SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-151258- -00000-0000

Fecha: 2012-09-04 16:00:58 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** MACROCICLOS COMO INHIBIDORES DEL FACTOR DE COAGULACION (FXIA)

51. **CLASIFICACIÓN INTERNACIONAL** _____

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

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA ORDOÑEZ

22. **BOGOTÁ, D. C.,** SEPTIEMBRE 03, 2012

(FORMA P-10)

115198-Imprenta Nacional de Colombia-2011

PETITOR

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-151258- -00000-0000
Fecha: 2012-09-04 16:00:58 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

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, (US) 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: CORTE, James, R.; FANG, Tianan; DECICCO, Carl, P.; PINTO, Donald, J., P.; ROSSI, Karen, A.; HU, Zilun; JEON, Yoon; QUAN, Mimi, L.; SMALLHEER, Joanne, M.; WANG, Yufeng; YANG, Wu **Dirección:** c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 (US); c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 (US); c/o Bristol-Myers Squibb Company Route 206 & Province Line Road Lawrenceville, New Jersey 08543 (US); c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 (US); y otros **Nacionalidad o Domicilio**: Estados unidos de América	

(5) **PCT (85)**

Solicitud Internacional No.	PCT/US2011/024305	Fecha	10-02-2011
Publicación Internacional No.	WO 2011/100401	Fecha	18-08-2011

(6) **Título (54)** MACROCICLOS COMO INHIBIDORES DEL FACTOR DE COAGULACION (FXIA)

(7) **Clasificación Internacional (51)** C07D 487/08; C07D 498/08

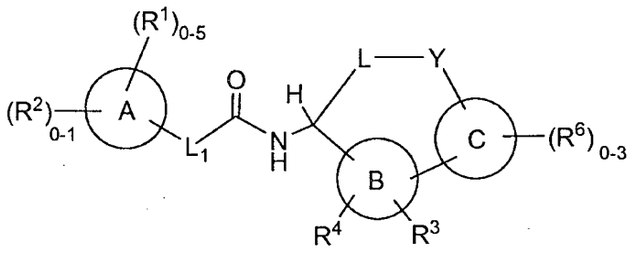
(8) **Prioridad**	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	11-02-2010	61/308,056
	US	21-10-2010	61/405338

(9) **Comprobante de pago No.** 12-0085730-12-00090450 **Fecha: 22-08-12 - 04-09-12**

(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: CD con Publicación Internacional, Traducción, Extractos, Documento de Cesión y Documento de poder

11 **FIGURA CARACTERÍSTICA**



(I)

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

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

2012/013

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0085730

Bogotá D.C., Agosto 22 de 2012 - 09:57:07

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	450027491	21/08/2012	73.321.000.00

*** 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. 12-151258- -00000-0000
Fecha: 2012-09-04 16:00:58 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0090450

Bogotá D.C., Septiembre 04 de 2012 - 07:57:19

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
RECIBO DE CA	999999999	77233	27/07/2012		140.000.00
RECIBO DE CA	999999999	85933	22/08/2012		5.000.00
RECIBO DE CA	999999999	85934	22/08/2012		5.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
5	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICICIALES	30.000.00	150.000.00
				$150.000.00

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

Responsable: _____
-********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-151258- -00000-0000

Fecha: 2012-09-04 16:00:58 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-151258- -00000-0000

Fecha: 2012-09-04 16:00:58 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 4

PATENTE DE INVENCIÓN ☐ MODELO DE

- ☐ 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 ☐

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: _____/_____/_____ AAAA MM DD	Recorrido:
Tipo de Radicación: Entrada: □ Salida: □ Traslado: □ Convenio: □		
Radicador:		Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1			
2			
3	12-151258-	0	2
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	**Otro**
Item	***Soporte Documental***
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	**Otro**

Observaciones:

Anexo 1 CD

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 August 2011 (18.08.2011)

PCT

(10) International Publication Number
WO 2011/100401 A1

(51) International Patent Classification:
C07D 487/08 (2006.01) *C07D 498/08* (2006.01)

(21) International Application Number:
PCT/US2011/024305

(22) International Filing Date:
10 February 2011 (10.02.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/303,423 11 February 2010 (11.02.2010) US
61/405,338 21 October 2010 (21.10.2010) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CORTE, James, R.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **FANG, Tianan** [CN/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **DECICCO, Carl, P.** [CA/US]; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Lawrenceville, New Jersey 08543 (US). **PINTO, Donald, J., P.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **ROSSI, Karen, A.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **HU, Zilun** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **JEON, Yoon** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **QUAN, Mimi, L.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **SMALLHEER, Joanne, M.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **WANG, Yufeng** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **YANG, Wu** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US).

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

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, 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:

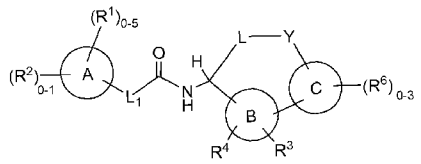
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *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))*

(54) **Title**: MACROCYCLES AS FACTOR XIA INHIBITORS



(I)

(57) **Abstract**: The present invention provides compounds of Formula (I): or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein all the variables are as defined herein. These compounds are selective Factor XIa inhibitors or dual inhibitors of fXIa and plasma kallikrein. This invention also relates to pharmaceutical compositions comprising these compounds and methods of treating thromboembolic and/or inflammatory disorders using the same.

WO 2011/100401 A1

MACROCYCLES AS FACTOR XIA INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates generally to novel macrocyclic compounds, and their analogues thereof, which are inhibitors of Factor XIa and/or plasma kallikrein, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of thromboembolic disorders.

BACKGROUND OF THE INVENTION

[0002] Thromboembolic diseases remain the leading cause of death in developed countries despite the availability of anticoagulants such as warfarin (COUMADIN®), heparin, low molecular weight heparins (LMWH), and synthetic pentasaccharides and antiplatelet agents such as aspirin and clopidogrel (PLAVIX®). The oral anticoagulant warfarin, inhibits the post-translational maturation of coagulation Factors VII, IX, X and prothrombin, and has proven effective in both venous and arterial thrombosis. However, its usage is limited due to its narrow therapeutic index, slow onset of therapeutic effect, numerous dietary and drug interactions, and a need for monitoring and dose adjustment. Thus, discovering and developing safe and efficacious oral anticoagulants for the prevention and treatment of a wide range of thromboembolic disorders has become increasingly important.

[0003] One approach is to inhibit thrombin generation by targeting the inhibition of coagulation Factor XIa (FXIa). Factor XIa is a plasma serine protease involved in the regulation of blood coagulation, which is initiated *in vivo* by the binding of tissue factor (TF) to Factor VII (FVII) to generate Factor VIIa (FVIIa). The resulting TF:FVIIa complex activates Factor IX (FIX) and Factor X (FX) that leads to the production of Factor Xa (FXa). The generated FXa catalyzes the transformation of prothrombin into small amounts of thrombin before this pathway is shut down by tissue factor pathway inhibitor (TFPI). The process of coagulation is then further propagated via the feedback activation of Factors V, VIII and XI by catalytic amounts of thrombin. (Gailani, D. et al., *Arterioscler. Thromb. Vasc. Biol.*, 27:2507-2513 (2007).) The resulting burst of thrombin converts fibrinogen to fibrin that polymerizes to form the structural framework of a blood clot, and activates platelets, which are a key cellular component of coagulation (Hoffman,

M., *Blood Reviews,* 17:S1-S5 (2003)). Therefore, Factor XIa plays a key role in propagating this amplification loop and is thus an attractive target for anti-thrombotic therapy.

SUMMARY OF THE INVENTION

[0004] The present invention provides novel macrocyclic compounds, their analogues, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, which are useful as selective inhibitors of serine protease enzymes, especially Factor XIa and/or plasma kallikrein.

[0005] The present invention also provides processes and intermediates for making the compounds of the present invention.

[0006] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0007] The compounds of the invention may be used in the treatment and/or prophylaxis of thromboembolic disorders.

[0008] The compounds of the present invention may be used in therapy.

[0009] The compounds of the present invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of a thromboembolic disorder.

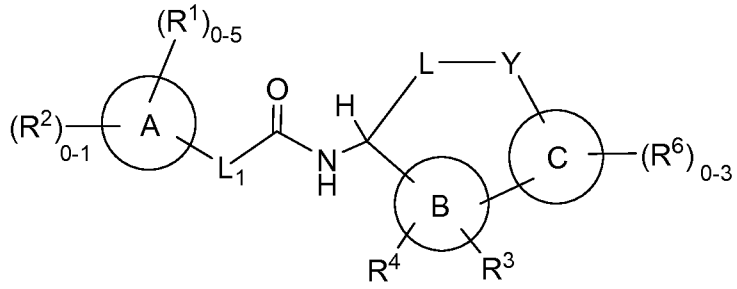
[0010] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two other agent(s).

[0011] These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

[0012] In a first aspect, the present invention provides, *inter alia*, a compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

ring A is independently a C_{3-10} carbocycle or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), O, and $S(O)_p$;

ring B is independently a benzene ring or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

ring C is independently a benzene ring or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), O, and $S(O)_p$;

L_1 is independently selected from the group consisting of: a bond, -CHR^5-, -CHR^5CHR^5-, -CR^5=CR^5-, -C≡C-, -OCH_2-, -CHR^5NH-, -CH_2O-, -SCH_2-, -SO_2CH_2-, -CH_2NH-, and -CR^5R^5-;

L is independently selected from the group consisting of: C_{3-8} alkylene, C_{3-8} alkenylene, and C_{4-8} alkynylene; wherein said alkylene, alkenylene and alkynylene are substituted with 0-2 R^7 and optionally one or more of the carbon atoms of said alkylene and alkenylene may be replaced by O, S, NH, N(C_{1-4} alkyl), CO, CONH, NHCO, OCONH, $NHCO_2$, -NHCONH-, SO_2NH, $NHSO_2$, CON(C_{1-4} alkyl), or N(C_{1-4} alkyl)CO;

Y is independently selected from the group consisting of: CH_2, CH(C_{1-4} alkyl), C(C_{1-4} alkyl)$_2$, CO, O, S, NH, N(C_{1-4} alkyl), N(CO_2(C_{1-4} alkyl)), -N(C_{1-4} alkyl)CH_2-, -N(CO_2(C_{1-4} alkyl))CH_2-, -N(CH_2CO_2(C_{1-4} alkyl))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -OCON(C_{1-4} alkyl)-, -NHCONH-, -SO_2NH-, -$NHCO_2$-, and -$NHSO_2$-;

alternatively, L-Y is -C_{3-6} alkylene-CH=N-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $CO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), $-CH_2NH_2$, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-OCH_2CO_2H$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-C(=NH)NH_2$, and phenyl substituted with 0-2 R^a;

R^2 is independently a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a} is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, $-CH_2OH$, C_{1-4} alkoxy, OH, CF_3, OCF_3, CN, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), COC_{1-4} alkyl, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl)$_2$, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_{1-4}$ alkyl), and $-SO_2N(C_{1-4}$ alkyl)$_2$;

R^3 is independently selected from the group consisting of: H, =O, halogen, OH, NH_2, CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, $-CH_2OH$, CO_2H, $CO_2(C_{1-4}$ alkyl), $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)$_2$, $-CH_2CO_2H$, and C_{3-6} cycloalkyl;

R^4 is independently selected from the group consisting of: H, and C_{1-4} alkyl;

R^5 is, independently at each occurrence, selected from the group consisting of: H, halogen, OH, and C_{1-4} alkyl;

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCOCF_3$, $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl)$_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH_2$, $-CONH(C_{1-4}$ alkyl),

-$CON(C_{1-4}$ alkyl$)_2$, -CH_2CONH_2, and -$NHCO_2(CH_2)_{0-2}R^9$;

R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, NH_2, CH_2NH_2, C_{1-4} haloalkyl, OCH_2F, $OCHF_2$, OCF_3, -$NH(C_{1-4}$ alkyl), -$N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, CH_2OH, $CH_2O(C_{1-4}$ alkyl), $CH_2O(CH_2)_{1-4}O(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $CO_2(CH_2)_2O(C_{1-4}$ alkyl), $CO_2(C_{1-4}$ haloalkyl), $CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl), CH_2CO_2H, $CH_2CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, -$OCO(C_{1-4}$ alkyl), -$CH_2NH(CH_2)_2O(C_{1-4}$ alkyl), -$CONH(C_{1-4}$ alkoxy), -$CO_2(CH_2)_2O(C_{1-4}$ alkyl), -$CO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, -$CONH(CH_2)_2O(C_{1-4}$ alkyl), -$CONH(CH_2)_2N(C_{1-4}$ alkyl$)_2$, -$CON(C_{1-4}$ alkyl$)(CH_2)_2O(C_{1-4}$ alkyl), -$CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkyl, -CONHBn, -CONH(OBn), -$(CO)_{0-1}(CH_2)_{0-3}$-C_{3-6} carbocycle, and -$(CH_2)_{0-1}$-$(CO)_{0-1}$-$(W)_{0-1}$-$(CH_2)_{0-2}$-(4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$); wherein said carbocycle and heterocycle are substituted with 0-2 R^8;

R^8 is, independently at each occurrence, selected from the group consisting of: halogen, OH, CHF_2, CF_3, C_{1-4} alkoxy, CH_2OH, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, and C_{1-4} alkyl;

R^9 is a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), O, and $S(O)_p$;

R^a is, independently at each occurrence, selected from the group consisting of: halogen, OH, CF_3, C_{1-4} alkoxy, and C_{1-4} alkyl;

W is independently selected from the group consisting of: O, NH and $N(C_{1-4}$ alkyl); and

p is, independently at each occurrence, selected from the group consisting of: 0, 1, and 2.

[0013] In a second aspect, the present invention provides compounds of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the first aspect, wherein:

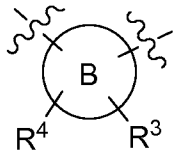
ring A is independently a 6-membered carbocycle, a 9- to 10-membered carbocycle, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-3 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$;

ring B is independently selected from the group consisting of: imidazole, oxazole, oxadiazole, triazole, pyridine, pyridazine, pyrimidine, and benzene; and

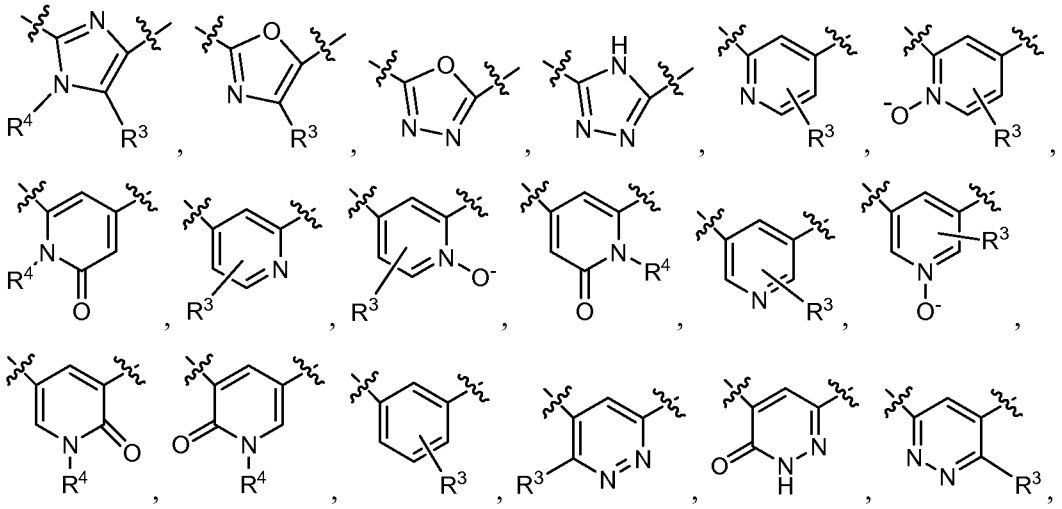
ring C is independently selected from the group consisting of: benzene, pyridine, indazole, indole, benzimidazole, quinoline, isoquinoline, tetrahydroquinoline, tetrahydroisoquinoline, and quinazoline.

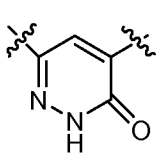
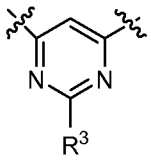
[0014] In a third aspect, the present invention provides compounds of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the first or second aspect, wherein:

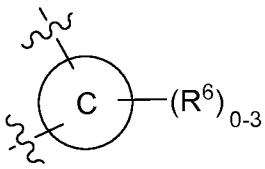
ring A is independently selected from the group consisting of: benzene, cyclohexane, indane, tetrahydronaphthalene, naphthalene, isoxazoline, isoxazole, pyrazole, imidazole, triazole, piperidine, pyridine, indazole, indole, benzimidazole, quinoline, isoquinoline, tetrahydroquinoline, and tetrahydroisoquinoline;

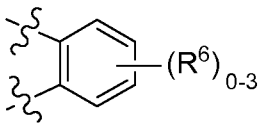
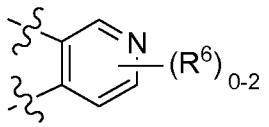
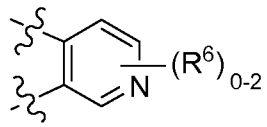


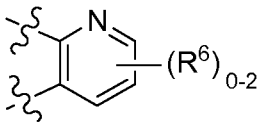
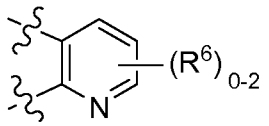
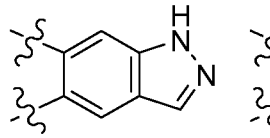
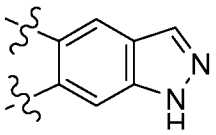
is independently selected from the group consisting of:

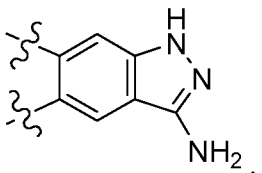
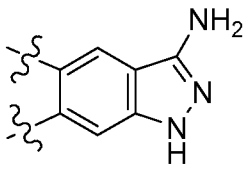
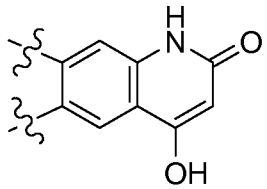



, and 
; and

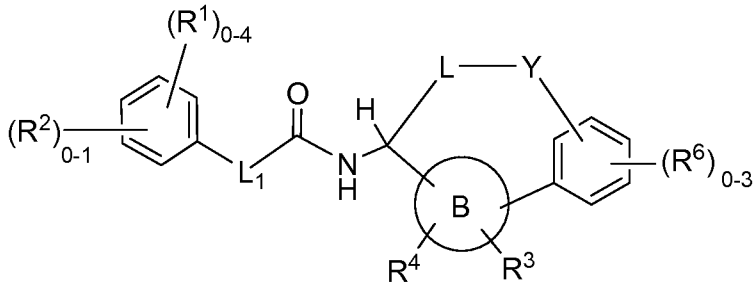

is independently selected from the group consisting of:


,

,

,

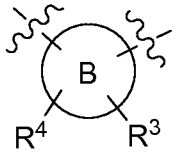

,

,

,

,

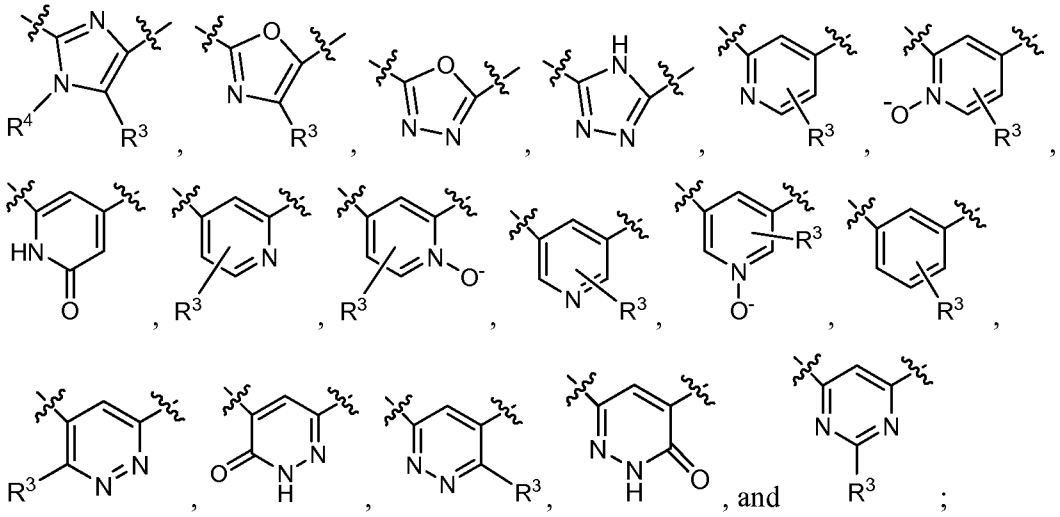

,

, and

.

