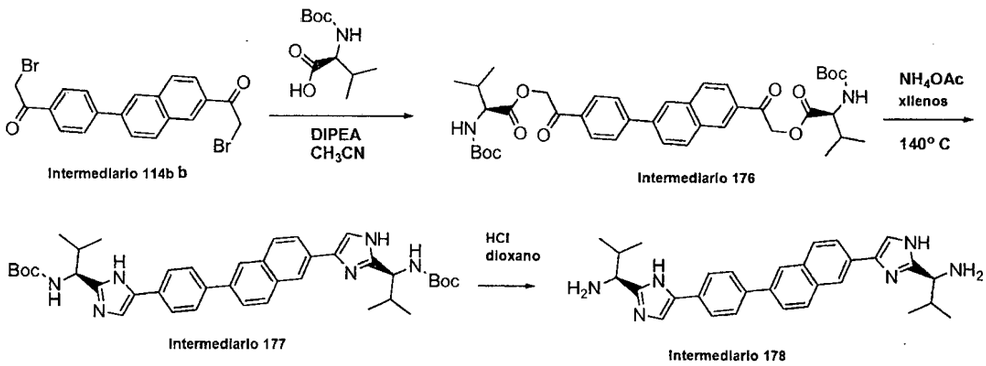
Intermediario 175

(1R,3S,5R)-3-(4-((6-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

A una solución de una sal en TFA de 3-(5-((6-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (115 mg, 0.131 mmol) en dioxano (1.5 ml) se añadió HCl 2M (0.33 ml, 0.66 mmol) en dioxano (2 ml) y la reacción se agitó enérgicamente durante la noche. La reacción se concentró para dar una sal HCl de (1R,3S,5R)-3-(4-((6-(2-((2S,4S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (87

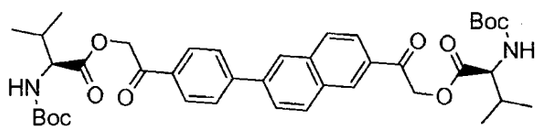
mg), que se usó sin purificación adicional. Tiempo de retención en la CL-EM 2.793 min; m/z 449.41 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 45



El Intermediario 178 se preparó de forma análoga a la preparación del intermediario 117 en el Esquema de reacción 29 usando ácido (S)-2-(*terc*-butoxicarbonilamino)-3-

metilbutanoico como material de partida en lugar de ácido (2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico. Los datos analíticos para los intermediarios se muestran a continuación:

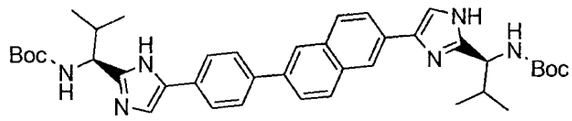


Intermediario 176

(S)-2-(4-(6-(2-((S)-2-(terc-butoxicarbonilamino)-3-metilbutanoiloxi)acetil)naftalen-2-il)fenil)-2-oxoetil 2-(terc-butoxicarbonilamino)-3-metilbutanoato

La reacción dio el producto deseado (700 mg) en forma de un sólido pardo. Tiempo de retención en la CL-EM 2.243 min; m/z 717.5 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 1.0 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma

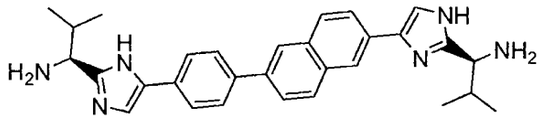
MICROMASS® para CL en modo de electrorrocío.



Intermediario 177

((1S)-1-(4-(4-(6-(2-((1S)-1-((terc-butoxicarbonil)amino-2-metilpropil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-metilpropil)carbamato de terc-butilo

La reacción dio el producto deseado (453 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.407 min; m/z 677.6 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 1.0 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

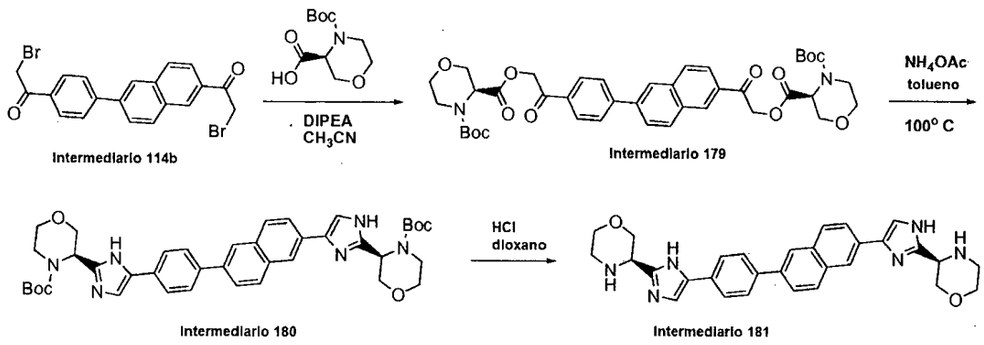


Intermediario 178

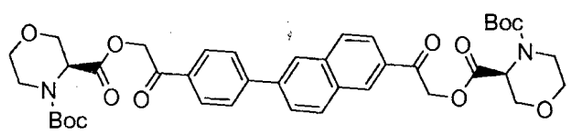
(S)-1-(5-(4-(6-(2-((S)-1-amino-2-metilpropil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-metilpropan-1-amina

La reacción dio una sal HCl del producto deseado (390 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.080 min; m/z 477.4 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 1.0 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 46



El Intermediario 181 se preparó de forma análoga a la preparación del intermediario 117 en el Esquema de reacción 29 usando ácido (S)-4-(*terc*-butoxicarbonil)morfolino-3-carboxílico como material de partida en lugar de ácido (2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico. Los datos analíticos para los intermediarios se muestran a continuación:

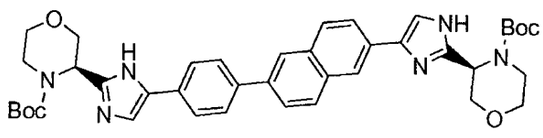


Intermediario 179

morfolina-3.4-dicarboxilato de (S)-3-(2-(4-(6-(2-((S)-4-(terc-butoxicarbonil)morfolina-3-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil) 4-terc-butilo

La reacción dio una sal HCl del producto deseado (1.60 g) en forma de una espuma solidificada blancuzca. Tiempo de retención en la CL-EM 4.413 min; m/z 770.29 (MNa+). Los datos de CL se registraron en un cromatógrafo de líquidos

Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 8.47 (s, 1 H), 8.13 (s, 1 H), 7.98 - 8.11 (m, 5 H), 7.86 (d, *J*=8.3 Hz, 3 H), 5.39 - 5.70 (m, 4 H), 4.66 - 4.83 (m, 2 H), 4.46 - 4.63 (m, 2 H), 3.91 - 4.03 (m, 2 H), 3.68 - 3.85 (m, 4 H), 3.49 - 3.59 (m, 3 H), 3.27 - 3.40 (m, 1 H), 1.51 (s, 18 H).

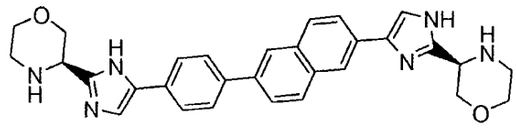


Intermediario 180

3-(5-(4-(6-(2-((R)-4-(terc-butoxicarbonil)morfolin-3-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-3-il)morfolin-1-carboxilato de (R)-terc-butilo

La reacción dio el producto deseado (1.12 g) en

forma de un sólido naranja. Tiempo de retención en la CL-EM 3.608 min; m/z 707.94 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.22 (s, ancho, 1 H), 8.09 (s, 1 H), 7.90 - 7.97 (m, 2 H), 7.75 - 7.89 (m, 6 H), 7.49 (s ancho, 1 H), 7.41 (s ancho, 1 H), 5.17 - 5.24 (m, 2 H), 4.42 (t, *J*=11.2 Hz, 2 H), 3.82 - 3.95 (m, 6 H), 3.59 (tt, *J*=11.6, 3.0 Hz, 2 H), 3.39 - 3.51 (m, 2 H), 1.50 (d, *J*=2.8 Hz, 18 H).



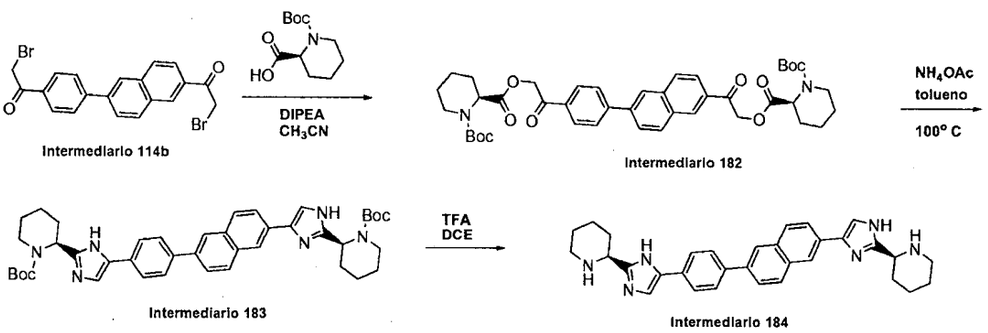
Intermediario 181

(R)-3-(5-(4-(6-(2-((R)-morfolin-3-il)-1H-imidazol-4-il)-

naftalen-2-il)fenil-1H-imidazol-2-il)morfolina

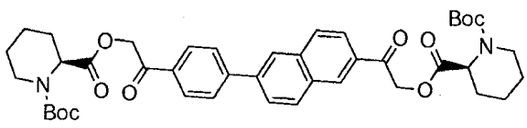
La reacción dio una sal HCl del producto deseado (312 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.988 min; m/z 507.72 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 47



El Intermediario 184 se preparó de forma análoga a

la preparación del intermediario 117 en el Esquema de reacción 29 usando ácido (S)-1-(*terc*-butoxicarbonil)piperidin-2-carboxílico como material de partida en lugar de ácido (2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico. Los datos analíticos para los intermediarios se muestran a continuación:

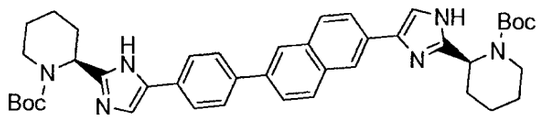


Intermediario 182

Piperidin-1,2-dicarboxilato de (S)-2-(2-(4-(6-(2-((2S)-1-(terc-butoxicarbonil)piperidin-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil) 1-terc-butilo

La reacción dio el producto deseado (1.67 g) en forma de una espuma amarillo claro. Tiempo de retención en la CL-EM 4.850 min; m/z 766.37 (MNa+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido

trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 8.47 (s, 1 H), 8.13 (s, 1 H), 7.99 - 8.10 (m, 5 H), 7.83 - 7.89 (m, 3 H), 5.32 - 5.67 (m, 4 H), 4.92 - 5.13 (m, 2 H), 3.93 - 4.11 (m, 2 H), 3.00 - 3.28 (m, 2 H), 2.40 (s ancho, 2 H), 1.68 - 1.84 (m, 6 H), 1.49 (s, 18 H), 1.39 - 1.67 (m, 4 H).



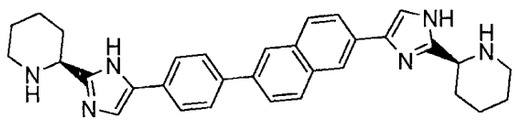
Intermediario 183

2-(5-(4-(6-(2-((S)-1-(terc-butoxicarbonil)piperidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)piperidin-1-carboxilato de (S)-terc-butilo

La reacción dio el producto deseado (1.18 g) en forma de un sólido amarillo brillante.

Tiempo de retención en la CL-EM 3.778 min; m/z 703.97 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0%

de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.22 (s ancho, 1 H), 8.09 (s, 1 H), 7.93 (t, *J*=7.7 Hz, 2 H), 7.73 - 7.88 (m, 6 H), 7.46 (s ancho, 1 H), 7.38 (s ancho, 1 H), 5.47 (s ancho, 2 H), 4.03 - 4.15 (m, 2 H), 2.99 - 3.12 (m, 2 H), 2.46 (s ancho, 2 H), 1.80 - 1.94 (m, 2 H), 1.50 (d, *J*=2.3 Hz, 18 H), 1.44 - 1.76 (m, 8 H).



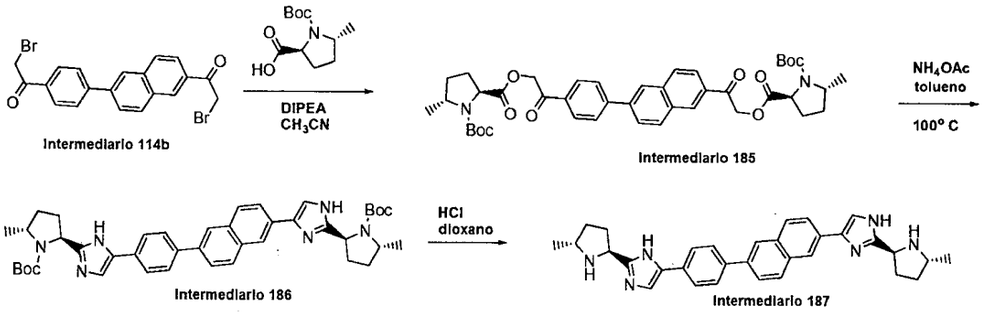
Intermediario 184

(S)-3-(5-(4-(6-(2-((S)-piperidin-2-il)-1H-imidazol-4-il)-naftalen-2-il)fenil-1H-imidazol-2-il)piperidina

La reacción dio una sal HCl del producto deseado (280 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.015 min; m/z 503.69 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de

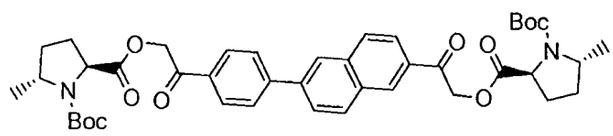
onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 10.06 (s ancho, 2 H), 9.85 (s ancho, 2 H), 8.48 (s, 1 H), 8.36 (s, 1 H), 8.09 - 8.19 (m, 3 H), 7.96 - 8.09 (m, 7 H), 4.70 (s ancho, 2 H), 3.42 - 3.53 (m, 2 H), 3.14 (s ancho, 2 H), 2.10 - 2.37 (m, 4 H), 1.60 - 2.00 (m, 8 H).

Esquema de reacción 48



El Intermediario 187 se preparó de forma análoga a la preparación del intermediario 117 en el Esquema de reacción 29 usando ácido (2S,5R)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico (preparado según JOC 1995, p.

5011) como material de partida en lugar de ácido (2S,5S)-1-(*terc*-butoxicarbonil)-5-metilpirrolidin-2-carboxílico. Los datos analíticos para los intermediarios se muestran a continuación:

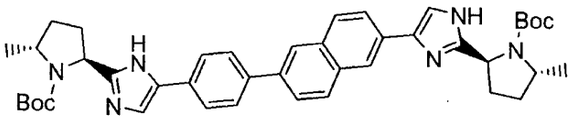


Intermediario 185

5-metilpirrolidin-1,2-dicarboxilato de (2S,5R)-2-(2-(4-(6-(2-((2S,5R)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-carboniloxi)acetil)naftalen-2-il)fenil)-2-oxoetil)· 1-terc-butilo

La reacción dio el producto deseado (979 mg). Tiempo de retención en la CL-EM 4.796 min; m/z 766.19 (MNa+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos

de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, CLOROFORMO-*d*) δ ppm 8.47 (s ancho, 1 H), 8.13 (d, *J*=2.5 Hz, 1 H), 7.99 - 8.11 (m, 5 H), 7.86 (dd, *J*=7.8, 2.3 Hz, 3 H), 5.21 - 5.77 (m, 4 H), 4.51 - 4.58 (m, 1 H), 4.47 (dd, *J*=7.8, 4.5 Hz, 1 H), 4.17 - 4.26 (m, 1 H), 4.07 - 4.14 (m, 1 H), 2.23 - 2.48 (m, 6 H), 1.60 - 1.68 (m, 2 H), 1.44 - 1.52 (m, 18 H), 1.25 (d, *J*=6.3 Hz, 3 H), 1.21 (d, *J*=6.3 Hz, 3 H).

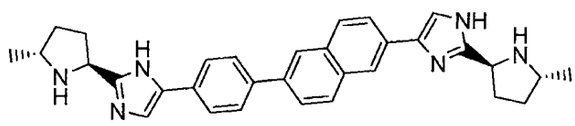


Intermediario 186

2-(5-(4-(6-(2-((2S,5r)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-5-metilpirrolidin-1-carboxilato de (2S,5R)-terc-butilo

La reacción dio el producto deseado (561 mg) en forma de una espuma solidificada naranja. Tiempo de retención en la CL-EM 3.673 min; m/z 703.95 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de

conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



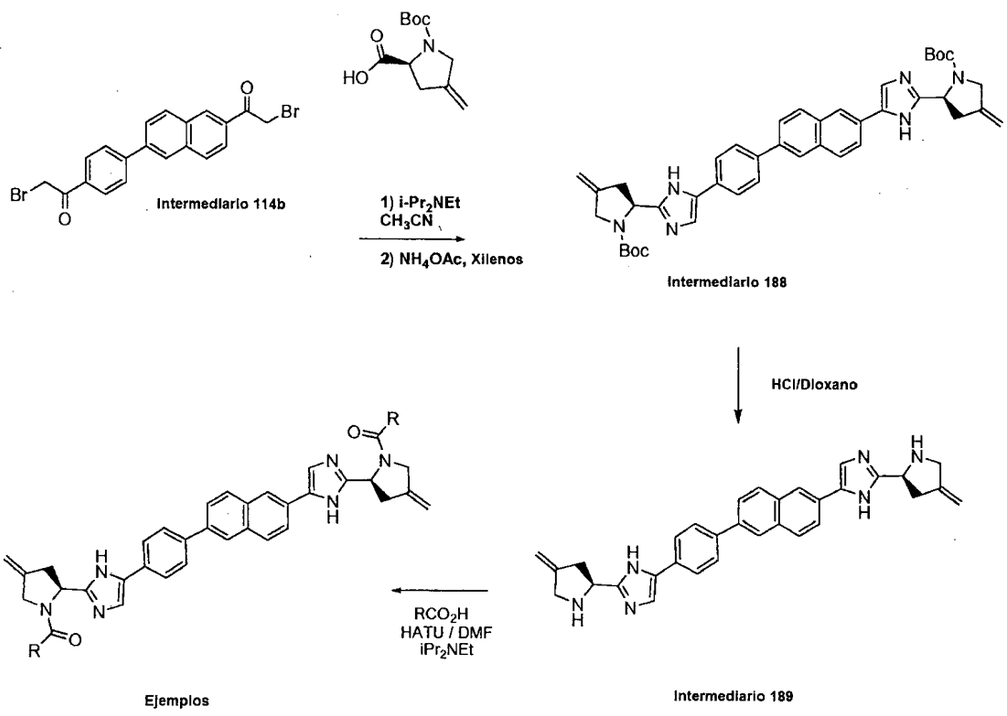
Intermediario 187

2-(-5-((2S,5R)-5-metilpirrolidin-2-il)-5-(4-(6-(2-((2S,5R)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol

La reacción dio una sal HCl del producto deseado (157 mg) en forma de un sólido naranja claro. Tiempo de retención en la CL-EM 2.975 min; m/z 503.71 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90%

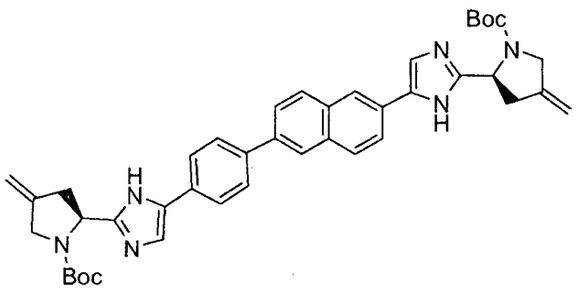
de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 9.84 - 10.25 (m, 4 H), 8.54 (s, 1 H), 8.36 (s, 1 H), 7.95 - 8.22 (m, 10 H), 5.15 (s ancho, 2 H), 4.00 (s ancho, 2 H), 2.53 - 2.63 (m, 4 H), 2.30 - 2.41 (m, 2 H), 1.67 - 1.82 (m, 2 H), 1.43 (d, *J*=4.3 Hz, 6 H).

Esquema de reacción 49



El Intermediario 189 se preparó como se muestra en el Esquema de reacción 49 usando ácido (S)-1-(*terc*-butoxicarbonil)-4-metilenpirrolidin-2-carboxílico como material de partida. Los datos analíticos para los

intermediarios se muestran a continuación:



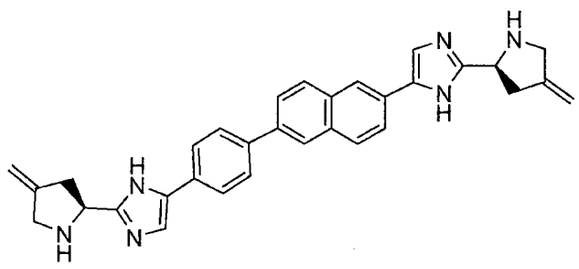
Intermediario 188

(2S,5S)-2-(4-(4-(6-(2-((2S)-1-(terc-butoxicarbonil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metilen-1-pirrolidincarboxilato de terc-butilo

A una suspensión espesa agitada de S)-1-(*terc*-butoxicarbonil)-4-metilenpirrolidin-2-carboxílico (509 mg, 2.241 mmol) y 2-bromo-1-4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (500 mg, 1.121 mmol) en MeCN (25 ml) se añadió Base de Hunig (0.43 ml, 2.47 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con agua, solución de bicarbonato sódico saturada y salmuera. Después de concentrado, el residuo se suspendió en xileno (25 ml) y se añadió acetato amónico (1.3 g, 16.85 mmol). El recipiente de presión se selló y se calentó a 140°C durante 2.5 horas La mezcla de reacción se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado y salmuera. Después de

concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 80 g (eluido con 15% B a 100% B en 1 l, donde el solvente B = acetato de etilo y el solvente A = hexanos) para dar (2S)-2-(4-(4-(6-(2-((2S)-1-(*terc*-butoxicarbonil)-4-metilen-2-pirrolidinil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-4-metilen-1-pirrolidincarboxilato de *terc*-butilo (380 mg, rendimiento del 45 %). Tiempo de retención en la CL-EM 3.32 min; Calculado para C42H47N6O4: 699.36 m/z Encontrado 699.41 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.21 (s, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.97 (s, 1H), 7.87-7.83 (m, 6H), 7.54 (s, 1H), 7.46 (s, 1H), 5.14 (s, 2H), 5.19

(s, 2H), 4.30 (s ancho, 2H), 4.15 (s ancho, 2H), 3.22-3.16 (m, 2H), 2.81 - 2.76 (m, 2H), 1.51/1.31 (s, 18H).



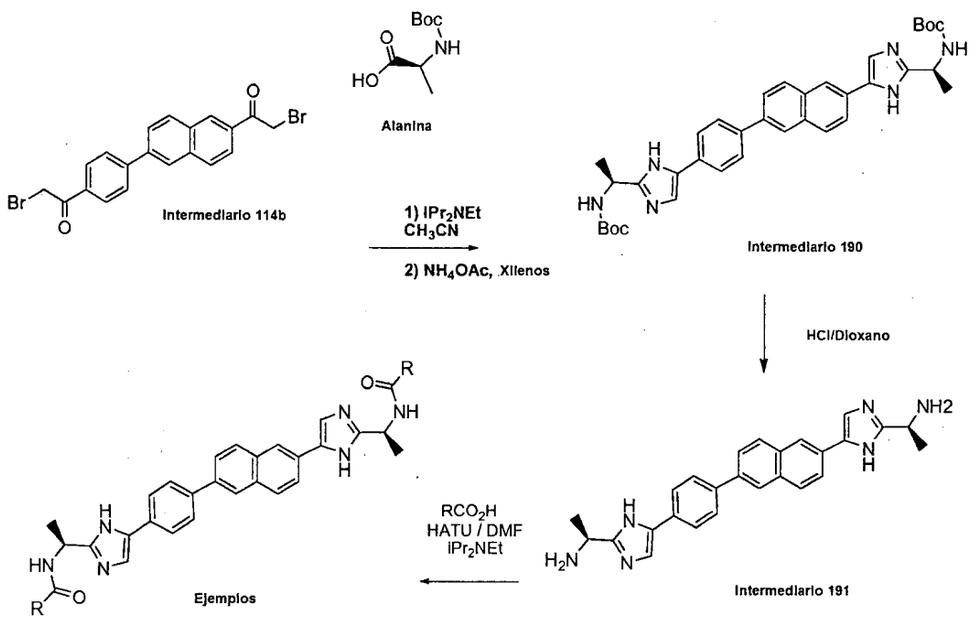
Intermediario 189

2((S)-4-metilenpirrolidin-2-il)-4-(4-(6-(2-((S)-5-metilENpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol

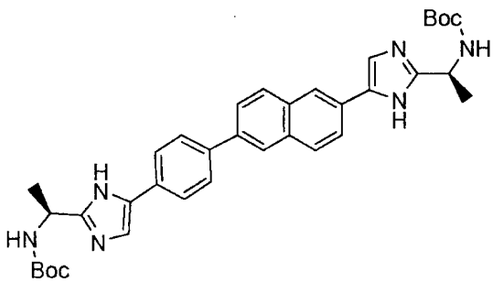
Una solución de HCl 4N en dioxano (10 ml) se añadió a (2S)-2-(4-(4-(6-(2-((2S)-1-(*terc*-butoxicarbonil)-4-metilen-2-pirrolidinil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-4-metilen-1-pirrolidincarboxilato de *terc*-butilo (380 mg, 0.544 mmol) en MeOH (10 ml) y se agitó en condiciones ambientales durante 4 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 350 mg). Tiempo de retención en la CL-EM 2.68 min; Calculado para C32H31N6: 499.26 m/z Encontrado 499.21 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un

velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 50



El Intermediario 191 se preparó como se muestra en el Esquema de reacción 50 usando ácido (S)-2-(*terc*-butoxicarbonilamino)propanoico como material de partida. Los datos analíticos para los intermediarios se muestran a continuación:

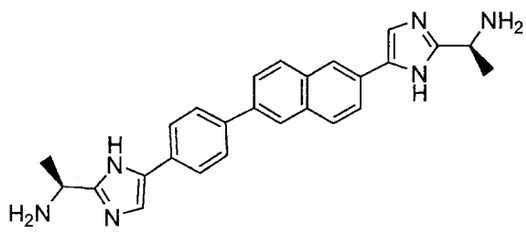


Intermediario 190

((1S)-1-(4-(4-(6-(2-((1S)-1-((terc-butoxicarbonil)amino-2-etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-etil)carbamato de terc-butilo

A una suspensión espesa agitada de ácido (S)-2-(*terc*-butoxicarbonil)propanoico (424 mg, 2.24 mmol) y 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (500 mg, 1.121 mmol) en MeCN (50 ml) se añadió Base de Hunig (0.39 ml, 2.24 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con agua, solución de bicarbonato sódico saturada y salmuera. Después de concentrado, el residuo se suspendió en xileno (25 ml) y se añadió acetato amónico (1.5 g, 20.18 mmol). El recipiente de presión se selló y se calentó a 140°C durante 3.5 horas La mezcla de reacción se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 90g (eluido con 15% B a 100% B en 1 l, donde el

solvente B = acetato de etilo y el solvente A = hexanos) para dar (1S)-1-(4-(4-(6-(2-((1S)-1-(*terc*-butoxicarbonil)amino)etil-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)etil)carbamato de *terc*-butilo (368 mg, rendimiento del 47 %). NOTA: La muestra fue sólo parcialmente soluble en cloruro de metileno. Tiempo de retención en la CL-EM 3.24 min; Calculado para $C_{36}H_{43}N_6O_4$: 623.33 m/z Encontrado 623.37 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.11 (s, 1H), 7.95 (t, J = 8.24 Hz, 2H), 7.86-7.79 (m, 6H), 7.46 (s, 1H), 7.37 (s, 1H), 4.93-4.89 (m, 2H), 1.57-1.48 (m, 24H).



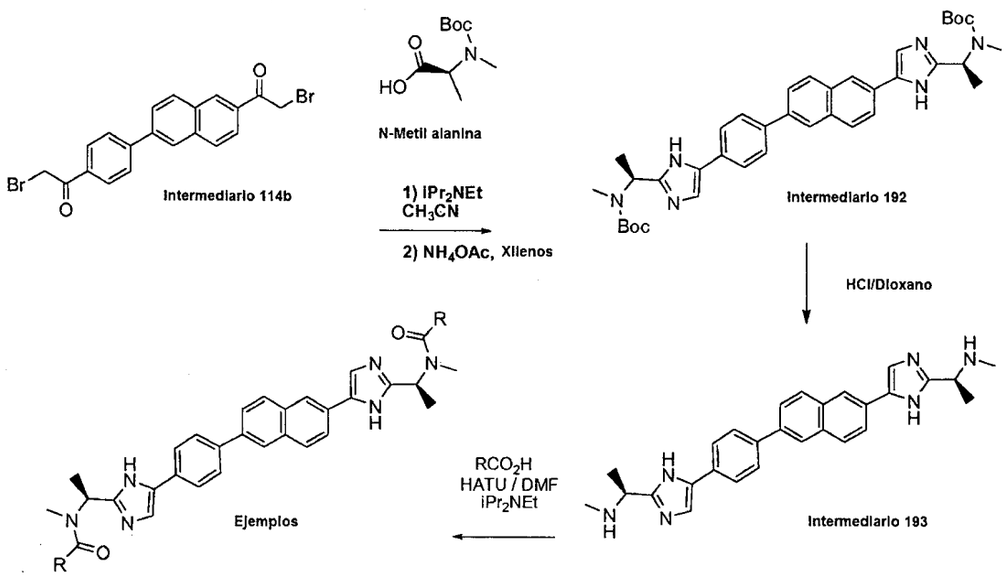
Intermediario 191

(S)-1-(4-(4-(6-(2-((S)-1-aminoetil)-1H-imidazol-4-il)-naftalen-2-il)fenil-1H-imidazol-2-il)etanamina

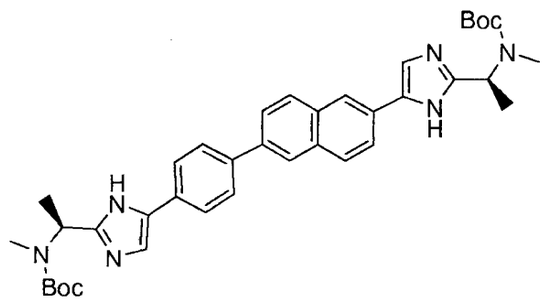
Una solución de HCl 4N en dioxano (10 ml) se añadió a (1S)-1-(4-(4-(6-(2-((1S)-1-(*terc*-butoxicarbonil)amino)etil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-etil)carbamato de *terc*-butilo (368 mg. 0.59 mmol) en MeOH (10 ml) y se agitó en condiciones ambientales durante 5 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 334 mg). Tiempo de retención en la CL-EM 1.33 min; Calculado para $C_{26}H_{27}N_6$: 423.23 m/z Encontrado 423.17 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua

al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 51



El Intermediario 193 se preparó como se muestra en el Esquema de reacción 51 usando ácido (S)-2-(*terc*-butoxicarbonil(metil)amino)propanoico como material de partida. Los datos analíticos para los intermediarios se muestran a continuación:



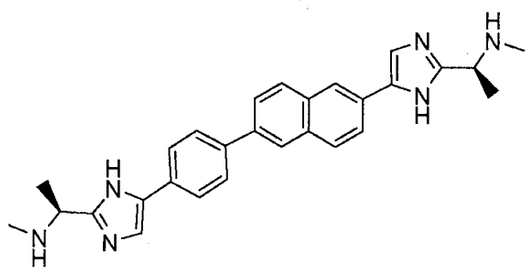
Intermediario 192

((1S)-1-(4-(4-(6-(2-((1S)-1-((terc-

butoxicarbonil)(metil)amino-2-etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-etil)metilcarbamato de terc-butilo

A una suspensión espesa agitada de ácido (S)-2-(*terc*-butoxicarbonil(metil)amino)propanoico (456 mg, 2.241 mmol) y 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (500 mg, 1.121 mmol) en MeCN (50 ml) se añadió Base de Hunig (0.78 ml, 4.48 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con agua, solución de bicarbonato sódico saturada y salmuera. Después de concentrado, el residuo se suspendió en xileno (25 ml) y se añadió acetato amónico (859 mg, 11.15 mmol). El recipiente de presión se selló y se calentó a 140°C durante 3 horas La mezcla de reacción se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 90g (eluido con 15% B a 100% B en 1 l, donde el solvente B = acetato de etilo y el solvente A = hexanos) para dar (1S)-1-(4-(4-(6-(2-((1S)-1-(*terc*-butoxicarbonil)(metil)amino)etil-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)etil)metilcarbamato de *terc*-butilo (460 mg, rendimiento del 58%). Tiempo de retención en la CL-EM 3.28 min; Calculado para $C_{38}H_{47}N_6O_4$: 651.37 m/z

Encontrado 651.34 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.24-8.12 (m, 2H), 7.98-7.82 (m, 8H), 7.52-7.42 (m, 2H), 5.47 (s ancho, 2H), 2.77 (s, 3H), 2.76 (s, 3H),1.64 (m, 6H), 1.52 (s, 18H).