[0015] In a fourth aspect, the present invention provides compounds of Formula (II):


(II)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:


is independently selected from the group consisting of:



L_1 is independently selected from the group consisting of: a bond, -CHR^5CHR^5-, -CR^5=CHR^5-, -C≡C-, -OCH_2-, -CHR^5NH-, -CH_2O-, -SCH_2-, -SO_2CH_2-, -CH_2NH-, and -CR^5R^5-;

L is independently selected from the group consisting of: C_{3-8} alkylene and C_{3-8} alkenylene; wherein said alkylene and alkenylene are substituted with 0-2 R^7 and optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, CO, S, NH, N(C_{1-4} alkyl), CONH-, NHCO, OCONH, SO_2NH, or CON(C_{1-4} alkyl);

Y is independently selected from the group consisting of: CH_2, CO, CH(C_{1-4} alkyl), C(C_{1-4} alkyl)$_2$, O, S, NH, N(C_{1-4} alkyl), N(CO_2(C_{1-4} alkyl), -N(C_{1-4} alkyl)CH_2-, -N(CO_2(C_{1-4} alkyl))CH_2-, -N(CH_2CO_2(C_{1-4} alkyl))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -OCON(C_{1-4} alkyl)-, -NHCONH-, and -SO_2NH-;

alternatively, L-Y is -C_{3-6} alkylene-CH=N-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, CO_2(C_{1-4} alkyl), CO(C_{1-4} alkyl), -OCH_2CO_2H, -CH_2NH_2, -$CONH_2$, -CONH(C_{1-4} alkyl), -SO_2NH_2, and -C(=NH)NH_2;

R^2 is independently a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a} is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, $-CH_2OH$, C_{1-4} alkoxy, OH, CF_3, CN, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), COC_{1-4} alkyl, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), and $-CON(C_{1-4}$ alkyl$)_2$;

R^3 is independently selected from the group consisting of: H, halogen, OH, NH_2, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $-CH_2OH$, CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl$)_2$, $-CH_2CO_2H$, and C_{3-6} cycloalkyl;

R^4 is independently selected from the group consisting of: H and C_{1-4} alkyl;

R^5 is, independently at each occurrence, selected from the group consisting of: H, halogen, OH, and C_{1-4} alkyl;

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl$)_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH(CH_2)_2O(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-CH_2CONH_2$, $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-NHCOCF_3$, and $-NHCO_2(CH_2)_{0-1}R^9$;

R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, C_{1-4} haloalkyl, C_{1-4} alkoxy, CH_2OH, $CH_2O(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $CO_2(CH_2)_2O(C_{1-4}$ alkyl)), $CO_2CH_2CF_3$, $CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl, CH_2CO_2H, $CH_2CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-OCO(C_{1-4}$ alkyl), $-CH_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-CON(C_{1-4}$ alkyl$)(CH_2)_2O(C_{1-4}$ alkyl), $-CONH(CH_2)_2N(C_{1-4}$ alkyl$)_2$,

-CON(C_{1-4} alkyl)$(CH_2)_2$N(C_{1-4} alkyl)$_2$, -CONH(C_{1-4} alkoxy), -CONHBn, -CONH(OBn), -$(CH_2)_{1-3}$Ph, C_{1-4} alkyl, and -$(CH_2)_{0-1}$-$(CO)_{0-1}$-$(W)_{0-1}$-$(CH_2)_{0-2}$-(4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), O, and $S(O)_p$); wherein said heterocycle is substituted with 0-2 R^8;

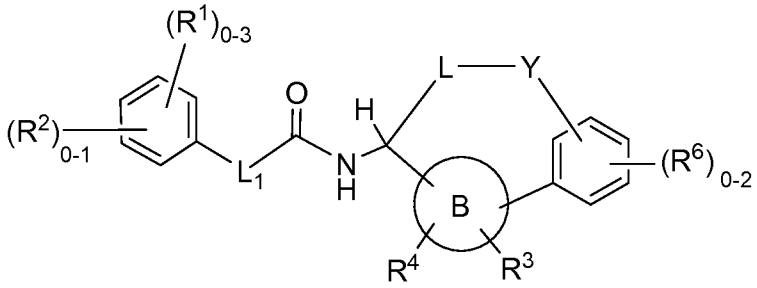
R^8 is, independently at each occurrence, selected from the group consisting of: halogen, OH, CHF_2, CF_3, C_{1-4} alkoxy, and C_{1-4} alkyl;

R^9 is a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), N(CO_2(C_{1-4} alkyl)), O, and $S(O)_p$;

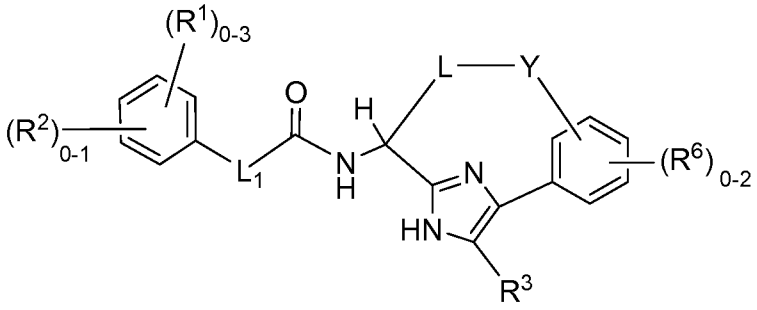
W is independently selected from the group consisting of: O and NH; and

p is, independently at each occurrence, selected from the group consisting of: 0, 1, and 2.

[0016] In a fifth aspect, the present invention provides compounds of Formula (IIa) or Formula (IIb):



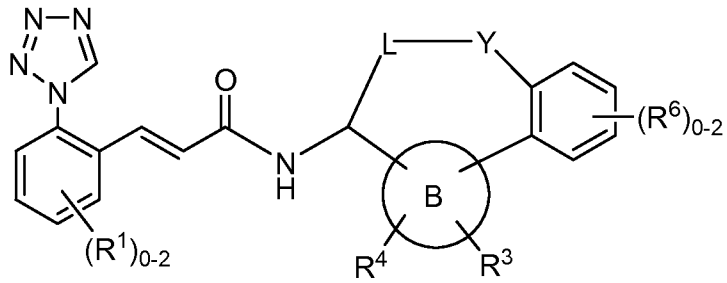
(IIa)



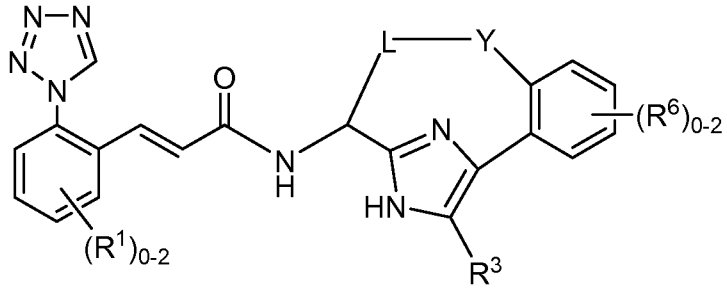
(IIb)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the fourth aspect.

[0017] In a sixth aspect, the present invention provides compounds of Formula (IIc) or Formula (IId):



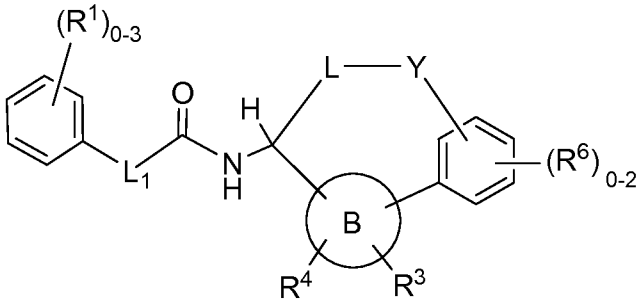
(IIc)



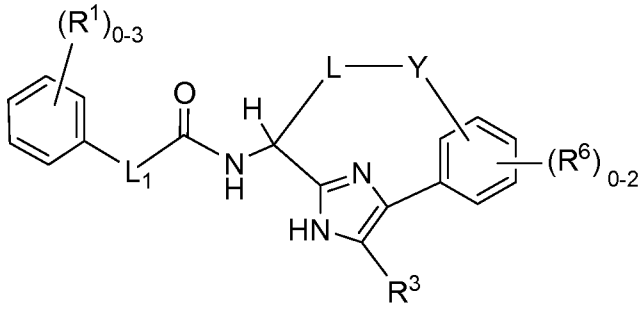
(IId)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the fourth aspect.

[0018] In a seventh aspect, the present invention provides compounds of Formula (IIe) or Formula (IIf):



(IIe)



(IIf)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the fourth aspect.

[0019] In an eighth aspect, the present invention includes compounds of Formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any of the above aspects, wherein:

L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$, -CH=CH-, -C(Me)=CH-, -C≡C-, and $-CH_2NH-$ in Formula (I), (II), (IIa), (IIb), (IIe) or (IIf);

L is independently selected from the group consisting of: C_{3-7} alkylene and C_{3-7} alkenylene; wherein said alkylene and alkenylene are substituted with 0-2 R^7 and optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, CO, NH, $N(C_{1-4}$ alkyl), CONH, NHCO, or $CON(C_{1-4}$ alkyl);

Y is independently selected from the group consisting of: CH_2, CO, $CH(C_{1-4}$ alkyl), $C(C_{1-4}$ alkyl$)_2$, O, S, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), $-N(C_{1-4}$ alkyl$)CH_2-$, $-N(CO_2(C_{1-4}$ alkyl$))CH_2-$, $-N(CH_2CO_2(C_{1-4}$ alkyl$))CH_2-$, -CONH-, -NHCO-, $-CONHCH_2-$, $-CON(C_{1-4}$ alkyl$)CH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$;

alternatively, L-Y is $-(CH_2)_{3-6}-CH=N-$;

R^1 is, independently at each occurrence, selected from: halogen, CN, OH, OCH_2F, $OCHF_2$, OCF_3, C_{1-4} haloalkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, and $-SO_2NH_2$;

R^3 is independently selected from the group consisting of: H, halogen, OH, NH_2, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $-CH_2OH$, CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl$)_2$, $-CH_2CO_2H$, and C_{3-6} cycloalkyl; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl),

-NHC(O)N(C_{1-4} alkyl)$_2$, -NHSO$_2$(C_{1-4} alkyl), -SO$_2$NH(CH$_2$)$_2$OH, -SO$_2$NH(CH$_2$)$_2$O(C_{1-4} alkyl), CONH$_2$, CONH(C_{1-4} alkyl), CON(C_{1-4} alkyl)$_2$, -NHCO$_2$(CH$_2$)$_2$N(C_{1-4} alkyl)$_2$, -NHCOCF$_3$, and -NHCO$_2$(CH$_2$)$_{0-1}$R^9.

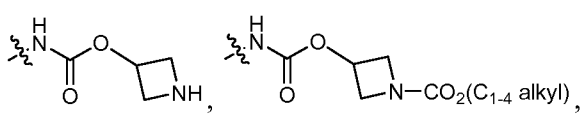
[0020] In a ninth aspect, the present invention includes compounds of Formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any of the above aspects, wherein:

L_1 is independently selected from the group consisting of: a bond, -CH$_2$CH$_2$- and -CH=CH- in Formula (I), (II), (IIa), (IIb), (IIe) or (IIf);

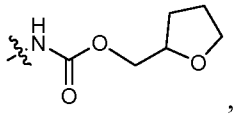
R^1 is, independently at each occurrence, selected from the group consisting of: halogen, CN, C_{1-4} alkyl, OH, C_{1-4} alkoxy, CH$_2$F, CHF$_2$, CF$_3$, OCH$_2$F, OCHF$_2$, OCF$_3$, CO(C_{1-4} alkyl), NH$_2$, NH(C_{1-4} alkyl)$_2$, N(C_{1-4} alkyl)$_2$, -CH$_2$NH$_2$, and -C(=NH)NH$_2$;

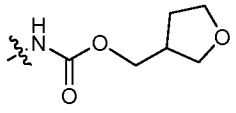
R^3 is independently selected from the group consisting of: H, halogen, CN, CF$_3$, CO$_2$H, CO$_2$(C_{1-4} alkyl), C_{1-4} alkyl, CONH$_2$, CON(C_{1-4} alkyl)$_2$, and C_{3-6} cycloalkyl; and

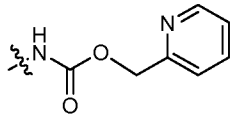
R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF$_3$, CO$_2$H, CO$_2$(C_{1-4} alkyl), -CH$_2$CO$_2$H, -CH$_2$CO$_2$(C_{1-4} alkyl), NH$_2$, -CH$_2$NH$_2$, -NHCO(C_{1-4} alkyl), -NHCO$_2$(C_{1-4} alkyl), -CH$_2$NHCO$_2$(C_{1-4} alkyl), -CONH$_2$, CONH(C_{1-4} alkyl), CON(C_{1-4} alkyl)$_2$, -NHCO$_2$(CH$_2$)$_2$OH, -NHCO$_2$(CH$_2$)$_2$O(C_{1-4} alkyl), -NHCO$_2$CH$_2$CO$_2$H, -NHCO$_2$CH$_2$CH(C_{1-4} alkyl)O(C_{1-4} alkyl), -NHCO$_2$(CH$_2$)$_2$N(C_{1-4} alkyl)$_2$, -NHCOCF$_3$,



,

,


,


,


.

[0021] In a tenth aspect, the present invention includes compounds of Formula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically

acceptable salt, a solvate, or a prodrug thereof, within the scope of any one of the above aspects, wherein:

L_1 is independently selected from the group consisting of: a bond and -CH=CH- in Formula (I), (II), (IIa), (IIb), (IIe) or (IIf);

L is independently selected from the group consisting of: $-(CH_2)_{3-6}-$, $-(CH_2)_{2-4}CH(C_{1-4}\text{ alkyl})(CH_2)_{0-2}-$, $-(CH_2)_{1-2}-CH=CH-(CH_2)_{0-3}-$, $-CH_2-CH=C(C_{1-4}\text{ alkyl})-(CH_2)_{1-2}-$, $-CH_2-C(C_{1-4}\text{ alkyl})=CH-(CH_2)_{1-2}-$, $-CH_2-CH=CH-CH_2CH(C_{1-4}\text{ alkyl})-$, $-CH_2-CH=CH-CH(C_{1-4}\text{ alkyl})-(CH_2)_{0-2}-$, $-CH_2-CH=CH-CH_2C(\text{halo})_2-$, $-CH_2-CH=CH-(CH_2)_{1-2}CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(\text{halo})-$, $-(CH_2)_{3-4}C(\text{halo})_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_{3-4}CH(C_{1-4}\text{ alkoxy})-$, $-(CH_2)_4CH(CH_2(C_{1-4}\text{ alkoxy}))-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_{4-5}CH(CO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CO_2CH_2CF_3)-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4C(C_{1-4}\text{ alkyl})(CO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4C(CF_3)(CO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CONH_2))-$, $-(CH_2)_4CH(CONH(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})_2)-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})CH(CONH_2)-$, $-(CH_2)_4CH(CO_2(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CH_2NH(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CONH(C_{1-4}\text{ alkoxy}))-$, $-(CH_2)_4CH(CONH(OBn))-$, $-(CH_2)_4CH((CH_2)_3Ph)-$, $-(CH_2)_4CH(CO_2(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$, $-(CH_2)_4CH(CONH(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CONH(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$, $-(CH_2)_4CH(CH(\text{halo})_2)-$, $-(CH_2)_{4-5}CH(CF_3)-$, $-(CH_2)_3C(\text{halo})_2CH_2-$, $-(CH_2)_{1-3}CH(OH)(CH_2)_{1-2}-$, $-CH_2CH(OH)CH(OH)CH_2-$, $-(CH_2)_3CH(OCO(C_{1-4}\text{ alkyl}))CH_2-$, $-(CH_2)_3C(O)CH_2-$, $-CH_2O(CH_2)_{2-4}-$, $-CH_2NH(CH_2)_{2-4}-$, $-(CH_2)_{2-3}NH(CH_2)_{1-2}-$, $-(CH_2)_{2-4}N(C_{1-4}\text{ alkyl})(CH_2)_{0-2}-$, $-CH_2CONH(CH_2)_{2-4}-$, $-CH_2CON(C_{1-4}\text{ alkyl})(CH_2)_{2-4}-$, $-CH_2NHCOC(\text{halo})_2CH_2-$,

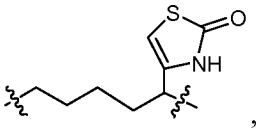
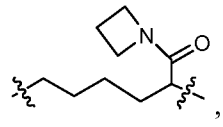
-$(CH_2)_4CH$(3-C_{1-4} alkyl-oxetan-3-yl)-, -$(CH_2)_4CH$(thiazol-4-yl)-,

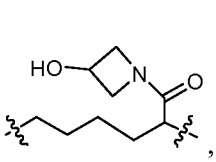
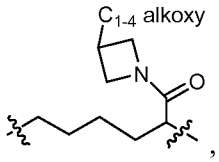
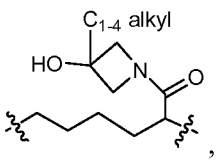
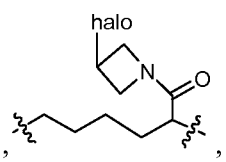
-$(CH_2)_4CH$(4-C_{1-4} alkyl-thiazol-2-yl)-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-imidazol-2-yl)-,

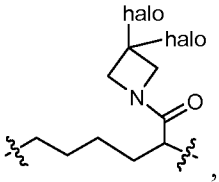
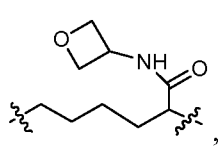
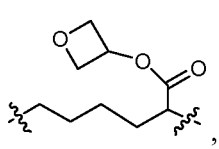
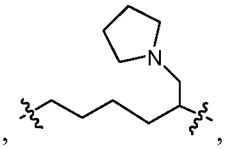
-$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-3-yl)-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-5-yl)-,

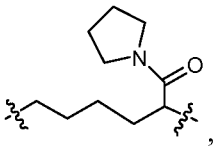
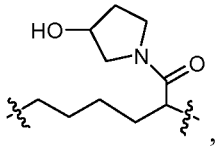
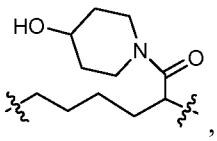
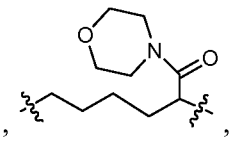
-CH_2-CH=CH-CH_2CH(1-C_{1-4} alkyl-pyrazol-5-yl)-,

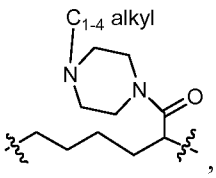
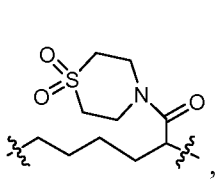
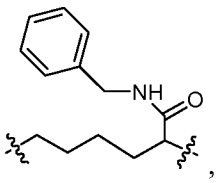
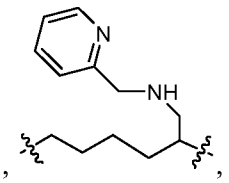
-$(CH_2)_4CH$(1-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)-,

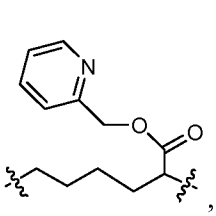
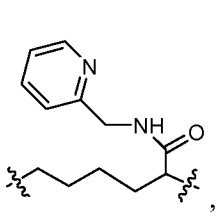
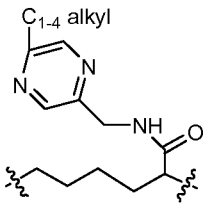
-$(CH_2)_4CH$(1-C_{1-4} alkyl-4-halo-pyrazol-3-yl)-,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  , and ;

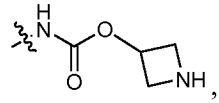
Y is independently selected from the group consisting of: CH_2, CO, O, NH, N(C_{1-4} alkyl), N(CO_2(C_{1-4} alkyl)), -N(C_{1-4} alkyl)CH_2-, -N(CO_2(C_{1-4} alkyl))CH_2-, -N(CH_2CO_2(C_{1-4} alkyl))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -NHCONH-, and -SO_2NH-; and

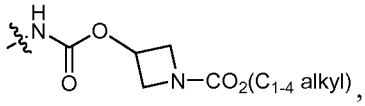
alternatively, L-Y is -$(CH_2)_{3-6}$-CH=N-;

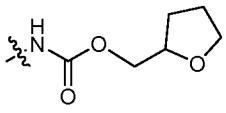
R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, OH, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), CN, CH_2F, CHF_2, CF_3, $OCHF_2$, NH_2, $N(C_{1-4}$ alkyl$)_2$, $-CH_2NH_2$, and $-C(=NH)NH_2$;

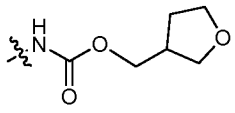
R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and C_{3-6} cycloalkyl; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-NHCOCF_3$,

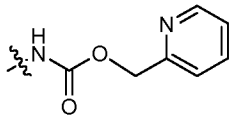






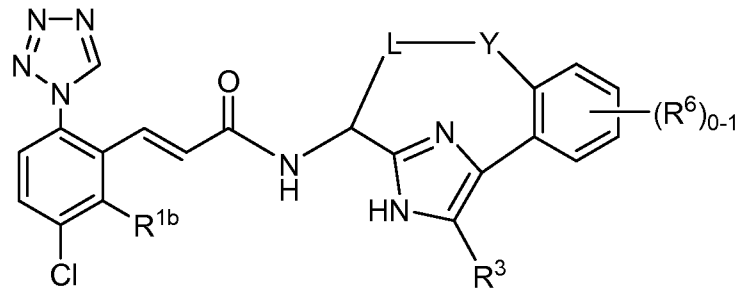


, and

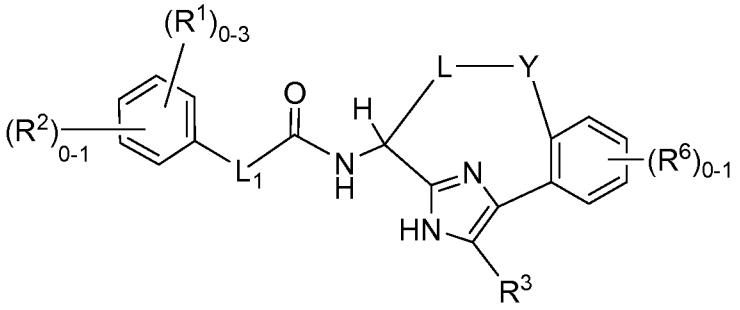


.

[0022] In an 11th aspect, the present invention includes compounds of Formula (III) or Formula (IIIa):



(III)



(IIIa)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L_1 is independently selected from the group consisting of: a bond and -CH=CH- in Formula (IIIa);

L is independently selected from the group consisting of: $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_3CH(C_{1-4}$ alkyl)-, $-(CH_2)_4CH(C_{1-4}$ alkyl)-, $-(CH_2)_2CH(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_3CH(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_2CH(C_{1-4}$ alkyl)$(CH_2)_2-$, $-(CH_2)_3CH(C_{1-4}$ alkyl)$(CH_2)_2-$, $-(CH_2)_4CH(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_4CH(C_{1-4}$ alkyl)$(CH_2)_2-$, $-(CH_2)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(C_{1-4}$ alkyl)$-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CH(C_{1-4}$ alkyl)-, $-CH_2-CH=CH-CH(C_{1-4}$ alkyl)CH_2-, $-CH_2-CH=CH-CH_2C(halo)_2-$, $-CH_2-CH=CH-CH_2CH(CF_3)-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(halo)-$, $-(CH_2)_3C(halo)_2-$, $-(CH_2)_4C(halo)_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_3CH(C_{1-4}$ alkoxy)-, $-(CH_2)_4CH(CH_2(C_{1-4}$ alkoxy))-, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_4CH(CO_2(C_{1-4}$ alkyl))-, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}$ alkyl))-, $-(CH_2)_4CH(CO_2CH_2CF_3)-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl))-, $-(CH_2)_5CH(CO_2(C_{1-4}$ alkyl))-, $-(CH_2)_4C(C_{1-4}$ alkyl)$(CO_2(C_{1-4}$ alkyl))-, $-(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl))-, $-(CH_2)_4CH(CONH_2)-$, $-(CH_2)_4CH(CONH(C_{1-4}$ alkyl))-, $-(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)-$, $-(CH_2)_3CH(C_{1-4}$ alkyl)$CH(CONH_2)-$, $-(CH_2)_4CH(CONH(C_{1-4}$ alkoxy))-, $-(CH_2)_4CH(CONH(OBn))-$, $-(CH_2)_4CH((CH_2)_3Ph)-$, $-(CH_2)_4CH(CON(C_{1-4}$ alkyl)$(CH_2)_2O(C_{1-4}$ alkyl))-,

-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-,

-$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-,

-$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-,

-$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_3C(O)CH_2$-,

-$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-,

-$(CH_2)_2N(C_{1-4}$ alkyl$)CH_2$-, -$(CH_2)_2N(C_{1-4}$ alkyl$)(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-,

-$CH_2CONH(CH_2)_3$-, -$CH_2CONH(CH_2)_4$-, -$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_2$-,

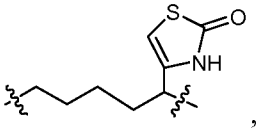
-$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_3$-, -$(CH_2)_4CH$(thiazol-4-yl)-,

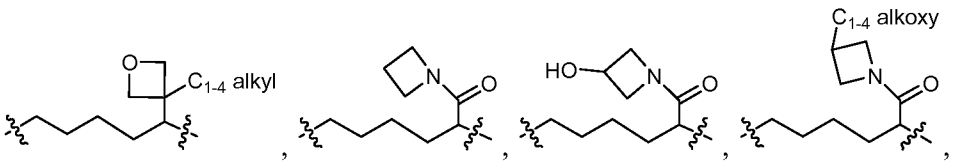
-$(CH_2)_4CH(4$-C_{1-4} alkyl-thiazol-2-yl)-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-imidazol-2-yl)-,

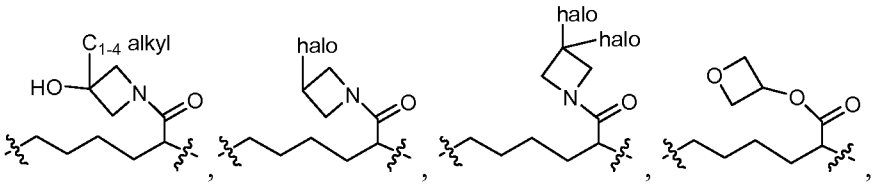
-$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-3-yl)-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-5-yl)-,

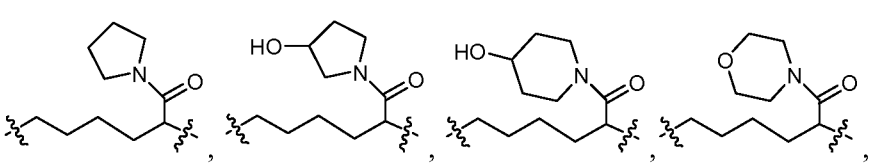
-CH_2-CH=CH-$CH_2CH(1$-C_{1-4} alkyl-pyrazol-5-yl)-,

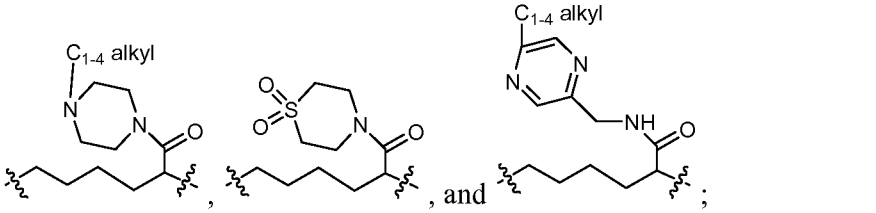
-$(CH_2)_4CH(1$-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)-,

-$(CH_2)_4CH(1$-C_{1-4} alkyl-4-halo-pyrazol-3-yl)-,  ,

 ,

 ,

 ,

 , and ;

Y is independently selected from the group consisting of: CH_2, CO, O, NH,

$N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), $-N(C_{1-4}$ alkyl)CH_2-, $-N(CO_2(C_{1-4}$ alkyl))CH_2-, $-N(CH_2CO_2(C_{1-4}$ alkyl))CH_2-, -CONH-, -NHCO-, $-CONHCH_2$-, $-CON(C_{1-4}$ alkyl)CH_2-, -OCONH-, -NHCONH-, and $-SO_2NH$-;

alternatively, L-Y is $-(CH_2)_4$-CH=N-;

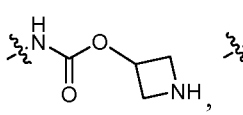
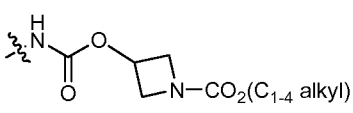
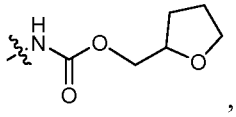
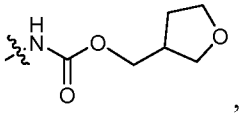
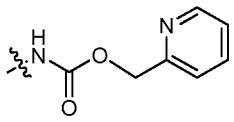
R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, OH, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), CN, CH_2F, CHF_2, CF_3, $OCHF_2$, NH_2, $N(C_{1-4}$ alkyl)$_2$, $-CH_2NH_2$, and $-C(=NH)NH_2$ in Formula (IIIa);

R^{1b} is independently selected from the group consisting of: H and halogen in Formula (III);

R^2 is independently a 5-membered heterocycle selected from: triazolyl and tetrazolyl in Formula (IIIa);

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl)$_2$, and C_{3-6} cycloalkyl; and

R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, $CO_2(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-NHCOCF_3$,

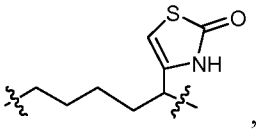

,

,

,

,

.

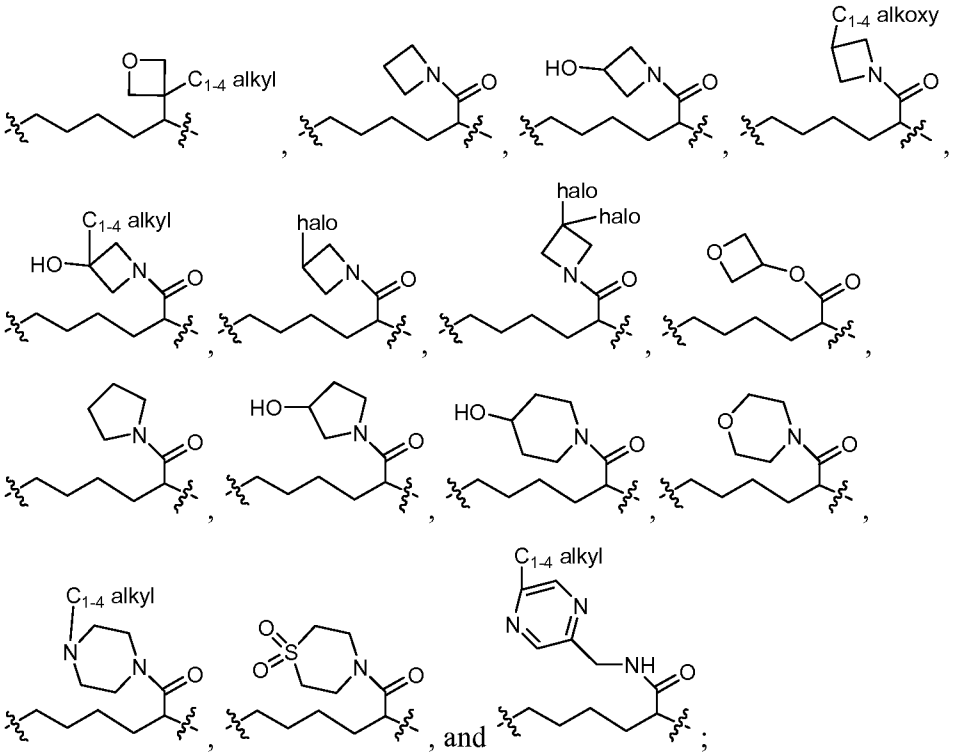
[0023] In a 12th aspect, the present invention includes compounds of Formula (III) or Formula (IIIa), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the 11th aspect, wherein:

L is independently selected from the group consisting of: $-(CH_2)_4$-, $-(CH_2)_5$-, $-(CH_2)_6$-, $-(CH_2)_3CH(C_{1-4}$ alkyl)-, $-(CH_2)_4CH(C_{1-4}$ alkyl)-, $-(CH_2)_2CH(C_{1-4}$ alkyl)CH_2-,

$-(CH_2)_3CH(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_2CH(C_{1-4}$ alkyl)$(CH_2)_2$-,

-$(CH_2)_3CH(C_{1-4}$ alkyl$)(CH_2)_2$-, -$(CH_2)_4CH(C_{1-4}$ alkyl$)CH_2$-,
-$(CH_2)_4CH(C_{1-4}$ alkyl$)(CH_2)_2$-, -$(CH_2)_2$-CH=CH-, -CH_2-CH=CH-CH_2-,
-CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C$(C_{1-4}$ alkyl$)$-$(CH_2)_2$-,
-CH_2-CH=CH-$CH_2CH(C_{1-4}$ alkyl$)$-, -CH_2-CH=CH-$CH(C_{1-4}$ alkyl$)CH_2$-,
-CH_2-CH=CH-CH_2C(halo$)_2$-, -CH_2-CH=CH-$CH_2CH(CF_3)$-,
-CH_2-CH=CH-$(CH_2)_2CH(CF_3)$-, -CH_2-CH=CH-CH(OH)CH_2-, -$(CH_2)_3CH$(halo)-,
-$(CH_2)_3C$(halo$)_2$-, -$(CH_2)_4C$(halo$)_2$-, -$(CH_2)_4CH(CH_2OH)$-,
-$(CH_2)_4CH(CH_2(C_{1-4}$ alkoxy$))$-, -$(CH_2)_3CH(C_{1-4}$ alkoxy$)$-, -$(CH_2)_4CH(C_{1-4}$ alkoxy$)$-,
-$(CH_2)_4CH(CO_2H)$-, -$(CH_2)_4CH(CH_2CO_2H)$-, -$(CH_2)_4CH(CO_2(C_{1-4}$ alkyl$))$-,
-$(CH_2)_4CH(CH_2CO_2(C_{1-4}$ alkyl$))$-, -$(CH_2)_4CH(CO_2CH_2CF_3)$-,
-$(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl$))$-, -$(CH_2)_5CH(CO_2(C_{1-4}$ alkyl$))$-,
-$(CH_2)_4C(C_{1-4}$ alkyl$)(CO_2(C_{1-4}$ alkyl$))$-, -$(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl$))$-,
-$(CH_2)_4CH(CONH_2)$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl$))$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CH(CONH_2)$-,
-$(CH_2)_4CH(CONH(C_{1-4}$ alkoxy$))$-, -$(CH_2)_4CH(CONH(OBn))$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2O(C_{1-4}$ alkyl$))$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-,
-$(CH_2)_4CH(CH$(halo$)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C$(halo$)_2CH_2$-,
-$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-,
-$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_3C(O)CH_2$-,
-$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-,
-$(CH_2)_2N(C_{1-4}$ alkyl$)CH_2$-, -$(CH_2)_2N(C_{1-4}$ alkyl$)(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-,
-$CH_2CONH(CH_2)_3$-, -$CH_2CONH(CH_2)_4$-, -$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_2$-,
-$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_3$-, -$(CH_2)_4CH$(thiazol-4-yl)-,
-$(CH_2)_4CH$(4-C_{1-4} alkyl-thiazol-2-yl)-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-imidazol-2-yl)-,
-$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-3-yl)-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-5-yl)-,
-CH_2-CH=CH-CH_2CH(1-C_{1-4} alkyl-pyrazol-5-yl)-,
-$(CH_2)_4CH$(1-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)-,

-$(CH_2)_4CH$(1-C_{1-4} alkyl-4-halo-pyrazol-3-yl)-,  ,

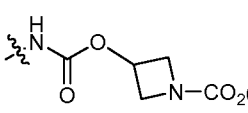
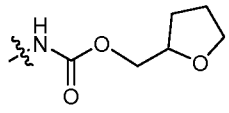
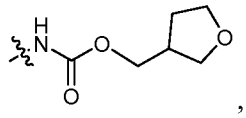


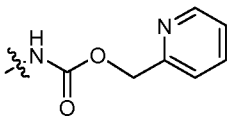
, and ;

Y is independently selected from the group consisting of: CH_2, O, NH, -CONH-, -NHCO-, -$CONHCH_2$-, -$CON(C_{1-4}$ alkyl)CH_2-, -$N(C_{1-4}$ alkyl)CH_2-, -$N(CO_2(C_{1-4}$ alkyl))CH_2-, -$N(CH_2CO_2(C_{1-4}$ alkyl))CH_2-, -OCONH-, -NHCONH-, and -SO_2NH-;

alternatively, L-Y is -$(CH_2)_4$-CH=N-; and

R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, -$NHCO_2(C_{1-4}$ alkyl), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), -$NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), -$NHCO_2CH_2CO_2H$,

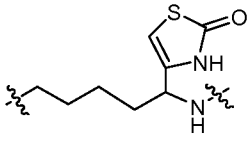
 ,  ,  ,

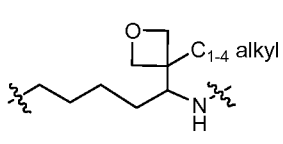
 .

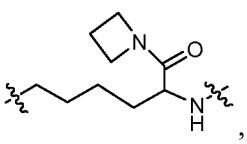
[0024] In a 13th aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L-Y is independently selected from the group consisting of: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)_2)CH_2-$, $-(CH_2)_4CF_2CO-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=CH-(CH_2)_4-$, $-CH_2CON(C_{1-4}\ alkyl)(CH_2)_3-$, $-CH_2CON(C_{1-4}\ alkyl)(CH_2)_4-$, $-(CH_2)_4N(C_{1-4}\ alkyl)CH_2-$, $-(CH_2)_4N(CO_2(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_4N(CH_2CO_2(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_5O-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(C_{1-4}\ alkyl)(CH_2)_2O-$, $-(CH_2)_4CH(C_{1-4}\ alkyl)CH_2O-$, $-CH_2CONH(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-CH_2-CH=CH-(CH_2)_2O-$, $-CH_2-CH=CH-(CH_2)_3O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_3CH(C_{1-4}\ alkyl)CH_2NH-$, $-(CH_2)_4CH(C_{1-4}\ alkyl)NH-$, $-(CH_2)_4CH(C_{1-4}\ alkyl)CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2(C_{1-4}alkoxy))NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH((CH_2)_3Ph)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_5CH(CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)_2)NH-$, $-(CH_2)_4C(C_{1-4}\ alkyl)(CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4C(CF_3)(CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_3CH(C_{1-4}\ alkyl)CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(C_{1-4}\ alkoxy))NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)(CH_2)_2O(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)(CH_2)_2N(C_{1-4}\ alkyl)_2)NH-$, $-CH_2-CH=CH-(CH_2)_2NH-$, $-CH_2-CH=CH-(CH_2)_3NH-$, $-(CH_2)_4CH(CHF_2)NH-$, $-(CH_2)_4CH(CF_3)NH-$, $-(CH_2)_5CH(CF_3)NH-$, $-(CH_2)_3CF_2CH_2NH-$, $-CH_2-CH=CH-CH_2CH(CF_3)NH-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH-$,

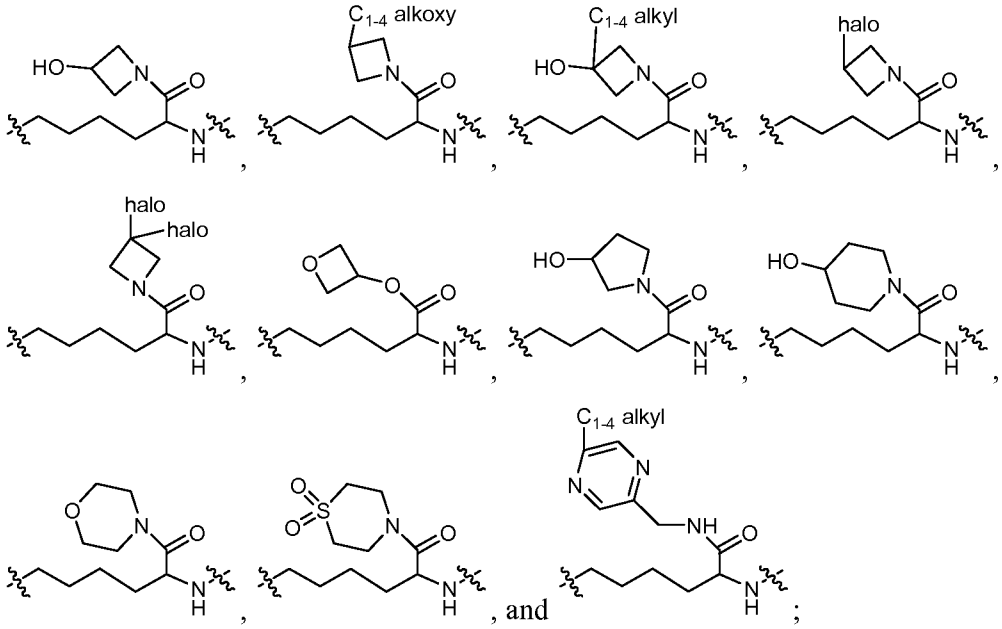
-$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-, -$CH_2NHCOCF_2CH_2NH$-, -$CH_2CONH(CH_2)_4NH$-, -$(CH_2)_4CH$(CO-pyrrolidin-1-yl)NH-, -$(CH_2)_4CH$(thiazol-4-yl)NH-, -$(CH_2)_4CH$(4-C_{1-4} alkyl-thiazol-2-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-imidazol-2-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-3-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-4-halo-pyrazol-3-yl)NH-, -CH_2-CH=CH-CH_2CH(1-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_6N(C_{1-4}$ alkyl)-, -$(CH_2)_5N(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CONH-, -$(CH_2)_4CH(C_{1-4}$ alkyl)CONH-, -$(CH_2)_2CH(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_2CH(C_{1-4}$ alkyl)$(CH_2)_2CONH$-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2CONH$-, -CH_2-CH=CH-$(CH_2)_3CONH$-, -CH_2-CH=CH-$CH_2CH(C_{1-4}$ alkyl)CONH-, -CH_2-CH=CH-CH(C_{1-4} alkyl)CH_2CONH-, -CH_2-CH=C(C_{1-4} alkyl)$(CH_2)_2CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CONH-, -$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3CH(CF_3)CONH$-, -$CH_2CH(OH)(CH_2)_2CONH$-, -$(CH_2)_2CH(OH)CH_2CONH$-, -$(CH_2)_3CH(OH)CH_2CONH$-, -$CH_2CH(OH)CH(OH)CH_2CONH$-, -CH_2-CH=CH-CH(OH)CH_2CONH-, -$(CH_2)_3CH(C_{1-4}$ alkoxy)CONH-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl))CH_2CONH-, -$(CH_2)_3C(O)CH_2CONH$-, -$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-, -$CH_2NH(CH_2)_2CONH$-, -$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2CONH$-, -$(CH_2)_5NHCO$-, -CH_2-CH=CH-$(CH_2)_2NHCO$-, -$(CH_2)_3OCONH$-, -$(CH_2)_4OCONH$-, -CH_2-CH=CH-CH_2OCONH-, -CH_2-CH=CH-$CH_2NHCONH$-, -$(CH_2)_4SO_2NH$-, -CH_2-CH=CH-CH_2SO_2NH-,

-$(CH_2)_4$-CH=N-, 

, 

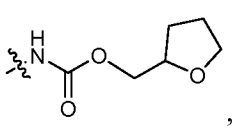
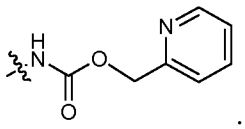
, 

,



R^{1b} is independently selected from the group consisting of: H and halogen;

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl)$_2$, and C_{3-6} cycloalkyl; and

R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl),  , and  .