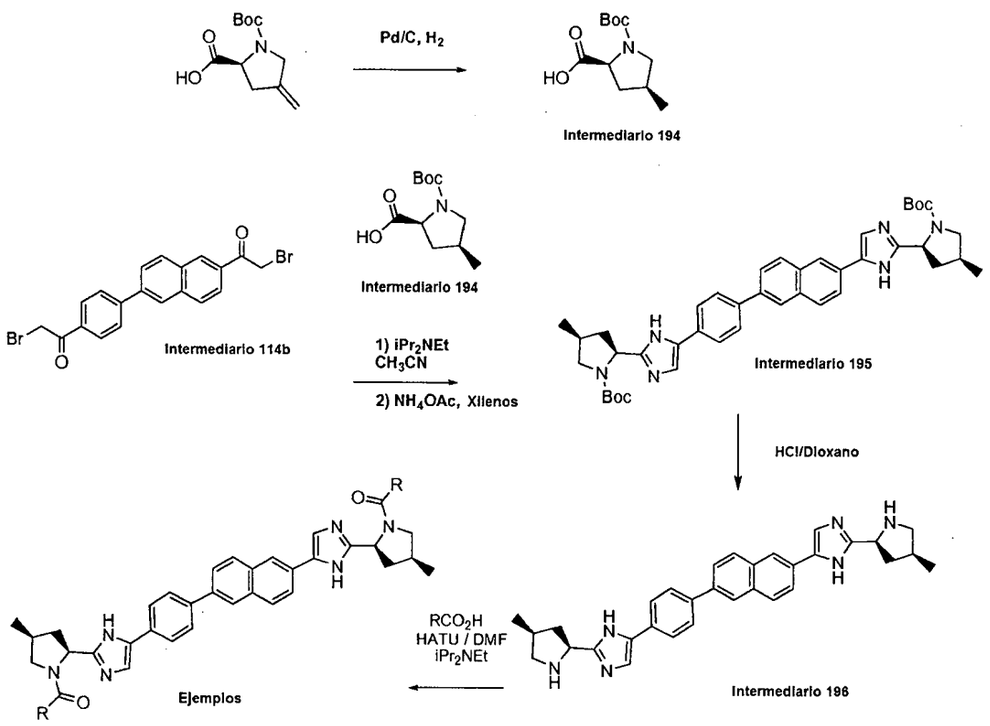
Intermediario 193

(S)-N-metil-1-(4-(4-(6-(2-((S)-1-(metilamino)etil)-1H-imidazol-4-il)-naftalen-2-il)fenil-1H-imidazol-2-il)etanamina

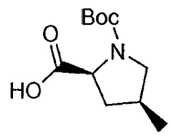
Una solución de HCl 4N en dioxano (10 ml) se añadió a (1S)-1-(4-(4-(6-(2-((1S)-1-(*terc*-

butoxicarbonil)(metil)amino)etil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-etil)metilcarbamato de *terc*-butilo (434 mg. 0.667 mmol) en MeOH (10 ml) y se agitó en condiciones ambientales durante 3 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 396 mg). Tiempo de retención en la CL-EM 1.44 min; Calculado para $C_{28}H_{31}N_6$: 451.26 m/z Encontrado 451.17 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 52



El Intermediario 196 se preparó como se muestra en el Esquema de reacción 52 usando ácido (2S,4S)-1-(*terc*-butoxicarbonil)-4-metilenpirrolidin-2-carboxílico como material de partida. Los datos analíticos para los intermediarios se muestran a continuación:



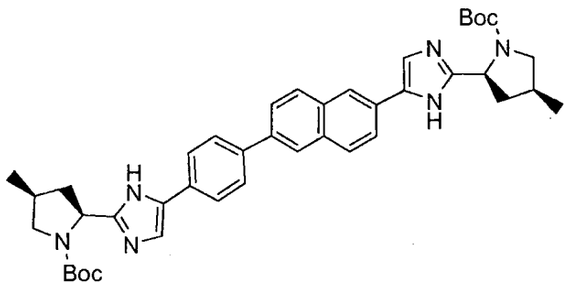
Intermediario 194

Ácido (2S,4S)-1-(terc-butoxicarbonil)-4-metilpirrolidin-2-carboxílico

Una solución de ácido (S)-1-(*terc*-butoxicarbonil)-

4-metilenpirrolidin-2-carboxílico (4 g, 17.60 mmol) en 2-propanol (10 ml) se añadió a una suspensión purgada con nitrógeno de 10% de paladio sobre carbono (936 mg) en 2-propanol (240 ml) y el matraz se cargó con gas hidrógeno (1 atm). Después de agitar 18, se retiró el catalizador mediante filtración sobre CELITE® y el filtrado se concentró. El análisis CL mostró que la muestra contenía ~14% del isómero trans y la recristalización del tolueno enriqueció el isómero cis a 96% (16:1). Tiempo de retención en la CL-EM 3.26 min; Calculado para $C_{11}H_{20}N_6O_4$:: 230.14 m/z Encontrado 252.14 $[M+Na]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® de 2 x5 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 10%/agua al 90%/TFA al 0.1% y el solvente B fue metanol al 90%/agua al 10%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 4.21 - 4.17 (m, 1H), 3.76 - 3.67 (m, 1H), 2.96 - 2.92 (m, 1H), 2.49 - 2.46 (m, 1H), 2.30 - 2.29 (m, 1H), 1.59 - 1.51 (m, 1H), 1.47/1.43 (m, 9H), 1.10

-1.06 (m, 3H).



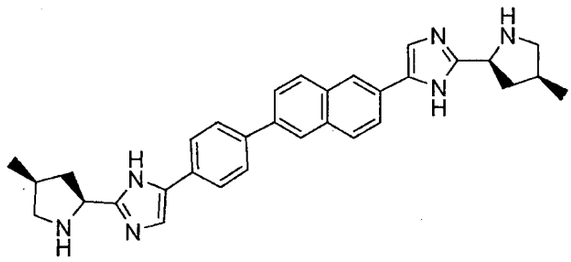
Intermediario 195

(2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(terc-butoxicarbonil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidincarboxilato de terc-butilo

A una suspensión espesa agitada de ácido (2S,4S)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-carboxílico (500 mg, 2.18 mmol) y 2-bromo-1-4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (486 mg, 1.09 mmol) en acetonitrilo (11 ml) se añadió Base de Hunig (0.381 ml, 2.181 mmol). La mezcla heterogénea se agitó durante 18 horas a TA y se añadió base de Hunig adicional (1 equiv.) y la mezcla se agitó durante 24 h. El solvente se eliminó *al vacío* y el residuo se suspendió en cloruro de metileno y se lavó con solución de bicarbonato sódico saturada, salmuera y se secó sobre sulfato sódico. El lavado se repitió 2 veces. El producto bruto, asilado en forma de una espuma parda, se suspendió en xileno (15 ml) y se añadió acetato amónico (1.261 g, 16.36 mmol). El recipiente de presión se selló y se introdujo en un baño de aceite precalentado (140 °C) y se agitó durante 2 horas. La

mezcla de reacción se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 80 g (eluido con 25% B a 100% B en 1.5 l, y se conservó 0.5 l B. solvente B = acetato de etilo y el solvente A = hexanos) para dar (2S,4S)-2-(4-(4-(6-(2-((2S, 4S)-1-(*terc*-butoxicarbonil)-4-metil-2-pirrolidinil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-4-metil-1-pirrolidincarboxilato de *terc*-butilo (214.2 mg, 27.9 %) en forma de una espuma amarilla. Tiempo de retención en la CL-EM 3.32 min; Calculado para $C_{42}H_{51}N_6O_4$: 703.40 m/z Encontrado 703.28 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.12 (s, 1H), 7.96-7.94 (m, 2H), 7.87-7.82 (m, 6H), 7.50

(s, 1H), 7.42 (s, 1H), 4.87 (s ancho, 2H), 3.81 (s ancho, 2H), 3.24-3.18 (m, 2H), 2.53-2.50 (m, 2H), 2.36 (s ancho, 2H), 1.82-1.74 (m, 2H), 1.46/1.23 (s, 18H), 1.17-1.16 (m, 6H).



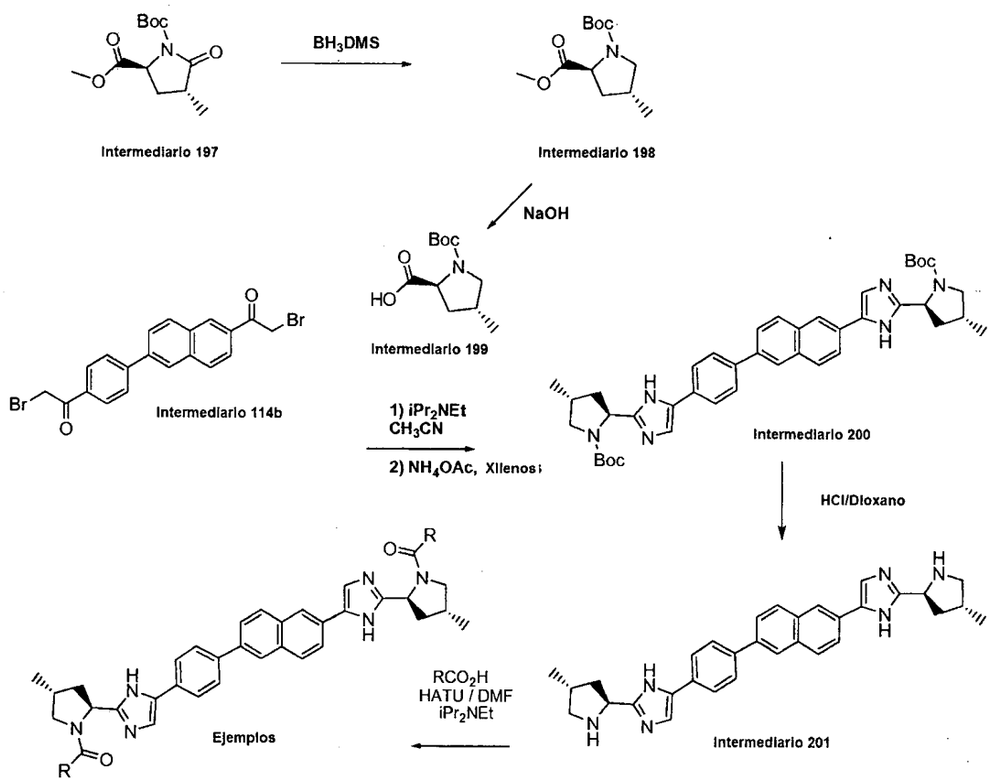
Intermediario 196

2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol

Una solución de HCl 4N en dioxano (15 ml) se añadió a (2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(*terc*-butoxicarbonil)-4-metil-2-pirrolidinil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-4-metil-1-pirrolidincarboxilato de *terc*-butilo (200 mg. 0.285 mmol) en MeOH (5 ml) y se agitó en condiciones ambientales durante 2 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 185 mg). Tiempo de retención en la CL-EM 2.64 min; Calculado para $C_{32}H_{35}N_6$: 503.29 m/z Encontrado 503.20 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad

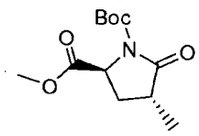
de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 53



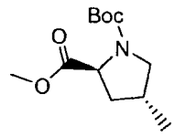
El Intermediario 201 se preparó como se muestra en el Esquema de reacción 53 usando ácido (2S,4R)-1-(*terc*-butoxicarbonil)-4-metilenpirrolidin-2-carboxílico como

material de partida. Los datos analíticos para los intermediarios se muestran a continuación:



Intermediario 197

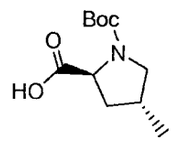
El isómero trans se aisló de una mezcla de cis, trans, y el análogo de dimetil que podría obtenerse a partir de la alquilación con yoduro de metilo de 2-metil-5-oxopirrolidin-1,2-dicarboxilato de (S)-1-*terc*-butilo de conformidad con el proceso descrito en Tetrahedron Letters, 2003, 3203-3205, RMN de ^{1}H (500 MHz, MeOD) δ ppm 4.66-4.64 (m, 1H), 3.80 (s, 3H), 2.34-2.29 (m, 1H), 2.04-1.99 (m, 1H), 1.49 (s, 9H), 1.21-1.19 (m, 3H).



Intermediario 198

A una solución del Intermediario 197 (6.06 g, 23.55 mmol) en THF (180 ml) se añadió complejo de sulfuro de borano-metilo (17.67 ml, 35.3 mmol) y la mezcla de reacción se c calentó a 40 °C durante 16 horas. El solvente se eliminó al vacío y el residuo se repartió entre acetato de etilo y agua (250 ml de cada uno). La capa acuosa se extrajo con EtOAc (2 X 60 ml) y la fase orgánica combinada se secó con Na_2SO_4, y se concentró al vacío. El aceite incoloro resultante

se purificó con una cromatografía instantánea (10-65% de EtOAc/hexano) para dar el Intermediario 198 en forma de un aceite incoloro (3.65 g). RMN de ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.36-4.33 (dd, J=2.4, 10, 0.4H), 4.26-4.23 (dd, J=3, 8.9, 0.6 H), 3.73-3.63 ('s' superpuesta con 'm', 4H), 2.97-2.85 (m, 1H), 2.37 (m, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 1.44-1.39 (dos 's', 9H), 1.03-1.00 (dos 's', 3H).

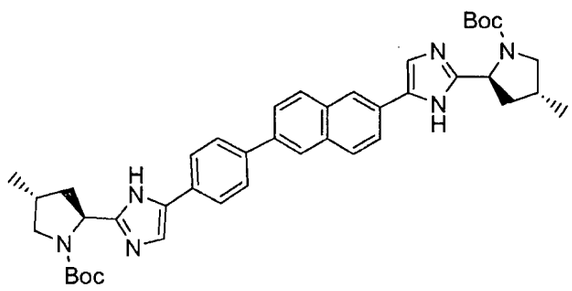


Intermediario 199

Ácido (2S,4R)-1-(terc-butoxicarbonil)-4-metilpirrolidin-2-carboxílico

A una solución del éster Intermediario 198 (3.63 g, 14.92 mmol) en etanol (36 ml) se añadió solución de LiOH (0.393 g, 10.42 mmol) en agua (18.00 ml), y la mezcla de reacción se agitó a temperatura ambiente durante 22 h. El solvente orgánico se evaporó a vacío y el residuo se diluyó con agua (30 ml) y se lavó con acetato de etilo (50 ml). Se enfrió en un baño de agua y hielo, y se acidificó a un intervalo de pH de ~2 con HCl 1 N. Después se extrajo con EtOAc (50 ml, 2x). La capa orgánica se secó con Na_2SO_4 y se concentró a vacío para dar el Intermediario 199 en forma de un aceite incoloro, que se convirtió en un sólido blanco tras la exposición extendida a alto vacío (3.3 g). RMN de ^{1}H NMR

($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.37-4.27 ('m' superpuesta 1H), 3.72-3.50 (m, 1H), 3.01-2.83 ('m' superpuesta, 1H), 2.50-2.11 (m, 2H), 1.89-1.57 (m, 1H), 1.47-1.39 (dos 's', 9H), 1.04-1.03 (dos 's', 3H).



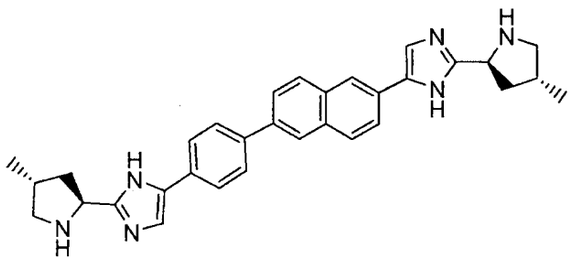
Intermediario 200

(2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-(terc-butoxicarbonil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidincarboxilato de terc-butilo

A una suspensión espesa agitada de ácido (2S,4R)-1-(*terc*-butoxicarbonil)-4-metilpirrolidin-2-carboxílico (500 mg, 2.18 mmol) y 2-bromo-1-4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (486 mg, 1.09 mmol) en acetonitrilo (11 ml) se añadió Base de Hunig (0.381 ml, 2.181 mmol). La mezcla heterogénea se agitó durante 18 h a TA y se añadió base de Hunig adicional (1 equiv.) y la mezcla se agitó durante 24 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en cloruro de metileno y se lavó con solución de bicarbonato sódico saturada, salmuera y se secó sobre sulfato sódico. El lavado se repitió 2 veces. El producto bruto, aislado en forma de una espuma parda, se suspendió en xileno

(15 ml) y se añadió acetato amónico (1.261 g, 16.36 mmol). El recipiente de presión se selló y se introdujo en un baño de aceite precalentado (140 °C) y se agitó durante 2 horas. La mezcla de reacción se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 80 g (eluido con 25% B a 100% B en 1.5 l, y se conservó 0.5 l B. solvente B = acetato de etilo y el solvente A = hexanos) para dar (2S,4R)-2-(4-(4-(6-(2-((2S, 4R)-1-(*terc*-butoxicarbonil)-4-metil-2-pirrolidinil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-4-metil-1-pirrolidincarboxilato de *terc*-butilo (214.2 mg, 27.9 %) en forma de una espuma amarilla. Tiempo de retención en la CL-EM 3.32 min; Calculado para $C_{42}H_{51}N_6O_4$: 703.40 m/z Encontrado 703.28 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se

determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.12 (s, 1H), 7.96-7.94 (m, 2H), 7.87-7.82 (m, 6H), 7.50 (s, 1H), 7.42 (s, 1H), 4.87 (s ancho, 2H), 3.81 (s ancho, 2H), 3.24-3.18 (m, 2H), 2.53-2.50 (m, 2H), 2.36 (s ancho, 2H), 1.82-1.74 (m, 2H), 1.46/1.23 (s, 18H), 1.17-1.16 (m, 6H).



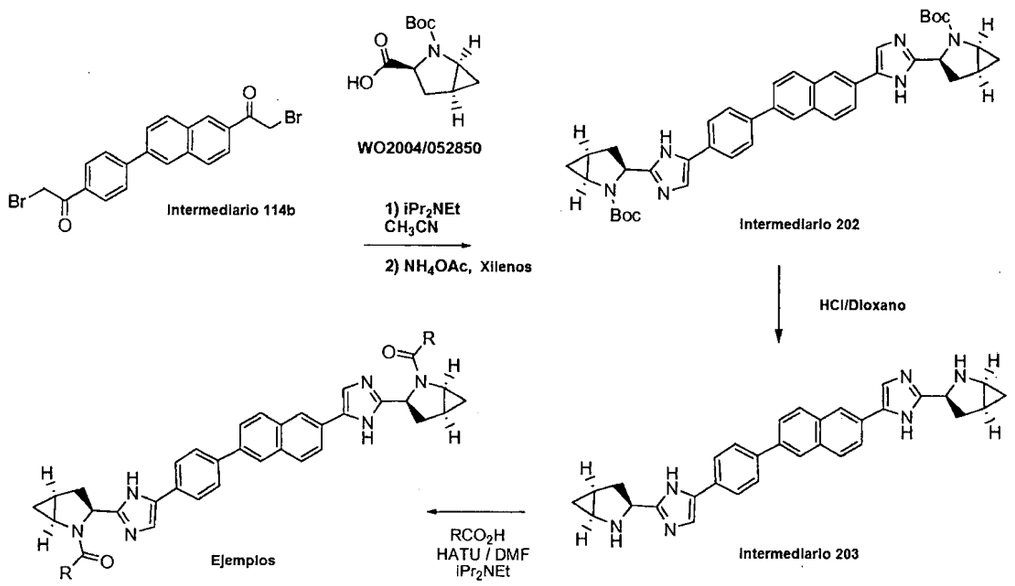
Intermediario 201

2-((2S,4R)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4R)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol

Una solución de HCl 4N en dioxano (15 ml) se añadió a (2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-(*terc*-butoxicarbonil)-4-metil-2-pirrolidinil)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-4-metil-1-pirrolidincarboxilato de *terc*-butilo (200 mg, 0.285 mmol) en MeOH (5 ml) y se agitó en condiciones ambientales durante 2 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 185 mg). Tiempo de retención en la CL-EM 2.64 min; Calculado para $C_{32}H_{35}N_6$: 503.29 m/z Encontrado 503.20 [M+H]+. Los datos de CL se registraron

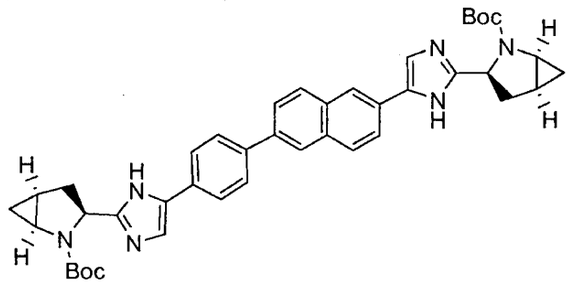
en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Esquema de reacción 54



El intermediario 203 se preparó como se muestra en el Esquema de reacción 54 usando como material de partida

ácido (1S,3S,5S)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (que podría prepararse de conformidad con el documento WO2004/052850). Los datos analíticos para los intermediarios se muestran a continuación:



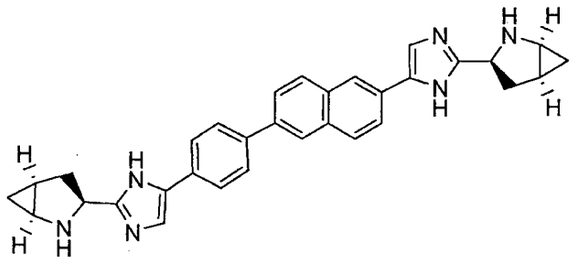
Intermediario 202

(1S,3S,5R)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución agitada de 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (0.491 g, 1.100 mmol) y ácido (1S,3S,5S)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico (500 mg, 1.1 mmol) en acetonitrilo (11 ml) se añadió Base de Hunig (0.384 ml, 2.2 mmol). La mezcla heterogénea se agitó durante 20 horas a temperatura ambiente, el solvente se retiró *a vacío*. El residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado, salmuera y se secó sobre sulfato sódico. El lavado se repitió 2 veces. El

producto bruto se suspendió en xileno (11 ml) y se añadió acetato amónico (1.27 g, 16.5 mmol). El recipiente de presión se selló y se introdujo en un baño de aceite precalentado (140 °C) y se agitó durante 2 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato sódico saturada y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 80 g (eluido con 25% B a 100% B en 1.5 l, y se conservó 0.5 l B. solvente B = acetato de etilo y el solvente A = hexanos) para dar (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-il)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (418.9 mg, 43%) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.46 min; Calculado para $C_{42}H_{47}N_6O_4$: 699.37 m/z Encontrado 699.33 [M+H]+. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de

solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.11 (s, 1H), 7.96-7.93 (m, 2H), 7.85-7.80 (m, 6H), 7.45 (s ancho, 1H), 7.37 (s ancho, 1H), 5.36 (s ancho, 2H), 3.72 (s ancho, 1H), 3.64 (s ancho, 1H), 2.82 (s ancho, 1H), 2.72 (s ancho, 1H), 2.43 (s ancho, 1H), 2.15 (s ancho, 1H), 1.70 (s ancho, 2H), 1.55/1.33 (s, 18H), 1.10 (s ancho, 1H), 0.94 (s ancho, 1H), 0.88 (s ancho, 1H), 0.81 (s ancho, 1H).



Intermediario 203

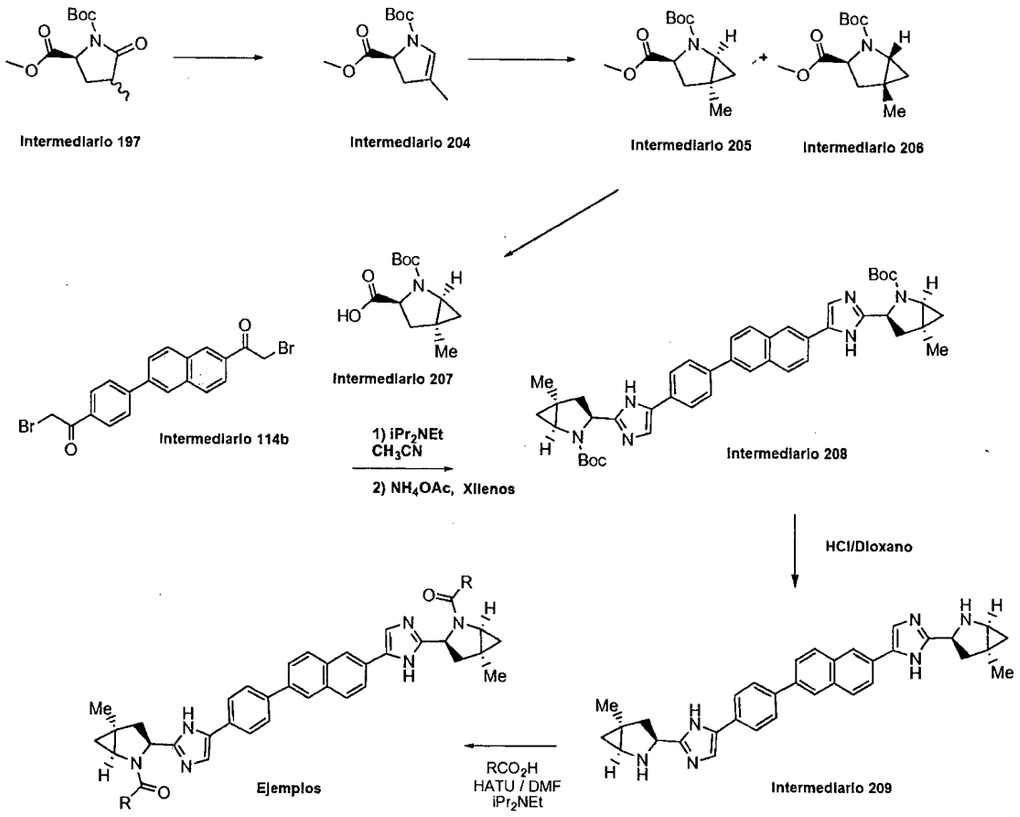
(1R,3S,5S)-3-(4-(4-(6-(2-((1R,3S,5S)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hexano

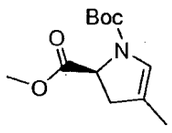
Una solución de HCl 4N en dioxano (10 ml) se añadió a (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*terc*-butoxicarbonil)-2-azabiciclo[3.1.0]hex-3-Il)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (375 mg. 0.537 mmol) en MeOH (3 ml) y se agitó en condiciones ambientales durante 2 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 346 mg). Tiempo de retención en la CL-EM 2.75 min; Calculado para $C_{32}H_{31}N_6$: 499.26 m/z Encontrado 499.22 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL

en modo de electrorrocío.

Esquema de reacción 55



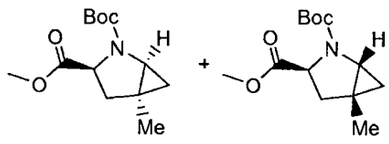
El intermediario 209 se preparó como se muestra en el Esquema de reacción 55 usando como material de partida ácido (1S,3S,5S)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexan-3-carboxílico (que podría prepararse de conformidad con el documento WO2004/052850). Los datos analíticos para los intermediarios se muestran a continuación:



Intermediario 204

A una solución de la mezcla diastereomérica (en el

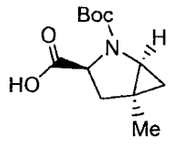
carbono que porta el grupo metilo) del Intermediario 197 (4.75g, 18.46 mmol) se añadió superhidruro (19.20 ml, 19.20 mmol) gota a gota a -50 °C en un baño de hielo seco/acetona en 10 min. Se añadió base de Hunig (13.58 ml, 78 mmol), se agitó durante 10 min, se añadió DMAP (0.122 g, 0.997 mmol) en forma de un sólido, se agitó durante 15 min y se añadió, gota a gota, anhídrido trifluoroacético (2.98 ml, 21.08 mmol) en 15 min. El baño en hielo seco/acetona se retiró y la mezcla de reacción se agitó durante 4 h dejando calentarse a temperatura ambiente. La mezcla de reacción se lavó con agua (50 mL), NaCl sat. (30 ml) y se concentró a vacío. El material bruto resultante se purificó con una cromatografía instantánea (8-60% de EtOAc/hexano) para dar el éster Intermediario 204 en forma de un aceite amarillo (2.85 g). RMN de ^{1}H-(CD_3, 400 MHz): 6.36 (s, 0.5H), 6.25 (s, 0.5H), 4.70-4.57 (m, 1H), 3.78 (s, 3H), 2.96 (m, 1H), 2.54 (m, 1H), 1.70 (s, 3H), 1.50 (s, 4.5H), 1.44 (s, 4.5H).



Intermediarios 205 y 206

Gota a gota se añadió dietilzinc (1.1 M en tolueno, 59.1 ml, 65.0 mmol) durante 20 min la una solución de tolueno enfriado (-23 °C) (60 ml) del Intermediario 203 (5.23 g, 21.68 mmol) y se agitó durante 10 min. Gota a gota se añadió

cloroyodometano (9.44 ml, 130 mmol) en 10 min y la mezcla de reacción se agitó a -21 °C durante 16 horas. A la mezcla de reacción se añadió $NaHCO_3$ sat. (60 ml), se retiró el baño de enfriamiento y la mezcla se agitó durante 10 min. Después se filtró y la torta del filtro se lavó con tolueno (50 ml). El filtrado se repartió y la capa orgánica se secó con Na2SO4, y se concentró al vacío. El material bruto resultante se purificó con cromatográfica instantánea (2-10% EtOAc/Hexano) para dar el Intermediario 205 (primer eluato; aceite incoloro; 2.88 g) e Intermediario 206 (Segundo eluato; aceite incoloro; 1.01g). La asignación de las estereoquímicas relativas se realizó basándose en estudios NOE. Intermediario 205: RMN de ^1H-(CD_3, 400 MHz): 4.65-4.52 (m, 1H), 3.72 (s, 3H), 3.28-3.17 (m, 1H), 2.44-2.32 (m, 1H), 2.16-2.10 (m, 1H), 1.51-1.42 (dos s, 9H), 1.24 (s, 3H), 1.07 (m, 1H), 0.69-0.60 (m, 1H).