[0025] In a 14th aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L-Y is independently selected from the group consisting of: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(C_{1-4}$ alkyl))CH_2-, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(C_{1-4}$ alkyl))CH_2-, $-(CH_2)_4CH(CON(C_{1-4}$ alkyl)$_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=CH-(CH_2)_4-$, $-CH_2CON(C_{1-4}$ alkyl)$(CH_2)_3-$, $-(CH_2)_5O-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(C_{1-4}$ alkyl)$(CH_2)_2O-$, $-(CH_2)_4CH(C_{1-4}$ alkyl)CH_2O-, $-CH_2NH(CH_2)_4O-$,

-CH_2-CH=CH-$(CH_2)_3$O-, -$(CH_2)_5$NH-, -$(CH_2)_6$NH-, -$(CH_2)_3$CH(C_{1-4} alkyl)CH_2NH-,
-$(CH_2)_4$CH(C_{1-4} alkyl)NH-, -$(CH_2)_4$CH(C_{1-4} alkyl)CH_2NH-, -$(CH_2)_4$CH(CH_2OH)NH-,
-$(CH_2)_4$CH(CH_2(C_{1-4} alkoxy))NH-, -$(CH_2)_4$CH(CO_2H)NH-,
-$(CH_2)_4$CH(CH_2CO_2H)NH-, -$(CH_2)_4$CH(CH_2CO_2(C_{1-4} alkyl))NH-,
-$(CH_2)_4$CH(CO_2(C_{1-4} alkyl))NH-, -$(CH_2)_4$CH($CO_2CH_2CF_3$)NH-,
-$(CH_2)_4$CH($CO_2(CH_2)_2SO_2$(C_{1-4} alkyl))NH-, -$(CH_2)_5$CH(CO_2(C_{1-4} alkyl))NH-,
-$(CH_2)_4$CH($CONH_2$)NH-, -$(CH_2)_4$CH(CONH(C_{1-4} alkyl))NH-,
-$(CH_2)_4$CH(CON(C_{1-4} alkyl)$_2$)NH-, -$(CH_2)_4$C(C_{1-4} alkyl)(CO_2(C_{1-4} alkyl))NH-,
-$(CH_2)_4$C(CF_3)(CO_2(C_{1-4} alkyl))NH-, -$(CH_2)_3$CH(C_{1-4} alkyl)CH($CONH_2$)NH-,
-$(CH_2)_4$CH(CONH(C_{1-4} alkoxy))NH-, -$(CH_2)_4$CH(CONH(OBn))NH-,
-$(CH_2)_4$CH(CON(C_{1-4} alkyl)$(CH_2)_2$O(C_{1-4} alkyl))NH-,
-$(CH_2)_4$CH(CON(C_{1-4} alkyl)$(CH_2)_2$N(C_{1-4} alkyl)$_2$)NH-,
-CH_2-CH=CH-$(CH_2)_2$NH-, -CH_2-CH=CH-$(CH_2)_3$NH-, -$(CH_2)_4$CH(CHF_2)NH-,
-$(CH_2)_4$CH(CF_3)NH-, -$(CH_2)_5$CH(CF_3)NH-, -$(CH_2)_3CF_2CH_2$NH-,
-CH_2-CH=CH-$(CH_2)_2$CH(CF_3)NH-, -$CH_2CONH(CH_2)_2$NH-, -$CH_2CONH(CH_2)_3$NH-,
-$(CH_2)_4$CH(3-C_{1-4} alkyl-oxetan-3-yl)NH-, -$(CH_2)_4$CH(CO-pyrrolidin-1-yl)NH-,
-$(CH_2)_4$CH(thiazol-4-yl)NH-, -$(CH_2)_4$CH(4-C_{1-4} alkyl-thiazol-2-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-imidazol-2-yl)NH-, -$(CH_2)_4$CH(1-C_{1-4} alkyl-pyrazol-3-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-4-halo-pyrazol-3-yl)NH-,
-CH_2-CH=CH-CH_2CH(1-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_4$N(CO_2(C_{1-4} alkyl))CH_2-,
-$(CH_2)_4$N(CH_2CO_2(C_{1-4} alkyl))CH_2-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-, -$(CH_2)_6$CONH-,
-$(CH_2)_3$CH(C_{1-4} alkyl)CONH-, -$(CH_2)_4$CH(C_{1-4} alkyl)CONH-,
-$(CH_2)_2$CH(C_{1-4} alkyl)CH_2CONH-, -$(CH_2)_3$CH(C_{1-4} alkyl)CH_2CONH-,
-$(CH_2)_2$CH(C_{1-4} alkyl)$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-,
-CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-,
-CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-CH=CH-CH_2CH(C_{1-4} alkyl)CONH-,
-CH_2-CH=CH-CH(C_{1-4} alkyl)CH_2CONH-, -CH_2-CH=C(C_{1-4} alkyl)-$(CH_2)_2$CONH-,

-$(CH_2)_3CH(C_{1-4}$ alkyl)CONH-,

-$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-,

-CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3CH(CF_3)CONH$-, -$CH_2CH(OH)(CH_2)_2CONH$-,

-$(CH_2)_2CH(OH)CH_2CONH$-, -$(CH_2)_3CH(OH)CH_2CONH$-,

-$CH_2CH(OH)CH(OH)CH_2CONH$-, -CH_2-CH=CH-$CH(OH)CH_2CONH$-,

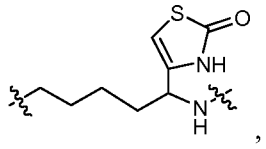
-$(CH_2)_3CH(C_{1-4}$ alkoxy)CONH-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl))CH_2CONH-,

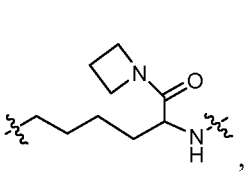
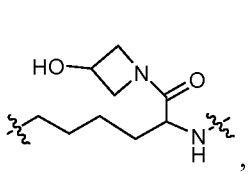
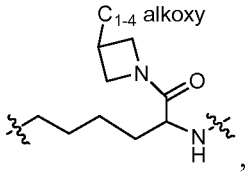
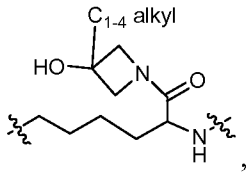
-$(CH_2)_3C(O)CH_2CONH$-, -$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-,

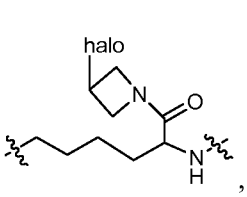
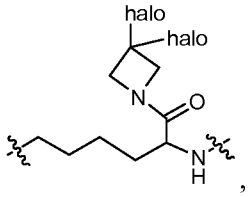
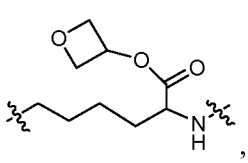
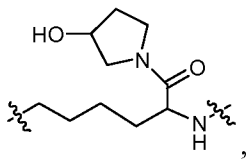
-$CH_2NH(CH_2)_2CONH$-, -$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(C_{1-4}$ alkyl)CH_2CONH-,

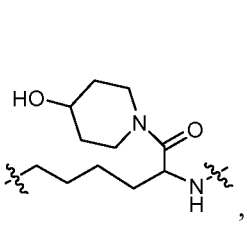
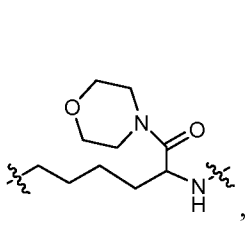
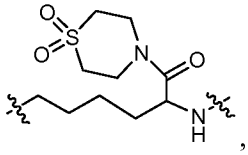
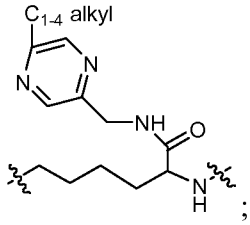
-$(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2CONH$-, -$(CH_2)_5NHCO$-, -CH_2-CH=CH-$(CH_2)_2NHCO$-,

-CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4OCONH$-, -CH_2-CH=CH-$CH_2NHCONH$-,

-$(CH_2)_4SO_2NH$-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,  ,

 ,  ,  ,  ,

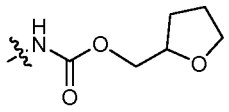
 ,  ,  ,  ,

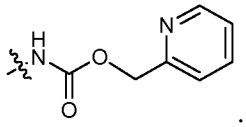
 ,  ,  , and  ;

R^{1b} is independently selected from the group consisting of: H and halogen;

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and cyclopropyl; and

R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, -$NHCO_2(C_{1-4}$ alkyl), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O(C_{1-4}$ alkyl),

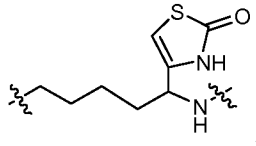
-$NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), and  , and

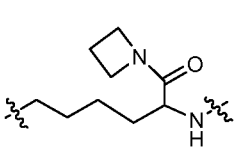
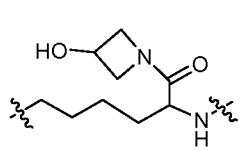
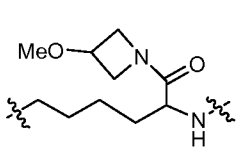
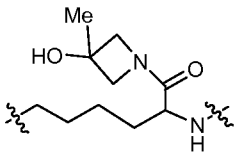
 .

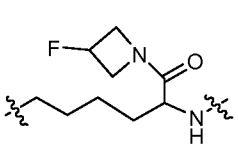
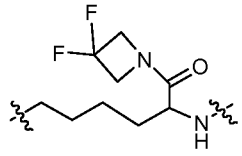
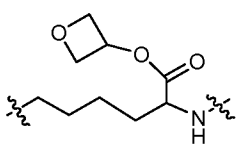
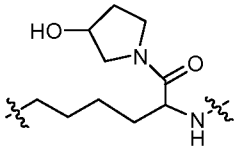
[0026] In a 15th aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

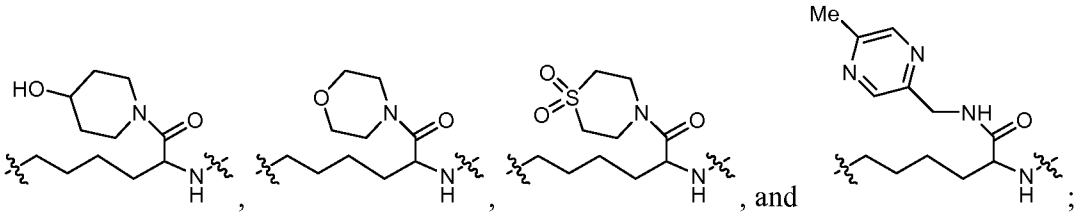
L-Y is independently selected from the group consisting of: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2Me)CH_2$-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONHMe)CH_2$-, -$(CH_2)_4CH(CON(Me)_2)CH_2$-, -$CH_2$-CH=CH-$(CH_2)_3$-, -$CH_2$-CH=CH-$(CH_2)_4$-, -$CH_2CON(CH_3)(CH_2)_3$-, -$(CH_2)_4N(CO_2Me)CH_2$-, -$(CH_2)_4N(CH_2CO_2Et)CH_2$-, -$(CH_2)_5O$-, -$(CH_2)_6O$-, -$(CH_2)_3CH(Me)(CH_2)_2O$-, -$(CH_2)_4CH(Me)CH_2O$-, -$CH_2NH(CH_2)_4O$-, -$CH_2$-CH=CH-$(CH_2)_3O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_3CH(Me)CH_2NH$-, -$(CH_2)_4CH(Me)NH$-, -$(CH_2)_4CH(Me)CH_2NH$-, -$(CH_2)_4CH(CH_2OH)NH$-, -$(CH_2)_4CH(CH_2OMe)NH$-, -$(CH_2)_4CH(CO_2H)NH$-, -$(CH_2)_4CH(CO_2Me)NH$-, -$(CH_2)_4CH(CO_2Et)NH$-, -$CH_2CONH(CH_2)_4NH$-, -$(CH_2)_4CH(CO_2(i\text{-}Pr))NH$-, -$(CH_2)_4CH(CO_2(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH$-, -$(CH_2)_5CH(CO_2Me)NH$-, -$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2Me)NH$-, -$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(Me))NH$-, -$(CH_2)_4CH(CONH(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CON(Me)_2)NH$-, -$(CH_2)_4CH(CONH(OMe))NH$-, -$(CH_2)_4CH(CONH(OBn))NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH$-, -$(CH_2)_4C(Me)(CO_2Me)NH$-, -$(CH_2)_4C(CF_3)(CO_2Me)NH$-, -$(CH_2)_3CH(Me)CH(CONH_2)NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH$-, -$CH_2$-CH=CH-$(CH_2)_2NH$-, -$CH_2$-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-, -$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_5CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-, -$CH_2$-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-, -$(CH_2)_4CH$(3-Me-oxetan-3-yl)NH-, -$(CH_2)_4CH$(CO-pyrrolidin-1-yl)NH-,

-$(CH_2)_4$CH(thiazol-4-yl)NH-, -$(CH_2)_4$CH(4-Me-thiazol-2-yl)NH-,
-$(CH_2)_4$CH(1-Me-imidazol-2-yl)NH-, -$(CH_2)_4$CH(1-Me-pyrazol-3-yl)NH-,
-$(CH_2)_4$CH(1-(n-Pr)-pyrazol-3-yl)NH-, -$(CH_2)_4$CH(1-Me-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1,3-di-Me-pyrazol-5-yl)NH-, -$(CH_2)_4$CH(1-Me-4-Cl-pyrazol-3-yl)NH-,
-CH_2-CH=CH-CH_2CH(1-Me-pyrazol-5-yl)NH-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-,
-$(CH_2)_6$CONH-, -$(CH_2)_3$CH(Me)CONH-, -$(CH_2)_4$CH(Me)CONH-,
-$(CH_2)_2$CH(Me)CH_2CONH-, -$(CH_2)_3$CH(Me)CH_2CONH-,
-$(CH_2)_2$CH(Me)$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-,
-CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-,
-CH_2-CH=CH-CH_2CH(Me)CONH-, -CH_2-CH=CHCH(Me)CH_2CONH-,
-CH_2-CH=CHCH(Et)CH_2CONH-, -CH_2-CH=C(Me)-$(CH_2)_2$CONH-,
-$(CH_2)_3$CH(Et)CONH-, -$(CH_2)_3$CH(i-Pr)CONH-, -$(CH_2)_3$CHFCONH-,
-$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-,
-$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-,
-$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-
CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OMe)CONH-, -$(CH_2)_3$CH(OCOMe)CH_2CONH-,
-$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-,
-$CH_2NH(CH_2)_2$CONH-, -$CH_2NH(CH_2)_3$CONH-, -$(CH_2)_2$N(Me)CH_2CONH-,
-$(CH_2)_2$N(Me)$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-,
-CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-,
-$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,


,


,

,

,

,

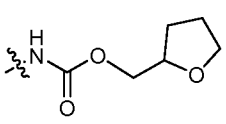
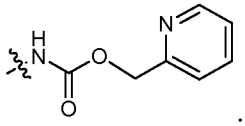

,

,

,

,



, , , and ;

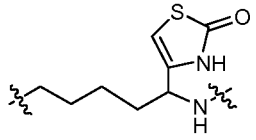
R^{1b} is independently selected from the group consisting of: H and F;

R^3 is independently selected from the group consisting of: H, F, Cl, Br, CH_3, CN, CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$, and cyclopropyl; and

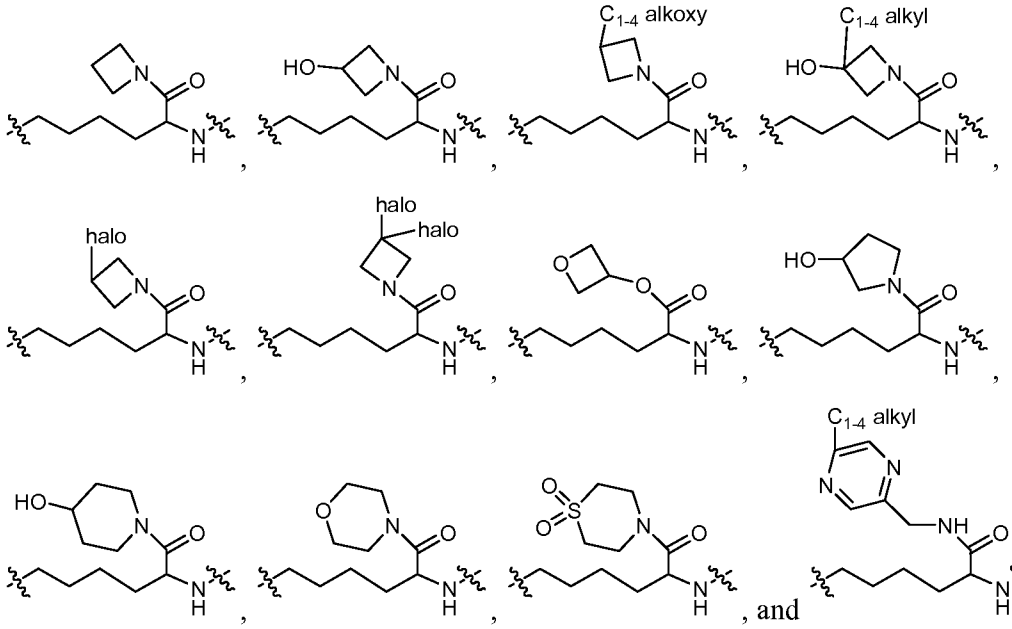
R^6 is independently selected from the group consisting of: F, NH_2, CO_2H, $CONH_2$, $-NHCO_2Me$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2OMe$, $-NHCO_2(CH_2)_2OEt$, $-NHCO_2CH_2CH(Et)OMe$, and  , and  .

[0027] In a 16th aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L-Y is independently selected from the group consisting of: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(C_{1-4}\text{ alkyl}))CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(C_{1-4}\text{ alkyl}))CH_2-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2(C_{1-4}\text{ alkyl}))CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_4CH(C_{1-4}\text{ alkyl})NH-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})CH_2NH-$, $-(CH_2)_4CH(C_{1-4}\text{ alkyl})CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2(C_{1-4}\text{ alkoxy}))NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}\text{ alkyl}))NH-$, $-(CH_2)_4CH(CO_2(C_{1-4}\text{ alkyl}))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}\text{ alkyl}))NH-$, $-(CH_2)_5CH(CO_2(C_{1-4}\text{ alkyl}))NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(C_{1-4}\text{ alkyl}))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})_2)NH-$, $-(CH_2)_4CH(CONH(C_{1-4}\text{ alkoxy}))NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2O(C_{1-4}\text{ alkyl}))NH-$,

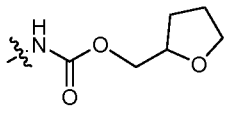
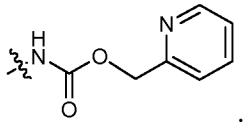
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2)NH$-, -CH_2-CH=CH-$(CH_2)_2NH$-, -CH_2-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-, -$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-, -CH_2-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$(CH_2)_4CH(3$-C_{1-4} alkyl-oxetan-3-yl$)NH$-, -$(CH_2)_4CH($CO-pyrrolidin-1-yl$)NH$-, -$(CH_2)_4CH($thiazol-4-yl$)NH$-, -$(CH_2)_4CH(4$-C_{1-4} alkyl-thiazol-2-yl$)NH$-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-imidazol-2-yl$)NH$-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-3-yl$)NH$-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-5-yl$)NH$-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl$)NH$-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-4-halo-pyrazol-3-yl$)NH$-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CONH$-, -$(CH_2)_4CH(C_{1-4}$ alkyl$)CONH$-, -$(CH_2)_2CH(C_{1-4}$ alkyl$)CH_2CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CH_2CONH$-, -$(CH_2)_2CH(C_{1-4}$ alkyl$)(CH_2)_2CONH$-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2CONH$-, -CH_2-CH=CH-$(CH_2)_3CONH$-, -CH_2-CH=CH-$CH_2CH(C_{1-4}$ alkyl$)CONH$-, -CH_2-CH=CH-$CH(C_{1-4}$ alkyl$)CH_2CONH$-, -CH_2-CH=C$(C_{1-4}$ alkyl$)$-$(CH_2)_2CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CONH$-, -$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3CH(CF_3)CONH$-, -$CH_2CH(OH)(CH_2)_2CONH$-, -$(CH_2)_2CH(OH)CH_2CONH$-, -$(CH_2)_3CH(OH)CH_2CONH$-, -$CH_2CH(OH)CH(OH)CH_2CONH$-, -CH_2-CH=CH-$CH(OH)CH_2CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkoxy$)CONH$-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl$))CH_2CONH$-, -$(CH_2)_3C(O)CH_2CONH$-, -$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-, -$CH_2NH(CH_2)_2CONH$-, -$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(C_{1-4}$ alkyl$)CH_2CONH$-, -$(CH_2)_2N(C_{1-4}$ alkyl$)(CH_2)_2CONH$-, -$(CH_2)_5NHCO$-, -CH_2-CH=CH-$(CH_2)_2NHCO$-, -CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4OCONH$-, -CH_2-CH=CH-$CH_2NHCONH$-, -$(CH_2)_4SO_2NH$-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-, 

,



R^{1b} is independently selected from the group consisting of: H and halogen;

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and cyclopropyl; and

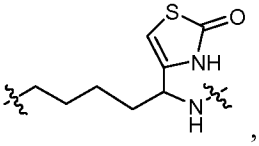
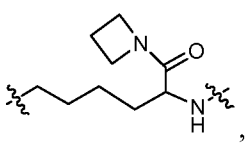
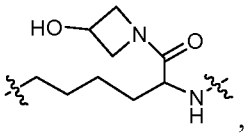
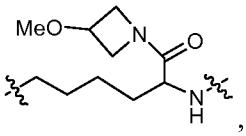
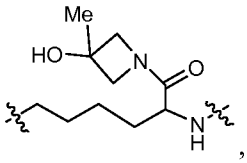
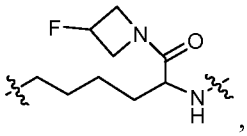
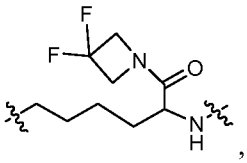
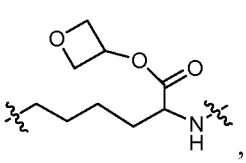
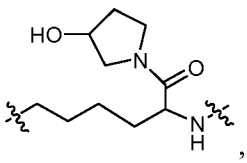
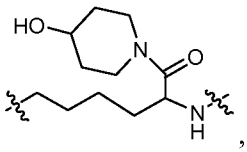
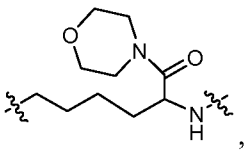
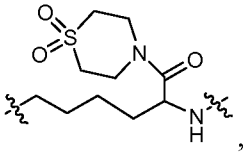
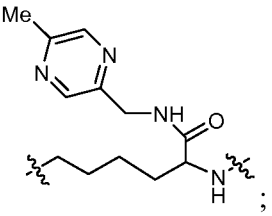
R^6 is independently selected from the group consisting of: F, NH_2, CO_2H, $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), and  , and  .

[0028] In a 17th aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L-Y is independently selected from the group consisting of: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2Me)CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONHMe)CH_2-$, $-(CH_2)_4CH(CON(Me)_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2Me)CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(Me)(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$,

-$(CH_2)_5$NH-, -$(CH_2)_6$NH-, -$(CH_2)_4$CH(Me)NH-, -$(CH_2)_3$CH(Me)CH_2NH-,
-$(CH_2)_4$CH(Me)CH_2NH-, -$(CH_2)_4$CH(CH_2OH)NH-, -$(CH_2)_4$CH(CH_2OMe)NH-,
-$(CH_2)_4$CH(CO_2H)NH-, -$(CH_2)_4$CH(CO_2Me)NH-, -$(CH_2)_4$CH(CO_2Et)NH-,
-$(CH_2)_4$CH(CO_2(i-Pr))NH-, -$(CH_2)_4$CH(CO_2(t-Bu))NH-, -$(CH_2)_4$CH($CO_2CH_2CF_3$)NH-,
-$(CH_2)_4$CH($CO_2(CH_2)_2SO_2$Me)NH-, -$(CH_2)_5$CH(CO_2Me)NH-,
-$(CH_2)_4$CH(CH_2CO_2H)NH-, -$(CH_2)_4$CH(CH_2CO_2Me)NH-, -$(CH_2)_4$CH($CONH_2$)NH-,
-$(CH_2)_4$CH(CONH(Me))NH-, -$(CH_2)_4$CH(CONH(t-Bu))NH-,
-$(CH_2)_4$CH($CON(Me)_2$)NH-, -$(CH_2)_4$CH(CONH(OMe))NH-,
-$(CH_2)_4$CH(CONH(OBn))NH-, -$(CH_2)_4$CH(CON(Me)$(CH_2)_2$OMe)NH-,
-$(CH_2)_4$CH(CON(Me)$(CH_2)_2N(Me)_2$)NH-, -CH_2-CH=CH-$(CH_2)_2$NH-,
-CH_2-CH=CH-$(CH_2)_3$NH-, -$(CH_2)_4$CH(CHF_2)NH-, -$(CH_2)_4$CH(CF_3)NH-,
-$(CH_2)_3CF_2CH_2$NH-, -CH_2-CH=CH-$(CH_2)_2$CH(CF_3)NH-,
-$(CH_2)_4$CH(3-Me-oxetan-3-yl)NH-, -$(CH_2)_4$CH(CO-pyrrolidin-1-yl)NH-,
-$(CH_2)_4$CH(thiazol-4-yl)NH-, -$(CH_2)_4$CH(4-Me-thiazol-2-yl)NH-,
-$(CH_2)_4$CH(1-Me-imidazol-2-yl)NH-, -$(CH_2)_4$CH(1-Me-pyrazol-3-yl)NH-,
-$(CH_2)_4$CH(1-(n-Pr)-pyrazol-3-yl)NH-, -$(CH_2)_4$CH(1-Me-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1,3-di-Me-pyrazol-5-yl)NH-, -$(CH_2)_4$CH(1-Me-4-Cl-pyrazol-3-yl)NH-,
-$(CH_2)_4N(CO_2Me)CH_2$-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-, -$(CH_2)_6$CONH-,
-$(CH_2)_3$CH(Me)CONH-, -$(CH_2)_4$CH(Me)CONH-, -$(CH_2)_2$CH(Me)CH_2CONH-,
-$(CH_2)_3$CH(Me)CH_2CONH-, -$(CH_2)_2$CH(Me)$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-,
-CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-,
-CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-CH=CH-CH_2CH(Me)CONH-,
-CH_2-CH=CH-CH(Me)CH_2CONH-, -CH_2-CH=CHCH(Et)CH_2CONH-,
-CH_2-CH=C(Me)-$(CH_2)_2$CONH-, -$(CH_2)_3$CH(Me)CONH-, -$(CH_2)_3$CH(Et)CONH-,
-$(CH_2)_3$CH(i-Pr)CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-
,
-CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-,
-$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-,
-CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH_2CONH-,

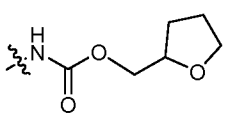
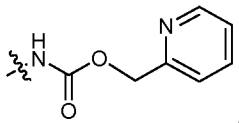
-$(CH_2)_3CH(OMe)CONH$-, -$(CH_2)_3CH(OCOMe)CH_2CONH$-, -$(CH_2)_3C(O)CH_2CONH$-, -$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-, -$CH_2NH(CH_2)_2CONH$-, -$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(Me)CH_2CONH$-, -$(CH_2)_2N(Me)(CH_2)_2CONH$-, -$(CH_2)_5NHCO$-, -$CH_2$-CH=CH-$(CH_2)_2NHCO$-, -$CH_2$-CH=CH-$CH_2OCONH$-, -$(CH_2)_4OCONH$-, -$CH_2$-CH=CH-$CH_2NHCONH$-, -$(CH_2)_4SO_2NH$-, -$CH_2$-CH=CH-$CH_2SO_2NH$-, -$(CH_2)_4$-CH=N-,


,

,

,

,

,

,

,

,

,

,

,

, and

;

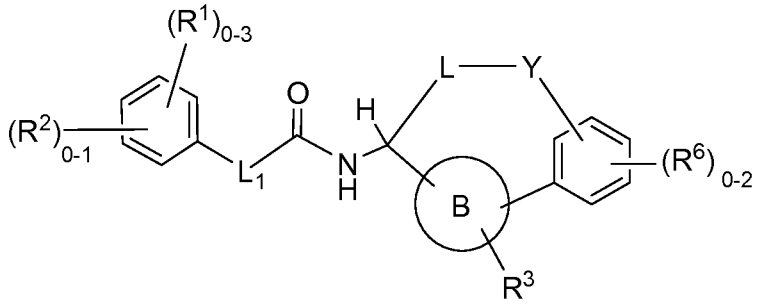
R^{1b} is independently selected from the group consisting of: H and F;

R^3 is independently selected from the group consisting of: H, F, Cl, Br, CH_3, CN, CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$, and cyclopropyl; and

R^6 is independently selected from the group consisting of: F, NH_2, CO_2H, -$NHCO_2Me$, -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2OMe$, -$NHCO_2(CH_2)_2OEt$, -$NHCO_2CH_2CH(Et)OMe$, and

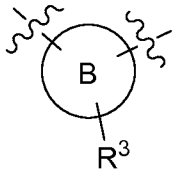

, and

.

[0029] In an 18th aspect, the present invention includes compounds of Formula (IV):

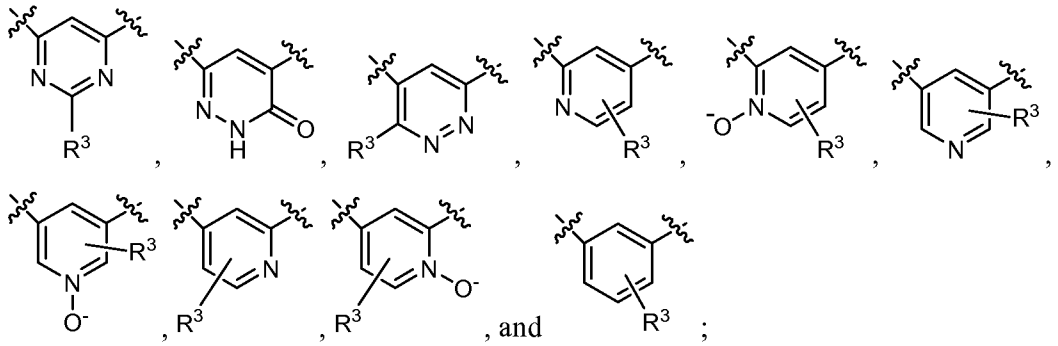


(IV)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any one of the first to tenth aspects, wherein:

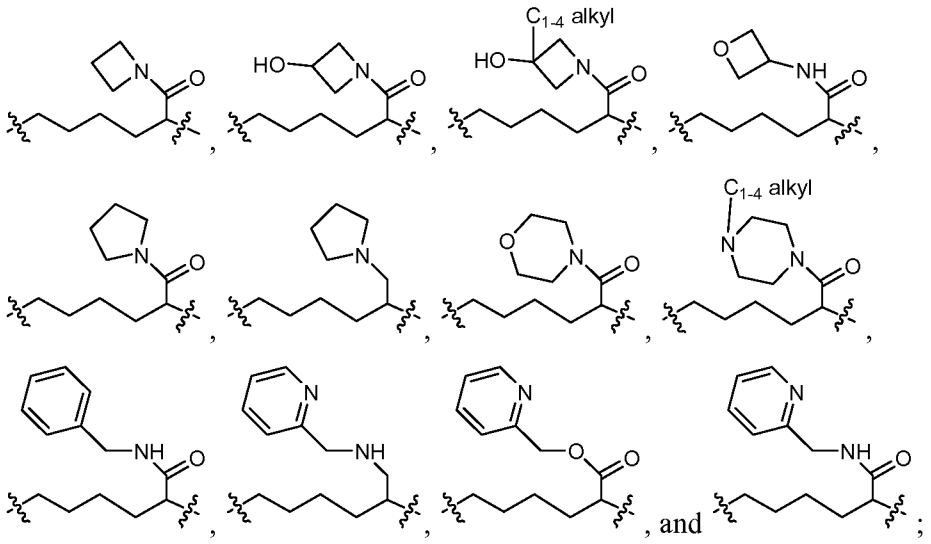


is independently selected from the group consisting of:



L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$ and $-CH=CH-$;

L is independently selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})-$, $-CH_2-CH=CH-CH_2CH(CF_3)-$, $-(CH_2)_4CH(CF_3)-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CO_2(C_{1-4}\text{ alkyl}))-$, $-CH_2CONH(CH_2)_2-$, $-(CH_2)_4CH(CO_2(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CH_2NH(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CO_2(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$,



Y is independently -CONH-, O, or NH;

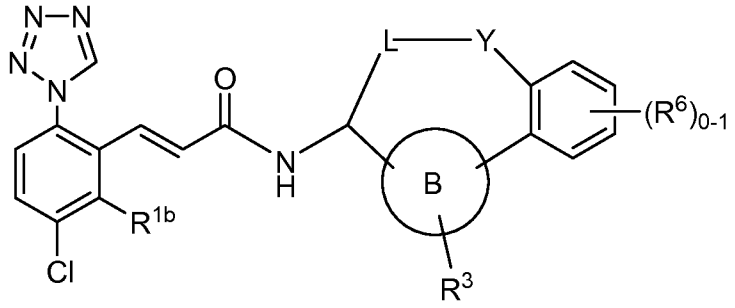
R^1 is, independently at each occurrence, selected from: halogen, CN, OCF_3, CHF_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), NH_2, $-C(=NH)NH_2$, $-C(O)NH_2$, and $-CH_2NH_2$;

R^2 is independently a 5-membered heterocycle selected from: pyrazolyl, imidazolyl, triazolyl, and tetrazolyl;

R^3 is independently selected from the group consisting of: H, halogen, and C_{1-4} alkyl; and

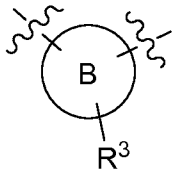
R^6 is, independently at each occurrence, selected from the group consisting of: H, halogen, CN, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), CO_2H, and $CONH_2$.

[0030] In a 19th aspect, the present invention includes compounds of Formula (IVa):

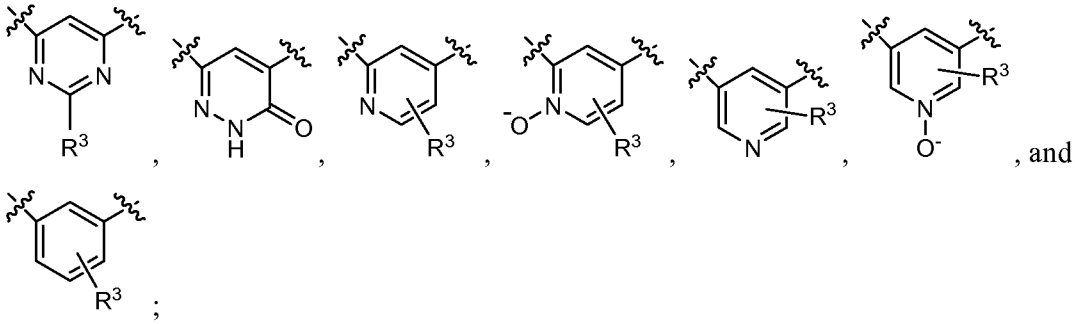


(IVa)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the 18th aspect, wherein:



is independently selected from the group consisting of:



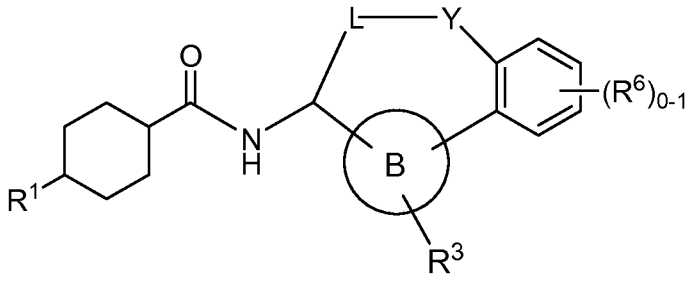
;

Y is independently -CONH- or NH;

R^3 is independently selected from the group consisting of: H, F, Cl, and C_{1-4} alkyl; and

R^6 is independently selected from the group consisting of: F, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), CO_2H, $CONH_2$, and $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl).

[0031] In a 20th aspect, the present invention includes compounds of Formula (V):



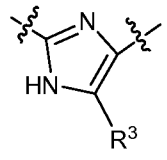
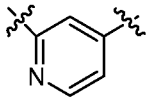
(V)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the first, second or third aspect, wherein:

ring B is independently selected from the group consisting of: imidazole and pyridine; and

R^1 is independently selected from the group consisting of: C_{1-4} alkyl and CH_2NH_2.

[0032] In another aspect, the present invention includes compounds of Formula (V): or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

ring B is independently selected from the group consisting of:  and  ;

L is independently selected from the group consisting of: $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CF_2-$, $-(CH_2)_4-$, and $-(CH_2)_4CH(CF_3)-$;

Y is independently selected from the group consisting of: $-CH_2-$, -CONH-, and NH;

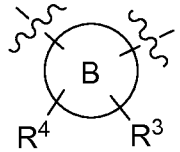
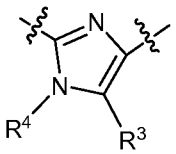
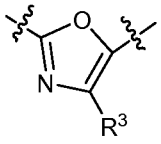
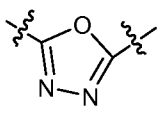
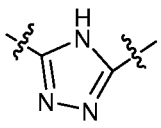
R^3 is independently selected from the group consisting of: H, F, Cl, and Me; and

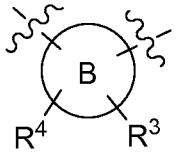
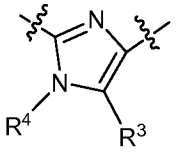
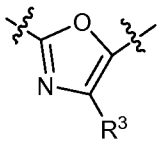
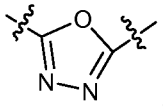
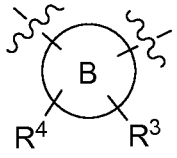
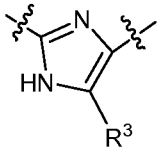
R^{6a} is independently selected from the group consisting of: H and $-NHCO_2Me$.

[0033] In a 21st aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

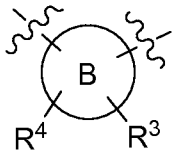
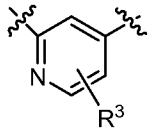
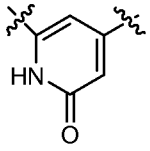
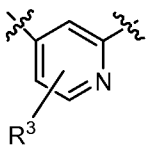
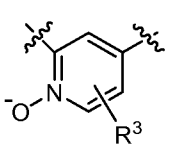
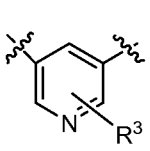
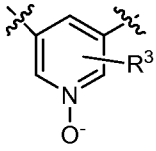
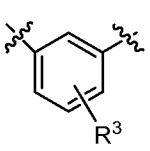
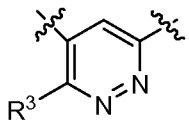
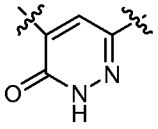
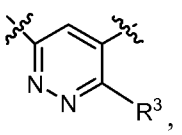
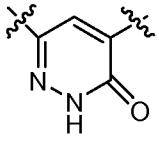
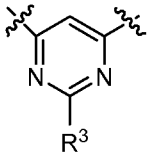
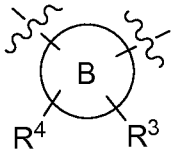
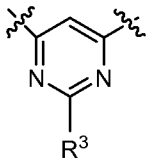
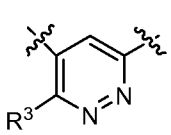
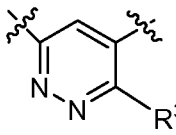
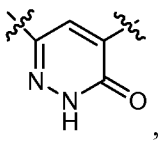
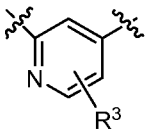
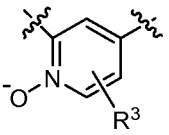
[0034] In another aspect, the present invention provides a compound selected from any subset list of compounds within the scope of the 24th aspect.

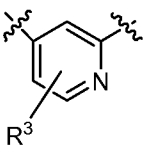
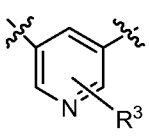
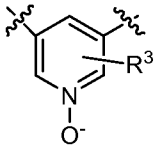
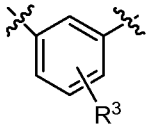
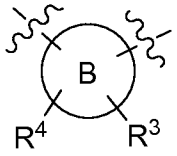
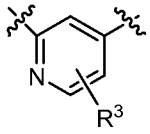
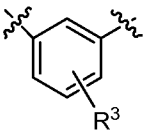
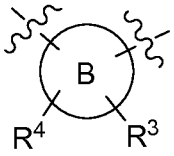
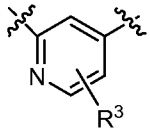
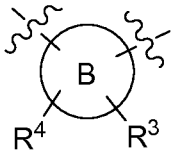
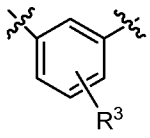
[0035] In another aspect, the present invention provides compounds of Formula (I), (II), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the fourth aspect, wherein:

 is independently selected from the group consisting of:  ,  ,  , and  . In another aspect wherein:

 is independently selected from the group consisting of:  ,  and  . In another aspect, wherein:  is  .

[0036] In another aspect, the present invention provides compounds of Formula (I), (II), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of the fourth aspect, wherein:

 is independently selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In another aspect wherein:  is independently selected from the group consisting of:  ,  ,  ,  ,  ,  ,




, and  . In another aspect wherein:  is independently selected from the group consisting of:  and  . In another aspect wherein:  is  . In another aspect wherein:  is  .

[0037] In another aspect, the present invention includes compounds of Formula (I), (II), (IIa), or (IIb), a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any of the above aspects, wherein:

R^2 is independently a 5-membered heterocycle substituted with 0-1 R^{2a}, wherein said heterocycle is selected from: pyrazolyl, imidazolyl, triazolyl, and tetrazolyl; and

R^{2a} is, independently at each occurrence, selected from the group consisting of: halogen, OH, NH_2, CH_2OH, CO_2H, C_{1-4} alkyl, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), and $-CON(C_{1-4}$ alkyl$)_2$.

[0038] In another aspect, the present invention includes compounds of Formula (I), (II), (IIa), or (IIb), a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any of the above aspects, wherein:

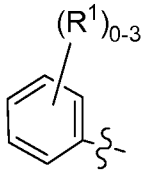
R^2 is independently selected from the group consisting of: triazolyl and tetrazolyl.

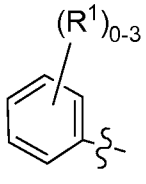
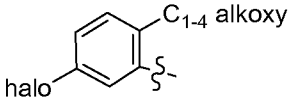
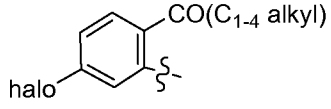
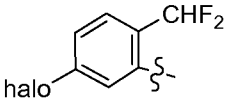
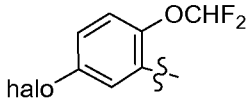
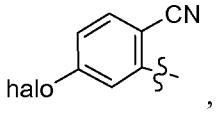
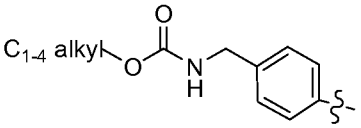
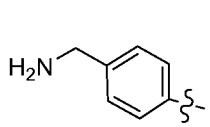
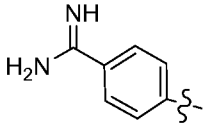
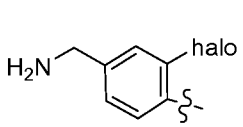
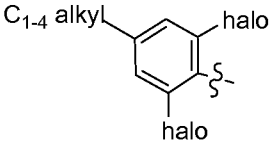
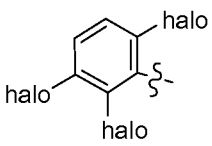
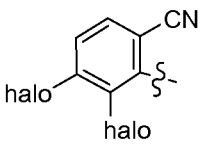
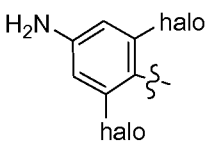
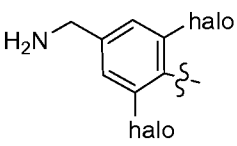
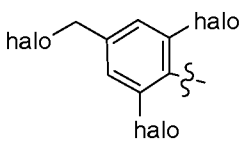
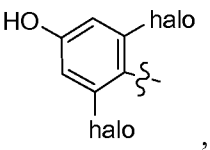
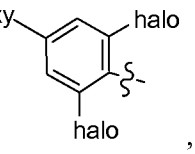
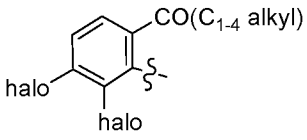
[0039] In another embodiment, ring A is independently selected from the group consisting of: phenyl, cyclohexyl, and 5,6,7,8-tetrahydroisoquinolinyl.

[0040] In another embodiment, ring A is phenyl.

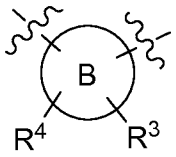
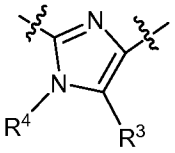
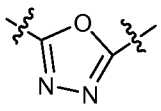
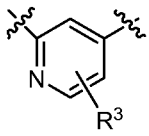
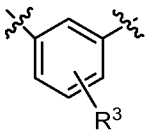
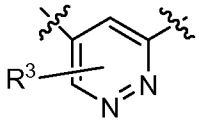
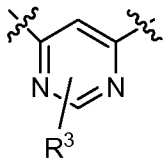
[0041] In another embodiment, ring A is cyclohexyl.

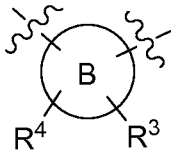
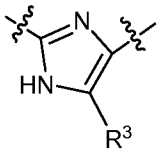
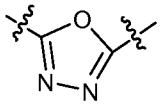
[0042] In another embodiment, ring A is tetrahydroisoquinoline.