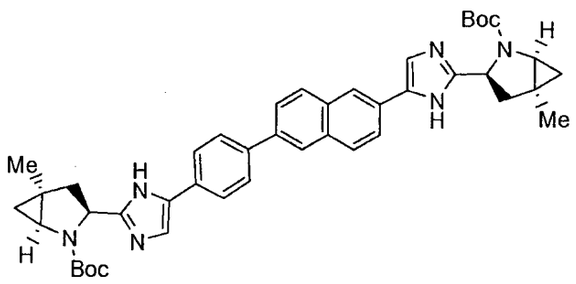


Intermediario 207

Ácido (1S,3S,5S)-2-(terc-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexan-3-carboxílico

A una solución del éster Intermediario 205 (2.88 g, 11.28 mmol) en etanol (36 ml) se añadió solución de LiOH (0.324 g, 13.54 mmol) en agua (10.00 ml), y la mezcla se

agitó a temperatura ambiente durante 6 h. La mayor parte del componente volátil se eliminó a vacío y el residuo se fraccionó entre agua (20 ml) y éter (20 ml). La fase acuosa se enfrió en un baño de agua y hielo, se acidificó con HCl 1 N a una región de pH de 2, y se extrajo con EtOAc (30 ml, 4x). La fase orgánica combinada se secó con Na2SO4, se evaporó al vacío para dar el Intermediario 207 en forma de un sólido pegajoso (2.55g). RMN de ^{1}H-(CD_3, 400 MHz): 4.64 (m, 1H), 3.25 (appt s, 1H), 2.70-2.40 (m, 1H), 2.14 (m, 1H), 1.54-1.44 (m, 9H), 1.27 (s, 3H), 1.10-0.80 (m, 1H), 0.67 (m, 1H).



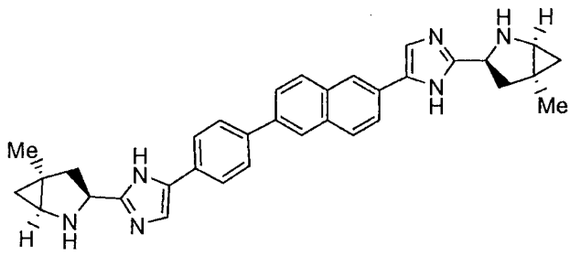
Intermediario 208

(1S,3S,5R)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(terc-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución agitada de 2-bromo-1-(4-(6-(2-bromoacetil)naftalen-2-il)fenil)etanona (0.607 g, 1.36 mmol) y ácido (1S,3S,5S)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexano-3-carboxílico (729.0 mg, 2.72 mmol)

en acetonitrilo seco (12 ml) se añadió Base de Hunig (0.475 ml, 2.72 mmol). La mezcla heterogénea se agitó durante 20 horas a temperatura ambiente, el solvente se retiró *a vacío*. El residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado, salmuera y se secó sobre sulfato sódico. El lavado se repitió 2 veces. El producto bruto se suspendió en xileno (12 ml) y se añadió acetato amónico (1.57 g, 20.39 mmol). El recipiente de presión se selló y se introdujo en un baño de aceite precalentado (140 °C) y se agitó durante 2 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato sódico saturada y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 80 g (eluido con 25% B a 100% B en 1.5 l, y se conservó 0.5 l B. solvente B = acetato de etilo y el solvente A = hexanos) para dar (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (279 mg, 27%) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.56 min; Calculado para $C_{44}H_{51}N_6O_4$: 727.40 m/z Encontrado 727.41 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® de 2.0 x 50 mm usando un

detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.18 (s, 1H), 8.11 (s, 1H), 7.96-7.93 (m, 2H), 7.83-7.80 (m, 6H), 7.43 (s ancho, 1H), 7.35 (s ancho, 1H), 5.35 (s ancho, 2H), 3.42 (s ancho, 1H), 3.36 (s ancho, 1H), 2.61 (s ancho, 1H), 2.53 (s ancho, 2H), 2.72 (s ancho, 1H), 1.55/1.33 (s, 25H), 1.06 (s ancho, 1H), 0.85 (s ancho, 1H), 0.72 (s ancho, 1H).



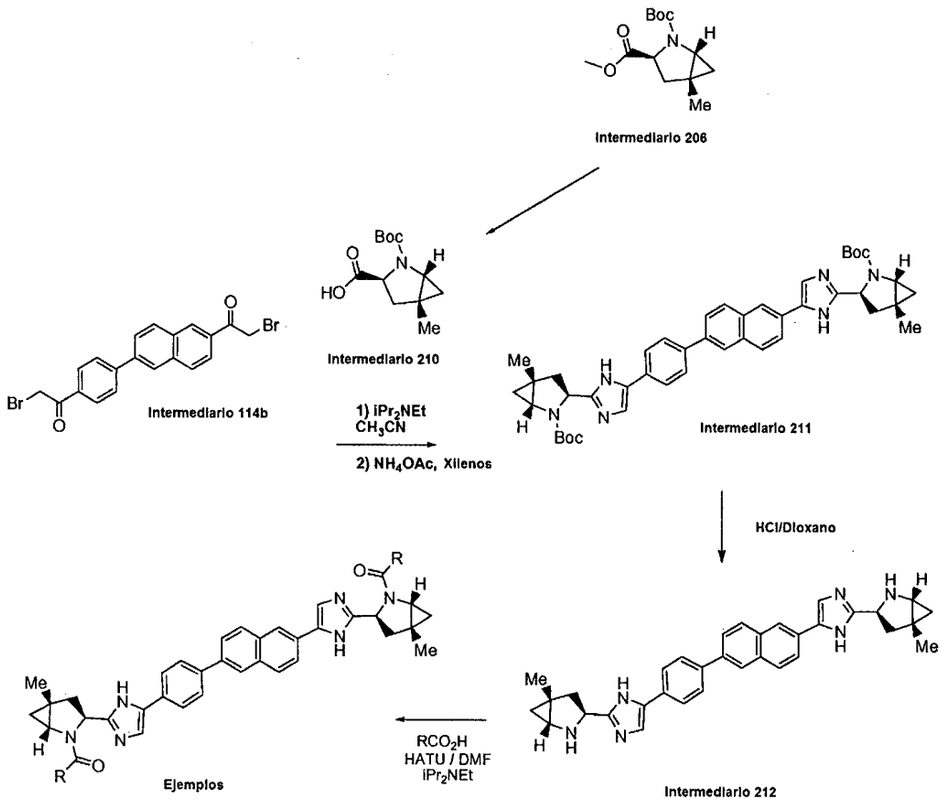
Intermediario 209

(1S,3S,5S)-5-metil-3-(4-(4-(6-(2-((1S,3S,5S)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

Una solución de HCl 4N en dioxano (15 ml) se

añadió a (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-Il)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-5-metil2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (250 mg, 0.344 mmol) en MeOH (5 ml) y se agitó en condiciones ambientales durante 2 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 231 mg). Tiempo de retención en la CL-EM 3.09 min; Calculado para $C_{34}H_{35}N_6$: 527.29 m/z Encontrado 527.35 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

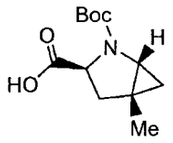
Esquema de reacción 56



El intermediario 212 se preparó como se muestra en el Esquema de reacción 56 usando como material de partida ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexan-3-carboxílico (que podría prepararse de conformidad con el documento WO2004/052850). Los datos analíticos para

El intermediario 212 se preparó tal como se muestra en el esquema de reacción 56 usando como material de partida ácido (1R,3S,5R)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexan-3-carboxílico (que podría prepararse

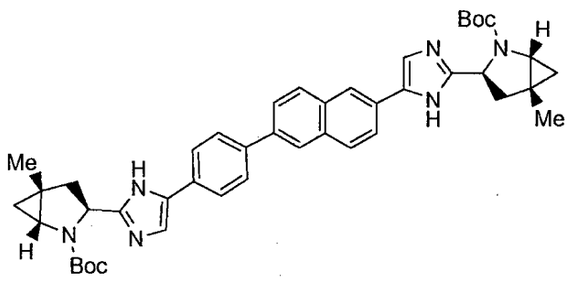
conforme al documento WO2004/052850). Los datos analíticos para los intermediarios se muestran a continuación:



Ácido (1R,3S,5R)-2-(terc-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexan-3-carboxílico

Intermediario 210

El intermediario 210 se preparó a partir del Intermediario 206 como se ha descrito con anterioridad para el Intermediario 207, RMN de ^1H ($CDCl_3$, 400 MHz): 4.13 (app s ancho, 1H), 3.06 (app s ancho, 1H), 2.55/2.41 (app s ancho solapante, 2H), 1.51 (s, 9H), 1.27 (s, 3H), 0.76 (app t, J = 5.6, 1H), 0.60 (app s ancho, 1H).



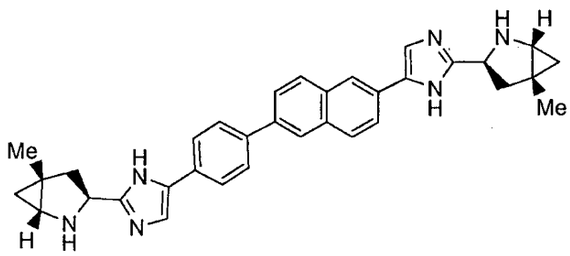
Intermediario 211

(1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hexan-2-carboxilato de terc-butilo

A una solución agitada de 2-bromo-1-(4-(6-(2-

bromoacetil)naftalen-2-il)fenil)etanona (0.37 g, 0.83 mmol) y ácido (1R,3R,5S)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hexano-3-carboxílico (0.40 g, 1.66 mmol) en acetonitrilo seco (9 ml) se añadió Base de Hunig (0.29 ml, 1.66 mmol). La mezcla heterogénea se agitó durante 20 horas a temperatura ambiente, el solvente se retiró *a vacío*. El residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato de sodio saturado, salmuera y se secó sobre sulfato sódico. El lavado se repitió 2 veces. El producto bruto se suspendió en xileno (9 ml) y se añadió acetato amónico (1.3 g, 16.6 mmol). El recipiente de presión se selló y se introdujo en un baño de aceite precalentado (140 °C) y se agitó durante 2 horas. El solvente se eliminó *al vacío* y el residuo se suspendió en acetato de etilo y se lavó con solución de bicarbonato sódico saturada y salmuera. Después de concentrar, el producto bruto se cargo (cloruro de metileno) en un cartucho de gel de sílice Thompson de 90 g (eluido con 25% B a 100% B en 1.5 l, y se conservó 0.5 l B. solvente B = acetato de etilo y el solvente A = hexanos) para dar (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (80 mg, 10%). Tiempo de retención en la CL-EM 3.37 min; Calculado para $C_{44}H_{51}N_6O_4$: 727.40 m/z Encontrado 727.38 $[M+H]^+$. Los datos

de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.19 (s, 1H), 8.08 (s, 1H), 7.92-7.91 (m, 2H), 7.85-7.77 (m, 6H), 7.47 (s, 1H), 7.38 (s, 1H), 4.67 (s ancho, 2H), 3.93-3.90 (m, 2H), 2.63-2.57 (m, 2H), 2.20-2.14 (m, 2H), 1.31-1,23 (m, 24H), 0.92 (app, d, J=6.7 Hz, 1H), 0.82 (s ancho, 1H), 0.77-0.75 (m, 2H).



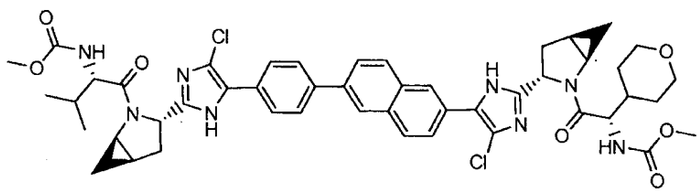
Intermediario 212

(1R,3S,5R)-5-metil-3-(4-(4-(6-(2-((1R,3S,5R)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

Una solución de HCl 4N en dioxano (5 ml) se

añadió a (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-Il)-1*H*-imidazol-4-il)-2-naftil)fenil)-1*H*-imidazol-2-il)-5-metil2-azabiciclo[3.1.0]hexan-2-carboxilato de *terc*-butilo (48 mg, 0.066 mmol) en MeOH (1 ml) y se agitó en condiciones ambientales durante 2 horas, se concentró y se secó a vacío. Sal tetra de HCl (teoría supuesta: a 44 mg). Tiempo de retención en la CL-EM 2.82 min; Calculado para $C_{34}H_{35}N_6$: 527.29 m/z Encontrado 527.26 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min donde el solvente A fue metanol al 5%/agua al 95%/TFA al 0.1% y el solvente B fue metanol al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

Ejemplos



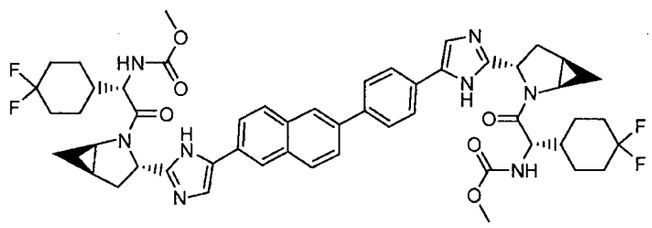
Ejemplo 64

((1S)-2-(((1R,3S,5R)-3-4-cloro-5-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo

A una solución agitada de ((1S)-2-(((1R,3S,5R)-3-(54-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo (Ejemplo 61) (60 mg, 0.071 mmol) en DMF (1.5 ml) se añadió N-clorosuccinimida (10.4 mg, 0.078 mmol) y el vaso de reacción se selló y se calentó a 50°C durante 16 horas. La reacción se enfrió, se concentró parcialmente y después se diluyó con MeOH. La solución se filtró y purificó mediante HPLC preparativa (MeOH/H_2O, w TFA al 0.1%) para dar una sal en TFA de ((1S)-2-(((1R,3S,5R)-3-(5-(6-(4-cloro-5-(6-(4-(4-cloro-2-((2-1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (21.4 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.798 min; m/z 462.34 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, MeOD) δ ppm 8.18 (s, 2 H), 8.03 (d, J=8.8 Hz, 1 H), 7.99 (d, J=8.8 Hz, 1 H), 7.80 - 7.92 (m, 6 H), 5.06 (ddd, J=9.0, 5.8, 3.5 Hz, 2 H), 4.63 (d, J=7.5 Hz, 1 H), 4.57 (d, J=6.5 Hz, 1 H), 3.92 - 3.98 (m, 2 H), 3.71 - 3.81 (m, 2 H), 3.67 (s, 6 H), 3.35 - 3.44 (m, 2 H), 2.42 - 2.57 (m, 4 H), 1.99 - 2.24 (m, 4 H), 1.40 - 1.66 (m, 4 H), 1.06 - 1.14 (m, 2 H), 1.03 (d, J=6.8 Hz, 3 H), 0.95 (d, J=6.8 Hz, 3 H),

0.82 (d, *J*=2.8 Hz, 2 H).

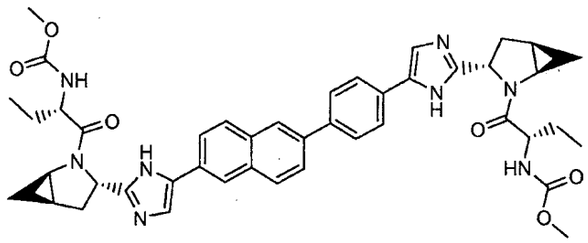


Ejemplo 65

((1S)-1-(4,4-difluorociclohexil)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorociclohexil)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 69) (38.0 mg, 0.059 mmol) y ácido (S)-2-(4,4-diflurociclohexil)-2-(metoxicarbonilamino)acético (44.5 mg, 0.177 mmol) en DMF (0.7 ml) y DIPEA (0.103 ml, 0.590 mmol) se añadió HATU (67.3 mg, 0.177 mmol). La reacción se diluyó con MeOH, se filtró, se purificó mediante HPLC preparativa (agua/MeOH p/TFA al 0.1%) y se repurificó mediante HPLC preparativa (agua/MeOH p/acetato amónico) para dar ((1S)-1-(4,4-difluorociclohexil)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-(4,4-difluorociclohexil)-2-((metoxicarbonil)amino)acetil)-2-

azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil)carbamato de metilo (22.1 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 2.713 min; m/z 483.13 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.16 (s, 1 H), 8.11 (s, 1 H), 7.94 (d, J=8.5 Hz, 2 H), 7.77 - 7.85 (m, 5 H), 7.47 (s, 1 H), 7.39 (s, 1 H), 7.08 (d, J=8.5 Hz, 1 H), 5.15 (ddd, J=8.2, 6.3, 6.1 Hz, 2 H), 4.68 (s ancho, 2 H), 3.69 - 3.76 (m, 2 H), 3.68 (s, 6 H), 2.41 - 2.57 (m, 4 H), 1.65 - 2.12 (m, 16 H), 1.33 - 1.59 (m, 4 H), 1.06 - 1.17 (m, 2 H), 0.78 (s ancho, 2 H).

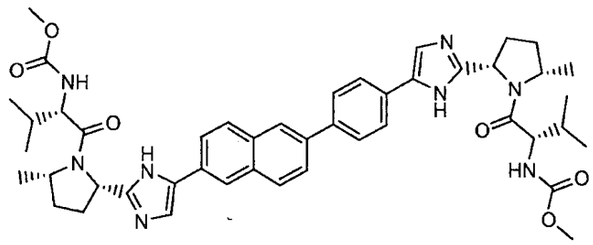


Ejemplo 66

((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-butanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil(fenil)--1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-propil)carbamato de metilo

A una solución agitada de una sal en TFA de (1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 69) (80 mg, 0.084 mmol) y ácido (S)-2-(metoxicarbonilamino)butanoico (37.8 mg, 0.235 mmol) en DMF (0.8 ml) y DIPEA (0.15 ml, 0.84 mmol) se añadió HATU (89 mg, 0.24 mmol). La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (agua/MeOH P/TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-butanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil(fenil)--1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-propil)carbamato de

metilo (70.1 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 1.688 min; m/z 785.55 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.26 (s, 1 H), 8.12 (d, *J*=8.8 Hz, 1 H), 8.07 (d, *J*=8.5 Hz, 1 H), 7.93 - 8.00 (m, 4 H), 7.82 - 7.90 (m, 4 H), 5.12 - 5.21 (m, 2 H), 4.58 - 4.65 (m, 2 H), 3.74 - 3.81 (m, 2 H), 3.67 (s, 6 H), 2.70 (ddd, *J*=13.7, 9.0, 4.9 Hz, 2 H), 2.49 (dc, *J*=14.2, 7.1 Hz, 2 H), 2.09 (s ancho, 2 H), 1.86 - 1.99 (m, 2 H), 1.64 - 1.77 (m, 2 H), 1.09 - 1.17 (m, 2 H), 1.02 (t, *J*=7.4 Hz, 6 H), 0.92 (s ancho, 2 H).

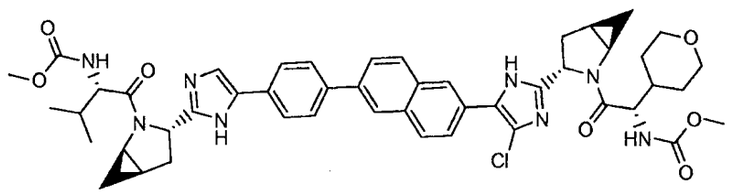


Ejemplo 67

((1S)-1-(((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (intermediario 117) (102 mg, 0.106 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (46.6 mg, 0.266 mmol) en DMF (1.0 ml) y DIPEA (0.18 ml, 1.1 mmol) se añadió HATU (101 mg, 0.266 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (MeOH/H_2O p/ TFA al 0.1%) y después se volvió a purificar mediante HPLC preparativa (agua/acetonitrilo/TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((2S,5S)-2-(4-(4-(6-(2-((2S)-1-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-

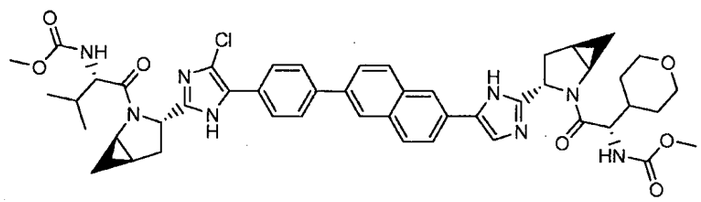
metilpropil)carbamato de metilo (63.8 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 1.900 min; m/z 817.59 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H se presenta como una mezcla ~4:1 de regioisómeros. RMN de ^1H (para el regioisómero mayoritario) (400 MHz, MeOD) δ ppm 8.31 (s, 1 H), 8.27 (s, 1 H), 8.13 (d, *J*=8.5 Hz, 1 H), 8.09 (d, *J*=8.5 Hz, 1 H), 7.94 - 8.02 (m, 5 H), 7.84 - 7.92 (m, 3 H), 5.15 - 5.24 (m, 2 H), 4.13 (dd, *J*=8.7, 1.4 Hz, 2 H), 3.74 (d, *J*=2.8 Hz, 2 H), 3.67 (s, 6 H), 2.50 - 2.60 (m, 2 H), 2.26 - 2.45 (m, 4 H), 1.95 - 2.10 (m, 4 H), 1.57 (dd, *J*=6.5, 3.0 Hz, 6 H), 1.32 (t, *J*=6.4 Hz, 2 H), 0.99 (d, *J*=6.8 Hz, 6 H), 0.89 (d, *J*=6.8 Hz, 6 H).



Ejemplo 68

((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

y



Ejemplo 69

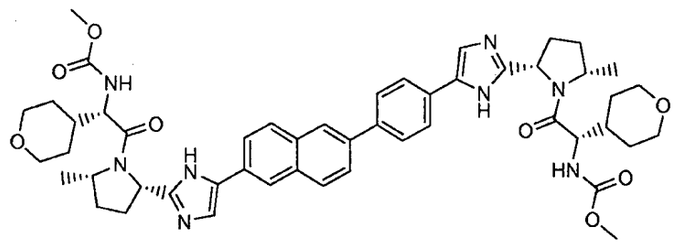
((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)fenil-1H-imidazol-4-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

Una mezcla de dos regioisómeros de cloromidazol en forma de sales en TFA (Ejemplos 68 y 69) (21.4 mg) se aisló del mismo reacción que preparó una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-

azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (Ejemplo 64). Los dos compuestos regioisómeros se separaron en múltiples inyecciones usando cromatografía SCF (columna SCF de 2-etilpiridina (4.6 x 250mm, 5μm) y 80% de CO_2 - 20% EtOH/0.1%DEA). La regioquímica absoluta de los materiales separados se determine mediante correlación HMBC. La reacción dio ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (7.4 mg) y ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (4.5 mg), cada uno un sólido blancuzco. Para el Ejemplo 68: Tiempo de retención en la CL-EM 2.683 min; m/z 889.17 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna

PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. Para el Ejemplo 69: Tiempo de retención en la CL-EM 2.695 min; m/z 889.22 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de

EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

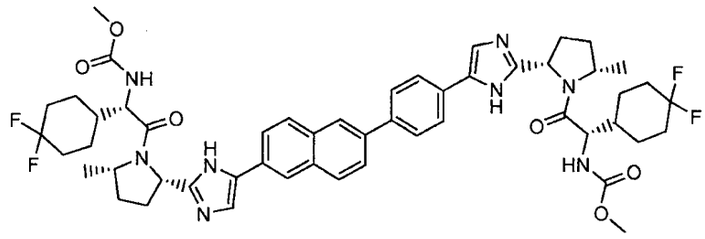


Ejemplo 70

((1S)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 117) (73.9 mg, 0.077 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (41.9 mg, 0.193 mmol) en DMF (1.0 ml) y DIPEA (0.14 ml, 0.77 mmol) se añadió HATU (73.3 mg, 0.93 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa ($MeOH/H_2O$ p/ TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-

2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (51.2 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 1.897 min; m/z 901.39 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



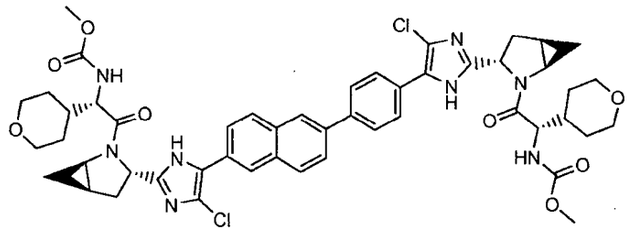
Ejemplo 71

((1S)-1-(4,4-difluorociclohexil)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-2-((2S)-2-(4,4-difluorociclohexil)-2-((metoxicarbonil)amino)acetil)-5-metil-2-pirrolidinil-H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-

pirrolidinil-2-oxoetil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (intermediario 117) (70.8 mg, 0.074 mmol) y ácido (S)-2-(4,4-difluorociclohexil)-2-(metoxicarbonilamino)acético (46.8 mg, 0.186 mmol) en DMF (1.0 ml) y DIPEA (0.13 ml, 0.75 mmol) se añadió HATU (71.4 mg, 0.186 mmol) y la reacción se agitó a temperatura ambiente durante 1.5 horas. La mezcla de reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/H_2O p/ TFA al 0.1%) para dar el producto deseado en forma de una sal en TFA de ((1S)-1-(4,4-difluorociclohexil)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-(4,4-difluorociclohexil)-2-((metoxicarbonil)amino)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo (43.3 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 2.828 min; m/z 485.22 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al

100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



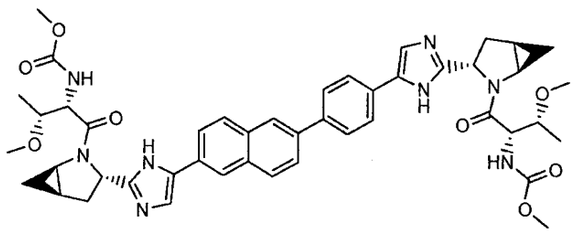
Ejemplo 72

((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(4-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de ((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (Ejemplo 34) (22.7 mg, 0.025 mmol) en DMF (0.5 ml) se añadió N-clorosuccinimida (71, mg, 0.053 mmol) y el vaso de reacción se selló y la reacción se

calentó a 50°C durante 12 horas. La reacción se enfrió hasta la temperatura ambiente, se añadió N-clorosuccinimida adicional (~3mg) y el vaso de reacción se selló y se agitó a 50 °C durante 2h. La reacción se enfrió hasta la temperatura ambiente, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (Metanol/agua p/TFA al 0.1%) para dar ((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(4-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (12 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.708 min; m/z 483.25 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma

MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (400 MHz, MeOD) δ ppm 8.18 (s, 2 H), 8.04 (d, *J*=8.8 Hz, 1 H), 7.99 (d, *J*=8.8 Hz, 1 H), 7.80 - 7.92 (m, 6 H), 5.02 - 5.09 (m, 2 H), 4.63 (d, *J*=6.0 Hz, 2 H), 3.91 - 3.99 (m, 4 H), 3.73 - 3.80 (m, 2 H), 3.67 (s, 6 H), 3.34 - 3.45 (m, 4 H), 2.43 - 2.54 (m, 4 H), 1.98 - 2.13 (m, 4 H), 1.38 - 1.67 (m, 8 H), 1.06 - 1.15 (m, 2 H), 0.81 (s ancho, 2 H).



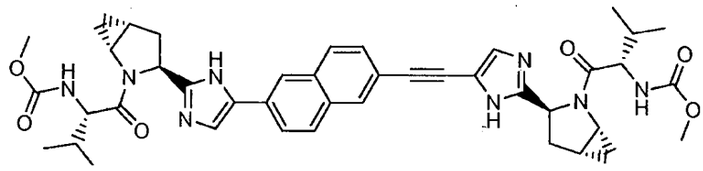
Ejemplo 73

((1S,2R)-2-metoxi-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(N-(metoxicarbonil)-O-metil-L-treonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)propil)carbamato de metilo

A una solución agitada de una sal en TFA de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (intermediario 133) (66 mg, 0.069 mmol) y ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico (33.0 mg, 0.173 mmol) en DMF (0.8 ml) y DIPEA (0.121 ml, 0.691 mmol) se añadió HATU (65.7 mg, 0.173 mmol) y la reacción se agitó a temperatura ambiente durante la noche. La reacción se diluyó con MeOH, se

filtró y se purificó mediante HPLC preparativa (Metanol/agua p/acetato amónico 10 mM) para dar una sal en TFA de ((1S,2R)-2-metoxi-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-(N-(metoxicarbonil)-O-metil-L-treonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)propil)carbamato de metilo (51.9 mg, 0.048 mmol, rendimiento del 98%) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 2.383 min; m/z 845.42 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 10u, C18 de 3.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (MeOD, 400 MHz) δ 8.29 (s ancho, 1H), 8.26 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.00 - 7.93 (m, 4H), 7.91 - 7.82 (m, 4H), 5.18 (td, J = 9.0, 7.0 Hz, 2H), 4.78 (dd, J = 3.9, 1.7 Hz, 2H), 3.92 -

3.79 (m, 4H), 3.68 (s, 6H), 3.35 (s, 3H), 3.35 (m, 3H), 2.76 - 2.65 (m, 2H), 2.59 - 2.47 (m, 2H), 2.15 - 2.05 (m, 2H), 1.19 (d, J = 6.3 Hz, 6H), 1.16 - 1.07 (m, 2H), 0.94 - 0.84 (m, 2H).



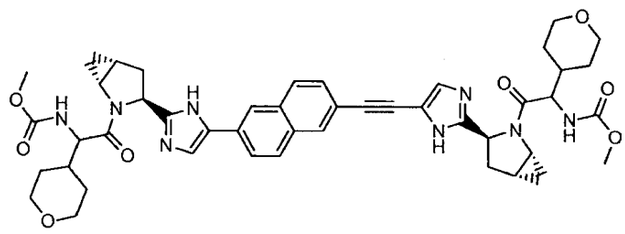
Ejemplo 74

((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-etinil-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 124) (100 mg, 0.169 mmol) y ácido (R)-2-(metoxicarbonilamino)-3-metilbutanoico (89 mg, 0.51 mmol) en DMF (1.5 ml) y DIPEA (0.24, 1.4 mmol) se añadió HATU (193 mg, 0.506 mmol) y la solución naranja transparente se agitó a temperatura ambiente durante 3 horas. La reacción se diluyó con metanol, se filtró y se purificó mediante HPLC preparativa (agua/MeOH con amortiguador acetato amónico) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil-2-naftil(fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (71 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.706 min; m/z 761.22 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 4 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, MeOD) δ ppm 8.15 (s, 1 H), 7.96 (s, 1 H), 7.80 - 7.88 (m, 3 H), 7.51 (dd, J=8.4, 1.6 Hz, 1 H), 7.46 (s, 1 H), 7.27 (s, 1 H), 5.18 (dd, J=9.0, 4.8 Hz, 1 H), 5.13 (dd, J=8.8, 4.3 Hz, 1 H), 4.59 (dd, J=11.8, 6.8 Hz, 2 H), 3.68 - 3.72 (m, 1 H), 3.67 (s, 3 H), 3.67 (s, 3 H), 3.59 - 3.64 (m, 1 H), 2.31 - 2.60 (m, 4 H), 2.08 - 2.22 (m, 2 H), 1.99 - 2.08 (m, 2 H), 1.13 (ddd, J=8.6, 5.8, 5.5 Hz, 2 H), 1.00 (dd,

J=12.9, 6.9 Hz, 6 H), 0.93 (dd, J=6.7, 2.9 Hz, 6 H), 0.79 (s ancho, 2 H).