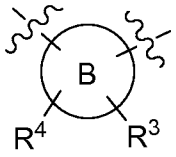
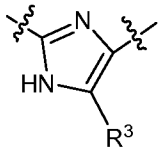
[0043] In another aspect, ring A is  wherein R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, OH, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), CN, CH_2F, CHF_2, $OCHF_2$, NH_2, $N(C_{1-4}$ alkyl$)_2$, $-CH_2NH_2$, $-CH_2NHCO_2(C_{1-4}$ alkyl), and $-C(=NH)NH_2$.

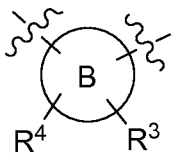
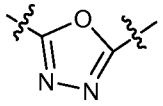
[0044] In another aspect, ring A is  is independently selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

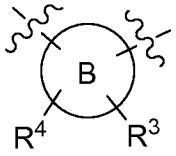
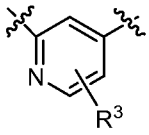
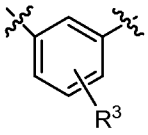
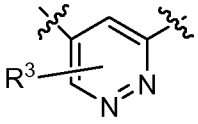
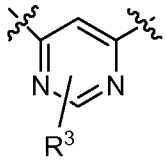
[0045] In another embodiment, ring B is independently selected from the group consisting of: imidazole, oxadiazole, pyridine, pyridazine, and benzene.

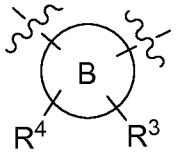
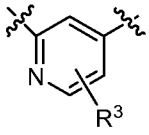
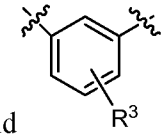
[0046] In another embodiment,  is independently selected from the group consisting of:  ,  ,  ,  ,  , and  .

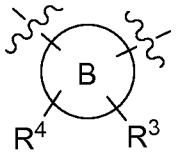
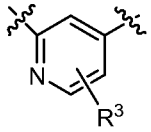
[0047] In another embodiment,  is independently selected from the group consisting of:  and  .

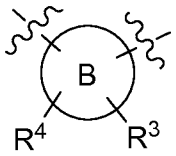
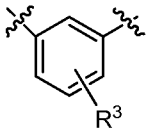
[0048] In another embodiment,  is  .

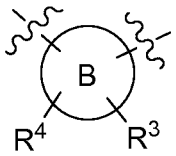
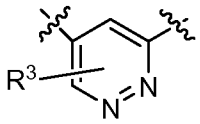
[0049] In another embodiment,  is  .

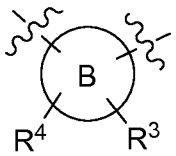
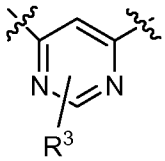
[0050] In another embodiment,  is independently selected from the group consisting of:  ,  ,  , and  .

[0051] In another embodiment,  is independently selected from the group consisting of:  and  .

[0052] In another embodiment,  is  .

[0053] In another embodiment,  is  .

[0054] In another embodiment,  is  .

[0055] In another embodiment,  is  .

[0056] In another embodiment, L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$, -CH=CH-, -C(Me)=CH-, -C≡C-, and $-CH_2NH-$.

[0057] In another embodiment, L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$, -CH=CH-, and -C(Me)=CH.

[0058] In another embodiment, L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$ and -CH=CH-.

[0059] In another embodiment, L_1 is a bond.

[0060] In another embodiment, L_1 is -CH=CH-.

[0061] In another embodiment, L is independently selected from the group consisting of: C_{3-7} alkylene and C_{3-7} alkenylene; wherein said alkylene and alkenylene are substituted with 0-2 R^7 and optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, NH, N(C_{1-4} alkyl), CONH, NHCO, or CON(C_{1-4} alkyl).

[0062] In another embodiment, L is independently selected from the group consisting of: C_{3-7} alkylene and C_{4-7} alkenylene; wherein said alkylene and alkenylene are optionally substituted with 1-2 R^7; optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, NH, N(C_{1-4} alkyl), CONH, or CON(C_{1-4} alkyl).

[0063] In another embodiment, L is C_{3-7} alkylene, wherein said alkylene is optionally substituted with 1-2 R^7; optionally one or two of the carbon atoms of said alkylene may be replaced by O, NH, N(C_{1-4} alkyl), CONH, or CON(C_{1-4} alkyl).

[0064] In another embodiment, L is C_{4-7} alkenylene, wherein said alkenylene is optionally substituted with 1-2 R^7; optionally one or two of the carbon atoms of said alkenylene may be replaced by O, NH, N(C_{1-4} alkyl), CONH, or CON(C_{1-4} alkyl).

[0065] In another embodiment, Y is independently selected from the group consisting of: $-CH_2-$, O, NH, N(C_{1-4} alkyl), -NHCO-, -CONH-, $-CONHCH_2-$, $-CON(C_{1-4}\text{ alkyl})CH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$.

[0066] In another embodiment, Y is independently selected from the group consisting of: $-CH_2-$, O, NH, NMe, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$.

[0067] In another embodiment, Y is -CONH-.

[0068] In another embodiment, R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, OH, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, $NH(C_{1-4}$ alkyl$)_2$, $N(C_{1-4}$ alkyl$)_2$, $CO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), $-OCH_2CO_2H$, $-CH_2NH_2$, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, and $-C(=NH)NH_2$.

[0069] In another embodiment, R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, OH, CHF_2, CF_3, OCF_3, CN, NH_2, $CO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), $-OCH_2CO_2H$, $-CH_2NH_2$, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-SO_2NH_2$, and $-C(=NH)NH_2$.

[0070] In another embodiment, R^1 is, independently at each occurrence, selected from: halogen, CN, OH, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl$)_2$, $N(C_{1-4}$ alkyl$)_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, $-CH_2NHCO_2(C_{1-4}$ alkyl), and $-SO_2NH_2$.

[0071] In another embodiment, R^1 is, independently at each occurrence, selected from: halogen, CN, OH, OCF_3, CHF_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), NH_2, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, and $-SO_2NH_2$.

[0072] In another embodiment, R^1 is selected from the group consisting of: halogen, C_{1-4} alkyl, CHF_2, and $CO(C_{1-4}$ alkyl).

[0073] In another embodiment, R^2 is a 5-membered heterocycle substituted with 0-1 R^{2a}, wherein said heterocycle is independently selected from: pyrazolyl, imidazolyl, triazolyl, and tetrazolyl.

[0074] In another embodiment, R^2 is independently selected from the group consisting of: triazolyl and tetrazolyl.

[0075] In another embodiment, R^2 is tetrazolyl.

[0076] In another embodiment, R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, and cyclopropyl.

[0077] In another embodiment, R^3 is independently selected from the group consisting of: H, C_{1-4} alkyl, and halogen.

[0078] In another embodiment, R^3 is independently selected from the group consisting of: H and halogen.

[0079] In another embodiment, R^3 is independently selected from the group consisting of: H and Cl.

[0080] In another embodiment, R^3 is H.

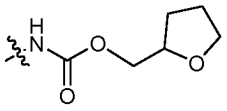
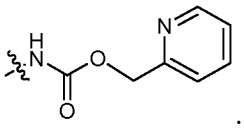
[0081] In another embodiment, R^3 is Cl.

[0082] In another embodiment, R^4 is H.

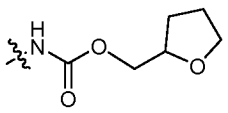
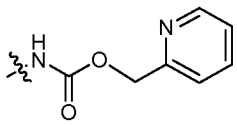
[0083] In another embodiment, R^5 is, independently at each occurrence, selected from the group consisting of: H and C_{1-4} alkyl.

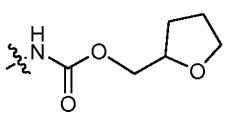
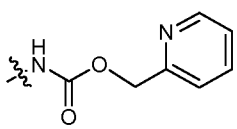
[0084] In another embodiment, R^5 is, independently at each occurrence, selected from the group consisting of: H and methyl.

[0085] In another embodiment, R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl$)_2$, $-NHSO_2(C_{1-4}$ alkyl),

$-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-C(O)NH(CH_2)_2O(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-CH_2CONH_2$,  , and  .

[0086] In another embodiment, R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl$)_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), and $-CONH_2$.

[0087] In another embodiment, R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-CONH_2$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl),  , and  .

[0088] In another embodiment, R^6 is, independently at each occurrence, selected from the group consisting of: halogen, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl),  , and  .

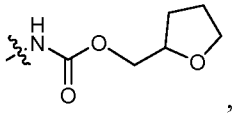
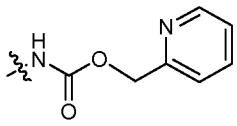
[0089] In another embodiment, R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl),

$-CH_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), and $-CONH_2$.

[0090] In another embodiment, R^6 is, independently at each occurrence, selected from the group consisting of: halogen, CO_2H, $CO_2(C_{1-4}$ alkyl), NH_2, $NHCO_2(C_{1-4}$ alkyl), and $-CH_2NHCO_2(C_{1-4}$ alkyl).

[0091] In another embodiment, R^6 is, independently at each occurrence, is selected from the group consisting of: halogen, NH_2, $NHCO_2(C_{1-4}$ alkyl), and $-CH_2NHCO_2(C_{1-4}$ alkyl).

[0092] In another embodiment, R^6 is, independently at each occurrence, is selected from the group consisting of: F, NH_2, $NHCO_2Me$, and $-CH_2NHCO_2Me$.

[0093] In another embodiment, R^{6a} is independently selected from the group consisting of: H, halogen, NH_2, CO_2H, $CONH_2$, $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl),  , and  .

[0094] In another embodiment, R^{6a} is independently selected from the group consisting of: H, halogen, $NH(C_{1-4}$ alkyl), and $NHCO_2(C_{1-4}$ alkyl).

[0095] In another embodiment, R^{6a} is independently selected from the group consisting of: H, halogen, and $NHCO_2(C_{1-4}$ alkyl).

[0096] In another embodiment, R^{6a} is independently selected from the group consisting of: H, F, and $NHCO_2Me$.

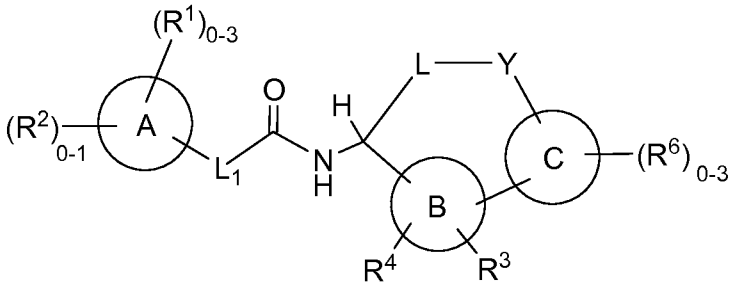
[0097] In another embodiment, R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, CHF_2, CF_3, C_{1-4} alkoxy, CH_2OH, $CH_2O(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), CH_2CO_2H, $CH_2CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-OCO(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-CONH(C_{1-4}$ alkoxy), C_{1-4} alkyl, and

-$(CO)_{0-1}$-(4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), O, and $S(O)_p$); wherein said heterocycle is substituted with 0-2 R^8.

[0098] In another embodiment, R^7 is independently selected from the group consisting of: halogen, C_{1-4} alkyl, and N(C_{1-4} alkyl)$_2$.

[0099] In another embodiment, R^7 is independently selected from the group consisting of: halogen, and C_{1-4} alkyl.

[00100] In another aspect, the present invention provides, *inter alia*, a compound of Formula (I-1):



(I-1)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

ring A is a C_{3-10} carbocycle or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

ring B is a benzene ring or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

ring C is a benzene ring or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

L_1 is selected from the group consisting of: a bond, -CHR^5CHR^5-, -CR^5=CR^5-, -C≡C-, -OCH_2-, -CHR^5NH-, -CH_2O-, -SCH_2-, -SO_2CH_2-, -CH_2NH-, and -CR^5R^5-;

L is selected from the group consisting of: C_{3-8} alkylene, C_{4-8} alkenylene and C_{4-8} alkynylene; wherein said alkylene, alkenylene and alkynylene are optionally substituted with 1-2 R^7; optionally one or more of the carbon atoms of said alkylene and

alkenylene may be replaced by O, S, NH, N(C_{1-4} alkyl), CO, CONH, NHCO, OCONH, SO_2NH, or CON(C_{1-4} alkyl);

Y is selected from the group consisting of: O, S, NH, N(C_{1-4} alkyl), CH_2, CH(C_{1-4} alkyl), C(C_{1-4} alkyl)$_2$, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -OCON(C_{1-4} alkyl)-, -NHCONH-, -SO_2NH-, -$NHCO_2$-, and -$NHSO_2$-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, OH, CHF_2, CF_3, OCF_3, CN, NH_2, -CO_2(C_{1-4} alkyl), -CO(C_{1-4} alkyl), -CH_2NH_2, -$CONH_2$, -CONH(C_{1-4} alkyl), -OCH_2CO_2H, -NHCO(C_{1-4} alkyl), -$NHCO_2$(C_{1-4} alkyl), -$NHSO_2$(C_{1-4} alkyl), -SO_2NH_2, and -C(=NH)NH_2;

R^2 is a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a} is, independently at each occurrence, selected from the group consisting of: C_{1-4} alkyl, -CH_2OH, C_{1-4} alkoxy, OH, CF_3, OCF_3, CN, NH_2, CO_2H, CO_2(C_{1-4} alkyl), COC_{1-4} alkyl, -$CONH_2$, -CONH(C_{1-4} alkyl), -CON(C_{1-4} alkyl)$_2$, -SO_2(C_{1-4} alkyl), -SO_2NH_2, -SO_2NH(C_{1-4} alkyl), and -SO_2N(C_{1-4} alkyl)$_2$;

R^3 is selected from the group consisting of: H, halogen, OH, NH_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, -CH_2OH, CO_2H, CO_2(C_{1-4} alkyl), -C(O)NH_2, -C(O)NH(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)$_2$, and -CH_2CO_2H;

R^4 is selected from the group consisting of: H and C_{1-4} alkyl;

R^5 is, independently at each occurrence, selected from the group consisting of: H, halogen, OH, and C_{1-4} alkyl;

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, CO_2(C_{1-4} alkyl), -CH_2CO_2H, -$(CH_2)_2CO_2H$, -CH_2CO_2(C_{1-4} alkyl), -$(CH_2)_2CO_2$(C_{1-4} alkyl), NH_2, -CH_2NH_2, -NHCO(C_{1-4} alkyl), -$NHCO_2$(C_{1-4} alkyl), -$NHCO_2(CH_2)_2O$(C_{1-4} alkyl), -$NHCO_2(CH_2)_3O$(C_{1-4} alkyl), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2NH_2$,

$-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl)$_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl)$_2$, and $-CH_2CONH_2$;

R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, NH_2, $-CH_2NH_2$, CHF_2, CF_3, $-NH(C_{1-4}$ alkyl), $-N((C_{1-4}$ alkyl)$_2$, C_{1-4} alkoxy, and C_{1-4} alkyl; and

p is, independently at each occurrence, selected from the group consisting of: 0, 1, and 2.

[00101] In another aspect, the present invention provides compounds of Formula (I-1), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

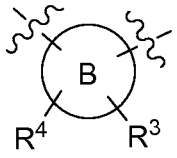
ring A is a 6-membered carbocycle or 5,6,7,8-tetrahydroisoquinoline;

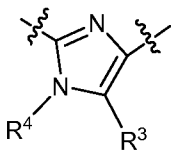
ring B is selected from the group consisting of: imidazole, oxadiazole, pyridine, pyridazine, pyrimidine, and benzene; and

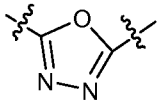
ring C is selected from the group consisting of: benzene and pyridine.

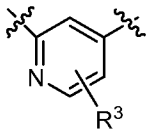
[00102] In another aspect, the present invention provides compounds of Formula (Ia), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

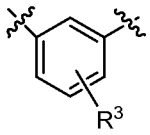
ring A is selected from the group consisting of: benzene, cyclohexane, and 5,6,7,8-tetrahydroisoquinoline;

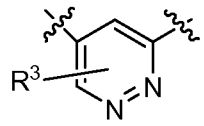


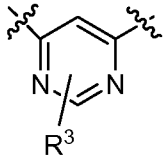
is selected from the group consisting of:


,


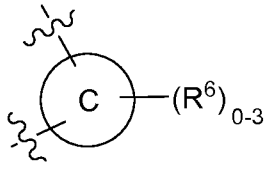
,


,


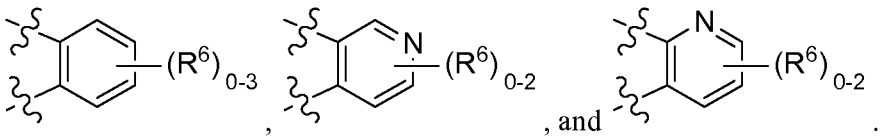
,


, and


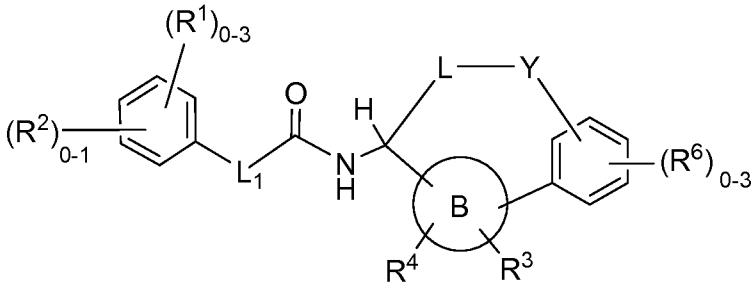
; and



is selected from the group consisting of:



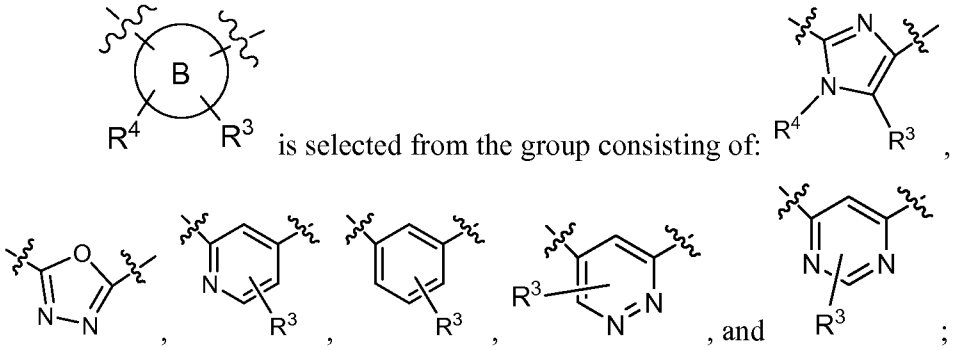
[00103] In another aspect, the present invention provides compounds of Formula (II-1):



(II-1)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

is selected from the group consisting of:



L_1 is selected from the group consisting of: a bond, $-CHR^5CHR^5-$, $-CR^5=CHR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR^5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CH_2NH-$, and $-CR^5R^5-$;

L is selected from the group consisting of: C_{3-8} alkylene and C_{4-8} alkenylene; wherein said alkylene and alkenylene are optionally substituted with 1-2 R^7; optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, S, NH, $N(C_{1-4}$ alkyl), CONH-, or $CON(C_{1-4}$ alkyl);

Y is selected from the group consisting of: CH_2, $CH(C_{1-4}$ alkyl), $C(C_{1-4}$ alkyl)$_2$, O, S, NH, $N(C_{1-4}$ alkyl), -CONH-, -NHCO-, $-CONHCH_2-$, $-CON(C_{1-4}$ alkyl)CH_2-, -OCONH-, $-OCON(C_{1-4}$ alkyl)-, -NHCONH-, and $-SO_2NH-$;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, OH, CHF_2, CF_3, OCF_3, CN, NH_2, $CO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), $-OCH_2CO_2H$, $-CH_2NH_2$, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-SO_2NH_2$, and $-C(=NH)NH_2$;

R^2 is a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a} is, independently at each occurrence, selected from the group consisting of: C_{1-4} alkyl, $-CH_2OH$, C_{1-4} alkoxy, OH, CF_3, CN, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), COC_{1-4} alkyl, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), and $-CON(C_{1-4}$ alkyl)$_2$;

R^3 is selected from the group consisting of: H, halogen, OH, NH_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $-CH_2OH$, CO_2H, $CO_2(C_{1-4}$ alkyl), $-C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)$_2$, and $-CH_2CO_2H$;

R^4 is selected from the group consisting of: H and C_{1-4} alkyl;

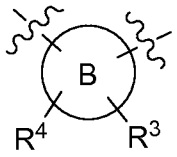
R^5 is, independently at each occurrence, selected from the group consisting of: H, halogen, OH, and C_{1-4} alkyl;

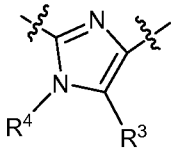
R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl)$_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH_2$, $-C(O)NH(CH_2)_2O(C_{1-4}$ alkyl), and $-CH_2CONH_2$;

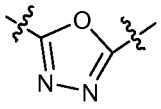
R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, CF_3, C_{1-4} alkoxy and C_{1-4} alkyl; and

p is, independently at each occurrence, selected from the group consisting of: 0, 1, and 2.

[00104] In another aspect, the present invention provides compounds of Formula (I), (II), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

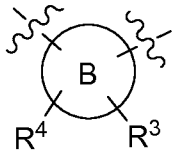


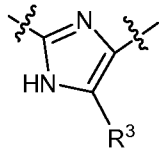
is selected from the group consisting of:


and


.

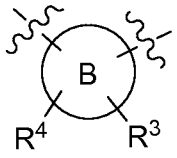
[00105] In another aspect, the present invention provides compounds of Formula (I-1), (II-1), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

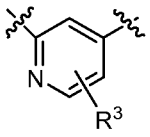


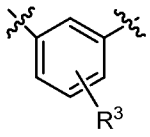
is


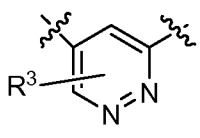
.