Ejemplo 75

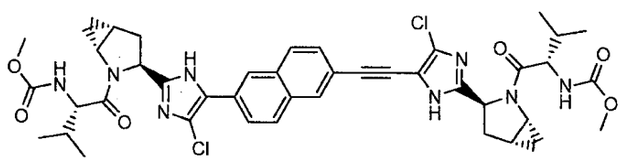
(mezcla de diastereómeros)

(2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-(((metoxicarbonil)amino)(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-4-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 124) (57 mg, 0.096 mmol) y ácido (R)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético racémico (62.7 mg, 0.289 mmol) en DMF (1.0 ml) y DIPEA (0.134, 0.770 mmol) se añadió HATU (110 mg, 0.289 mmol) y la solución naranja transparente se agitó a temperatura ambiente durante 3 horas. La reacción se diluyó con metanol, se filtró y se purificó mediante HPLC preparativa (agua/MeOH con amortiguador acetato amónico) para dar 2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-

(((metoxicarbonil)amino)(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (37.3 mg) en forma de un sólido amarillo y una mezcla de diaestereómeros. Tiempo de retención en la CL-EM 1.522 min; m/z 845.36 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. Mezcla de diastereómeros. RMN de ^1H NMR (400 MHz, MeOD) δ ppm 8.15 (d, J=12.8 Hz, 1 H), 7.96 (s, 1 H), 7.80 - 7.90 (m, 3 H), 7.51 (dd, J=8.5, 1.5 Hz, 1 H), 7.46 (d, J=5.5 Hz, 1 H), 7.27 (d, J=5.3 Hz, 1 H), 5.08 - 5.24 (m, 2 H), 4.61 - 4.69 (m, 1 H), 4.57 (dd, J=8.3, 4.5 Hz, 1 H), 3.85 - 4.03 (m, 5 H), 3.63 - 3.79 (m, 8 H), 3.34 - 3.49 (m, 5 H), 2.30 - 2.63

(m, 4 H), 1.99 - 2.16 (m, 3 H), 1.70 - 1.80 (m, 1 H), 1.35 - 1.66 (m, 6 H), 1.16 - 1.26 (m, 1 H), 1.07 - 1.16 (m, 1 H), 0.70 - 0.83 (m, 2 H).



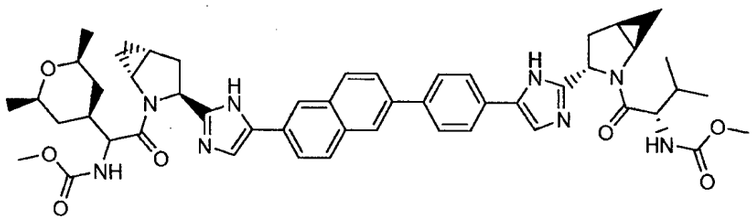
Ejemplo 76

((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(6-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)etinil)fenil)-1H-imidazol-2-il)-2-az[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

A una solución agitada de ((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-etinil-2-naftil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (38 mg, 0.050 mmol) en DMF (1 ml) se añadió N-clorosuccinimida (13.3 mg, 0.100 mmol) y, después, el vaso de reacción se aclaró con nitrógeno, se selló y se calentó a 50°C durante 16 horas. La reacción se enfrió hasta la TA y se añadió N-clorosuccinimida (7.4 mg) adicional. La reacción se recalentó a 50°C durante 3 horas, se enfrió hasta la TA, se diluyó con MeOH (~ 0.5 ml), se filtró y se purificó mediante HPLC preparativa (MeOH/agua/amortiguador TFA) para dar una sal en TFA de

((1S)-1-(((1R,3S,5R)-3-(5-(6-(4-cloro-5-(6-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-etinil-2-naftil-1H-bencimidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (5.0 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 4.153 min; m/z 831.02 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.19 (s, 1 H), 8.07 (s, 1 H), 7.87 - 7.99 (m, 3 H), 7.58 (dd, *J*=8.5, 1.3 Hz, 1 H), 5.07 (t, *J*=7.2 Hz, 1 H), 4.98 - 5.03 (m, 1 H), 4.54 - 4.59 (m, 2 H), 3.67 (s, 6 H), 3.62 - 3.75 (m, 2 H), 2.45 - 2.50 (m, 2 H), 2.41 (dd, *J*=7.3, 3.5 Hz, 2 H), 2.09 - 2.21 (m, 2 H), 1.96 - 2.08 (m, 2 H), 1.08 - 1.16 (m, 2 H),

1.02 (t, *J*=6.1 Hz, 6 H), 0.92 - 0.97 (m, 6 H), 0.75 - 0.85 (m, 2 H).



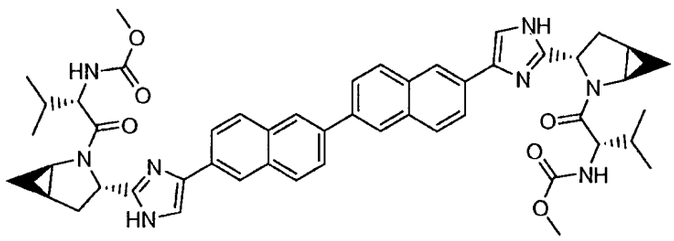
Ejemplo 77

((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (S)-1-((1R,3S,5R)-3-(5-(4-(6-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (Intermediario 128) (42 mg, 0.061 mmol), ácido 2-((2R,4R,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético (*Cap-179 estereoisómero 2)* (14.9 mg, 0.061 mmol) y DIEA (0.053 ml, 0.30 mmol) en DMF (2 ml) se añadió HATU (25.4 mg, 0.067 mmol) y la solución amarillenta resultante se agitó a TA durante 2 horas. La reacción se concentró a presión reducida y el residuo se redisolvió en

metanol y se purificó mediante HPLC preparativa. solvente A: MeCN al 0.5%/ agua al 95%/ NH_4Ac 10 mM ; solvente B: MeCN al 95%/ agua al 5%/ NH_4Ac 10 mM ; Columna: Sunfire Prep MS C18 de 30 x 100 mm S10; Longitud de onda: 220 nM; Velocidad de flujo: 40 ml/min; gradiente: 0% de B a 80% de B durante 30 minutos con un tiempo de conservación de 5 min) para dar ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (26 mg) en forma de un sólido blanco. CL/EM [M+H]+= 883; Tr = 2.99 min es el producto. Columna Luna de 3u C18 de 2x50mm; inicio %B: 0, final %B: 100 solvente A: ACN al 5%/ H_2O al 95% + Acetato amónico 10 mM; solvente B: ACN al 95%/ H_2O al 5%+ acetato amónico 10 mM; velocidad de flujo 4 ml/min. Tiempo de recorrido: 5 min. Pureza = 97 %. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 11.85 (1 H, s ancho,), 11.73 (1 H, s ancho,), 8.14 - 8.27 (2 H, m), 7.90 - 7.98 (3 H, m), 7.82 - 7.89 (3 H, m), 7.79 (2 H, d, *J*=8.24 Hz), 7.64 (1 H, s), 7.57 (1 H, s), 7.19 (2 H, t, *J*=9.31 Hz), 5.03 - 5.13 (2 H, m), 4.51 (1 H, t, *J*=7.93 Hz), 4.44 (1 H, t, *J*=7.78 Hz), 3.65 (1 H, s ancho,), 3.51 - 3.60 (7 H, m), 3.29 - 3.42 (7 H, m), 2.35 - 2.47 (2 H, m), 2.20 - 2.33 (2 H, m), 2.01 - 2.11 (2 H, m), 1.83 - 1.92 (3 H, m), 1.63 (1 H, d, *J*=12.21 Hz), 1.57 (1

H, d, *J*=11.60 Hz), 0.96 - 1.09 (12 H, m), 0.89 (4 H, d, *J*=6.71 Hz), 0.72 (2 H, s ancho).

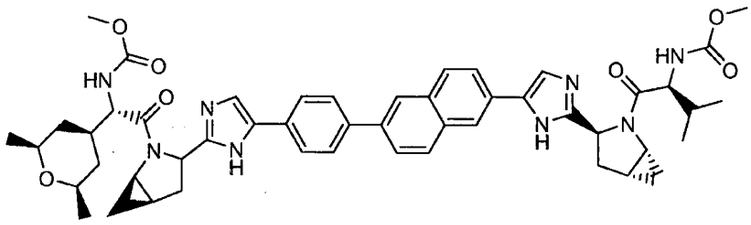


Ejemplo 78

((1S)-1-(((1R,3S,5R)-3-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2,2'-binaftalen-6-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de 6,6-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)-2,2'-binaftilo (Intermediario 133) (43.9 mg, 0.080 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (42.0 mg, 0.240 mmol) en DMF (1 ml) y DIPEA (0.14 ml, 0.80 mmol) se añadió HATU (91 mg, 0.240 mmol) y la solución marrón transparente se agitó durante 2 horas. La mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (agua/MeOH con TAF al 0.15) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2,2'-binaftalen-6-il)1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (28.9 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 1.788 min; m/z 863.46 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.37 (s, 2 H), 8.29 (d, J=1.0 Hz, 2 H), 8.15 (d, J=8.8 Hz, 2 H), 8.06 - 8.13 (m, 4 H), 7.97 (s, 2 H), 7.86 (dd, J=8.7, 1.6 Hz, 2 H), 5.17 (dd, J=9.3, 7.0 Hz, 2 H), 4.57 (d, J=6.8 Hz, 2 H), 3.80 - 3.86 (m, 2 H), 3.68 (s, 6 H), 2.71 (dd, J=13.7, 9.4 Hz, 2 H), 2.46 - 2.56 (m, 2 H), 2.15 - 2.25 (m, 2 H), 2.09 (d, J=8.0 Hz, 2 H), 1.08 - 1.16 (m, 2 H), 1.03 (d, J=6.8 Hz, 6 H), 0.92 - 0.96 (m, 6 H), 0.88 - 0.96 (m, 2 H).

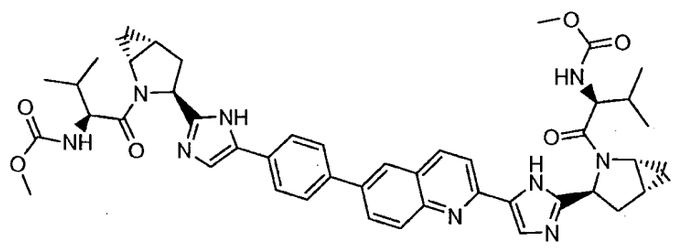


Ejemplo 79

((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,5R)-2-((2S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal en TFA de (2S)-1-((1R,3S,5R)-3-(5-(6-(4-(2-((1R,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (47 mg, 0.072 mmol) y ácido (S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético (23 mg, 0.093 mmol) en DMF (1 ml) y DIPEA (0.050 ml, 0.29 mmol) se añadió HATU (35.4 mg, 0.093 mmol) y la reacción se agitó durante 3 horas. La mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (MeOH/agua con CFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,5R)-2-((2S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-

1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (31.3 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 1.670 min; m/z 883.43 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.28 (d, J=1.0 Hz, 1 H), 8.26 (s, 1 H), 8.12 (d, J=8.8 Hz, 1 H), 8.07 (d, J=8.5 Hz, 1 H), 7.93 - 7.99 (m, 4 H), 7.82 - 7.92 (m, 4 H), 5.15 (td, J=9.6, 6.9 Hz, 2 H), 4.58 (t, J=7.4 Hz, 2 H), 3.79 - 3.86 (m, 2 H), 3.68 (s, 6 H), 3.43 - 3.53 (m, 2 H), 2.65 - 2.75 (m, 2 H), 2.50 (ddd, J=13.6, 6.7, 6.5 Hz, 2 H), 2.04 - 2.24 (m, 4 H), 1.54 - 1.62 (m, 1 H), 1.45 - 1.53 (m, 1 H), 0.84 - 1.21 (m, 18 H).

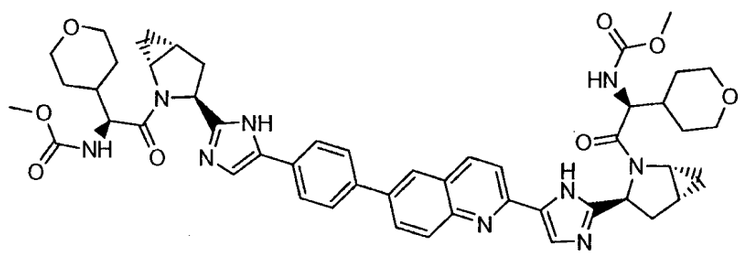


Ejemplo 80

((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal HCl de 2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)quinolina (Intermediario 139) (50 mg, 0.073 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (29.5 mg, 0.169 mmol) en DMF (1 ml) y DIPEA (0.115, 0.660 mmol) se añadió HATU (64.1 mg, 0.169 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O/MeOH con TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-ilfenil)-2-quinolinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-

il)carbonil)-2-metilpropil)carbamato de metilo (55.3 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.883 min; m/z 814.65 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



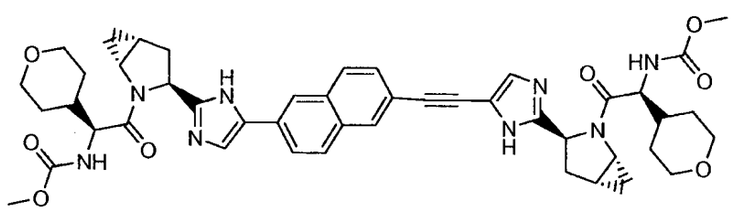
Ejemplo 81

((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-

oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de una sal de HCl de 2-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-6-(4-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)quinolinA (Intermediario 139) (50 mg, 0.073 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (36.6 mg, 0.169 mmol) en DMF (1 ml) y DIPEA (0.12 ml, 0.66 mmol) se añadió HATU (64.1 mg, 0.169 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (64.8 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.553 min; m/z 898.70 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un

tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



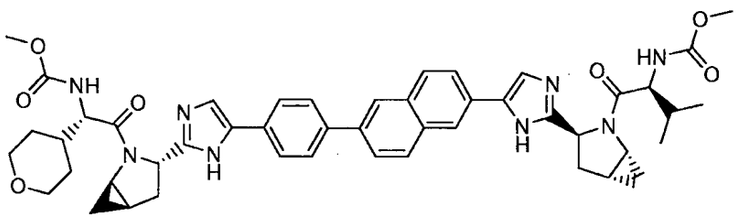
Ejemplo 82

((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-4-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (60 mg, 0.134 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético (58.4 mg, 0.269 mmol) en DMF (1.2 ml) y DIPEA (0.134, 0.19 ml, 1.1 mmol) se añadió HATU (102 mg, 0.269 mmol) y la reacción se agitó durante 2 horas. La reacción se diluyó con metanol y se purificó mediante HPLC preparativa

(MeOH/agua con amortiguador de acetato amónico) para dar ((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (48.9 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 2.572 min; m/z 845.65 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) □ ppm 8.14 (s, 1 H), 7.96 (s, 1 H), 7.80 - 7.87 (m, 3 H), 7.51 (dd, *J*=8.5, 1.5 Hz, 1 H), 7.45 (s, 1 H), 7.27 (s, 1 H), 5.16 (dd, *J*=8.8, 5.0 Hz, 1 H), 5.11 (dd, *J*=8.8, 4.5 Hz, 1 H), 4.66 (d, *J*=7.5 Hz, 1 H), 4.63 (d, *J*=7.8 Hz, 1 H), 3.90 - 3.98 (m, 4 H), 3.67 (s, 6

H), 3.63 - 3.76 (m, 2 H), 3.33 - 3.44 (m, 4 H), 2.32 - 2.56 (m, 4 H), 1.98 - 2.10 (m, 4 H), 1.35 - 1.67 (m, 8 H), 1.08 - 1.16 (m, 2 H), 0.78 (s ancho, 2 H).



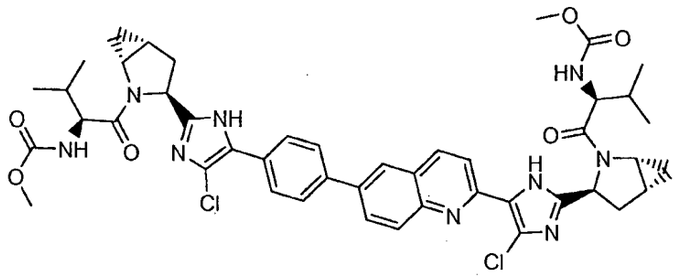
Ejemplo 83

((1S)-2-((1R,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-naftil)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de (2S)-1-((1R,3S,5R)-3-(5-(6-(4-(2-((1R,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)fenil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (Intermediario 131) (40 mg, 0.061 mmol) y ácido (S)-2(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (15.90 mg, 0.073 mmol) se añadió HATU (27.8 mg, 0.073 mmol) y se disolvieron en DMF (0.5 ml) y DIPEA (0.053 ml, 0.31 mmol) y la reacción se agitó a TA durante 2 horas. La reacción se diluyó con metanol y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador acetato amónico) para dar ((1S)-2-(((1R,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (3.5 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 2.785 min; m/z 855.74 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.17 (s, 1 H), 8.10 (s, 1 H), 7.93 (dd, J=8.5, 3.0 Hz, 2 H), 7.77 - 7.86 (m, 6 H), 7.44 (s, 1 H), 7.35 (s, 1 H), 5.20 (dd, J=8.9, 4.6 Hz, 1 H), 5.15 (dd, J=8.8, 5.0 Hz, 1 H), 4.66 (d, J=7.8 Hz, 1 H), 4.61 (d, J=6.8 Hz, 1 H), 3.90 - 3.99 (m, 2 H), 3.68 (s, 6 H), 3.64 - 3.76 (m, 3 H), 3.34 - 3.43 (m, 3 H), 2.39 - 2.61 (m, 4 H), 2.12 - 2.23 (m, 1 H), 1.99 - 2.10 (m, 2 H), 1.52 -

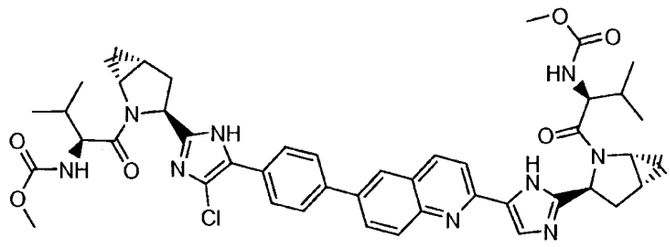
1.67 (m, 2 H), 1.41 - 1.51 (m, 1 H), 1.08 - 1.18 (m, 2 H), 1.02 (d, *J*=6.8 Hz, 3 H), 0.94 (d, *J*=6.8 Hz, 3 H), 0.76 - 0.84 (m, 2 H).



Ejemplo 84

((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-az[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

y



Ejemplo 85

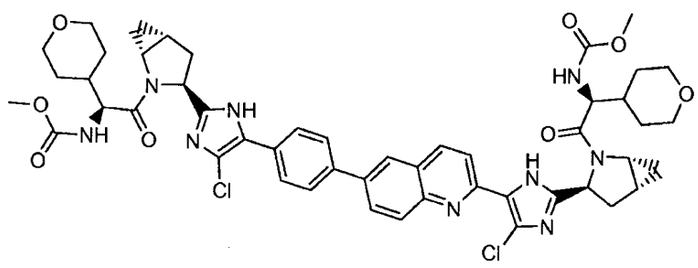
((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal en TFA de ((1S)-

1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-ilfenil)-2-quinolinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (Ejemplo 80) (26 mg, 0.022 mmol) en DMF (0.5 ml) se añadió N-clorosuccinimida (6.01 mg, 0.045 mmol) y la mezcla de reacción se agitó a 50°C durante 16 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador TFA al 0.1%) para dar dos productos: 1) Una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (12.4 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.871 min; m/z 882.55 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de

0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.53 (d, *J*=8.8 Hz, 1 H), 8.26 (d, *J*=8.8 Hz, 1 H), 8.23 (s, 1 H), 8.17 (s, 2 H), 7.82 - 7.93 (m, 4 H), 5.16 (dd, *J*=8.8, 5.3 Hz, 1 H), 5.06 (t, *J*=7.2 Hz, 1 H), 4.53 - 4.63 (m, 2 H), 3.68 - 3.76 (m, 2 H), 3.67 (s, 6 H), 2.44 - 2.60 (m, 4 H), 2.11 - 2.24 (m, 2 H), 1.97 - 2.09 (m, 2 H), 1.09 - 1.18 (m, 2 H), 1.03 (dd, *J*=6.8, 3.3 Hz, 6 H), 0.95 (dd, *J*=6.8, 2.4 Hz, 6 H), 0.75 - 0.87 (m, 2 H). 2) Una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (4.8 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.98 min; m/z 848.60 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0%

de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.64 (d, *J*=8.8 Hz, 1 H), 8.34 (s, 1 H), 8.32 (s, 1 H), 8.25 - 8.29 (m, 2 H), 8.09 (d, *J*=8.8 Hz, 1 H), 7.86 - 7.96 (m, 4 H), 5.18 - 5.25 (m, 1 H), 5.03 - 5.09 (m, 1 H), 4.53 - 4.62 (m, 2 H), 3.64 - 3.83 (m, 2 H), 3.64 - 3.69 (m, 6 H), 2.42 - 2.70 (m, 4 H), 1.97 - 2.24 (m, 4 H), 1.08 - 1.17 (m, 2 H), 1.02 (dd, *J*=6.8, 2.4 Hz, 6 H), 0.94 (t, *J*=6.8 Hz, 6 H), 0.76 - 0.91 (m, 2 H).



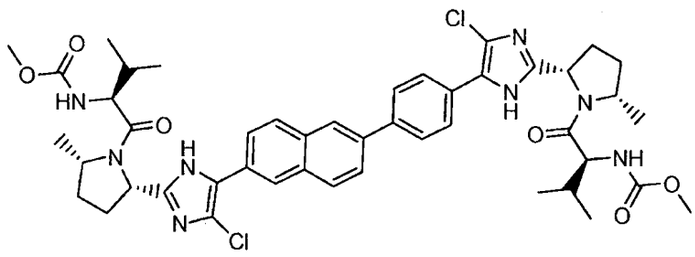
Ejemplo 86

((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil-3-quinolinil-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (Ejemplo 81) (31 mg, 0.025 mmol) en DMF (0.5 ml) se añadió N-clorosuccinimida (6.68 mg, 0.050 mmol) y la mezcla de reacción se agitó a 50 °C durante 16 h. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de CFA al 0.1%) para dar ((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-(4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (12.1 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.511 min; m/z 484.17 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad

de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.60 (d, *J*=8.8 Hz, 1 H), 8.27 - 8.33 (m, 2 H), 8.21 (s, 2 H), 7.89 - 7.95 (m, 2 H), 7.83 - 7.88 (m, 2 H), 5.15 (dd, *J*=8.7, 5.6 Hz, 1 H), 5.05 (dd, *J*=8.3, 6.3 Hz, 1 H), 4.64 (dd, *J*=11.3, 7.8 Hz, 2 H), 3.87 - 4.00 (m, 4 H), 3.73 - 3.81 (m, 2 H), 3.68 (s, 6 H), 3.33 - 3.48 (m, 4 H), 2.41 - 2.61 (m, 4 H), 1.95 - 2.16 (m, 4 H), 1.39 - 1.70 (m, 8 H), 1.06 - 1.18 (m, 2 H), 0.81 (m, 2 H).



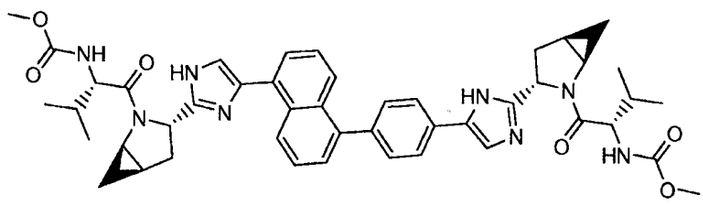
Ejemplo 87

((1S)-1-(((2S,5S)-2-(4-cloro-5-(4-(6-(4-cloro-2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-

metilpropil)carbamato de metilo

A una solución agitada de una sal en TFA de ((1S)-1-(((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (105 mg, 0.129 mmol) en DMF (3.0 ml) se añadió N-clorosuccinimida (18.88 mg, 0.141 mmol) y, después, el vaso de reacción se aclaró con nitrógeno, se selló y se calentó a 50°C durante la noche. Mediante CLEM una proporción 1.3:1.6:1 del material de partida : mono-Cl (presumiblemente ambos regioisómeros : dicloro). La reacción se concentró, se disolvió en MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con un amortiguador de TFA) para dar un material de partida recuperado (36.2 mg), una mezcla de los dos regioisómeros mono-cloroimidazol (56.6 mg) (Ejemplo 94 y Ejemplo 95) y una sal en TFA de ((1S)-1-(((2S,5S)-2-(4-cloro-5-(4-(6-(4-cloro-2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (20.4 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.482 min; m/z 885.84 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una

columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



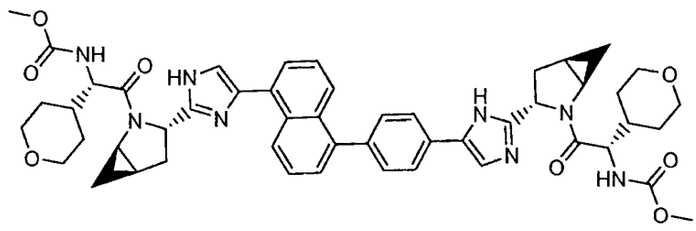
Ejemplo 88

((1S)-1-(((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-1-naftil(fenil)--1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

(Intermediario 144) (42.6 mg, 0.066 mmol) y ácido (S)-2-(metoxicarbonilamino)metilbutanoico (28.9 mg, 0.165 mmol) en DMF (0.8 ml) y DIPEA (0.092 ml, 0.53 mmol) se añadió HATU (62.8 mg, 0.165 mmol) y la reacción se agitó a TA durante 2 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-ilfenil)-2-quinolinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-1-metilpropil)carbamato de metilo (53.7 mg) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 2.821 min; m/z 813.88 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se

determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.06 (d, *J*=8.5 Hz, 1 H), 7.98 (d, *J*=8.5 Hz, 1 H), 7.95 (s, 1 H), 7.91 (d, *J*=8.5 Hz, 2 H), 7.78 (s, 1 H), 7.65 - 7.73 (m, 4 H), 7.59 - 7.64 (m, 2 H), 5.18 (ddd, *J*=12.5, 9.2, 7.0 Hz, 2 H), 4.59 (dd, *J*=6.4, 3.4 Hz, 2 H), 3.80 - 3.87 (m, 2 H), 3.69 (s, 6 H), 2.73 (dt, *J*=13.4, 9.2 Hz, 2 H), 2.48 - 2.59 (m, 2 H), 2.18 - 2.28 (m, 2 H), 2.10 (s ancho, 2 H), 1.08 - 1.15 (m, 2 H), 1.06 (d, *J*=7.0 Hz, 3 H), 1.04 (d, *J*=7.0 Hz, 3 H), 0.99 (d, *J*=6.7 Hz, 3 H), 0.95 (d, *J*=6.7 Hz, 3 H), 0.89 - 0.94 (m, 2 H).



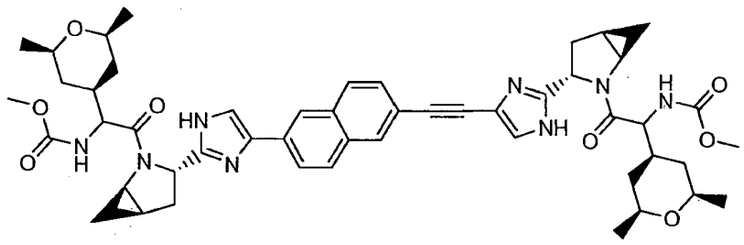
Ejemplo 89

((1S)-2-((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-1-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-3-(5-(4-(5-(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)naftalen-1-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

(Intermediario 144) (42.6 mg, 0.066 mmol) y ácido (S)-2-(metoxicarbonilamino)2-tetrahidro-2H-piran-4-il)acético (35.9 mg, 0.165 mmol) en DMF (0.8 ml) y DIPEA (0.092 ml, 0.53 mmol) se añadió HATU (62.8 mg, 0.165 mmol) y la reacción se agitó a TA durante 4 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de acetato amónico) para dar ((1S)-2-((1R,3S,5R)-3-(4-(4-(5-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (42.6 mg, 0.066 mmol) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 1.965 min; m/z 897.59 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 4 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 1 min donde el solvente A fue MeOH al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/MeOH al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron

usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8.23 (d, *J*=8.2 Hz, 1 H), 7.91 (d, *J*=8.5 Hz, 1 H), 7.82 (d, *J*=8.2 Hz, 2 H), 7.52 - 7.59 (m, 2 H), 7.44 - 7.51 (m, 4 H), 7.41 (s, 1 H), 7.21 (s, 1 H), 5.23 (dd, *J*=8.9, 4.6 Hz, 1 H), 5.18 (dd, *J*=8.9, 4.9 Hz, 1 H), 4.68 (dd, *J*=7.5, 2.6 Hz, 2 H), 3.89 - 4.01 (m, 4 H), 3.70 - 3.77 (m, 2 H), 3.69 (s, 6 H), 3.35 - 3.45 (m, 4 H), 2.43 - 2.63 (m, 4 H), 2.00 - 2.14 (m, 4 H), 1.52 - 1.71 (m, 6 H), 1.41 - 1.52 (m, 2 H), 1.10 - 1.18 (m, 2 H), 0.79 - 0.86 (m, 2 H).



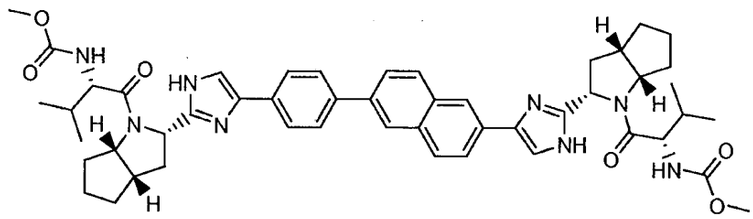
Ejemplo 90

((1S)-1-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((1R,3S,5R)-3-(4-((6-(2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil)carbamato de metilo

Una sal HCl de (1R,3S,5R)-4-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 124) (50 mg, 0.073

mmol), ácido 2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético (*Cap-179 estereoisómero 2)* (36.9 mg, 0.151 mmol) HATU (58.6 mg, 0.154 mmol) y DIEA (0.077 ml, 0.441 mmol) se combinaron en DMF (3 ml) y la solución amarilla resultante se agitó a TA durante 15 horas. Los volátiles se retiraron a presión reducida y el residuo se redisolvió en metanol y se purificó mediante HPLC preparativa (solvente A: MeOH al 10%/agua al 90%/TFA al 0.1% ; solvente B: MeOH al 90%/agua al 10%/TFA al 0.1% ; Columna: Sunfire Prep MS C18 de 30 x 100 mm de 5u; Longitud de onda: 220 nM; Velocidad de flujo: 40 ml/min; gradiente: 10 % de B a 80% de B durante 30 min, con un tiempo de conservación de 5 min) para dar una sal en TFA de ((1S)-1-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((1R,3S,5R)-3-(4-((6-(2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil)carbamato de metilo (43 mg) en forma de un sólido blanco. CL/EM [M+H]+= 902; Tr = 1.93 min es el producto. Columna PHENOMENEX® de 10u C18 de 3.0x50mm; inicio %B: 0, final %B: 100 solvente A: MeOH al 10%/H_2O al 90% + TFA al 1%; solvente B: MeOH al 90%/ H_2O al 10%+ TFA al 1%; velocidad de flujo 4 ml/min. Tiempo de recorrido: 5 min. Pureza = 98 %. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 8.38 (1 H,

s ancho,), 8.14 - 8.22 (1 H, m), 8.09 (1 H, d, *J*=8.85 Hz), 7.93 - 8.00 (2 H, m), 7.62 (1 H, d, *J*=8.85 Hz), 7.25 (2 H, t, *J*=7.48 Hz), 5.02 (2 H, t, *J*=6.87 Hz), 4.51 (1 H, dd, *J*=7.78, 6.56 Hz), 4.45 (1 H, t, *J*=7.93 Hz), 3.82 (1 H, s ancho,), 3.67 (1 H, d, *J*=13.73 Hz), 3.54 (6 H, s), 3.31 - 3.42 (3 H, m), 2.33 (2 H, s ancho,), 1.85 - 1.97 (2 H, m), 1.43 - 1.52 (1 H, m), 1.22 - 1.31 (1 H, m), 1.03 - 1.12 (10 H, m), 0.89 - 1.01 (9 H, m), 0.82 (1 H, s ancho,), 0.75 (1 H, s ancho.).

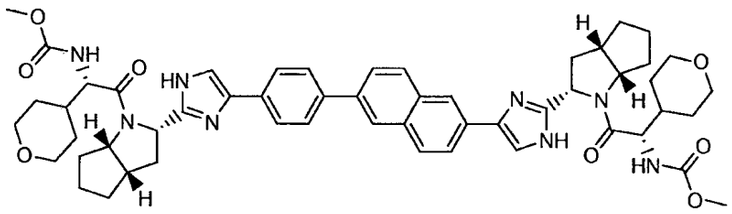


Ejemplo 91

((1S)-1-(((2S,3aS,6aS)-2-(4-(6-(4-(2-((2S,3aS,6aS)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)octahidrociclopenta[b]pirrol-2-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)hexahidrociclopenta[b]pirrol-1(2H)-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de 2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)octahidrociclopenta[b]pirrol (51 mg, 0.073 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (Intermediario 147) (28.1 mg, 0.160 mmol) y

DIPEA (0.076 ml, 0.44 mmol) en DCM (1.5 ml) se añadió HATU (60.9 mg, 0.160 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. La mezcla de reacción bruta se concentró hasta sequedad y se purificó mediante HPLC preparativa (amortiguador TFA) para dar una sal en TFA de ((1S)-1-(((2S,3aS,6aS)-2-(4-(6-(4-(2-((2S,3aS,6aS)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)octahidrociclopenta[b]pirrol-2-il)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)hexahidrociclopenta[b]pirrol-1(2H)-il)carbonil)-2-metilpropil)carbamato de metilo (23.7 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 2.462 min; m/z 867.8 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 1 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

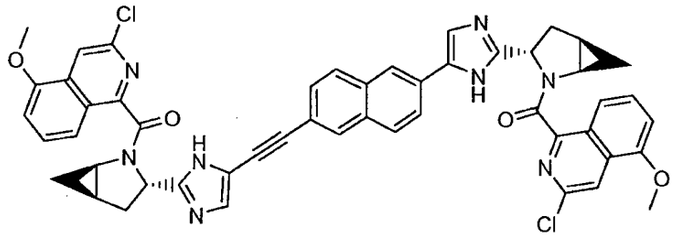


Ejemplo 92

((1S)-2-((2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)hexahidrociclopenta[b]pirrol-2(2H)-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)hexahidrociclopenta[b]pirrol-1(2H)-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal HCl de (2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)octahidrociclopenta[b]pirrol (51 mg, 0.073 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (Intermediario 147) (52 mg, 0.074 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (35.5 mg, 0.163 mmol) y DIPEA (0.078 ml, 0.45 mmol) en DCM (1.5 ml) se añadió HATU (62.1 mg, 0.163 mmol) y la mezcla se agitó a TA durante 2 horas. La mezcla de reacción bruta se concentró hasta sequedad y se purificó mediante HPLC preparativa con amortiguador de TFA) para dar una sal en TFA de ((1S)-2-((2S,3aS,6aS)-2-(4-(4-(6-(2-((2S,3aS,6aS)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-

2H-piran-4-il)acetil)hexahidrociclopenta[b]pirrol-2(2H)-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)hexahidrociclopenta[b]pirrol-1(2H)-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (25.8 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 2.350 min; m/z 477.5 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 1 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



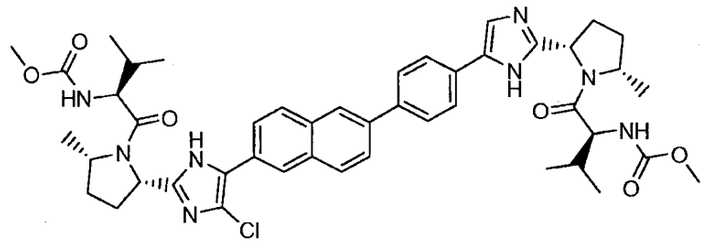
Ejemplo 93

3-cloro-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-azabiciclo[3.1.0]hex-3-

il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-5-metoxisoquinolina

A una solución agitada de una sal HCl de (1R,3S,5R)-5-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 124) (30 mg, 0.051 mmol) y ácido 3-cloro-5-metoxiisoquinolin-1-carboxílico (30.1 mg, 0.127 mmol) en DMF (0.88 ml) y DIPEA (0.071, 0.45 mmol) se añadió HATU (48.1 mg, 0.127 mmol) y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con un amortiguador de NH_4OAc) y se volvió a purificar mediante HPLC preparativa MeOH/agua con un amortiguador de TFA) para dar una sal en TFA DE (3-cloro-1-(((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((3-cloro-5-metoxi-1-isoquinolinil)carbonil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-5-metoxiisoquinolina (40.0 mg) en forma de sólido amarillo. Tiempo de retención en la CL-EM 3.621 min; m/z 887.34 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente

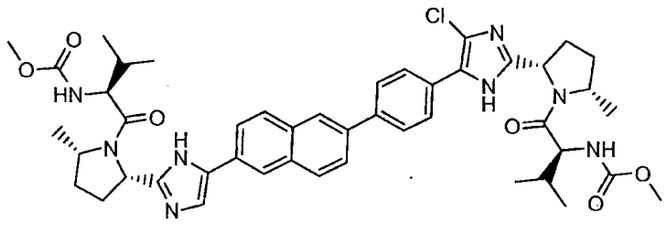
A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



Ejemplo 94

((1S)-1-(((2S,5S)-2-(4-(4-((4-cloro-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

y



Ejemplo 95

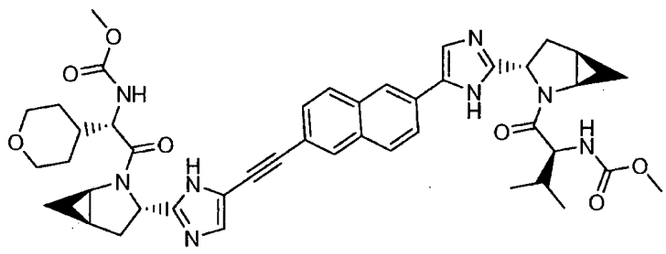
((1S)-1-(((2S,5S)-2-(4-cloro-5(-4-6-(2-((2S,5S)-1-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

Estos dos compuestos se prepararon en la reacción que preparó ((1S)-1-(((2S,5S)-2-(4-cloro-5-(4-(6-(4-cloro-2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-5-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (Ejemplo 87) y se aislaron como una mezcla de mono-cloroimidazol regioisómeros. Los dos regioisómeros se separaron mediante SCFC en una columna CHIRALCEL® OJ-H (30 x 250mm, 5µm) usando solventes: 75% de CO_2 - 25% de EtOH/0.1% de DEA. La regioquímica absoluta de los dos mono-cloroimidazol regioisómeros no se determinó de modo que cada uno fue asignado de forma arbitraria. Ejemplo 94: ((1S)-1-(((2S,5S)-2-(4-(4-((4-cloro-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (18.6 mg) se aisló en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.756 min; m/z 851.62 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un

detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. Ejemplo 95: ((1S)-1-(((2S,5S)-2-(4-cloro-5-(4-(6-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (24.1 mg) se aisló en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.770 min; m/z 851.64 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de

análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



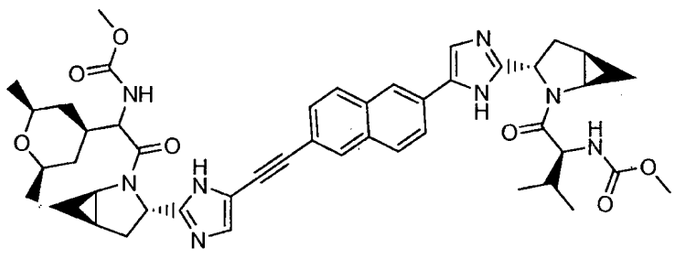
Ejemplo 96

((1S)-2-(((1R,3S,5R)-3-(4-(6-(2-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)etinil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etilcarbamato de metilo

A una solución de 3-(5-((6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (Intermediario 150) (69 mg, 0.074 mmol) en dioxano (2 ml) se añadió HCl 4M (0.370 ml, 1.48 mmol) en dioxano y la suspensión espesa se agitó durante 1.5 horas. La mezcla de reacción se concentró después bajo corriente de nitrógeno y el producto intermediario se trató con ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-

piran-4-il)acético (20.9 mg, 0.096 mmol), DMF (1.5 ml), DIPEA (0.078 ml, 0.44 mmol) y, por último, HATU (36.6 mg, 0.096 mmol). La mezcla de reacción se agitó durante la noche a TA, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador TFA al 0.1%) para dar una sal en TFA de ((1S)-2-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (35.3 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.726 min; m/z 803.74 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm

8.27 (s, 1 H), 8.18 (s, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.02 (m, 2 H), 7.88 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.74 (s, 1 H), 7.67 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.15 (dd, *J*=9.3, 7.0 Hz, 1 H), 5.09 (dd, *J*=9.0, 6.3 Hz, 1 H), 4.59 (d, *J*=7.8 Hz, 1 H), 4.56 (d, *J*=6.5 Hz, 1 H), 3.91 - 4.00 (m, 2 H), 3.74 - 3.84 (m, 2 H), 3.67 (s, 6 H), 3.34 - 3.45 (m, 2 H), 2.70 (dd, *J*=13.6, 9.5 Hz, 1 H), 2.61 (dd, *J*=13.8, 8.8 Hz, 1 H), 2.40 - 2.54 (m, 2 H), 2.14 - 2.23 (m, 1 H), 2.01 - 2.13 (m, 3 H), 1.56 - 1.64 (m, 1 H), 1.38 - 1.55 (m, 3 H), 1.05 - 1.14 (m, 2 H), 1.01 (d, *J*=6.8 Hz, 3 H), 0.92 (d, *J*=6.8 Hz, 3 H), 0.82 - 0.92 (m, 2 H).



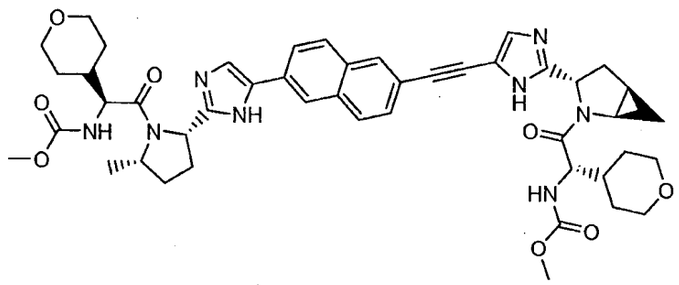
Ejemplo 97

((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de 3-(5-((6-(2-((1R,3S,5R)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)naftalen-2-

il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (Intermediario 150) (62.7 mg, 0.067 mmol) en dioxano (2 ml) se añadió HCl 4M (0.34 ml, 1.3 mmol) en dioxano y la suspensión espesa se agitó durante 1.5 horas. La reacción se concentró después bajo corriente de nitrógeno hasta sequedad y después se trató con ácido 2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético (*Cap-179 estereoisómero 2)* (21.45 mg, 0.087 mmol), DMF (1.5 ml), DIPEA (0.071 ml, 0.40 mmol) y, por último, HATU (33.3 mg, 0.087 mmol). La mezcla de reacción se agitó durante la noche a TA con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,5R)-2-((2S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (28 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.898 min; m/z 831.80 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un

gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.27 (s, 1 H), 8.17 (s, 1 H), 8.05 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.02 (m, 2 H), 7.88 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.74 (s, 1 H), 7.66 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.15 (dd, *J*=9.2, 6.9 Hz, 1 H), 5.10 (dd, *J*=9.0, 6.3 Hz, 1 H), 4.56 (t, *J*=6.0 Hz, 2 H), 3.73 - 3.85 (m, 2 H), 3.67 (s, 6 H), 3.43 - 3.54 (m, 2 H), 2.70 (dd, *J*=13.7, 9.4 Hz, 1 H), 2.61 (dd, *J*=13.6, 9.0 Hz, 1 H), 2.40 - 2.54 (m, 2 H), 2.01 - 2.23 (m, 4 H), 1.55 - 1.64 (m, 1 H), 1.46 (d, *J*=12.0 Hz, 1 H), 1.17 (dd, *J*=6.0, 4.3 Hz, 6 H), 1.04 - 1.13 (m, 3 H), 1.01 (d, *J*=6.8 Hz, 3 H), 0.96 - 1.03 (m, 1 H), 0.92 (d, *J*=6.8 Hz, 3 H), 0.88 - 0.93 (m, 1 H), 0.82 - 0.87 (m, 1 H).



Ejemplo 98

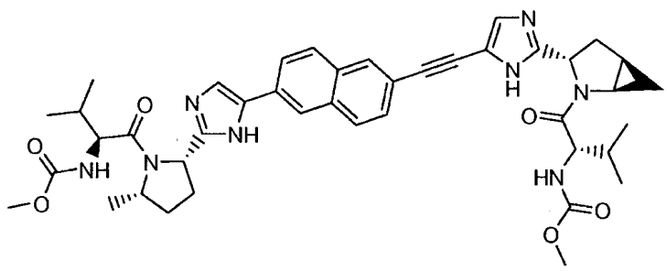
((1S)-2-((2S,5S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-

((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una sal HCl de (1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 154) (27 mg, 0.045 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético (24.7 mg, 0.114 mmol) en DMF (1 ml) y DIPEA (0.056, 0.32 ml, 0.32 mmol) se añadió HATU (43.2 mg, 0.114 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. La reacción se concentró en una corriente de nitrógeno, se disolvió en MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de TFA al 0.1%) para dar una sal en TFA de((1S)-2-((2S,5S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (31.4 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.658 min; m/z 847.80 (MH+). Los datos de CL se registraron en un cromatógrafo de

líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H se presenta como una mezcla ~1:3:5 de rotámeros. L RMN de ^1H para el rotámero mayoritarios es: RMN de ^1H (400 MHz, MeOD) δ ppm 8.29 (s, 1 H), 8.18 (s, 1 H), 8.06 (d, *J*=8.5 Hz, 1 H), 8.01 (d, *J*=8.8 Hz, 1 H), 7.99 (s, 1 H), 7.89 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.74 (s, 1 H), 7.67 (dd, *J*=8.4, 1.4 Hz, 1 H), 5.19 (dd, *J*=10.5, 7.0 Hz, 1 H), 5.09 (dd, *J*=8.9, 6.4 Hz, 1 H), 4.59 (d, *J*=7.5 Hz, 1 H), 4.22 (d, *J*=9.3 Hz, 1 H), 3.86 - 4.00 (m, 4 H), 3.72 - 3.82 (m, 2 H), 3.67 (s, 6 H), 3.23 - 3.45 (m, 4 H), 2.50 - 2.70 (m, 2 H), 2.24 - 2.50 (m, 3 H), 1.90 - 2.13 (m, 4 H), 1.70 - 1.85 (m, 1 H), 1.57 (d, *J*=6.5 Hz, 3 H), 1.30 - 1.64 (m, 6

H), 1.23 (d, *J*=11.5 Hz, 1 H), 1.04 - 1.12 (m, 1 H), 0.85 (s ancho, 1 H).



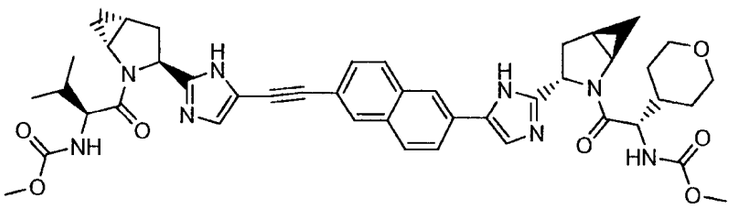
Ejemplo 99

((1S)-1-(((1R,3S,5R)-3-(4-((6-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (1R,3S,5R)-3-(4-((6-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 154) (10.1 mg, 0.017 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (7.44 mg, 0.042 mmol) en DMF (0.5 ml) y DIPEA (0.021, 0.119 ml) se añadió HATU (43.2 mg, 0.114 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. La reacción se concentró disuelta en MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de ((1S)-1-(((2S,5S)-((1S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil-1H-imidazol-4-i)naftil)etinil-1H-imidazol-2-il)-

2-azabiciclo[3.1.0]hex-2-il)carbonil)-1-metilpropil)carbamato de metilo (9.3 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 2.930 min; m/z 763.75 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H representa una mezcla de ~1:3 de rótamelos, los datos para el rotámero mayoritario son: RMN de ^1H (400 MHz, MeOD) δ ppm 8.30 (s, 1 H), 8.19 (s, 1 H), 8.07 (d, J=8.8 Hz, 1 H), 7.99 - 8.03 (m, 2 H), 7.90 (dd, J=8.5, 1.5 Hz, 1 H), 7.77 (s, 1 H), 7.65 - 7.71 (m, 1 H), 5.19 (dd, J=10.2, 6.9 Hz, 1 H), 5.10 (dd, J=9.2, 6.4 Hz, 1 H), 4.55 (d, J=6.5 Hz, 1 H), 4.13 (d, J=8.8 Hz, 1 H), 3.67 (s, 6 H), 3.65 - 3.79 (m, 2 H), 1.95 - 2.68 (m, 8 H), 1.57 (d, J=6.5 Hz, 3 H), 1.31 (d, J=6.3 Hz, 1 H), 1.01 (d, J=7.0 Hz, 3 H), 0.98 (d, J=7.0 Hz, 3 H), 0.93 (d, J=6.8 Hz, 3 H),

0.88 (d, *J*=6.8 Hz, 3 H), 0.84 - 1.14 (m, 2 H).



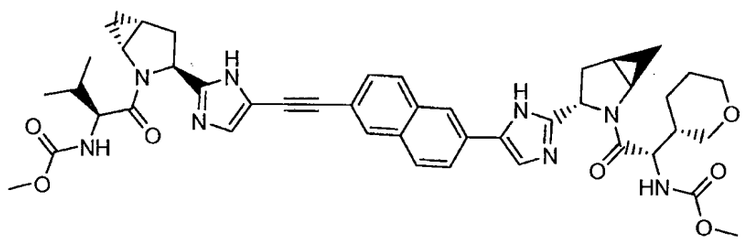
Ejemplo 100

((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una mezcla de una sal en TFA de 1,3-(6-(4-(5-(2-((1R,3S,5R)-2-(metoxicarbonilamino)-3-metilbutanoil-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)etinil)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (60 mg, 0.064 mmol) en dioxano (0.5 ml) se añadió HCl 4M (0.32 ml, 1.3 mmol) en dioxano y la reacción se agitó enérgicamente durante 4 horas. La reacción se concentró hasta sequedad.. Después, se añadieron ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (18.2 mg, 0.084 mmol), DMF (0.5 ml), DIPEA (0.067 ml, 0.39 mmol) y, por último, HATU (31.8 mg) al material bruto y la reacción se agitó a TA durante 1 hora. La reacción se concentró parcialmente con una corriente de nitrógeno, se

diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa ((MeOH/agua con un amortiguador de TFA) y después se volvió a purificar mediante HPLC preparativa ((MeOH/agua con un amortiguador de acetato amónico.). El material se purificó una tercera vez mediante HPLC preparativa (MeOH/agua con amortiguador TFA) para dar una sal en TFA de ((1S)-2-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil-2-naftil)-1H-imidazol-2-il)-2-azabiciclo-[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2-H-piran-4-il)carbamato de metilo (27.7 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 3.291 min; m/z 803.67 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo

de electrorrocío. RMN de ^{1}H (400 MHz, MeOD) δ ppm 8.27 (s, 1 H), 8.19 (s, 1 H), 8.06 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.03 (m, 2 H), 7.88 (dd, *J*=8.5, 1.8 Hz, 1 H), 7.78 (s, 1 H), 7.68 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.15 (dd, *J*=9.0, 7.0 Hz, 1 H), 5.09 (dd, *J*=9.3, 6.5 Hz, 1 H), 4.80 (d, 2 H), 4.54 (d, *J*=6.5 Hz, 1 H), 3.87 - 3.93 (m, 1 H), 3.70 - 3.79 (m, 3 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.54 - 3.63 (m, 1 H), 3.34 - 3.40 (m, 1 H), 2.59 - 2.74 (m, 2 H), 2.40 - 2.55 (m, 2 H), 2.00 - 2.22 (m, 4 H), 1.71 - 1.81 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.05 - 1.14 (m, 2 H), 1.01 (d, *J*=6.8 Hz, 3 H), 0.93 (d, *J*=6.8 Hz, 3 H), 0.88 (s ancho, 2 H).



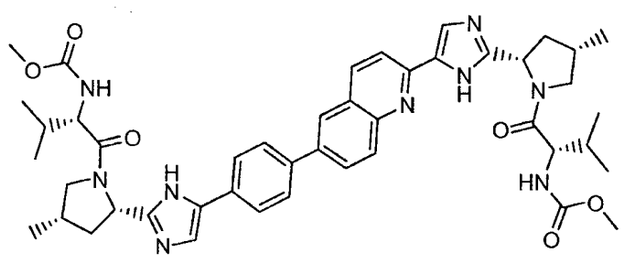
Ejemplo 101

((1S)-2-((1R,3S,5R)-3-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-((3S)-tetrahidro-2H-piran-3-il)etil)carbamato de metilo

A una mezcla de una sal en TFA de 1,3-(6-(4-(5-(2-((1R,3S,5R)-2-(metoxicarbonilamino)-3-metilbutanoil-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-il)etinil)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-

azabiciclo[3.1.0]hexan-2-carboxilato de (1R,3S,5R)-*terc*-butilo (60 mg, 0.064 mmol) en dioxano (0.5 ml) se añadió HCl 4M (0.3 ml, 1.3 mmol) en dioxano y la reacción se agitó enérgicamente durante 4 horas. La reacción se concentró hasta sequedad. Después, se añadieron ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-3-il)acético (18.2 mg, 0.084 mmol) (Cap. 177a), DMF (0.5 ml), DIPEA (0.067 ml, 0.39 mmol) y, por último, HATU (32 mg) al material bruto y la reacción se agitó a TA durante 1 hora. La reacción se concentró parcialmente, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador TFA) y se volvió a purificar en una inyección mediante HPLC preparativa (MeOH/agua con amortiguador acetato amónico) para dar una sal en TFA de ((1S)-2-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil-2-naftil)-1H-imidazol-2-il)-2-azabiciclo-[3.1.0]hex-2-il)-2-oxo-1-(3S)-(tetrahidro-2-H-piran-3-il)carbamato de metilo (30.5 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 3.376 min; m/z 803.66 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un

velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.14 (s, 1 H), 7.94 (s, 1 H), 7.78 - 7.86 (m, 3 H), 7.49 (dd, *J*=8.5, 1.5 Hz, 1 H), 7.45 (s, 1 H), 7.26 (s, 1 H), 5.15 (ddd, *J*=12.9, 8.7, 4.5 Hz, 2 H), 4.57 (d, *J*=6.8 Hz, 1 H), 3.70 - 3.86 (m, 3 H), 3.67 (s ancho, 3 H), 3.66 (s ancho, 3 H), 3.58 - 3.64 (m, 1 H), 3.53 (t, *J*=8.3 Hz, 1 H), 3.45 (dd, *J*=11.4, 8.2 Hz, 1 H), 2.31 - 2.57 (m, 4 H), 1.93 - 2.17 (m, 5 H), 1.67 - 1.84 (m, 2 H), 1.50 - 1.63 (m, 2 H), 1.08 - 1.17 (m, 2 H), 0.98 (d, *J*=6.8 Hz, 3 H), 0.92 (d, *J*=6.8 Hz, 3 H), 0.78 (s ancho, 2 H).



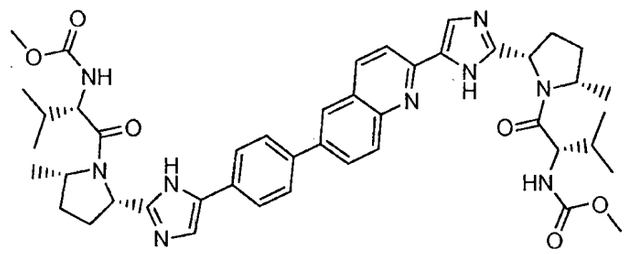
Ejemplo 102

((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal de HCl de 2-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)-6-(4-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina (Intermediario 164) (16.5 mg, 0.024 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-(metilbutanoico (9.7 mg, 0.055 mmol) en DMF (0.5 ml) y DIPEA (0.038 ml, 0.22 mmol) se añadió HATU (20.99 mg, 0.055 mmol) y la mezcla de reacción se agitó a TA durante 16 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (8.3 mg, 6.94 µmol, rendimiento 28.9%) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.555 min; m/z 818.78 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de

elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.60 (d, *J*=8.5 Hz, 1 H), 8.34 (d, *J*=1.8 Hz, 1 H), 8.32 (s, 1 H), 8.26 - 8.31 (m, 1 H), 8.21 - 8.26 (m, 1 H), 8.06 (d, *J*=8.5 Hz, 1 H), 7.97 - 8.03 (m, 1 H), 8.00 (d, *J*=8.5 Hz, 1 H), 7.93 (s, 1 H), 7.87 - 7.92 (m, 2 H), 5.19 - 5.36 (m, 2 H), 4.29 - 4.41 (m, 2 H), 4.24 (t, *J*=6.9 Hz, 2 H), 3.67 (s, 6 H), 3.44 (c, *J*=11.0 Hz, 2 H), 2.62 - 2.74 (m, 2 H), 2.46 - 2.61 (m, 2 H), 1.97 - 2.12 (m, 2 H), 1.82 - 1.97 (m, 2 H), 1.26 (dd, *J*=6.3, 3.3 Hz, 6 H), 0.91 - 0.96 (m, 6 H), 0.89 (dd, *J*=6.7, 5.1 Hz, 6 H).



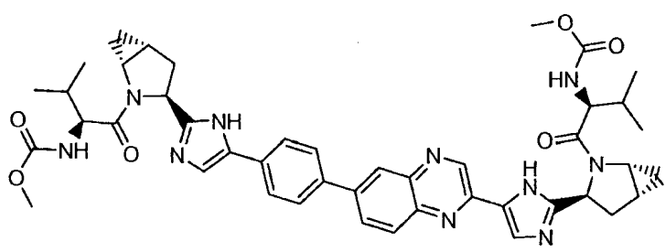
Ejemplo 103

((1S)-1-(((2S,5S)-2-(4-(6-(4-(2-((2S,5S)-1-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución de una sal de HCl bruta de 2-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)-6-(4-(2-((2S,5S)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina (Intermediario 167) (12.35 mg, 0.018 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-(metilbutanoico (7.25 mg, 0.041 mmol) en DMF (0.5 ml) y DIPEA (0.028 ml, 0.16 mmol) se añadió HATU (15.74 mg, 0.041 mmol) y la mezcla de reacción se agitó a TA durante 16 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador TFA al 0.1%) para dar una sal en TFA de ((1S)-1-(((2S,5S)-2-(4-(6-(4-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (3.9 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.616 min; m/z 818.73 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad

de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.68 (d, *J*=8.8 Hz, 1 H), 8.39 (d, *J*=1.3 Hz, 1 H), 8.30 - 8.35 (m, 2 H), 8.26 - 8.31 (m, 1 H), 8.16 (d, *J*=8.8 Hz, 1 H), 7.99 - 8.06 (m, 3 H), 7.89 - 7.94 (m, 2 H), 5.14 - 5.31 (m, 2 H), 4.14 (dd, *J*=8.8, 5.0 Hz, 2 H), 3.68 (s, 6 H), 2.47 - 2.59 (m, 2 H), 2.23 - 2.43 (m, 4 H), 1.95 - 2.10 (m, 4 H), 1.56 (dd, *J*=6.7, 3.6 Hz, 6 H), 1.01 - 1.07 (m, 2 H), 0.99 (dd, *J*=6.7, 3.4 Hz, 6 H), 0.89 (dd, *J*=6.8, 1.8 Hz, 6 H).



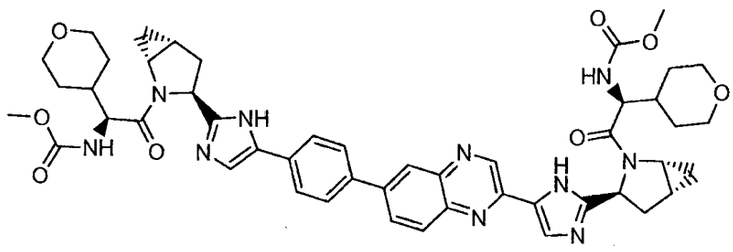
Ejemplo 104

((1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-

quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución de sal HCl de ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (Intermediario 173) (41.7 mg, 0.058 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (23.4 mg, 0.133 mmol) en DMF (1 ml) y DIPEA (0.09 ml, 0.5 mmol) se añadió HATU (50.7 mg, 0.133 mmol) y la mezcla de reacción se agitó a TA durante 16 horas. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador de TFA al 0.1%) para dar una sal en TFA de (1S)-1-(((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (22.3 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.451 min; m/z 815.72 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un

velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 9.41 (s, 1 H), 8.43 (d, *J*=8.5 Hz, 1 H), 8.41 - 8.47 (m, 1 H), 8.28 (d, *J*=1.3 Hz, 2 H), 8.03 (d, *J*=8.5 Hz, 1 H), 8.00 - 8.07 (m, 1 H), 7.87 - 7.95 (m, 3 H), 5.10 - 5.26 (m, 2 H), 4.57 (t, *J*=6.7 Hz, 2 H), 3.76 - 3.89 (m, 2 H), 3.68 (s, 6 H), 2.70 (dd, *J*=13.7, 9.2 Hz, 2 H), 2.44 - 2.56 (m, 2 H), 2.14 - 2.26 (m, 2 H), 2.04 - 2.14 (m, 2 H), 1.07 - 1.16 (m, 2 H), 1.02 (dd, *J*=6.8, 2.0 Hz, 6 H), 0.93 (dd, *J*=6.8, 2.0 Hz, 6 H), 0.83 - 0.99 (m, 2 H).



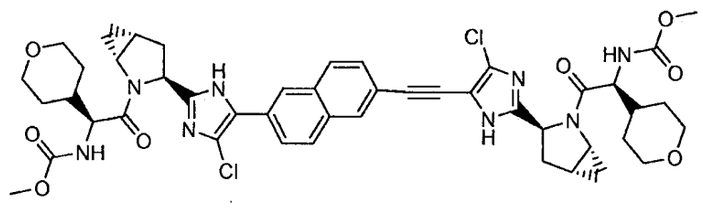
Ejemplo 105

((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-

2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de sal HCl de ((1S)-1-(((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (Intermediario 173) (10.1 mg, 0.014 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (7.0 mg, 0.032 mmol) en DMF (0.5 ml) y DIPEA (0.022 ml, 0.13 mmol) se añadió HATU (12.24 mg, 0.032 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. . La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/H2O con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-(6-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)-2-quinoxalinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (7.3 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.251 min; m/z 899.79 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un

detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 9.41 (s, 1 H), 8.41 - 8.47 (m, 2 H), 8.27 - 8.31 (m, 2 H), 8.03 (d, *J*=8.5 Hz, 1 H), 8.01 - 8.06 (m, 1 H), 7.87 - 7.95 (m, 3 H), 5.09 - 5.26 (m, 2 H), 4.61 (t, *J*=7.2 Hz, 2 H), 3.90 - 4.01 (m, 4 H), 3.80 - 3.90 (m, 2 H), 3.68 (s, 6 H), 3.34 - 3.47 (m, 4 H), 2.70 (dd, *J*=13.6, 9.3 Hz, 2 H), 2.45 - 2.57 (m, 2 H), 1.99 - 2.19 (m, 4 H), 1.36 - 1.68 (m, 8 H), 1.02 - 1.16 (m, 2 H), 0.79 - 0.96 (m, 2 H).