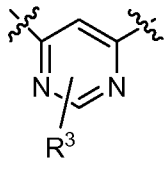
[00106] In another aspect, the present invention provides compounds of Formula (I-1), (II-1), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:



is selected from the group consisting of:


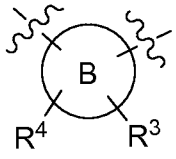


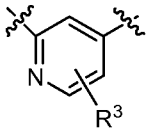
,


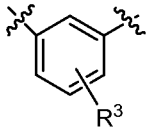
, and


.

[00107] In another aspect, the present invention provides compounds of Formula (I-1), (II-1), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

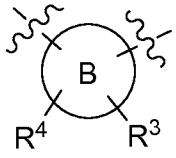


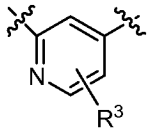
is selected from the group consisting of:


and


.

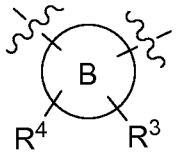
[00108] In another aspect, the present invention provides compounds of Formula (I-1), (II-1), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

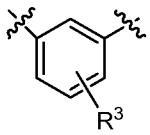


is


.

[00109] In another aspect, the present invention provides compounds of Formula (I-1), (II-1), (IIa), (IIc), or (IIe), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:



is


.

[00110] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), or (IIb), a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

R^2 is a 5-membered heterocycle substituted with 0-1 R^{2a}, wherein said heterocycle is selected from: pyrazolyl, imidazolyl, triazolyl, and tetrazolyl; and

R^{2a} is, independently at each occurrence, selected from the group consisting of: OH, NH_2, CH_2OH, CO_2H, C_{1-4} alkyl, -$CONH_2$, -$CONH(C_{1-4}$ alkyl), and -$CON(C_{1-4}$ alkyl)$_2$

[00111] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), or (IIb), a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

R^2 is selected from the group consisting of: triazolyl and tetrazolyl.

[00112] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L_1 is selected from the group consisting of: a bond, -CH_2CH_2-, -CH=CH-, -C(Me)=CH-, -C≡C-, and -CH_2NH-;

L is selected from the group consisting of: C_{3-7} alkylene and C_{4-7} alkenylene; wherein said alkylene and alkenylene are optionally substituted with 1-2 R^7; optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, NH, N(C_{1-4} alkyl), CONH, or CON(C_{1-4} alkyl);

Y is selected from the group consisting of: CH_2, CH(C_{1-4} alkyl), C(C_{1-4} alkyl)$_2$, O, S, NH, N(C_{1-4} alkyl), -CONH-, -NHCO-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -NHCONH-, and -SO_2NH-;

R^1 is, independently at each occurrence, selected from: halogen, CN, OH, OCF_3, CHF_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, CO(C_{1-4} alkyl), NH_2, -C(=NH)NH_2, -C(O)NH_2, -CH_2NH_2, and -SO_2NH_2;

R^3 is selected from the group consisting of: H, halogen, OH, NH_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, -CH_2OH, CO_2H, $CO_2(C_{1-4}$ alkyl), -C(O)NH_2, -C(O)NH(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)$_2$, and -CH_2CO_2H; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), -CH_2CO_2H, -$(CH_2)_2CO_2H$, -$CH_2CO_2(C_{1-4}$ alkyl), -$(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, -CH_2NH_2,

-NHCO(C_{1-4} alkyl), -NHCO$_2$(C_{1-4} alkyl), -NHCO$_2$(CH_2)$_2$O(C_{1-4} alkyl), -NHCO$_2$(CH_2)$_3$O(C_{1-4} alkyl), -NHCO$_2$(CH_2)$_2$OH, -NHCO$_2$(CH_2)$_2$NH$_2$, -CH_2NHCO$_2$(C_{1-4} alkyl), -NHC(O)NH(C_{1-4} alkyl), -NHC(O)N(C_{1-4} alkyl)$_2$, -NHSO$_2$(C_{1-4} alkyl), -SO$_2$NH(CH_2)$_2$OH, -SO$_2$NH(CH_2)$_2$O(C_{1-4} alkyl), and -$CONH_2$.

[00113] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L_1 is selected from the group consisting of: a bond, -CH_2CH_2- and -CH=CH-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, CN, C_{1-4} alkyl, CHF_2, CF_3, CO(C_{1-4} alkyl), NH_2, -CH_2NH_2, and -C(=NH)NH_2;

R^3 is selected from the group consisting of: H, halogen, CF_3, CO_2H, CO_2(C_{1-4} alkyl), and C_{1-4} alkyl; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, CO_2(C_{1-4} alkyl), -CH_2CO_2H, -CH_2CO_2(C_{1-4} alkyl), NH_2, -CH_2NH_2, -NHCO(C_{1-4} alkyl), -NHCO$_2$(C_{1-4} alkyl), -CH_2NHCO$_2$(C_{1-4} alkyl), and -$CONH_2$.

[00114] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L_1 is selected from the group consisting of: a bond, -CH_2CH_2- and -CH=CH-;

L is selected from the group consisting of: -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-(CH_2)$_2$-, -CH_2-CH=CH-(CH_2)$_3$-, -CH_2-CH=C(C_{1-4} alkyl)-(CH_2)$_2$-, -CH_2-CH=CH-CH(C_{1-4} alkyl)-CH_2-, -CH_2-C(C_{1-4} alkyl)=CH-(CH_2)$_2$-, -(CH_2)$_3$CH(C_{1-4} alkyl)CH_2-, -(CH_2)$_2$CH(C_{1-4} alkyl)(CH_2)$_2$-, -(CH_2)$_3$CH(C_{1-4} alkyl)(CH_2)$_2$-, -(CH_2)$_3$CH(C_{1-4} alkyl)-, -(CH_2)$_3$-, -(CH_2)$_4$-, -(CH_2)$_5$-, -(CH_2)$_6$-, -CH_2O(CH_2)$_3$-, -CH_2O(CH_2)$_4$-, -(CH_2)$_4CF_2$-, -(CH_2)$_4$CH(CF_3)-,

$-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(C_{1-4}$ alkyl)$-(CH_2)_2-$, $-CH_2-CON(C_{1-4}$ alkyl)$-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

Y is selected from the group consisting of: $-CH_2-$, O, NH, $N(C_{1-4}$ alkyl), -NHCO-, -CONH-, $-CONHCH_2-$, $-CON(C_{1-4}$ alkyl)CH_2-, -OCONH-, -NHCONH-, and $-SO_2NH-$;

R^3 is selected from the group consisting of: H, C_{1-4} alkyl, and halogen; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, CO_2H, $CO_2(C_{1-4}$ alkyl), NH_2, $NHCO_2(C_{1-4}$ alkyl), and $-CH_2NHCO_2(C_{1-4}$ alkyl).

[00115] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L is selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(C_{1-4}$ alkyl)$-(CH_2)_2-$, $-CH_2-CH=CH-CH(C_{1-4}$ alkyl)$-CH_2-$, $-CH_2-C(C_{1-4}$ alkyl)$=CH-(CH_2)_2-$, $-(CH_2)_3CH(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_3CH(C_{1-4}$ alkyl)$(CH_2)_2-$, $-(CH_2)_3CH(C_{1-4}$ alkyl)-, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(C_{1-4}$ alkyl)CH_2-, $-(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(C_{1-4}$ alkyl)$-(CH_2)_2-$, $-CH_2-CON(C_{1-4}$ alkyl)$-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

Y is selected from the group consisting of: CH_2, O, NH, N(C_{1-4} alkyl), -NHCO-, -CONH-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -NHCONH-, and -SO_2NH-;

R^1 is selected from the group consisting of: halogen, C_{1-4} alkyl, CHF_2, CN, and $CO(C_{1-4}$ alkyl);

R^3 is selected from the group consisting of: H, C_{1-4} alkyl, and halogen; and

R^6 is, independently at each occurrence, is selected from the group consisting of: halogen, NH_2, $NHCO_2(C_{1-4}$ alkyl), and -$CH_2NHCO_2(C_{1-4}$ alkyl).

[00116] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L is selected from the group consisting of: -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C(CH_3)-$(CH_2)_2$-, -CH_2-CH=CH-CH$(CH_3)CH_2$-, -$(CH_2)_3CH(CH_3)CH_2$-, -$(CH_2)_2CH(CH_3)(CH_2)_2$-, -$(CH_2)_3CH(CH_3)$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$(CH_2)_4CF_2$-, -$(CH_2)_4CH(CF_3)$-, -CH_2-CH=CH-CH_2CF_2-, -$CH_2NHCOCF_2CH_2$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-, -$(CH_2)_2NHCH_2$-, -$(CH_2)_2N(CH_3)CH_2$-, -$(CH_2)_2N(CH_3)(CH_2)_2$-, -CH_2-CONH-$(CH_2)_2$-, -CH_2-CONH-$(CH_2)_3$-, -CH_2-CONH-$(CH_2)_4$-, -CH_2-CON(CH_3)-$(CH_2)_2$-, -CH_2-CON(CH_3)-$(CH_2)_3$-, -$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, and -$CH_2CH(OH)CH(OH)CH_2$-;

Y is selected from the group consisting of: CH_2, O, NH, NMe, -CONH-, -NHCO-, -$CONHCH_2$-, -$CONMeCH_2$-, -OCONH-, -NHCONH-, and -SO_2NH-;

R^1 is selected from the group consisting of: H, F, Cl, Me, COMe, and CHF_2;

R^3 is selected from the group consisting of: H, Me, and Cl; and

R^6 is, independently at each occurrence, selected from the group consisting of: F, NH_2, $NHCO_2Me$, and -CH_2NHCO_2Me.

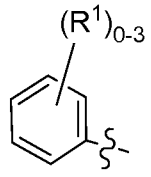
[00117] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any one of the above aspects, wherein:

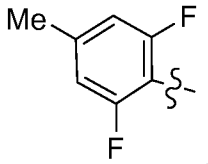
L is selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

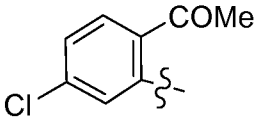
Y is selected from the group consisting of: CH_2, O, NH, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$; and

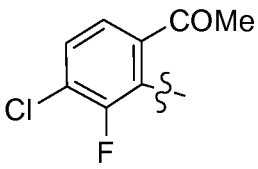
R^3 is selected from the group consisting of: H and Cl.

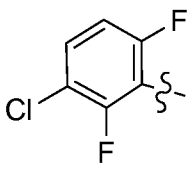
[00118] In another aspect, the present invention includes compounds of Formula (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

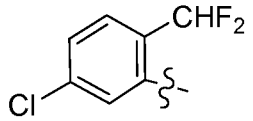


is selected from the group consisting of:


,


,


,


, and


.

[00119] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L is selected from the group consisting of: $-CH_2-CH=CH-CH_2-$,

$-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_3CH(CH_3)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, $-CH_2-CON(CH_3)-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

Y is selected from the group consisting of: CH_2, O, NH, NMe, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$;

R^1 is selected from the group consisting of: H, F, Cl, Me, COMe, and CHF_2;

R^3 is selected from the group consisting of: H, Me, and Cl; and

R^6 is, independently at each occurrence, selected from the group consisting of: F, NH_2, $NHCO_2Me$, and $-CH_2NHCO_2Me$.

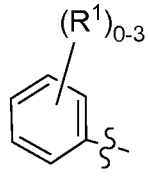
[00120] In another aspect, the present invention includes compounds of Formula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L is selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

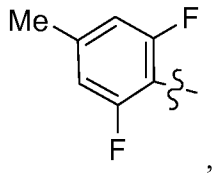
Y is selected from the group consisting of: CH_2, O, NH, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$; and

R^3 is selected from the group consisting of: H and Cl.

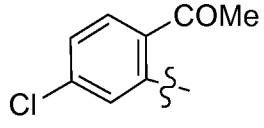
[00121] In another aspect, the present invention includes compounds of Formula (IIe) or (IIf) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:



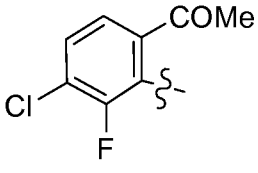
is selected from the group consisting of:



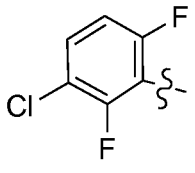
,



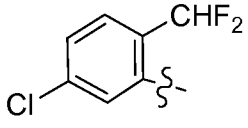
,



,

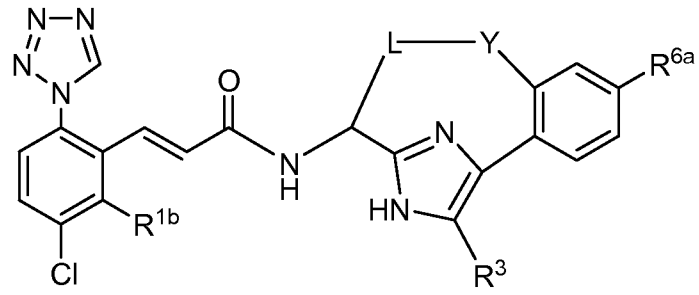


, and



.

[00122] In another aspect, the present invention includes compounds of Formula (III):



(III)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L is selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_3CH(CH_3)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, $-CH_2-CON(CH_3)-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

Y is selected from the group consisting of: CH_2, O, NH, NMe, -CONH-, -NHCO-, -$CONHCH_2$-, -$CONMeCH_2$-, -OCONH-, -NHCONH-, and -SO_2NH-;

R^{1b} is selected from the group consisting of: H and F;

R^3 is selected from the group consisting of: H, Me, and Cl; and

R^{6a} is selected from the group consisting of: H, F, NH_2, and $NHCO_2Me$.

[00123] In another aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

L is selected from the group consisting of: -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C(CH_3)-$(CH_2)_2$-, -CH_2-CH=CH-CH$(CH_3)CH_2$-, -$(CH_2)_3CH(CH_3)CH_2$-, -$(CH_2)_2CH(CH_3)(CH_2)_2$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$(CH_2)_4CF_2$-, -CH_2-CH=CH-CH_2CF_2-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$(CH_2)_2N(CH_3)CH_2$-, -$(CH_2)_2N(CH_3)(CH_2)_2$-, -CH_2-CONH-$(CH_2)_3$-, -CH_2-CONH-$(CH_2)_4$-, -CH_2-CON(CH_3)-$(CH_2)_2$-, and -$CH_2CH(OH)CH(OH)CH_2$-;

Y is selected from the group consisting of: CH_2, O, NH, -CONH-, -NHCO-, -$CONHCH_2$-, -$CONMeCH_2$-, -OCONH-, -NHCONH-, and -SO_2NH-;

R^{1b} is selected from the group consisting of: H and F;

R^3 is selected from the group consisting of: H and Cl; and

R^{6a} is selected from the group consisting of: H, F, NH_2, and $NHCO_2Me$.

[00124] In another aspect, the present invention includes compounds of Formula (III), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

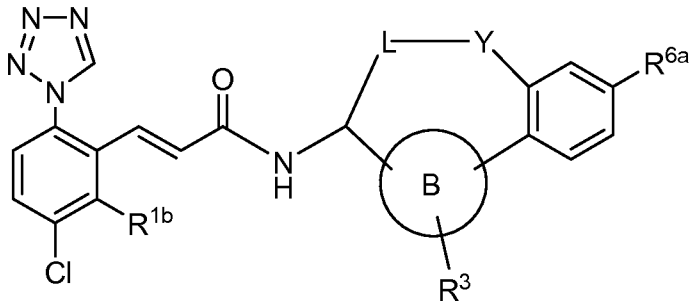
L is selected from the group consisting of: -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C(CH_3)-$(CH_2)_2$-, -CH_2-CH=CH-CH$(CH_3)CH_2$-, -$(CH_2)_3CH(CH_3)$-, -$(CH_2)_3CH(CH_3)CH_2$-, -$(CH_2)_2CH(CH_3)(CH_2)_2$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$(CH_2)_4CF_2$-, -$(CH_2)_4CH(CF_3)$-, -CH_2-CH=CH-CH_2CF_2-,

$-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$, and $-CH_2CH(OH)CH(OH)CH_2-$;

Y is selected from the group consisting of: CH_2, O, NH, -CONH-, -NHCO-, -OCONH-, -NHCONH-, $-CONHCH_2-$, and $-SO_2NH-$; and

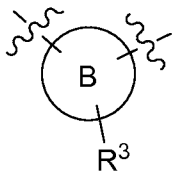
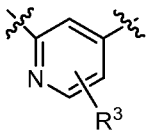
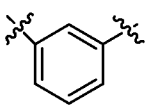
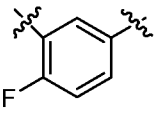
R^3 is selected from the group consisting of: H and Cl.

[00125] In another aspect, the present invention includes compounds of Formula (IV):



(IV)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, within the scope of any one of the above aspects, wherein:

is selected from the group consisting of: , and ;

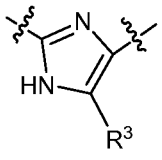
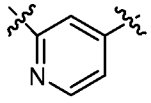
L is selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-(CH_2)_4-$, and $-(CH_2)_5-$;

Y is -CONH-;

R^3 is selected from the group consisting of: H and Cl; and

R^{6a} is selected from the group consisting of: H, F, $-NHCO_2Me$, and $-CH_2NHCO_2Me$.

[00126] In another aspect, the present invention includes compounds of Formula (V): or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, or a prodrug thereof, wherein:

ring B is selected from the group consisting of:  and  ;

L is selected from the group consisting of: $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CF_2-$, and $-(CH_2)_4-$;

Y is selected from the group consisting of: CH_2 and -CONH-;

R^3 is selected from the group consisting of: H and Cl; and

R^{6a} is selected from the group consisting of: H and $-NHCO_2Me$.

[00127] In another embodiment, the compounds of the present invention have Factor XIa Ki values ≤ 10 μM.

[00128] In another embodiment, the compounds of the present invention have Factor XIa Ki values ≤ 1 μM.

[00129] In another embodiment, the compounds of the present invention have Factor XIa Ki values ≤ 0.5 μM.

[00130] In another embodiment, the compounds of the present invention have Factor XIa Ki values ≤ 0.1 μM.

II. OTHER EMBODIMENTS OF THE INVENTION

[00131] In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00132] In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate, thereof.

[00133] In another embodiment, the present invention provides a pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically

effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00134] In another embodiment, the present invention provides a process for making a compound of the present invention.

[00135] In another embodiment, the present invention provides an intermediate for making a compound of the present invention.

[00136] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s). In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent(s) are an anti-platelet agent or a combination thereof. Preferably, the anti-platelet agent(s) are clopidogrel and/or aspirin, or a combination thereof.

[00137] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of a thromboembolic disorder comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00138] In another embodiment, the present invention provides a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, for use in therapy.

[00139] In another embodiment, the present invention provides a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, for use in therapy for the treatment and/or prophylaxis of a thromboembolic disorder.

[00140] In another embodiment, the present invention also provides the use of a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of a thromboembolic disorder.

[00141] In another embodiment, the present invention provides a method for treatment and/or prophylaxis of a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention or a

stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, and the second therapeutic agent is at least one agent selected from a second Factor Xa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, and a fibrinolytic agent. Preferably, the second therapeutic agent is at least one agent selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, desulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase. Preferably, the second therapeutic agent is at least one anti-platelet agent. Preferably, the anti-platelet agent(s) are clopidogrel and/or aspirin, or a combination thereof.

[00142] The thromboembolic disorder includes arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, and venous cerebrovascular thromboembolic disorders. Examples of the thromboembolic disorder include, but are not limited to, unstable angina, an acute coronary syndrome, atrial fibrillation, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis.

[00143] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of an inflammatory disorder comprising: administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof. Examples of the inflammatory disorder include, but are not limited to, sepsis, acute respiratory distress syndrome, and systemic inflammatory response syndrome.

[00144] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

[00145] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in treatment and/or prophylaxis of a thromboembolic disorder.

[00146] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

[00147] Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the

end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

[00148] The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are examples of stereoisomers. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superimposable. The term "diastereomer" refers to stereoisomers that are not mirror images. The term "racemate" or "racemic mixture" refers to a composition composed of equimolar quantities of two enantiomeric species, wherein the composition is devoid of optical activity.

[00149] The symbols "R" and "S" represent the configuration of substituents around a chiral carbon atom(s). The isomeric descriptors "R" and "S" are used as described herein for indicating atom configuration(s) relative to a core molecule and are intended to be used as defined in the literature (*IUPAC Recommendations 1996, Pure and Applied Chemistry*, 68:2193-2222 (1996)).

[00150] The term "chiral" refers to the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image. The term "homochiral" refers to a state of enantiomeric purity. The term "optical activity" refers to the degree to which a homochiral molecule or nonracemic mixture of chiral molecules rotates a plane of polarized light.

[00151] As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_1 to C_{10} alkyl" or "C_{1-10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_1-C_6 alkyl" denotes alkyl having 1 to 6

carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl). When "C_0 alkyl" or "C_0 alkylene" is used, it is intended to denote a direct bond.

[00152] "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

[00153] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[00154] The term "alkoxy" or "alkyloxy" refers to an –O-alkyl group. "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

[00155] "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl

also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

[00156] "Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_1 to C_6 haloalkoxy" or "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

[00157] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. "C_3 to C_7 cycloalkyl" or "C_{3-7} cycloalkyl" is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl".

[00158] As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and indanyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a

bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00159] As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

[00160] "Aryl" groups refer to monocyclic or polycyclic aromatic hydrocarbons, including, for example, phenyl, naphthyl, and phenanthranyl. Aryl moieties are well known and described, for example, in *Hawley's Condensed Chemical Dictionary* (13th Edition), Lewis, R.J., ed., J. Wiley & Sons, Inc., New York (1997). "C_6 or C_{10} aryl" or "C_{6-10} aryl" refers to phenyl and naphthyl. Unless otherwise specified, "aryl", "C_6 or C_{10} aryl" or "C_{6-10} aryl" or "aromatic residue" may be unsubstituted or substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H, and CO_2CH_3.

[00161] The term "benzyl," as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group, wherein said phenyl group may optionally be substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H, and CO_2CH_3.

[00162] As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is

fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

[00163] Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,

1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00164] Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

[00165] Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00166] As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

[00167] The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic

group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

[00168] Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1H-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

[00169] As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

[00170] Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00171] The term "counterion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

[00172] When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

[00173] As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. When a substituent is keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (*e.g.*, carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (*i.e.*, within) of the ring. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

[00174] In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

[00175] When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R groups, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00176] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00177] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00178] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

[00179] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Easton, PA (1990), the disclosure of which is hereby incorporated by reference.