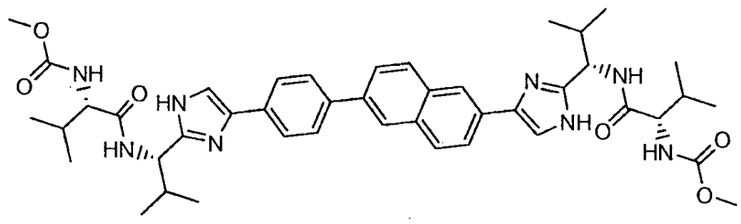
Ejemplo 106

((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-((4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-

il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)etinil-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de ((1S)-2-((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (Ejemplo 82) (21.0 mg, 0.025 mmol) en DMF se añadió N-clorosuccinimida (6.97 mg, 0.052 mmol) y después el vaso de reacción se aclaró con una corriente de nitrógeno, se selló y se calentó a 50°C durante 3 horas. Se añadió N-clorosuccinimida adicional (5.0 mg) y el vaso de reacción se aclaró con nitrógeno, se selló y se calentó a 50°C durante 3 horas, después la reacción se enfrió y se concentró en una corriente de nitrógeno. Los restos se disolvieron en MeOH, se filtraron y se purificaron mediante HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de ((1S)-2-((1R,3S,5R)-3-(4-cloro-5-(6-((4-cloro-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-

piran-4-il)etil)carbamato de metilo (8.1 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 4.276 min; m/z 457.47 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.18 (s, 1 H), 8.07 (s, 1 H), 7.98 (d, *J*=8.8 Hz, 1 H), 7.93 (d, *J*=8.5 Hz, 1 H), 7.88 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.59 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.05 (dd, *J*=8.5, 6.3 Hz, 1 H), 4.99 (t, *J*=6.9 Hz, 1 H), 4.62 (d, *J*=7.5 Hz, 2 H), 3.91 - 3.98 (m, 4 H), 3.74 - 3.81 (m, 1 H), 3.68 - 3.72 (m, 1 H), 3.67 (s, 6 H), 3.34 - 3.45 (m, 4 H), 2.45 - 2.56 (m, 2 H), 2.39 - 2.44 (m, 2 H), 1.96 - 2.11 (m, 4 H), 1.37 - 1.66 (m, 8 H), 1.05 - 1.14 (m, 2 H), 0.74 - 0.84 (m, 2 H).

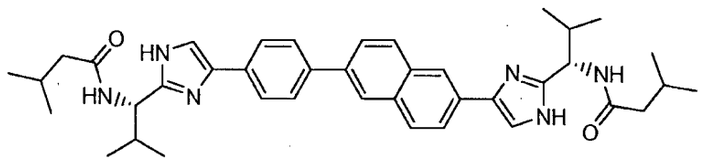


Ejemplo 107

((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)amino)-2-metilpropil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-metilpropil)carbamoil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (S)-1-(5-(4-(6-(2-((S)-1-amino-2-metilpropil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-metilpropan-1-amina (Intermediario 178) (57.4 mg, 0.092 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-metilbutanoico (35.4 mg, 0.202 mmol) y DIPEA (0.096 ml, 0.55 mmol) en DMF (1.5 ml) se añadió HATU (77 mg, 0.20 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. La mezcla de reacción bruta se concentró hasta sequedad y se purificó mediante HPLC preparativa (amortiguador de TFA) para dar una sal en TFA de ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)amino)-2-metilpropil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-metilpropil)carbamoil)-2-metilpropil)carbamato de metilo (60.4 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 2.253 min; m/z 759.6 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 1 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

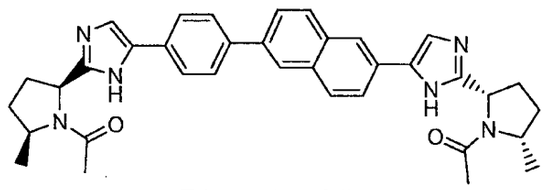


Ejemplo 108

3-metil-N-((1S)-2-metil-1-(4-(4-(6-(2-((1S)-2-metil-1-((3-metilbutanoil)amino)propil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)propil)butanamida

A una solución agitada de una sal HCl de (S)-1-(5-(4-(6-(2-((S)-1-amino-2-metilpropil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)-2-metilpropan-1-amina (Intermediario 178) (89 mg, 0.142 mmol) y ácido

3-metilbutanoico (32 mg, 0.313 mmol) y DIPEA (0.149 ml, 0.855 mmol) en DMF (2 ml) se añadió HATU (119 mg, 0.31 mmol) y la mezcla de reacción se agitó a TA durante 2 horas. La mezcla de reacción bruta se concentró hasta sequedad y se purificó dos veces mediante HPLC preparativa (amortiguador de TFA) para dar una sal en TFA de 3-metil-N-((1S)-2-metil-1-(4-(4-(6-(2-((1S)-2-metil-1-((3-metilbutanoil)amino)propil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)propil)butanamida (54.6 mg) en forma de un sólido blanco. Tiempo de retención en la CL-EM 2.375 min; m/z 645.6 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usaron un velocidad de flujo de 1 ml/min, un gradiente del solvente A al 100%/solvente B al 0% a solvente A al 0%/solvente B al 100%, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue acetonitrilo al 5%/H_2O al 95%/acetato de amonio 10 mM y el solvente B fue H_2O al 5%/acetonitrilo al 95%/acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.

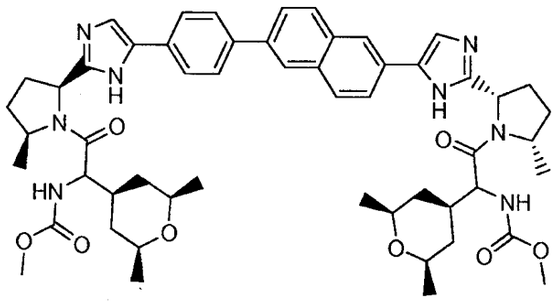


Ejemplo 109

2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol

A una solución de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (intermediario 117) (contaminado con acetato amónico) (38 mg, 0.076 mmol) y ácido (S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético (40.8 mg, 0.166 mmol) en DMF (1.0 ml) y DIPEA (0.053 ml, 0.30 mmol) se añadió HATU (63.2 mg, 0.166 mmol) y la reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con un amortiguador de TFA) para dar una sal en TFA de 2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (20 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.123 min; m/z 587.62 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un

detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.30 (s, 1 H), 8.27 (s, 1 H), 8.13 (d, *J*=8.8 Hz, 1 H), 8.09 (d, *J*=8.8 Hz, 1 H), 7.93 - 8.01 (m, 4 H), 7.84 - 7.91 (m, 4 H), 5.25 (c, *J*=8.4 Hz, 2 H), 4.31 - 4.40 (m, 2 H), 2.53 - 2.66 (m, 2 H), 2.28 - 2.40 (m, 4 H), 2.25 (s, 3 H), 2.25 (s, 3 H), 1.88 - 1.97 (m, 2 H), 1.47 (dd, *J*=6.5, 3.5 Hz, 6 H), 1.14 - 1.19 (m, 1 H).



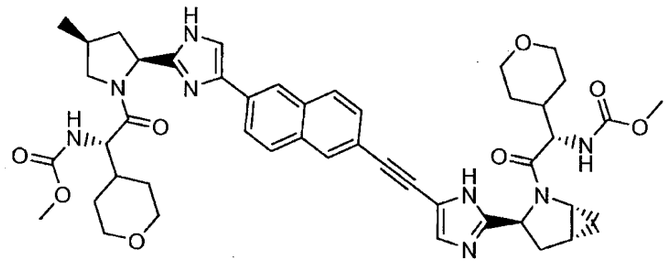
Ejemplo 110

(1-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-

((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)((metoxicarbonil)amino)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo

A una solución de una sal HCl de 2-((2S,5S)-5-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,5S)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (intermediario 117) (48 mg, 0.074 mmol) y ácido (S)-2-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-(metoxicarbonilamino)acético (*Cap-179 estereoisómero 2)* (39.9 mg, 0.163 mmol) en DMF (0.8 ml) y DIPEA (0.09 ml, 0.52 mmol) se añadió HATU (61.9 mg, 0.163 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La reacción se diluyó con MeOH, se filtró y se purificó en dos inyecciones mediante HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de (1-((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5S)-1-(((2R,4r,6S)-2.6-dimetiltetrahidro-2H-piran-4-il)((metoxicarbonil)amino)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo (55.5 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.506 min; m/z 479.54 (1/2MH+]. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS

equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H se presenta como una mezcla compleja de rotámeros.



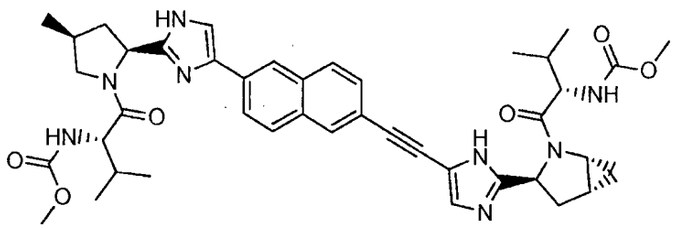
Ejemplo 111

((1S)-2-((2S,5S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de sal HCl de (1R,3S,5R)-3-(4-((6-

(2-((2S,4S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 175) (15 mg, 0.025 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético (13.70 mg, 0.063 mmol) en DMF (0.4 ml) y DIPEA (0.03, 0.2 ml, 0.2 mmol) se añadió HATU (23.99 mg, 0.063 mmol) y la mezcla de reacción se agitó a TA durante 1.5 horas. La reacción se diluyó con MeOH y se purificó en dos inyecciones mediante HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de((1S)-2-((2S,4S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (12.0 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.040 min; m/z 847.76 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en

el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.18 (s, 1 H), 8.05 (d, *J*=8.8 Hz, 1 H), 7.97 - 8.02 (m, 2 H), 7.88 (dd, *J*=8.8, 1.8 Hz, 1 H), 7.76 (s, 1 H), 7.67 (dd, *J*=8.4, 1.4 Hz, 1 H), 5.23 (dd, *J*=10.9, 6.9 Hz, 1 H), 5.09 (dd, *J*=9.0, 6.5 Hz, 1 H), 4.59 (d, *J*=7.8 Hz, 1 H), 4.34 - 4.41 (m, 1 H), 4.28 (d, *J*=8.0 Hz, 1 H), 3.86 - 4.00 (m, 4 H), 3.75 - 3.81 (m, 1 H), 3.67 (s, 3 H), 3.67 (s, 3 H), 3.32 - 3.50 (m, 5 H), 2.39 - 2.74 (m, 4 H), 1.87 - 2.13 (m, 4 H), 1.27 - 1.65 (m, 8 H), 1.25 (d, *J*=6.3 Hz, 3 H), 1.04 - 1.14 (m, 1 H), 0.86 (s ancho, 1 H).



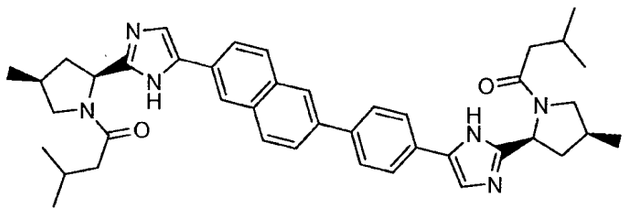
Ejemplo 112

((1S)-1-(((2S,4S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución de sal HCl de (1R,3S,5R)-3-(4-((6-

(2-((2S,4S)-5-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)etinil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 175) (38 mg, 0.064 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (28.0 mg, 0.160 mmol) en DMF (0.7 ml) y DIPEA (0.08, ml, 0.4 mmol) se añadió HATU (60.8 mg, 0.160 mmol) y se agitó a TA durante 1.5 horas. La reacción se diluyó con MeOH, se filtró y se purificó dos veces mediante HPLC preparativa (MeOH/agua con amortiguador de TFA) para dar una sal en TFA de ((1S)-1-(((2S,4S)-2-(4-(6-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (19.1 mg) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 3.288 min; m/z 763.74 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido

trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (400 MHz, MeOD) δ ppm 8.28 (s, 1 H), 8.18 (s, 1 H), 8.05 (d, *J*=8.8 Hz, 1 H), 7.98 - 8.03 (m, 2 H), 7.88 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.76 (s, 1 H), 7.67 (dd, *J*=8.5, 1.5 Hz, 1 H), 5.24 (dd, *J*=10.9, 7.2 Hz, 1 H), 5.10 (dd, *J*=9.0, 6.5 Hz, 1 H), 4.55 (d, *J*=6.5 Hz, 1 H), 4.30 - 4.37 (m, 1 H), 4.23 (d, *J*=7.3 Hz, 1 H), 3.72 - 3.79 (m, 1 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.43 (t, *J*=10.4 Hz, 1 H), 2.49 - 2.74 (m, 3 H), 2.44 (ddd, *J*=13.6, 6.7, 6.4 Hz, 1 H), 2.11 - 2.22 (m, 1 H), 1.98 - 2.11 (m, 2 H), 1.89 (c, *J*=12.0 Hz, 1 H), 1.25 (d, *J*=6.3 Hz, 3 H), 1.06 - 1.15 (m, 1 H), 1.00 (d, *J*=6.8 Hz, 3 H), 0.95 - 0.98 (m, 1 H), 0.94 (d, *J*=4.0 Hz, 3 H), 0.92 (d, *J*=3.8 Hz, 3 H), 0.88 (d, *J*=6.8 Hz, 3 H).



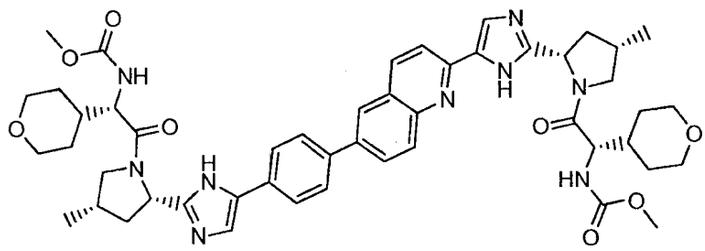
Ejemplo 113

2-((2S,4S)-4-metil-1-(3-metilbutanoil)-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-1-(3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol

A una solución de sal HCl de 2-((2S,4S)-4-metilpirrolidin-2-il)-5-(4-(6-(2-((2S,4S)-4-metilpirrolidin-

2-il)-1H-imidazol-5-il)naftalen-2-il)fenil)-1H-imidazol (Intermediario 196) (64.8 mg, 0.1 mmol), ácido 3-metilbutanoico (22.5 mg, 0.220 mmol) y DIPEA (0.122 ml, 0.700 mmol) en DCM (2 ml) se añadió HATU (76 mg, 0.200 mmol) y la mezcla se agitó a TA durante la noche. La mezcla de reacción se evaporó hasta sequedad y después se purificó mediante HPLC preparativa para dar una sal en TFA de 2-((2S,4S)-4-metil-1-(3-metilbutanoil)-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-1-(3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (61.7 mg) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 1.853 min; m/z 671.64 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL

en modo de electrorrocío.

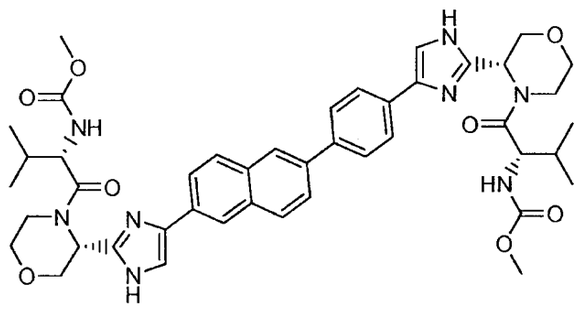


Ejemplo 114

((1S)-2-((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-quinolinil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de una sal de HCl de 2-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)-6-(4-(2-((2S,4S)-4-metilpirrolidin-2-il)-1H-imidazol-5-il)fenil)quinolina (Intermediario 164) (10 mg, 0.015 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (7.28 mg, 0.034 mmol) en DMF (0.5 ml) y DIPEA (0.023 ml, 0.13 mmol) se añadió HATU (12.75 mg, 0.034 mmol) y la mezcla de reacción se agitó a TA durante 16 horas. La reacción se concentró y el residuo se purificó mediante HPLC preparativa (H_2O-MeOH con amortiguador TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((2S,4S)-2-(4-(6-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-

quinolinil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (8.6 mg) en forma de un sólido amarillo. Tiempo de retención en la CL-EM 3.243 min; m/z 902.90 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (400 MHz, *MeOD*) δ ppm 8.61 (d, *J*=8.8 Hz, 1 H), 8.35 (d, *J*=1.8 Hz, 1 H), 8.22 - 8.33 (m, 3 H), 8.07 (d, *J*=8.8 Hz, 1 H), 8.00 (d, *J*=8.5 Hz, 1 H), 7.97 - 8.04 (m, 1 H), 7.89 (d, *J*=8.5 Hz, 1 H), 7.85 - 7.95 (m, 2 H), 5.17 - 5.33 (m, 2 H), 4.32 - 4.45 (m, 2 H), 4.28 (dd, *J*=8.2, 5.4 Hz, 2 H), 3.83 - 3.98 (m, 4 H), 3.67 (s, 6 H), 3.22 - 3.54 (m, 6 H), 2.63 - 2.75 (m, 2 H), 2.46 - 2.61 (m, 2 H), 1.83 - 2.04 (m, 4 H), 1.52 - 1.64 (m, 2 H), 1.30 - 1.53 (m, 6 H), 1.26 (dd, *J*=6.3, 4.0 Hz, 6 H).



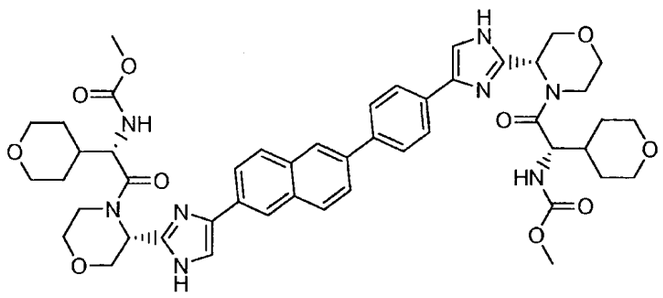
Ejemplo 115

(1S)-1-(((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-3-morfolinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-morfolinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (of (R)-3-(5-(4-(6-(2-((R)-morfolin-3-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)morfolina (Intermediario 181) (71.6 mg, 0.110 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (44.2 mg, 0.252 mmol) en DMF (1.0 ml) y DIPEA (0.13 ml, 0.77 mmol) se añadió HATU (96 mg, 0.252 mmol) y la mezcla reacción se lavó con nitrógeno, se selló y se agitó a TA durante 3 horas. La reacción se concentró en corriente de nitrógeno durante la noche, se diluyó con MeOH (~ 5 ml), se filtró y se purificó mediante HPLC preparativa (MeOH/agua con un amortiguador de TFA) para dar una sal en TFA de ((1S)-1-(((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((metoxicarbonil)amino)-3-

metilbutanoil)-3-morfolinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-morfolinil)carbonil)-2-metilpropil)carbamato de metilo (75.5 mg) en forma de un sólido blancuzco . Tiempo de retención el CLEM 3.351 min; m/z 822.07 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H presenta una mezcla de rotámeros. RMN de ^1H (400 MHz, MeOD) δ ppm 8.47 (s, 0.5 H), 8.33 (s, 0.5 H), 8.27 (s, 1 H), 7.85 - 8.17 (m, 10 H), 5.95 (d, J=4.5 Hz, 2 H), 4.71 (dd, J=12.5, 7.8 Hz, 1 H), 4.35 - 4.58 (m, 4 H), 3.94 - 4.20 (m, 5 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.53 - 3.78 (m, 3 H), 2.76 -

2.91 (m, 1 H), 2.12 (s ancho, 2 H), 1.05 - 1.19 (m, 6 H), 0.81 - 1.00 (m, 6 H).

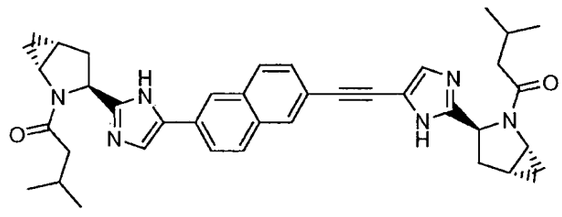


Ejemplo 116

((1S)-2-((3R)-3-(4-(4-(6-(2-((3R)-4-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-3-morfolinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-morfolinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal HCl de (of (R)-2-(5-(4-(6-(2-((R)-morfolin-3-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)morfolina (Intermediario 181) (65.5mg, 0.100 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (50.2 mg, 0.231 mmol) en DMF (1.0 ml) y DIPEA (0.12 ml, 0.70 mmol) se añadió HATU (88 mg, -4 mmol) y la mezcla reacción se lavó con nitrógeno, se selló y se agitó a TA durante 3 horas. La reacción se concentró en una corriente de nitrógeno durante la noche, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((3R)-3-(4-(4-(6-(2-((3R)-4-

((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-3-morfolinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-morfolinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (75 mg) en forma de un sólido blancuzco. Tiempo de retención en la CL-EM 3.120 min; m/z 906.15 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



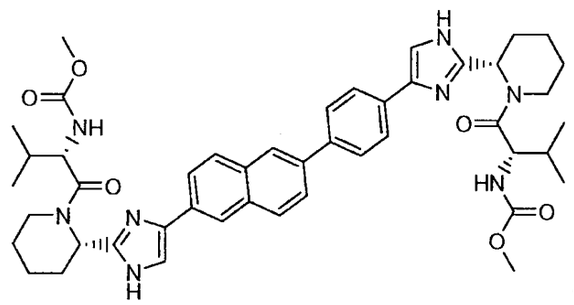
Ejemplo 117

(1R,3S,5R)-2-(3-metilbutanoil)-3-(4-(6-((2-((1R,3S,5R)-2-(3-

metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano

A una solución agitada de una sal HCl de (1R,3S,5R)-3-(5-(6-((2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)etinil)naftalen-2-il)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 124) (64.7 mg, 0.098 mmol), ácido 3-metilbutanoico (22.09 mg, 0.216 mmol) y DIPEA (0.103 ml, 0.590 mmol) en DCM (1.5 ml) se añadió HATU (74.8 mg, 0.197 mmol) y la mezcla de reacción se agitó a TA durante 2-3 horas. La reacción se concentró hasta sequedad mediante HPLC preparativo (amortiguador TFA) para dar una sal en TFA de (1R,3S,5R)-2-(3-metilbutanoil)-3-(4-(6-((2-((1R,3S,5R)-2-(3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)etinil)-2-naftil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (51.5 mg) en forma de una espuma beige. Tiempo de retención en la CL-EM 1.775 min; m/z 615.41 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 2 min, un tiempo de conservación de 1 min y un tiempo de

análisis de 3 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío.



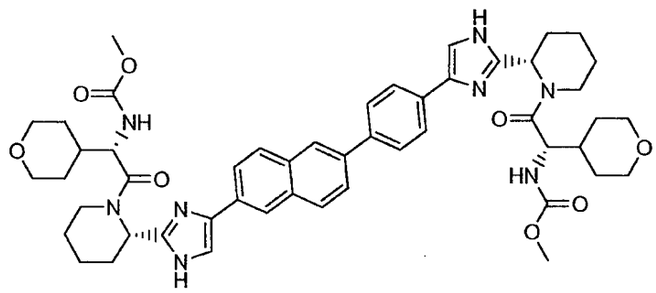
Ejemplo 118

((1S)-1-(((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-piperidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-piperidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de una sal HCl de (of (S)-2-(5-(4-(6-(2-((S)-piperidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)piperidina (Intermediario 184) (69.0 mg, 0.106 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (42.9 mg, 0.245 mmol) en DMF (1.0 ml) y DIPEA (0.13 ml, 0.75 mmol) se añadió HATU (93 mg, 0.245 mmol) y la mezcla reacción se lavó con nitrógeno, se selló y se agitó a TA durante 1 hora. La reacción se concentró en corriente de nitrógeno durante la noche, se diluyó con MeOH (~ 5 ml), se filtró y se purificó mediante HPLC preparativa (MeOH/agua con

un amortiguador de TFA) para dar una sal en TFA de ((1S)-1-(((2S)-3-(4-(4-(6-(2-((2S)-4-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-piperidinil)-1H-imidazol-1-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-piperidinil)carbonil)-2-metilpropil)carbamato de metilo (88.9 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.530 min; m/z 818.08 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H presenta una mezcla de rotámeros. RMN de ^1H (400 MHz, MeOD) δ ppm 8.46 (s. 0.65 H), 8.33 (s ancho. 0.35 H), 8.27 (s. 1 H), 7.84 - 8.15 (m, 10 H), 6.05 (s ancho. 1.3 H), 5.80 - 5.90 (m, 0.7 H), 4.67 - 4.78 (m,1.3 H), 4.42 - 4.50 (m, 2 H), 3.99 - 4.10 (m, 0.7 H), 3.78 (s ancho. 3.5 H), 3.69 (s ancho. 2.5 H), 3.40 - 3.52 (m, 0.7

H), 2.61 - 2.73 (m, 1.3 H), 2.46 - 2.59 (m, 1.3 H), 2.37 (s ancho. 0.7 H), 2.03 - 2.24 (m, 4 H), 1.91 - 2.02 (m, 1.3 H), 1.63 - 1.88 (m, 5.4 H), 1.45 - 1.62 (m, 1.4.H), 1.11 (t. *J*=6.8 Hz, 7.3 H), 0.93 - 1.03 (m, 4.7H).



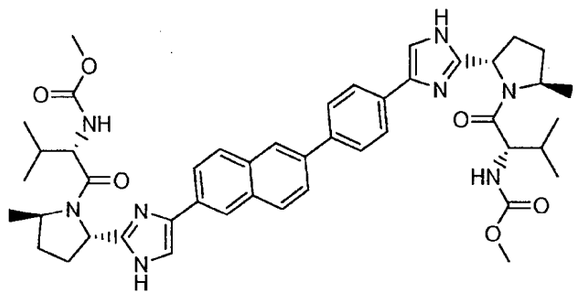
Ejemplo 119

((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-piperidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-piperidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de una sal HCl de ((S)-2-(5-(4-(6-(2-((S)-piperidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)piperidina (Intermediario 184) (62.5 mg, 0.096 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético (48.2 mg, 0.222 mmol) en DMF (1.0 ml) y DIPEA (0.12 ml, 0.68 mmol) se añadió HATU (84 mg, -4 mmol) y la mezcla reacción se lavó con nitrógeno, se selló y se agitó a TA durante 1 hora. La reacción se concentró en una corriente de nitrógeno durante la noche, se diluyó con MeOH, se filtró y se purificó mediante HPLC preparativa

(MeOH/agua con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((2S)-3-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-3-piperidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-1-piperidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (71.2 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.348 min; m/z 902.10 (MH+), Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H presenta una mezcla de rotámeros. RMN de ^1H (400 MHz, MeOD) δ ppm 8.45 (s, 0.6 H), 8.32 (s ancho, 0.4 H), 8.27 (s, 1 H), 8.02 - 8.15 (m, 4.4 H), 7.85 - 8.02 (m, 5.6 H), 6.08 (s ancho, 1.2 H), 5.90 (s ancho, 0.8 H), 4.70 (s ancho, 1.2 H), 4.45 - 4.59 (m, 2 H), 3.90 -

4.10 (m, 4 ,8 H), 3.77 (s, 3.6 H), 3.69 (s ancho, 2.4 H), 3.36 - 3.50 (m, 5 H), 2.35 - 2.73 (m, 3 H), 1.36 - 2.22 (m, 20 H).



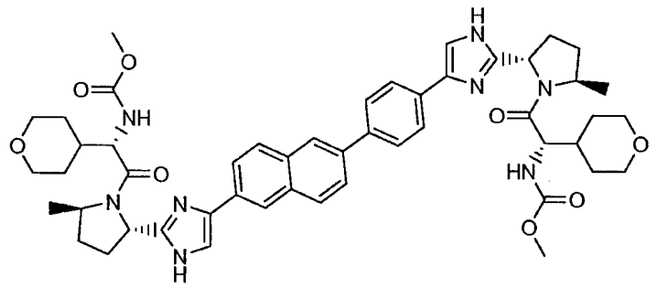
Ejemplo 120

((1S)-1-(((2S,5R)-2-(4-(4-((1S,2S)-2-(6-(2-((2S,5R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

A una solución de sal HCl de 2-((2S,5R)-5-metilpirrolidin-2-il)-5-(4-(6-(2-((2S,5R)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol (Intermediario 187) (46 mg, 0.071 mmol) y ácido (S)-2-(metoxicarbonilamino)-metilbutanoico (28.6 mg, 0.163 mmol) y DIPEA (0.09 ml, 0.5 mmol) en DMF (0.7 ml) se añadió HATU (62.0 mg, 0.163 mmol) y el vaso de reacción se aclaró con nitrógeno, se selló y se agitó a TA durante 1 hora. La reacción se concentró en corriente de nitrógeno durante la noche, se diluyó con MeOH (~ 3 ml), se filtró y se purificó mediante HPLC preparativa (MeOH/agua con un amortiguador de

TFA) para dar una sal en TFA de ((1S)-1-(((2S,5R)-3-(4-(4-(6-(2-((2S,5R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-1-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (53.3 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 3.255 min; m/z 818.08 (MH+), Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. La RMN de ^1H presenta una mezcla compleja de rotámeros. RMN de ^1H (400 MHz, MeOD) δ ppm 8.31 (s, 0.5 H), 8.26 - 8.30 (m, 1.5 H), 8.13 (d, J=8.8 Hz, 1 H), 8.08 (d, J=8.5 Hz, 1 H), 7.93 - 8.00 (m, 4 H), 7.83 - 7.93 (m, 4 H), 5.67 (t, J=7.8 Hz, 0.7 H), 5.38 - 5.45 (m, 1.3 H), 4.44 - 4.68 (m, 3.3 H), 3.92 (dd, J=8.2, 4.4 Hz, 0.7 H), 3.66

(s, 3.5 H), 3.41 (s, 1 H), 3.35 (s, 1.5 H), 2.53 - 2.92 (m, 3.3 H), 1.96 - 2.30 (m, 6 H), 1.78 - 1.87 (m, 0.7 H), 1.43 - 1.53 (m, 3.5 H), 1.33 (dd, *J*=6.3, 2.5 Hz, 2.5 H), 0.98 - 1.06 (m, 6 H), 0.96 (d, *J*=6.8 Hz, 2.4 H), 0.84 (d, *J*=6.8 Hz, 3.6 H).



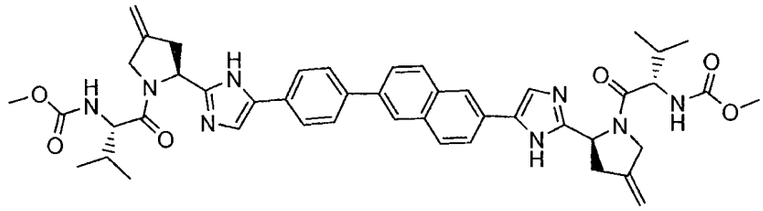
Ejemplo 121

((1S)-2-((2S,5S)-2-(4-(4-(6-(2-((2S,5R)-1-((2S,5R)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución de un vial de sal HCl de 2-((2S,5R)-5-metilpirrolidin-2-il)-5-(4-(6-(2-((2S,5R)-4-metilpirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol (Intermediario 187) (41.4 mg, 0.064 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro)-2H-piran-4-il)acético (31.9 mg, 0.147 mmol) en DMF (0.7 ml) y DIPEA (0.08 ml, 0.4 mmol)) se añadió HATU (55.8 mg, -4 mmol) y el vaso de reacción se aclaró con nitrógeno, se selló y se agitó a TA durante 1 hora. La reacción se concentró en una

corriente de nitrógeno durante la noche, se diluyó con MeOH (~ 3 ml), se filtró y se purificó mediante HPLC preparativa (MeOH/agua con amortiguador de TFA al 0.1%) para dar una sal en TFA de ((1S)-2-((2S,5R)-3-(4-(4-(6-(2-((2S,5R)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (27.6 mg) en forma de un sólido amarillo claro. El tiempo de retención en la CLEM fue 3.135 min; m/z 902.15 (MH+), Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna de 3u, C18 de 2 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 4 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 0.8 min y un tiempo de análisis de 5 min en el que el solvente A fue 10% de MeOH/90% de H_2O/0.1% de ácido trifluoroacético y el solvente B fue 10% de H_2O/90% de MeOH/0.1% de ácido trifluoroacético. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. Mezcla de rotámeros mediante RMN ^{1}H. RMN de ^{1}H (400 MHz, MeOD) δ ppm 8.31 (s, 0.5 H), 8.25 - 8.29 (m, 1.5 H), 8.13 (d, *J*=8.8 Hz, 1 H), 8.08 (dd, *J*=8.8, 2.5 Hz, 1 H),

7.93 - 8.00 (m, 4 H), 7.82 - 7.92 (m, 4 H), 5.71 (t, *J*=7.9 Hz, 0.8 H), 5.37 - 5.45 (m, 1.2 H), 4.47 - 4.69 (m, 3 H), 3.89 - 4.07 (m, 5 H), 3.67 (s, 3 H), 3.24 - 3.43 (m, 7 H), 2.57 - 2.92 (m, 3 H), 1.96 - 2.29 (m, 6 H), 1.79 - 1.87 (m, 1 H), 1.35 - 1.67 (m, 11 H), 1.33 (dd, *J*=6.5, 2.5 Hz, 3 H).



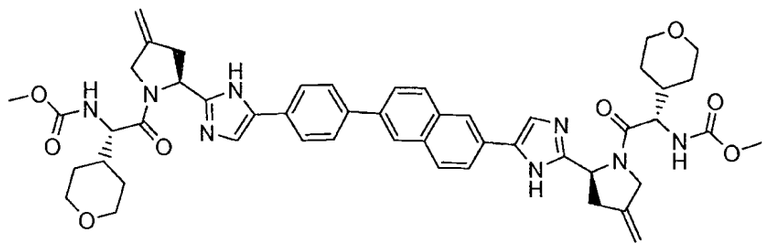
Ejemplo 122

((1S)-1-(((2S)-2-(4-(6-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-4-metilen-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((S)-4-metilenpirrolidin-2-il)-4-(4-(6-(2-((S)-4-metilenepirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol (Intermediario 189) (86 mg, 0.148 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (47.1 mg, 0.269 mmol) y base de Hunig (0.234 ml, 1134 mmol) en DMF (6 ml) se añadió HATU (102 mg, 0.269 mmol). La reacción se agitó 4 h a temperatura ambiente y se purificó mediante HPLC preparativa (MeOH/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((2S)-2-(4-(6-(4-(2-((2S)-

1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)fenil)-2-naftil)-1H-imidazol-2-il)-4-metilen-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (65 mg, 46%), Tiempo de retención en la CL-EM 3.22 min; Calculado para $C_{46}H_{53}N_8O_6$: 813.40 Encontrado m/z 813.7 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeCN al 5%/agua al 95%/NH4Oac 10 mM y el solvente B fue MeCN al 95%/agua al 5%/NH4Oac 10 mM . Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H NMR (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 8.0-7.85 (m, 8H), 5.50-5.45 (m, 2H), 5.32 (s, 2H), 5.28 (s, 2H), 4.72 (d, *J*=11.6 Hz, 2H), 4.60 (dd, *J*=11.3, 3.4 Hz, 2H), 4.21 (dd, *J*=7.6, 2.8 Hz, 2H), 3.68 (s, 6H), 2.98 - 2.92

(m, 2H), 2.10 - 2.06 (m, 2H), 1.06-1.02 (m, 2H), 0.97 - 0.94 (m, 12H).

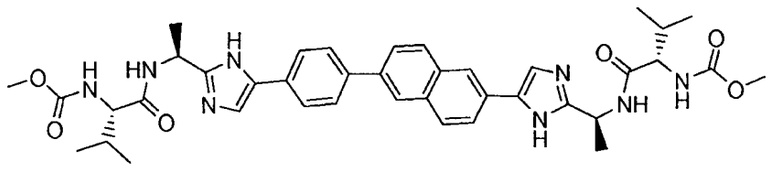


Ejemplo 123

((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metilen-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((S)-4-metilenepirrolidin-2-il)-4-(4-(6-(2-((S)-4-metilenepirrolidin-2-il)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol (Intermediario 189) (86 mg, 0.148 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (58.4 mg, 0.269 mmol) y base de Hunig (0.234 ml, 1134 mmol) en DMF (6 ml) se añadió HATU (102 mg, 0.269 mmol). La reacción se agitó 5 horas a TA y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-2-((2S)-2-(4-(4-(6-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)-

2-naftil)fenil)-1H-imidazol-2-il)-4-metilen-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo. Tiempo de retención en la CL-EM 2.81 min; Calculado para $C_{50}H_{57}N_8O_8$: 897.43 Encontrado m/z 897.41 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (s, 2H), 8.4 (d, J=8.8 Hz, 1H), 8.09 (d, J=9.0 Hz, 1H), 8.01-7.85 (m, 8H), 5.50-5.44 (m, 2H), 5.32 (s, 2H), 5.28 (s, 2H), 4.75 (d, J=14.6 Hz, 2H), 4.63 (dd, J=13.3, 4.5 Hz, 2H), 4.27 (dd, J=8.3, 3.5 Hz, 2H), 3.99-3.91 (m, 4H) 3.69 (s, 6H), 3.41-3.37 (m 4H), 3.0 -2.94 (m, 2H), 2.02 - 1.98 (m, 2H), 1.68-1.65 (m, 2H), 1.59-1.32 (m, 8H).

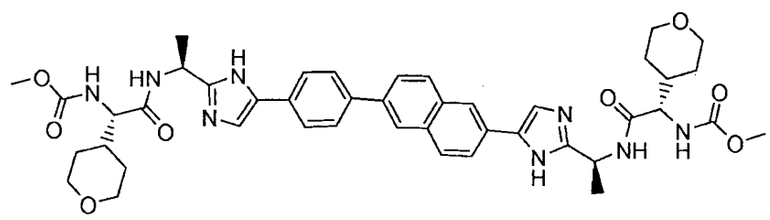


Ejemplo 124

((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)carbamoil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (S)-1-(4-(4-(6-(2-((S)-1-aminoetil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)etanamina (Intermediario 191) (111 mg, 0.148 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (47.1 mg, 0.393 mmol) y base de Hunig (0.343 ml, 1.96 mmol) en DMF (8 ml) se añadió HATU (149 mg, 0.393 mmol). La reacción se agitó 4 h a temperatura ambiente y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)carbamoil)-2-metilpropil)carbamato de metilo (91 mg, 47%), El tiempo de retención en la CLEM 2.96 min; Calculado para $C_{40}H_{49}N_8O_6$: 737.38 Encontrado m/z 737.45 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna

PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.35 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.9 Hz, 1H), 7.99-7.88 (m, 8H), 5.30-5.27 (m, 2H), 3.99-3.97 (m, 2H), 3.70 (s, 6H), 2.14 (s ancho, 2H), 1.78-1.75 (m, 6H), 0.99 -0.95 (m, 12H).



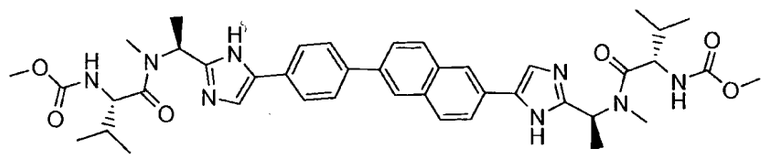
Ejemplo 125

((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)amino)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (S)-

1-(4-(4-(6-(2-((S)-1-aminoetil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)etanamina (Intermediario 191) (83 mg, 0.196 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (85 mg, 0.393 mmol) y base de Hunig (0.343 ml, 1.96 mmol) en DMF (8 ml) se añadió HATU (149 mg, 0.393 mmol). La reacción se agitó 5 h a temperatura ambiente y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)amino)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (89 mg, 42%), Tiempo de retención en la CL-EM 2.64 min; Calculado para $C_{44}H_{53}N_8O_8$: 821.40 Encontrado m/z 821.80 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 4 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue AcCN al 5%/agua al 95%/NH4Oac 10 mM y el solvente B fue AcCN al 95%/agua al 5%/NH4Oac 10 mM . Los datos de EM se

determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.34 (s, 1H), 8.2 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 7.99-7.87 (m, 8H), 5.29-5.26 (m, 2H), 4.02-4.00 (m, 2H), 3.98-3.93 (m, 4H) 3.71 (s, 6H), 3.41-3.37 (m 4H), 2.02 (s ancho, 2H), 1.79-1.76 (m, 6H), 1.62 (d, *J*=13.0 Hz, 2H), 1.49-1.39 (m, 6H).



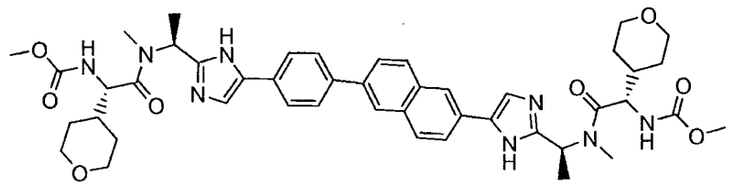
Ejemplo 126

((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil(metil))amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)(metil)carbamoil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (S)-N-metil-1-(4-(4-(6-(2-((S)-1-metilaminoetil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)etanamina (Intermediario 193) (66 mg, 0.111 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (38.9 mg, 0.222 mmol) y base de Hunig (0.194 ml, 1.11 mmol) en DMF (5 ml) se añadió HATU (84 mg, 0.222 mmol). La reacción se agitó 5 h a temperatura ambiente y se purificó mediante HPLC preparativa (MeCN/agua con TFA

al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)(metil)amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)(metil)carbamoil)-2-metilpropil)carbamato de metilo. Tiempo de retención en la CL-EM 1.78 min; Calculado para $C_{42}H_{53}N_8O_6$: 765.41 Encontrado m/z 765.41 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA; rotámeros, 500 MHz, MeOD) δ ppm 8.44/8.34 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.10-7.88 (m, 9H), 6.17-6.14/5.33-5.30 (m, 2H), 4.64-4.6/4.41-4.39 (m, 2H), 3.84/3.66 (s, 3H), 3.83/3.59 (s, 3H), 3.37 (s, 6H), 2.10-2.05 (m, 2H), 1.90-1.87/1.85-1.82 (m, 6H),

1.15 -0.90 (m, 12H).



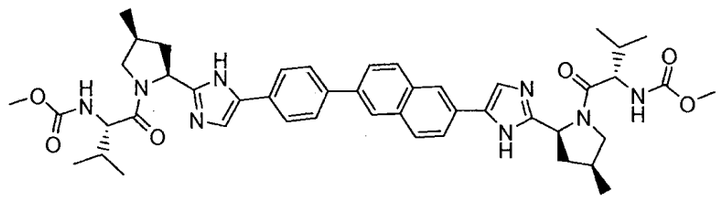
Ejemplo 127

((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)(metil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)amino)etil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)etil)(metil)amino)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (S)-N-metil-1-(4-(4-(6-(2-((S)-1-metilaminoetil)-1H-imidazol-4-il)naftalen-2-il)fenil)-1H-imidazol-2-il)etanamina (Intermediario 193) (66 mg, 0.111 mmol), ácido (S)-2-(metoxicarbonilamino)-2-tetrahidro-2H-piran-4-il)acético (48 mg, 0.222 mmol) y base de Hunig (0.194 ml, 1.11 mmol) en DMF (5 ml) se añadió HATU (84 mg, 0.222 mmol). La reacción se agitó 5 h a temperatura ambiente y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-2-(((1S)-1-(4-(4-(6-(2-((1S)-1-(((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)(metil)amino)etil)-1H-imidazol-4-il)-2-

naftil)fenil)-1H-imidazol-2-il)etil)(metil)amino)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo. Tiempo de retención en la CL-EM 1.58 min; Calculado para $C_{46}H_{57}N_8O_8$: 849.43 Encontrado m/z 849.46 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 30 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 1 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 3 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, rotámeros, 500 MHz, MeOD) δ ppm 8.45/8.34 (s, 1H), 8.28 (s, 1H), 8.14 (d, J=8.6 Hz, 1H), 8.09 (d, J=8.3 Hz, 1H), 8.06-7.88 (m, 8H), 6.21-6.18/5.38-5.34 (m, 2H), 4.73-4.70/4.47-4.45 (m, 2H), 4.02-3.94 (m, 4H) 3.84/3.63 (s, 3H), 3.83/3.60 (s, 3H), 3.46-3.38 (m 4H), 3.37/3.35 (s, 6H), 2.02 (s ancho, 2H), 1.91-1.88/1.84-1.81 (m, 6H), 1.68 (d, J=13.0 Hz, 2H), 1.53-1.42 (m,

6H).

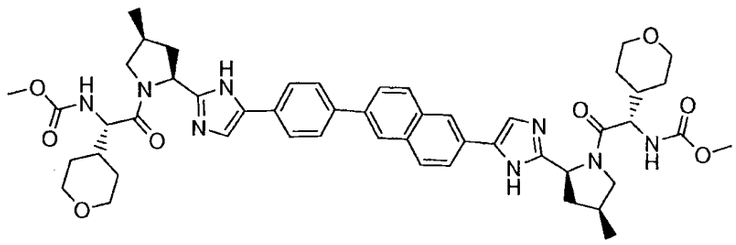


Ejemplo 128

((1S)-1-(((2S,4S)-2-(4-(4(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-ilnaftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (25 mg, 0.039 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (14.9 mg, 0.085 mmol) y base de Hunig (0.054 ml, 0.308 mmol) en DMF (1 ml) se añadió HATU (32 mg, 0.085 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-

metilpropil)carbamato de metilo (24.5 mg, 57.8%), Tiempo de retención en la CL-EM 3.05 min; Calculado para $C_{46}H_{57}N_8O_6$: 817.44 Encontrado m/z 817.36 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.99-7.85 (m, 8H), 5.27-5.22 (m, 2H), 4.37-4.33 (m, 2H), 4.25-4.23 (m, 2H), 3.68 (s, 6H), 3.47-3.41 (m, 2H), 2.72-2.68 (m 2H), 2.55 (s ancho, 2H), 2.07-2.03 (m, 2H), 1.92-1.87 (m, 2H), 1.27-1,26 (m, 6H), 0.95-0.9 (m, 12H).



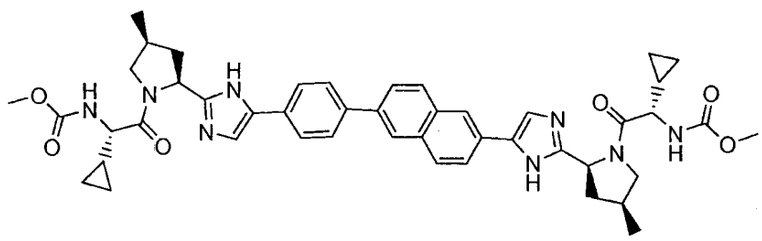
Ejemplo 129

(2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-

(((metoxicarbonil)amino)(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (50 mg, 0.077 mmol), ácido (S)-2-(metoxicarbonilamino)-22-(tetrahidro-2H-piran-4-il)acético (36.8 mg, 0.170 mmol) y base de Hunig (0.11 ml, 0.617 mmol) en DMF (1 ml) se añadió HATU (64.5 mg, 0.170 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de (2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(((metoxicarbonil)amino)(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo. Tiempo de retención en la CL-EM 2.84 min; Calculado para $C_{50}H_{61}N_8O_8$: 901.46 Encontrado m/z 901.42 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas

a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.85 (m, 8H), 5.25-5.21 (m, 2H), 4.42-4.39 (m, 2H), 4.30-4.27 (m, 2H), 3.96-3.92 (m, 4H), 3.68 (s, 6H), 3.49-3.35 (m 6H), 2.71-2.38 (m, 2H), 2.58-2.54 (m, 2H), 1.97 - 1.89 (m, 4H), 1.60 (d, *J*=13.0 Hz, 2H), 1.48-1,26 (m, 12H).



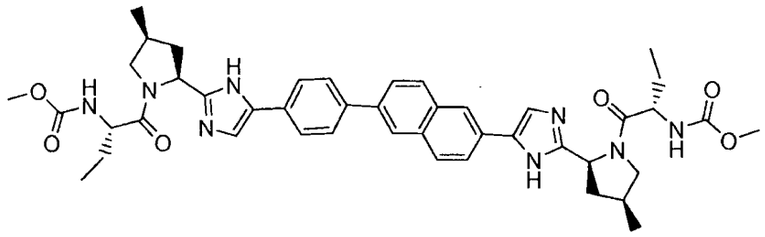
Ejemplo 130

(1-ciclopropil-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(ciclopropil((metoxicarbonil)amino)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-

2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (30 mg, 0.085 mmol), ácido (S)-2-ciclopropil-2-(metoxicarbonilamino)acético (17.62 mg, 0.085 mmol) y base de Hunig (0.065 ml, 0.37 mmol) en DMF (1 ml) se añadió HATU (39 mg, 0.102 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de (1-ciclopropil-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-(ciclopropil((metoxicarbonil)amino)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo (24.5 mg, 57.8%), Tiempo de retención en la CL-EM 3.08 min; Calculado para $C_{46}H_{53}N_8O_6$: 813.41 Encontrado m/z 813.45 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una

plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.32 (s, 1H), 8.27 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.99-7.87 (m, 8H), 5.29-5.24 (m, 2H), 4.30 (s ancho, 2H), 3.82-3.80 (m, 2H), 3.68 (s, 6H), 3.43-3.37 (m, 2H), 2.72-2.68 (m 2H), 2.55 (s ancho, 2H), 1.91-1.86 (m, 2H), 1.25-1,24 (m, 6H), 1.11 (s ancho, 2H), 0.60-0.58 (m, 4H), 0.53-0.51 (m, 2H), 0.04-0.38 (m, 2H).

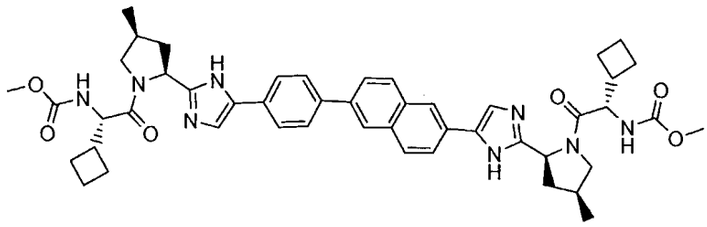


Ejemplo 131

((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)butanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)propil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (35 mg, 0.054 mmol), ácido (S)-2-(metoxicarbonilamino)butanoico (19.14 mg, 0.119 mmol) y base de Hunig (0.075 ml, 0.432 mmol) en DMF (1 ml) se añadió HATU (45 mg, 0.119 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El

residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)butanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)propil)carbamato de metilo (36.4 mg, 61.7%), Tiempo de retención en la CL-EM 2.91 min; Calculado para $C_{44}H_{53}N_8O_6$: 789.41 Encontrado m/z 789.41 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.14 (d, J=8.6 Hz, 1H), 8.09 (d, J=8.6 Hz, 1H), 8.00-7.86 (m, 8H), 5.27-5.22 (m, 2H), 4.37 (s ancho, 2H), 4.24-4.23 (m, 2H), 3.67 (s, 6H), 3.44-3.39 (m, 2H), 2.72-2.68 (m 2H), 2.58 (s ancho, 2H), 1.88-1.84 (m, 2H), 1.47-1,25 (m, 6H), 0.98 -0.92 (m, 10H).



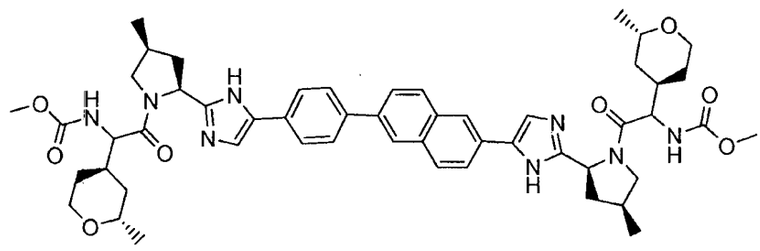
Ejemplo 132

((1S)-1-ciclobutil-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-ciclobutil-2-((metoxicarbonil)amino)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (35 mg, 0.054 mmol), ácido (S)-2-ciclobutil-2-(metoxicarbonilamino)acético (22.23 mg, 0.119 mmol) (preparado de un modo similar a lo indicado en *Cap-51* usando ácido (S)-2-(*terc*-butoxicarbonilamino)2-ciclobutilacético disponible comercialmente como material de partida) y base de Hunig (0.075 ml, 0.432 mmol) en DMF (1 ml) se añadió HATU (45 mg, 0.119 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar

una sal bis en TFA de ((1S)-1-ciclobutil-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-ciclobutil-2-((metoxicarbonil)amino)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo (25.6 mg, 43.6%), Tiempo de retención en la CL-EM 3.13 min; Calculado para $C_{48}H_{57}N_8O_6$: 841.44 Encontrado m/z 841.48 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.9 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.86 (m, 8H), 5.26-5.21 (m, 2H), 4.41-4.37 (m, 4H), 3.68 (s, 6H), 3.48-3.43 (m, 2H), 2.71-2.66 (m 4H), 2.56 (s

ancho, 2H), 1.96-1.87 (m, 14H), 1.27-1,26 (m, 6H).

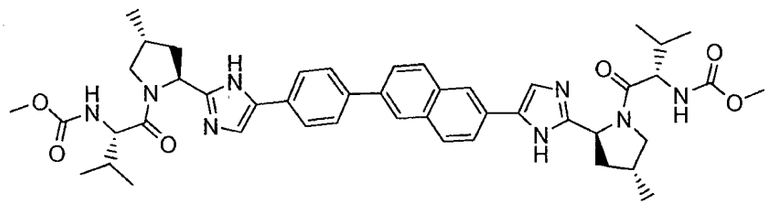


Ejemplo 133

((1S)-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-((2R,4S)-2-metiltetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-1-((2S,4R)-2-metiltetrahidro-2H-piran-4-il)-2-oxoetil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (25 mg, 0.039 mmol), ácido 2-(metoxicarbonilamino)-2((2R,4S)-2-metiltetrahidro-2H-piran-4-il)acético (*Cap-178, estereoisómero 1)* (19.61 mg, 0.085 mmol) y base de Hunig (0.054 ml, 0.308 mmol) en DMF (1 ml) se añadió HATU (32 mg, 0.085 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-((2R,4S)-2-

metiltetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-1-((2S,4R)-2-metiltetrahidro-2H-piran-4-il)-2-oxoetil)carbamato de metilo (21.3 mg, 45.2%), Tiempo de retención en la CL-EM 2.94 min; Calculado para $C_{52}H_{64}N_8O_8$: 929.49 Encontrado m/z 929.64 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.32 (s, 1H), 8.28 (s, 1H), 8.15 - 8.12 (m, 1H), 8.09-8.06 (m, 1H), 8.02-7.94 (m, 5H), 7.90-7.86 (m, 3H), 5.28-5.23 (m, 2H), 4.50-4.48 (m, 2H), 4.44 (s ancho, 2H), 3.95-3.91 (m, 2H), 3.71-3.68 (s, 10H), 3.46-3.41 (m, 2H), 2.72-2.67 (m, 2H), 2.55-2.52 (m, 2H), 2.19 (s ancho, 2H), 1.97 - 1.92 (m, 2H), 1.60 (s ancho, 2H), 1.48-1.46 (m, 2H), 1.39 (s ancho, 2H), 1.30-1,26 (m, 8H), 1.14-1.10 (m, 6H).

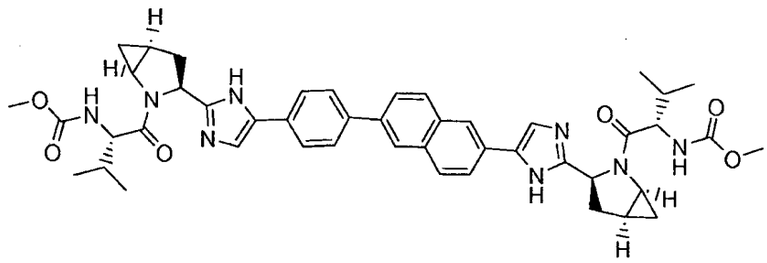


Ejemplo 134

((1S)-1-(((2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4R)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4R)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 201) (50 mg, 0.077 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (30 mg, 0.171 mmol) y base de Hunig (0.108 ml, 0.308 mmol) en DMF (1 ml) se añadió HATU (65 mg, 0.171 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((2S,4R)-2-(4-(4-(6-(2-((2S,4R)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (60.7 mg, 71%), Tiempo de retención en la CL-EM 3.12 min; Calculado para $C_{46}H_{57}N_8O_6$:

817.44 Encontrado m/z 817.46 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.00-7.86 (m, 8H), 5.43-5.38 (m, 2H), 4.26-4.24 (m, 2H), 4.09-4.05 (m, 2H), 3.69 (s, 6H), 3.64 (s ancho, 2H), 2.76-2.73 (m 2H), 235-2.32 (m, 2H), 2.25-2.22 (m, 2H), 2.11-2.09 (m, 2H), 1.22-1,20 (m, 6H), 0.98-0.93 (m, 12H).



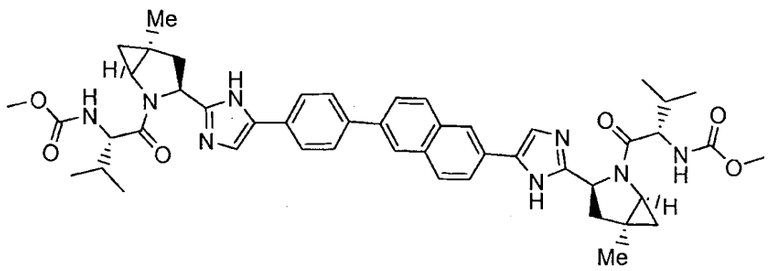
Ejemplo 135

((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-

azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano (Intermediario 203) (50 mg, 0.078 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (30 mg, 0.111 mmol) y base de Hunig (0.108 ml, 0.621 mmol) en DMF (8 ml) se añadió HATU (65 mg, 0.171 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (54 mg, 63%), Tiempo de retención en la CL-EM 3.15 min; Calculado para $C_{46}H_{53}N_8O_6$: 813.41 Encontrado m/z 813.45 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de

solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.26 (s, 1H), 8.12 (d, *J*=8.6 Hz, 1H), 8.07 (d, *J*=8.6 Hz, 1H), 7.98-7.86 (m, 8H), 5.80-5.74 (m, 2H), 4.36-4.34 (m, 2H), 4.02-3.99 (m, 2H), 3.73 (s, 6H), 2.99-2.95 (m, 2H), 2.28-2.25 (m 2H), 2.16 (s ancho, 2H), 2.04 (s ancho, 2H), 1.24-1,20 (m, 2H), 1.08 (s ancho, 2H), 1.02-1.00 (m, 12H).



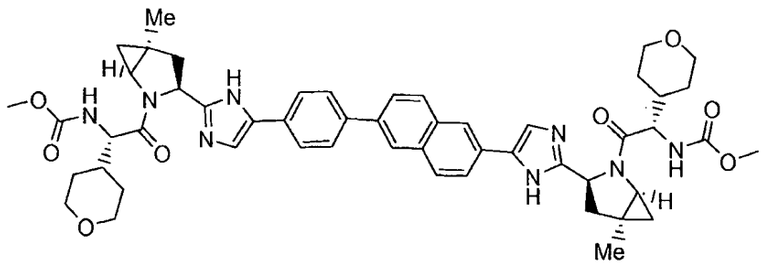
Ejemplo 136

((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de

(1S,3S,5S)-5-metil-3-(4-(4-(6-(2-((1S,3S,5S)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo [3.1.0]hexano (Intermediario 209) (50 mg, 0.074 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (28.7 mg, 0.164 mmol) y base de Hunig (0.104 ml, 0.595 mmol) en DMF (1 ml) se añadió HATU (62 mg, 0.164 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (45 mg, 54%), Tiempo de retención en la CL-EM 3.15 min; Calculado para $C_{48}H_{57}N_8O_6$: 841.44 Encontrado m/z 841.50 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A

fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.33 (s, 1H), 8.25 (s, 1H), 8.11 (d, *J*=8.5 Hz, 1H), 8.06 (d, *J*=8.7 Hz, 1H), 7.97-7.85 (m, 8H), 5.82-5.75 (m, 2H), 4.31-4.28 (m, 2H), 3.73-3.71 (m, 8H), 2.75-2.69 (m, 2H), 2.44-2.37 (m 2H), 2.17-2.12 (m, 2H), 1.40 (s, 6H), 1.1-1.11 (m, 4H), 1.01-0.99 (m, 12H).



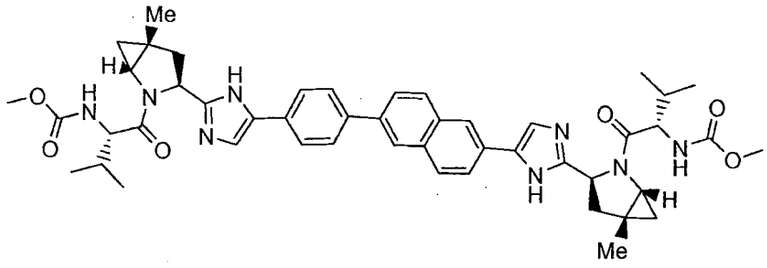
Ejemplo 137

((1S)-2-((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (1S,3S,5S)-5-metil-3-(4-(4-(6-(2-((1S,3S,5S)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo [3.1.0]hexano (Intermediario

209) (50 mg, 0.074 mmol), ácido (S)-2-(metoxicarbonilamino)-2--(tetrahidro-2H-piran-4-il)acético (35.5 mg, 0.164 mmol) y base de Hunig (0.104 ml, 0.595 mmol) en DMF (1 ml) se añadió HATU (62 mg, 0.164 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-2-((1S,3S,5S)-3-(4-(4-(6-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo (46.3 mg, 51%), Tiempo de retención en la CL-EM 3.15 min; Calculado para $C_{52}H_{61}N_8O8_6$: 925.46 Encontrado m/z 463.36 $[M/2+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se

determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.31 (s, 1H), 8.25 (s, 1H), 8.10 (d, *J*=8.8 Hz, 1H), 8.06 (d, *J*=8.8 Hz, 1H), 7.97-7.85 (m, 8H), 5.80-5.74 (m, 2H), 4.36-4.35 (m, 2H), 3.99-3.95 (m, 4H), 3.76-3.74 (m, 8H), 3.43-3.35 (m, 4 H), 2.75-2.68 (m, 2H), 2.44-2.37 (m 2H), 2.06-2.04 (m, 2H), 1.74 (app, d, *J*=13 Hz, 2H), 1.52-1.35 (m, 12H), 1.22-1.19 (m, 2H), 1.14-1.12 (m, 2H).



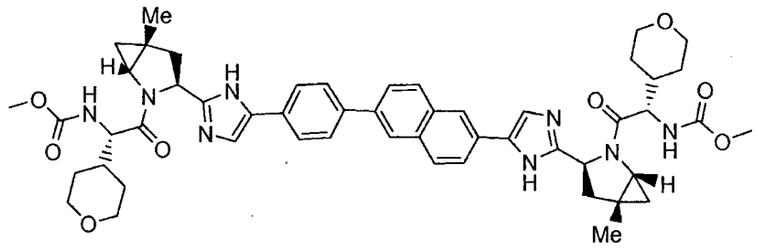
Ejemplo 138

((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hexan-2-carboxilato (Intermediario 211) (25 mg, 0.037 mmol), ácido (S)-2-(metoxicarbonilamino)-3-

metilbutanoico (14 mg, 0.082 mmol) y base de Hunig (0.052 ml, 0.297 mmol) en DMF (1 ml) se añadió HATU (31 mg, 0.082 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (17 mg, 41%), Tiempo de retención en la CL-EM 3.10 min; Calculado para $C_{48}H_{57}N_8O_6$: 841.44 Encontrado m/z 841.542 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMD de ^1H (sal en TFA, 500 MHz, MeOD) δ

ppm 8.27 (s, 1H), 8.26 (s, 1H), 8.12 (d, *J*=8.5 Hz, 1H), 8.07 (d, *J*=8.7 Hz, 1H), 7.98-7.93 (m, 4H), 7.88-7.85 (m, 4H), 5.09-5.04 (m, 2H), 4.55-4.53 (m, 2H), 3.38 (s, 6H), 3.57 (s ancho, 2H), 2.81-2.75 (m, 2H), 2.33-2.27 (m 2H), 2.22-2.16 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 1.05-0.93 (m, 16H).



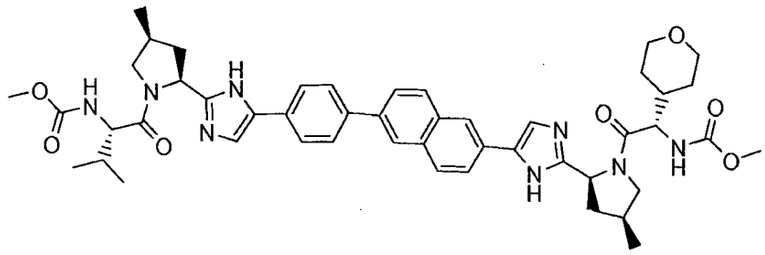
Ejemplo 139

((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de (1R,3S,5R)-2-(4-(4-(6-(2-((1R,3S,5R)-2-(*terc*-butoxicarbonil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hexan-2-carboxilato (Intermediario 211) (28 mg, 0.042 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (20 mg, 0.092 mmol) y base de Hunig (0.085 ml, 0.333 mmol) en DMF (2 ml) se añadió HATU (34.8 mg, 0.092 mmol). La reacción se agitó 1 hora a TA y se concentró parcialmente mediante purga del gas nitrógeno. El

residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((1R,3S,5R)-3-(4-(4-(6-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo (13 mg, 25%), Tiempo de retención en la CL-EM 2.92 min; Calculado para $C_{52}H_{61}N_8O8_6$: 925.46 Encontrado m/z 92.53 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Laś condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^1H (sal en TFA, 500 MHz, MeOD) δ ppm 8.28 (s, 2H), 8.14 (d, J=8.8 Hz, 1H), 8.07 (d, J=8.6 Hz, 1H), 8.00-7.96 (m, 4H), 7.91-7.84 (m, 4H), 5.08-5.02 (m, 2H), 4.59-4.56 (m, 2H), 4.00-3.94 (m, 4H), 3.69 (s, 6H), 3.62 (s ancho, 2H), 3.44-3.38 (m, 4H), 2.81-2.78 (m, 2H), 2.31-2.29

(m, 2H), 2.09 (s ancho, 2H), 1.60-1.47 (m, 8H), 1.43 (s, 3H), 1.44 (s, 3H), 1.04 (s ancho, 2H), 0.98-0.97 (m, 2H).



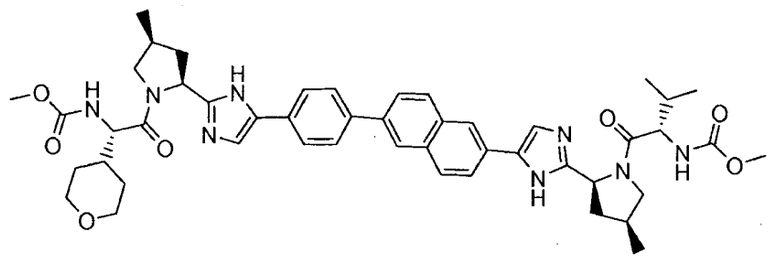
Ejemplo 140

((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

A una solución agitada de la sal tetra HCl de 2-((2S,4S)-4-metil-2-pirrolidinil)-4-(4-(6-(2-((2S,4S)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol (Intermediario 196) (150 mg, 0.231 mmol), ácido (S)-2-(metoxicarbonilamino)-22-(tetrahidro-2H-piran-4-il)acético (50 mg, 0.231 mmol) y base de Hunig (0.162 ml, 0.925 mmol) en DMF (1 ml) se añadió HATU (97 mg, 0.254 mmol). La reacción se agitó 1 h a temperatura ambiente antes de la adición de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (40.5 mg, 0.231 mmol) y la adición de base de Hunig (0.162 ml, 0.925 mmol) y HATU (97 mg, 0.254 mmol), La mezcla se agitó 1 hora a TA y se

concentró parcialmente mediante purga del gas nitrógeno. El residuo se suspendió en MeOH y se purificó mediante HPLC preparativa (MeCN/agua con TFA al 0.1%), Se aplicó un segundo proceso de cromatográfica para separar los isómeros: Columna SFC Diol-HL, 20% de metanol con 0.1 % de DEA; de 4.6 x 250 mm, de 5µm Fase móvil: 80% CO2 - 20% de metanol con 0.1% de DEA; Temp: 35 °C; Presión: 150 bares; Velocidad de flujo: 2 ml/min; UV monitorizada a 328 nm. La muestra aislada se suspendió en metanol (3 ml) y se añadió TFA neto (50 ml) a TA. La mezcla se concentró hasta sequedad y se introdujo en alto vacío para dar una sal en TFA bis de ((1S)-1-(((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (78.2 mg, rendimiento de 29.5%), Tiempo de retención en la CL-EM 2.95 min; Calculado para $C_{48}H_{59}N_8O_7$: 859.45 Encontrado m/z 859.50 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1

min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.30 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 8.01-7.85 (m, 8H), 5.26-5.22 (m, 2H), 4.42-4.36 (m, 2H), 4.30-4.27 (m, 1H), 4.24-4.23 (m, 1H), 3.95-3.91 (m, 2H), 3.68 (s, 6H), 3.47-3.36 (m 2H), 3.08-3.04 (m, 1H), 2.70 (s ancho, 2H), 2.55 (s ancho, 2H), 2.08-2.03 (m, 1H), 1.97 - 1.87 (m, 3H), 1.59 (d, *J*=13.0 Hz, 1H), 1.48-1,26 (m, 10H) 0.95-0.90 (m, 6H).

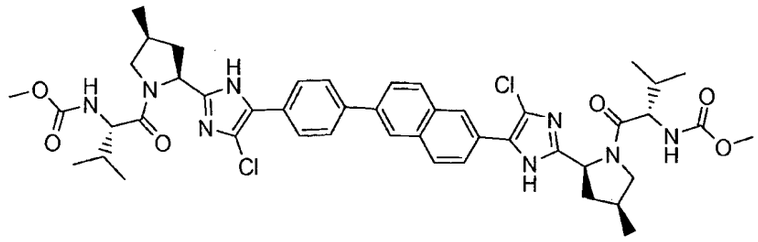


Ejemplo 141

((1S)-2-((2S,4S)-2-(4-(4-(6-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)-2-naftil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo

El otro isómero como se indica en el Ejemplo 140, El tiempo de retención CL-EM 2.98 min; Calculado para $C_{48}H_{59}N_8O_7$: 859.45 Encontrado m/z 859.58 $[M+H]^+$. Los datos de CL

se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8 ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.29 (s, 1H), 8.28 (s, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 7.99-7.86 (m, 4H), 7.91-7.85 (m, 4H), 5.26-5.21 (m, 2H), 4.41-4.36 (m, 4H), 4.28(d, *J*=8.24 Hz, 1H), 4.24 (d, *J*=7.32 Hz, 1H), 3.95-3.91 (m, 2H), 3.68 (s, 6H), 3.47-3.36 (m 2H), 2.73-2.66 (m, 2H), 2.59-2.53 (m, 2H), 2.07-2.03 (m, 1H), 1.97 - 1.87 (m, 3H), 1.59 (d, *J*=13.0 Hz, 1H), 1.51-1,25 (m, 11H) 0.95-0.90 (m, 6H).



Ejemplo 142

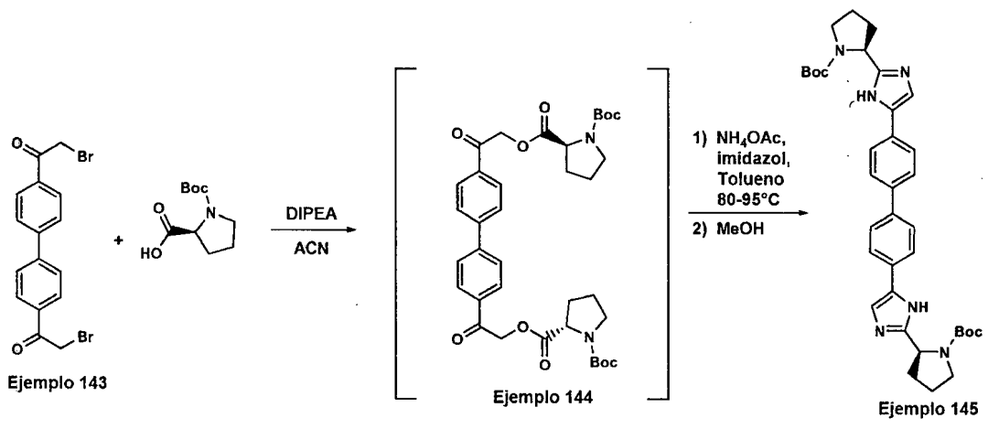
((1S)-1-(((2S,4S)-2-(4-cloro-5-(6-(4-(4-cloro-2-((2S,4S)-1-

((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-naftil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

La NCS (17.98 mg, 0.135 mmol) se añadió a la solución purgada del Ejemplo 128 (55 mg, 0.067 mmol) en DMF (1 ml) y la mezcla de reacción se agotó durante 18 horas a 50 °C. El solvente se retiró mediante concentrado y el producto bruto se suspendió en CH2Cl2 y se cargó en un cartucho Thompson de 4 g de gel de sílice. La elución de gradiente se realiza de 5-100% B en 1 l. A/B (A = CH_2Cl_2; B = 10% MeOH/EtOAc), Una muestra del producto purificado se suspendió en MeOH y se sometió a HPLC preparativa (MeCN/agua con TFA al 0.1%) para dar una sal bis en TFA de ((1S)-1-(((2S,4S)-2-(4-cloro-5-(6-(4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-naftil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo. Tiempo de retención en la CL-EM 4.48 min; Calculado para $C_{46}H_{55}Cl_2N_8O_6$: 885.36 Encontrado m/z 885.34 $[M+H]^+$. Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna C18 de 2.0 x 50 mm usando un detector SPD-10AV UV-Vis a una longitud de onda de detector de 220 nM. Las condiciones de elución usadas a un velocidad de flujo de 0.8

ml/min, un gradiente de solvente A de 100%/0% de solvente B a 0% de solvente A/100% de solvente B, un tiempo de gradiente de 3 min, un tiempo de conservación de 1 min y un tiempo de análisis de 5 min donde el solvente A fue MeOH al 5%/agua al 95%/TFA al 0.1% y el solvente B fue MeOH al 95%/agua al 5%/TFA al 0.1%. Los datos de EM se determinaron usando una plataforma MICROMASS® para CL en modo de electrorrocío. RMN de ^{1}H (sal en TFA, 500 MHz, MeOD) δ ppm 8.20 (s, 1H), 8.18 (s, 1H), 8.03 (d, *J*=8.6 Hz, 1H), 8.00 (d, *J*=8.6 Hz, 1H), 7.90-7.83 (m, 6H), 5.09-5.04 (m, 2H), 4.30-4.7 (m, 2H), 4.24-4.23 (m, 2H), 3.68 (s, 6H), 3.43-3.99 (m, 2H), 2.58-2.56 (m 2H), 2.43 (s ancho, 2H), 2.05-2.04 (m, 2H), 1.93-1.87 (m, 2H), 1.24-1,22 (m, 6H), 0.97-0.91 (m, 12H).

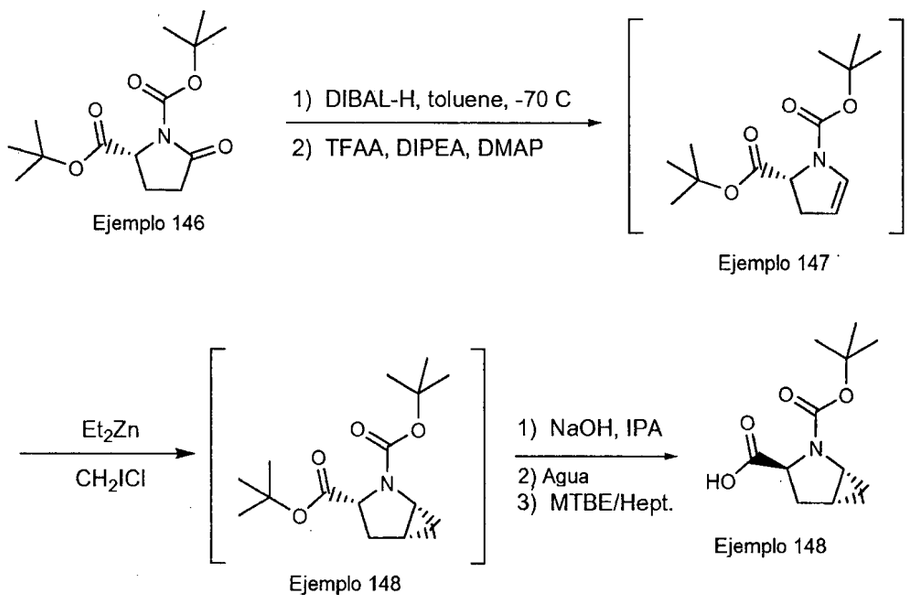
Ejemplo 145



Una suspensión agitada del Ejemplo 143 (10.0g, 25.3 mmol) y Boc-L-Prolina (11.4g, 53., mmol, 2.1 equiv.) en 100 ml of acetonitrilo se cargó con diisopropilamina (6.75 g, 52.3 mmol, 2.07 equiv.), La

mezcla resultante se calentó hasta 35 °C y se dejó agitar durante 3 horas. La mezcla se enfrió hasta 20 °C y la fase orgánica se lavó tres veces con 50 ml de NaCl acuoso al 13% p. La rica corriente orgánica se intercambió con solvente en tolueno puro mediante destilación al vacío para proporcionar el Ejemplo 144 como solución en aprox. 60 ml de tolueno. Un reactor con camisa de 500 ml se cargó con acetato amónico (38.9 g, 504.9 mmol, 20 equiv.), imidazol (6.9 g, 101.0 mmol, 4 equiv.) y 50 ml de tolueno. La suspensión resultante se calentó hasta una temperatura interna de 92-95 °C. La solución en tolueno del Ejemplo 144 se añadió manteniendo la temperatura a 92-95 °C. La mezcla resultante se dejó agitar a 92-95 °C durante 15 horas. La suspensión espesa resultante se enfrió a 55-60 °C y metanol (150 m) se añadió manteniendo la temperatura de 55-60 °C. La suspensión espesa se mantuvo a esta temperatura durante 3 horas, se enfrió hasta 20 °C durante 18 horas adicionales. Los cristales se recogieron mediante filtración y se lavó con metanol. La torta se deslicoró durante 2 horas y después se secó al vacío a 50-55°C durante 18 horas para dar 12.1 g del Ejemplo 145 en forma de un sólido amarillo claro (rendimiento 76.1°% con una HPLC AP de 97.8).

Ejemplo 149



En un reactor de 500 ml, se disolvió el Ejemplo 146 (comercialmente disponible, 17.5 g, 1.00 equiv.) en THF (87.5 ml). La solución resultante se enfrió hasta -75 °C y se cargó 1.5M DIBAL-H en tolueno (61.3 ml, 1.5 equiv.) manteniendo la temperatura por debajo de -70 °C. La solución resultante se agitó a -70 °C durante 1 hora. Se cargó ácido trifluoroacético (2.3 ml, 0.5 equiv.) en 10 minutos manteniendo la temperatura interna por debajo de -70 °C. Después se cargo trietilamina (51.3 ml, 6 equiv.) en 15 minutos manteniendo la temperatura interna por debajo de -70 °C. Se cargo ácido trifluoroacético (11.2 ml, 1.3 equiv.) en 10 minutos manteniendo la temperatura interna por debajo de -70 °C. Después, la reacción se dejó calentar hasta la

temperatura ambiente en 90 minutos y se inactivó mediante adición inversa a una solución de 20% en peso de ácido cítrico monohidrato acuoso (96.6 g, 1.5 equiv.) manteniendo la temperatura por debajo de 15°C. La mezcla resultante se agitó a temperatura ambiente durante 2 horas, después se descartó la capa acuosa inferior. La capa orgánica rica en producto se lavó dos veces con 70 ml de bicarbonato sódico acuoso saturado. El bicarbonato sódico sólido (1.7 g, 0.1 g/g del Ejemplo 146) se cargo y la solución se intercambió con el solvente en tolueno puro al vacío para proporcionar el Ejemplo 147 en forma de solución en 2 l/kg de tolueno.

Una solución del Ejemplo 147 (16.5g teóricos del Ejemplo 146) en 33 ml de tolueno se filtró en un reactor de 250 ml. Después, se cargaron trifluorotolueno (50 ml) y cloroyodometano (43.2 g, 4.0 equiv.) y la solución resultante se enfrió hasta -20 °C. Se cargó dietilzinc 1.1M en tolueno (111 ml, 2.0 equiv.) manteniendo la temperatura interna < -8 °C. La solución resultante se agitó a -15 a -20 °C durante 14 horas. La mezcla de reacción se calentó hasta 0 °C, después se inactivó mediante la adición inversa a una solución de 20 % en peso de ácido cítrico (135.7 g, 2.3 equiv.), El reactor se lavó con tolueno (82 ml) y el aclarado se añadió a la solución de inactivación. La mezcla bifásica resultante se agitó durante 20 minutos, después se dividió y se descartó la capa acuosa inferior. La capa orgánica rica se lavó dos veces

con 60 ml de NaCl acuoso 13% en peso de $NaHCO_3$ saturado. La solución resultante se intercambió con el solvente en IP puro al vacío para producir el ejemplo 148 en forma de una solución en 10 l/kg de IPA.

Un reactor de 250ml se cargó con una solución del Ejemplo 148 (147 ml, 14.7 g teóricos del Ejemplo 146) en IPA. La solución se calentó hasta 35°C y se añadió el hidróxido sódico sólido (6.2 g, 3.0 equiv.), La mezcla resultante se agitó a 35°C durante la noche. Se añadió agua (44 ml) y los solventes orgánicos se retiraron al vacío. Se añadió MTBE (145 ml) y el pH se ajustó a 3.0 con HCl 6N acuoso. La capa acuosa se dividió y se descartó. La capa orgánica rica en producto se lavó con 60 ml de agua, después se secó en azeotropismo al vacío mediante la adición de un volumen constante de MTBE. La solución se concentró hasta 55 ml y se agitó a 50 °C durante 30 minutos. La solución se enfrió hasta la temperatura ambiente en 1 hora durante la cual se formó una suspensión espesa. Se cargó heptano (90 ml) en 90 minutos y la suspensión espesa resultante envejeció durante 1 hora. Los sólidos se recogieron en una frita de vidrio con medio y se lavaron con 22.5 ml de 3:1 de heptano:MTBE seguido por 22.5 ml de heptano. El sólido se secó en un horno de vacío a 50 °C para proporcionar 5.48 g (46%) del Ejemplo 149 con una pureza LCAP de 94.9%.

El Ejemplo 149 bruto se disolvió en 55 ml de MTBE a

50 °C. La solución resultante se concentró hasta 20 ml y se enfrió hasta la temperatura ambiente en 1 hora. Después se añadió heptano (33 ml) en 90 minutos. Los sólidos resultantes se recogieron en una frita de vidrio con medio, se lavaron con heptano (15 ml) y se secaron en un horno de vacío a 50°C para proporcionar 4.45 g (98.8 AP, 98.8% de pureza quiral, 37% del Ejemplo 146) del producto deseado en forma de un polvo pardo.

Cabe esperar que la secuencia de reacciones anterior (para la formación del Ejemplo 149) sea lo suficientemente general como para toleran también otra funcionalidad. Por ejemplo, el grupo *terc*-butoxicarbonilo del carbono C2 del Ejemplo 147 podría ser sustituido potencialmente con una amida u otro éster. Asimismo, el grupo protector de *terc*-butoxicarbonilo en el nitrógeno podría estar sustituido por grupos protectores (tales como carbamatos, amidas, alquilo, arilo) o podrían estar completamente ausentes (sustituidos por hidrógeno),

ACTIVIDAD BIOLÓGICA

Se usó un ensayo VHC Replicón en la presente descripción, y se preparó, realizó y validó tal como se describe en la patente de propiedad conjunta PCT/US2006/022197 y en O'Boyle y col. *Antimicrob Agents Chemother.* **2005** Abril;49(4):1346-53, También se han usado procesos de ensayo que incorporan informadores de luciferasa

como se describe (Apath.com),

Se usaron células con el replicón VHC-neo y células con replicón que contenían sustituciones de resistencia en la región NS5A para analizar la familia de compuestos descritos en este documento. Se determinó que los compuestos tenían diferentes grados de actividad inhibitoria reducida sobre células que contenían mutaciones en comparación con el potencial inhibitorio correspondiente contra células de tipo silvestre. Así, los compuestos de la presente descripción pueden ser eficaces en la inhibición de la función de la proteína VHC NS5A y se entiende que son tan eficaces en combinaciones como se ha descrito previamente en la solicitud PCT/US2006/022197 y en el documento de patente de propiedad conjunta WO/04014852, Debería entenderse que los compuestos de la presente descripción pueden inhibir múltiples genotipos del VHC. La Tabla 2 muestra los valores de CE_{50} (Concentración eficaz inhibidora al 50 %) de compuestos representativos de la presente descripción contra el genotipo 1b de VHC. En una modalidad, los compuestos de la presente descripción son inhibidores de los genotipos 1a, 1b, 2a, 2b, 3a, 4a y 5a. Los valores de CE_{50} contra 1b de VHC son como sigue: A = 0.4 pM-10 pM; B = 10.1 pM - 1.00 nM; y C = 1.01 nM - 1 μM.

Los compuestos de la presente descripción pueden inhibir VHC mediante mecanismos además de, o distintos a, la inhibición de NS5A. En una modalidad, los compuestos de la

presente descripción inhiben el replicón de VHC y en otra modalidad los compuestos de la presente descripción inhiben NS5A.

Tabla 2

Número de ejemplo (salvo que se indique lo contrario	***CE_{50} (μM)***	***Intervalo***
Intermediario *52*		C
Intermediario *70*		C
Intermediario *114*		C
1		C
2	2.18E-06	A
3		B
4		C
5		B
6		A
7		B
8		B
9		A
10		A
11	1.82E-05	B
12		C
13		C
14		C
15		B
16		A
17		C
18		A
19		B
20		A

Número de ejemplo (salvo que se indique lo contrario	*CE_{50} (μM)*	*Intervalo*
21		A
22		B
23	8.88E-04	B
24		B
25A		C
25B		C
26		B
27	4.77E-06	A
28		B
29		A
30		A
31		B
32		B
33		A
34		A
35		A
36		A
37		A
38	4.21E-05	B
39		B
40		A
41		A
42		B
43		A
44		A
45		B
46	0.17	C
47		A
48		B
49		A

Número de ejemplo (salvo que se indique lo contrario	*CE_{50} (μM)*	*Intervalo*
50		B
51		B
52	5.90E-06	A
53	1.81E-03	C
54		A
55		A
56		A
57		A
58	8.49E-04	B
59		A
60		A
61		A
62		A
63		A
64		A
65	9.97E-07	A
66		A
67		A
68		A
69		A
70		A
71	2.11E-06	A
72		A
73		A
74		
75	1.23E-04	C
76		

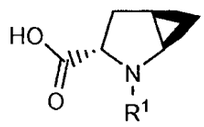
Número de ejemplo (salvo que se indique lo contrario	*CE_{50} (μM)*	*Intervalo*
77		A
78		A
79		A
80	1.08E-06	A
81		A
82	4.22E-05	B
83		A
84		A
85		A
86		A
87		A
88		A
89		A
90		A
91		A
92		A
93	0.04	C
94		A
95		A
96		B
97		A
98		B
99		A
100		A
101		A
102		A
103		A
104	2.01E-06	A
105		A
106		A
107		A
108		
109	0.18	C

Número de ejemplo (salvo que se indique lo contrario	***CE_{50} (μM)***	***Intervalo***
110		A
111		A
112		A
113		
114		B
115		A
116		B
117		
118	3.74E-05	B
119		A
120		A
121		A
122		A
123		A
124		B
125	1.36E-04	B
126	6.54E-04	B
127		A
128		A
129		B
130		A
131		---
132		A
133		A
134		A
135		B
136		A
137		A
138		A
139		A
140		A
141		A
142		A

Será evidente para un experto en la técnica que la presente descripción no se limita a los anteriores ejemplos ilustrativos, y que puede realizarse en otras formas específicas sin separarse de sus atributos esenciales. Por lo tanto se desea que los ejemplos sean considerados en todos los respectos como ilustrativos y como no restrictivos, haciendo referencia a las reivindicaciones anexas, en lugar de a los ejemplos anteriores, y por lo tanto se pretende que todos los cambios que entren dentro del significado y del alcance de equivalencia de las reivindicaciones estén incluidos en ellas.

REIVINDICACIONES

1. Un proceso para preparar un compuesto de fórmula (X)

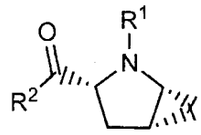


(I);

en donde R^1 se selecciona de hidrógeno y un grupo protector de nitrógeno;

caracterizado porque comprende:

i) hacer reaccionar un compuesto de fórmula (II),



(II);

o una sal farmacéuticamente aceptable del mismo; en donde

R^1 se selecciona de hidrógeno y un grupo protector de nitrógeno; y

R^2 se selecciona de amino, alcoxi y arilalcoxi; y

con una base, y

(b) tratar el producto de la etapa (a) con agua.

2. Proceso de conformidad con la reivindicación 1, caracterizado porque R^1 es hidrógeno.

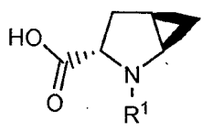
3. Proceso de conformidad con la reivindicación 1, caracterizado porque R^1 es un grupo protector de nitrógeno.

4. Proceso de conformidad con la reivindicación 3, caracterizado porque el grupo protector de nitrógeno es un grupo *terc*-butoxicarbonilo.

5. Proceso de conformidad con la reivindicación 1, caracterizado porque la base se selecciona de un alcóxido metálico y un hidróxido metálico.

6. Proceso de conformidad con la reivindicación 5, caracterizado porque la base se selecciona de etóxido de sodio, isopropóxido de sodio, *terc*-butóxido de sodio, hidróxido de sodio, hidróxido de litio, hidróxido de potasio, isopropóxido de potasio, *terc*-butóxido de potasio, *terc*-butóxido de litio e isopropóxido de litio.

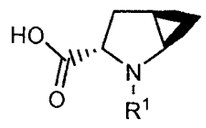
7. Proceso de conformidad con la reivindicación 1, caracterizado porque además comprende tratar un producto de fórmula (I)



(I),

en donde R^1 es hidrógeno;

con un reactivo protector de nitrógeno para proporcionar un compuesto de Fórmula (I)

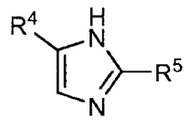


(I),

en donde R^1 es un grupo protector de nitrógeno.

8. Proceso de conformidad con la reivindicación 7, caracterizado porque el grupo protector de nitrógeno es *terc*-butoxicarbonilo.

9. Un proceso para preparar un compuesto de fórmula (Z)



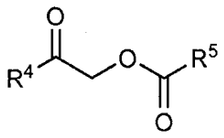
(III),

o una sal farmacéuticamente aceptable del mismo; en donde

R^4y R^5 se seleccionan independientemente de hidrógeno, alquilo, arilo, arilalquilo, heterociclilo y heterociclilalquilo;

caracterizado porque comprende:

tratar un compuesto de Fórmula (Q)



(IV),

con una base en presencia de acetato de amonio.

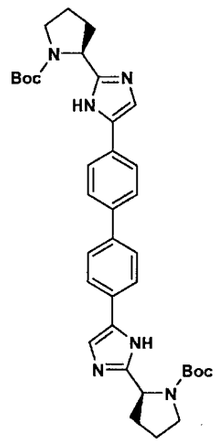
10. Proceso de conformidad con la reivindicación 9, caracterizado porque la base se selecciona de una amina terciaria, una amina aromática, una anilina y un imidazol sustituido.

11. Proceso de conformidad con la reivindicación

9, caracterizado porque la base se selecciona de 1,4-dimetilpiperazina, 3-quinuclidinol, 3-metilpiridina, 1-metilimidazol, dimetilbutilamina, N,N-dimetilanilina, dimerpranol, quinoxazolina, creatinina, 2-metilimidazol, 4-metilimidazol, imidazol, morfolina, N-metilmorfolina, 1.8-diazabicicloundec-7-eno, 1,4-diazabiciclo[2.2.2]octano, colidina, 4-cloroimidazol, 2-cloroimidazol, 4-cianoimidazol, bencimidazol, diisopropiletilamina y 2,6-lutidina.

12. Proceso de conformidad con la reivindicación 9, caracterizado porque la base es imidazol.

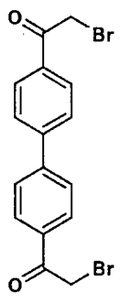
13. Un proceso de preparación del Ejemplo 145



.45.

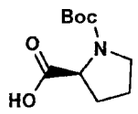
caracterizado porque comprende:

(a) tratar el Ejemplo 143



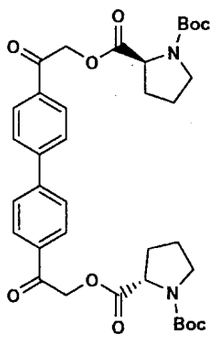
Ejemplo 143.

con el Ejemplo 144



Ejemplo 144

en presencia de una base, para producir un compuesto de Fórmula (V)



(V);

(b) tratar el compuesto de fórmula (V) con acetato de amonio en presencia de una base; y

(c) tratar el producto de la etapa (b) con metanol.

14. Proceso de conformidad con la reivindicación 13, caracterizado porque es un proceso continuo.

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a procesos para elaborar compuestos útiles en el tratamiento de infección por virus de hepatitis C (VHC).

CESIÓN DEL INVENTOR
AL SOLICITANTE

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 the international application No. PCT/US2010/055045 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 PACK, Shawn K. to BRISTOL-MYERS SQUIBB COMPANY, dated 16 November 2010 (16.11.2010)
VIII-2-1(iv)		an assignment from TYMONKO, Steven to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2010 (05.11.2010)
VIII-2-1(iv)		an assignment from PATEL, Bharat P. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2010 (05.11.2010)
VIII-2-1(iv)		an assignment from NATALIE, JR., Kenneth J. to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2010 (05.11.2010)
VIII-2-1(iv)		an assignment from BELEMA, Makonen to BRISTOL-MYERS SQUIBB COMPANY, dated 13 November 2009 (13.11.2009)

PODERES

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)

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

BOGDM5 # 82106

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

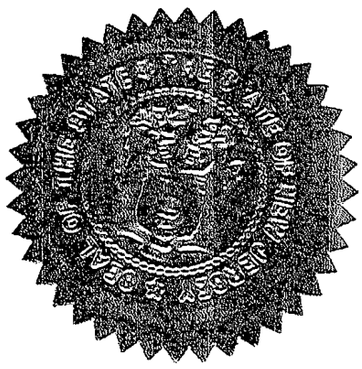
5. AT TRENTON, NEW JERSEY

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, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

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

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

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.

That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

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**

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.

That the grantor has in fact the referred to authority and that his/her representation is legal.

That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de

Abogados de Patentes Senior

de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

con sede en

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

está legalmente constituída, 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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-075545- -00000-0000
Fecha: 2012-05-08 16:43:08 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEiYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1395

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