[00180] In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, Bundgaard, H., ed., Elsevier (1985), and *Methods in Enzymology*, 112:309-396, Widder, K. et al., eds., Academic Press (1985);

b) Bundgaard, H., Chapter 5: "Design and Application of Prodrugs," *A Textbook of Drug Design and Development*, pp. 113-191, Krosgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988); and

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984).

[00181] Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.,* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

[00182] Preparation of prodrugs is well known in the art and described in, for example, *Medicinal Chemistry: Principles and Practice*, King, F.D., ed. The Royal Society of Chemistry, Cambridge, UK (1994); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and Wiley-VCH, Zurich, Switzerland (2003); *The Practice of Medicinal Chemistry*, Wermuth, C.G., ed., Academic Press, San Diego, CA (1999).

[00183] The present invention 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 have a variety of potential uses, *e.g.*, as standards and reagents in determining the ability of a potential

pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

[00184] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, $S(O)_2H$, or S(O)H group.

[00185] The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

[00186] Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, " °C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
i-Pr	isopropyl
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
Ph	phenyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
AcOH or HOAc	acetic acid
$AlCl_3$	aluminum chloride
AIBN	azobisisobutyronitrile
BBr_3	boron tribromide
BCl_3	boron trichloride
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BOP reagent	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Burgess reagent	1-methoxy-N-triethylammoniosulfonyl-methanimidate
CBz	carbobenzyloxy
CH_2Cl_2	dichloromethane
CH_3CN or ACN	acetonitrile
$CDCl_3$	deutero-chloroform
$CDCl_3$	chloroform
mCPBA or m-CPBA	*meta*-chloroperbenzoic acid
Cs_2CO_3	cesium carbonate
$Cu(OAc)_2$	copper (II) acetate

Cy_2NMe	N-cyclohexyl-N-methylcyclohexanamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2 dichloroethane
DCM	dichloromethane
DEA	diethylamine
Dess-Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-beniziodoxol-3-(1H)-one
DIC or DIPCDI	diisopropylcarbodiimide
DIEA, DIPEA or Hunig's base	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
cDNA	complimentary DNA
Dppp	(*R*)-(+)-1,2-bis(diphenylphosphino)propane
DuPhos	(+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene
EDC	*N*-(3-dimthylaminopropyl)-*N'*-ethylcarbodiimide
EDCI	*N*-(3-dimthylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
(*S,S*)-EtDuPhosRh(I)	(+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate
Et_3N or TEA	triethylamine
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
GMF	glass microfiber filter
Grubbs (II)	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene) (triycyclohexylphosphine)ruthenium
HCl	hydrochloric acid

HATU	O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)piperaxine-1-ethanesulfonic acid
Hex	hexane
HOBt or HOBT	1-hydroxybenzotriazole
H_2SO_4	sulfuric acid
K_2CO_3	potassium carbonate
KOAc	potassium acetate
K_3PO_4	potassium phosphate
LAH	lithium aluminum hydride
LG	leaving group
LiOH	lithium hydroxide
MeOH	methanol
$MgSO_4$	magnesium sulfate
MsOH or MSA	methylsulfonic acid
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
Na_2CO_3	sodium carbonate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
OTf	triflate or trifluoromethanesulfonate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	palladium(II) acetate

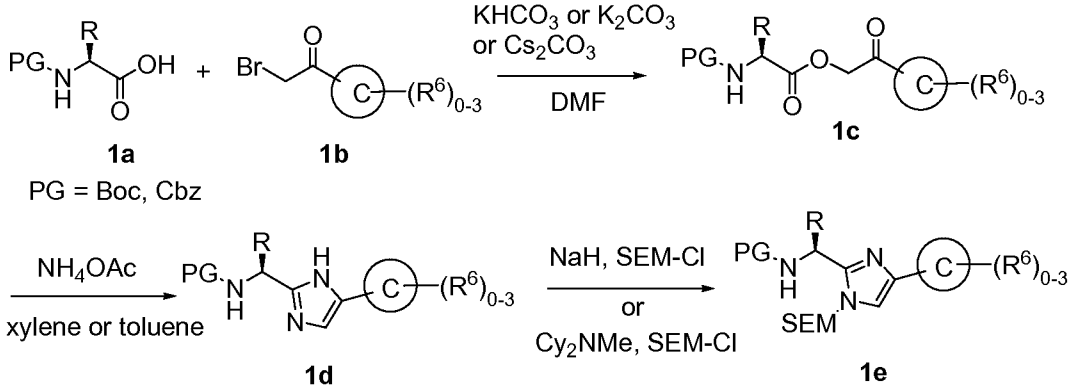
Pd/C	palladium on carbon
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)
Ph_3PCl_2	triphenylphosphine dichloride
PG	protecting group
PL-HCO_3 MP SPE	Solid phase anion exchange
$POCl_3$	phosphorus oxychloride
i-PrOH or IPA	isopropanol
PS	polystyrene
SEM-Cl	2-(trimethysilyl)ethoxymethyl chloride
SiO_2	silica oxide
$SnCl_2$	tin(II) chloride
TBAI	tetra-*n*-butylammonium iodide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$TMSCHN_2$	trimethylsilyldiazomethane
T3P	propane phosphonic acid anhydride
TRIS	tris(hydroxymethyl)aminomethane

[00187] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

[00188] It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, 4th Edition, Wiley-Interscience (2006)).

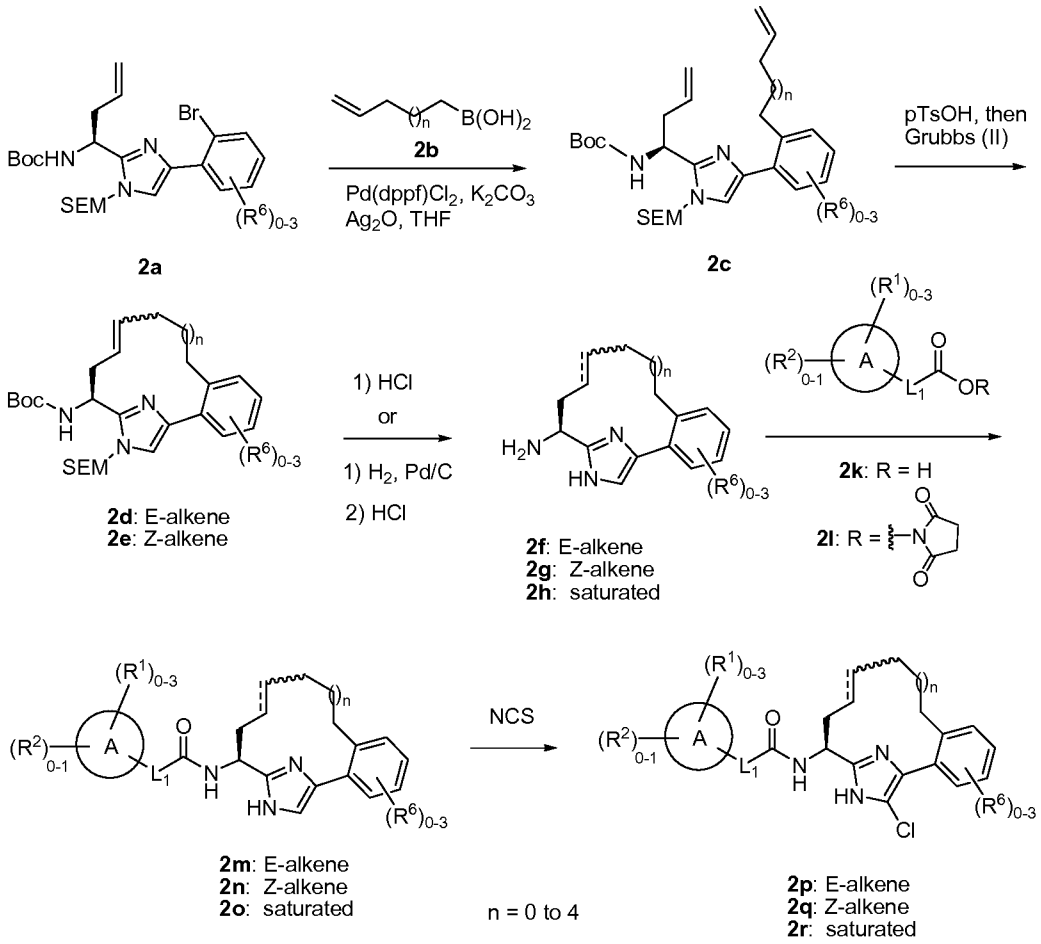
[00189] Imidazole derivatives useful for the synthesis of the compounds of this invention may be synthesized according to the general method outlined in Scheme 1 (Contour-Galcera et al., *Bioorg. Med. Chem. Lett.*, 11(5):741-745 (2001)). Alkylation of the potassium or cesium carboxylate of an appropriately protected or derivatized alpha amino acid 1a with a suitably substituted alpha-bromoketone 1b (ring C is aryl or heteroaryl) provides the keto ester 1c. The imidazole 1d is formed by heating the keto ester 1c to reflux in a suitable solvent, such as toluene or xylenes, in the presence of excess ammonium acetate using a Dean-Stark trap to remove water. Formation of the imidazole can also be carried out by combining the keto ester 1c and ammonium acetate in a suitable solvent, such as xylene or ethanol or a combination of solvents such as dimethylformamide and ethanol (1:1) and using microwave heating. Imidazole 1d can then be protected with as suitable protecting group. For example, imidazole 1d can be reacted with SEM-Cl, in the presence of base, such as sodium hydride or dicyclohexylmethyl amine, and in a solvent such as dimethylformamide or tetrahydrofuran to give 1e.

Scheme 1



[00190] Imidazole containing macrocycles of this invention wherein Y is $-CH_2-$ can be prepared according to Scheme 2. Suzuki-Miyaura coupling between 2a, prepared as described in Scheme 1, and a suitably substituted alkyl boronic acid 2b in the presence of silver(I) oxide and a base, such as potassium carbonate, using a precatalyst such as $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ complex, in a solvent such as tetrahydrofuran at elevated temperatures provides 2c (Falck, J.R., *Tetrahedron Letters*, 42:7213 (2001)). Using a modified procedure described by Lovely (*Tetrahedron Letters*, 44:1379 (2003)), 2c, following pretreatment with p-toluenesulfonic acid to form the imidazolium ion, can be cyclized via ring-closing metathesis using a catalyst, such as Grubbs (II), in a suitable solvent, such as dichloromethane, dichloroethane, or toluene at elevated temperature, to give the imidazole-containing macrocycle as a mixture of olefin isomers (E-alkene 2d and Z-alkene 2e). The olefins can be separated, and then deprotection of both the Boc and SEM groups with aqueous 5M hydrochloric acid in methanol or ethanol at elevated temperature provides amines 2f and 2g. Alternatively, the deprotection can be performed under anhydrous conditions with 4M hydrochloric acid in dioxane at elevated temperatures. The mixture of olefin isomers (E-alkene 2d and Z-alkene 2e) can be reduced with hydrogen over either palladium on carbon or platinum oxide and subsequent deprotection as described above gives the saturated amine 2h. Amide coupling between amines 2f-h, with an appropriately substituted carboxylic acid 2k, employing suitable coupling reagents, such as EDCI, HOBt, and base generates 2m-o (for alternative coupling reagents see: Han, S.-Y. et al., *Tetrahedron*, 60:2447 (2004)). Alternately, amines 2f-h can be coupled with an activated carboxylic ester 2l in the presence of a base such as Hunig's base and in a solvent such as dimethylformamide to give 2m-o. Further functional group incorporation on the imidazole ring may be achieved by chlorination of the C-5 of the imidazole ring with N-chlorosuccinimide, using a suitable solvent such as methylene chloride, acetonitrile or chloroform to give compounds 2p-r. Further functional group incorporation on the imidazole ring may also be achieved by fluorination of the C-5 of the imidazole ring with Accufluor, using a suitable solvent such as dimethylformamide in the presence of a base, such as sodium carbonate.

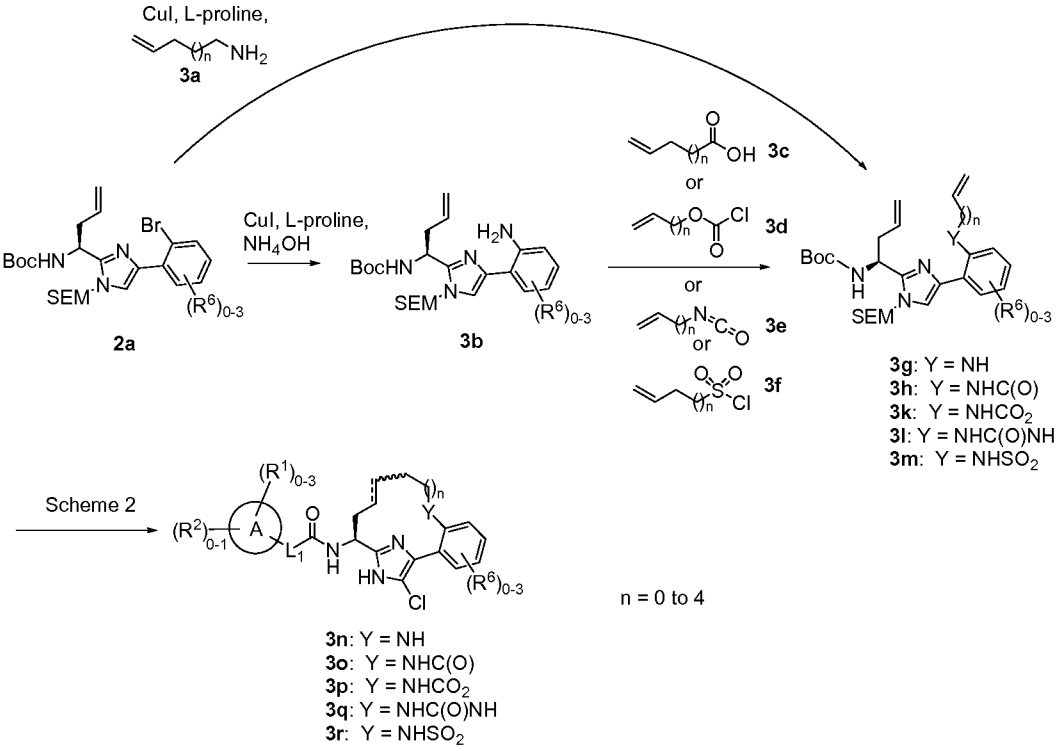
Scheme 2



[00191] Imidazole containing macrocycles of this invention wherein Y is NH, NHC(O), $NHCO_2$, NHC(O)NH, and $NHSO_2$ can be prepared according to Scheme 3. Using a modified procedure described by Ma (*Synthesis*, 3:496 (2005)), bromide 2a can be coupled with an appropriately substituted amine 3a employing copper (I) iodide and L-proline in the presence of a base such as potassium carbonate, in a solvent such as dimethylsulfoxide at elevated temperature to give the substituted aniline 3g. Alternatively, bromide 2a can be converted to the unsubstituted aniline 3b under similar reaction conditions (Chang, S., *Chem. Commun.*, 3052 (2008)). The aniline 3b can then be coupled with an appropriately substituted carboxylic acid 3c using T3P in a solvent such as ethyl acetate or dimethylformamide to give the amide 3h. The aniline 3b can also be coupled with an appropriately substituted chloroformate 3d, isocyanate 3e, or sulfonyl chloride 3f to provide the carbamate 3k, urea 3l, and the sulfonamide 3m, respectively.

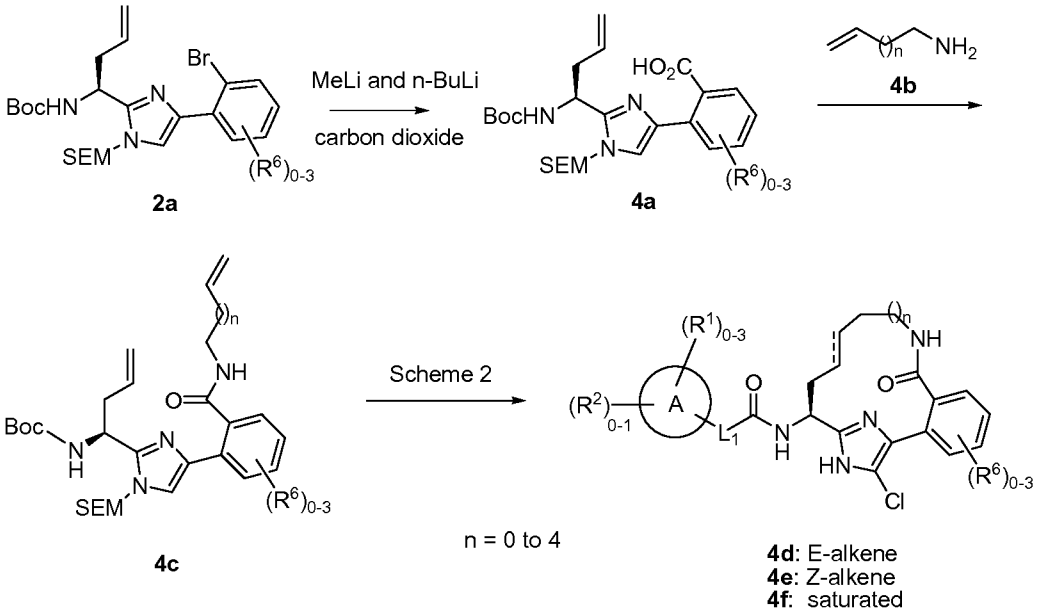
Compounds of the formula 3g, 3h, and 3k-m can be converted to compounds 3n-r according to Scheme 2. For the preparation of compounds of the formulae 3n, the preferred method for removing both the Boc and SEM, as described in Scheme 2, employs anhydrous 4M hydrochloric acid in dioxane at elevated temperatures with either cysteine or O-methyl hydroxylamine as a formaldehyde scavenger.

Scheme 3



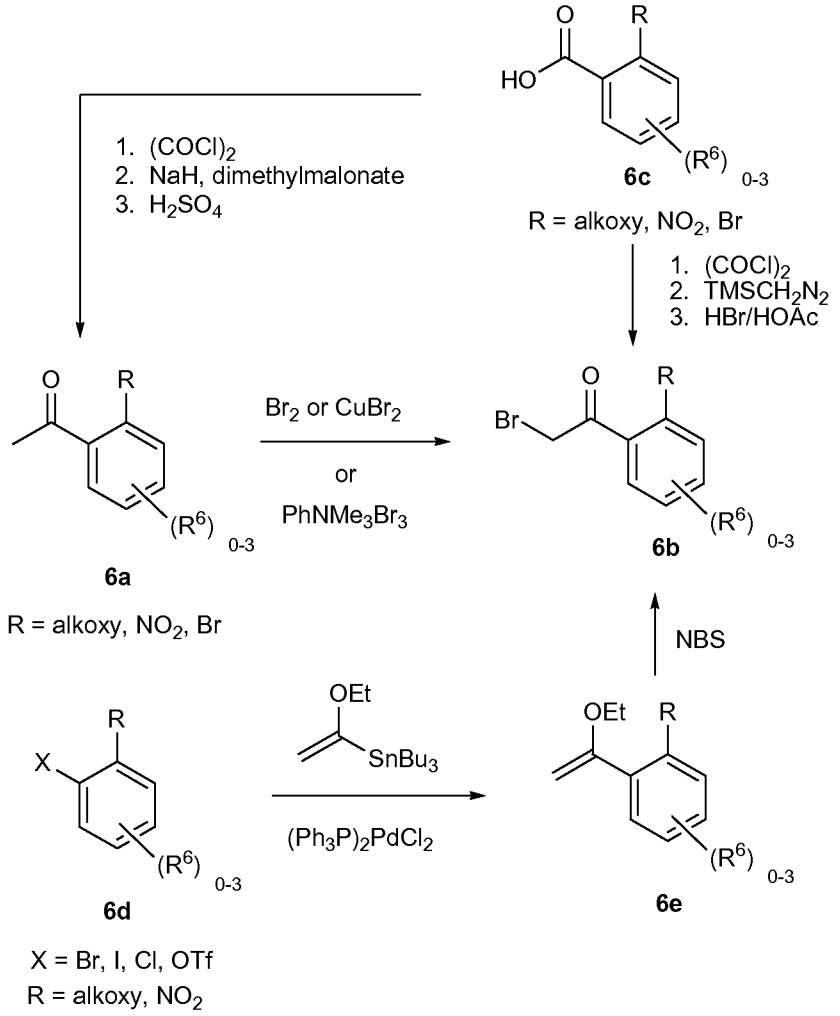
[00192] Imidazole-containing macrocycles of this invention wherein Y is C(O)NH can be prepared according to Scheme 4. Subjecting 2a to methyllithium followed by metal-halogen exchange with n-butyllithium and quenching the intermediate anion with carbon dioxide provides the carboxylic acid 4a. Amide coupling with an appropriately substituted amine 4b, as previously described for the conversion of 3b to 3h, gives amide 4c. Amide 4c can be converted to compounds 4d-f according to Scheme 2.

Scheme 4



[00193] Certain 2-bromoacetophenone analogs (1b, C = aryl) that are not commercially available may be synthesized from commercially available starting materials as described in Scheme 6. Acetophenone derivatives 6a can be treated with a brominating reagent such as bromine in a solvent such chloroform to give 6b. Alternatively, acetophenone derivatives 6a can be treated with either copper (II) bromide in a solvent such as ethyl acetate at elevated temperature or phenyltrimethylammonium tribromide in a solvent such as tetrahydrofuran at low temperature to provide 6b. Benzoic acid derivatives 6c can be treated sequentially with oxalyl chloride in a suitable solvent, such as dichloromethane, containing a few drops of DMF, and then treated with trimethylsilyldiazomethane in a suitable solvent or solvent combination, such as acetonitrile and hexane. The intermediate diazoketone is isolated and treated with aqueous hydrobromic acid and dichloromethane to provide 6b. Alternatively the benzoic acid derivatives 6c can be converted to the acetophenone derivatives 6a in three steps as described in Scheme 6. Alternatively, Stille coupling between a suitably substituted aryl halide or triflate and tributyl-(1-ethoxyvinyl) stannane with a palladium catalyst, such as *bis*-(triphenylphosphine)palladium dichloride, in a suitable solvent, such as toluene, at elevated temperature yields the enol ether 6e. The resulting enol ether 6e can be converted to 6b with N-bromosuccinimide.

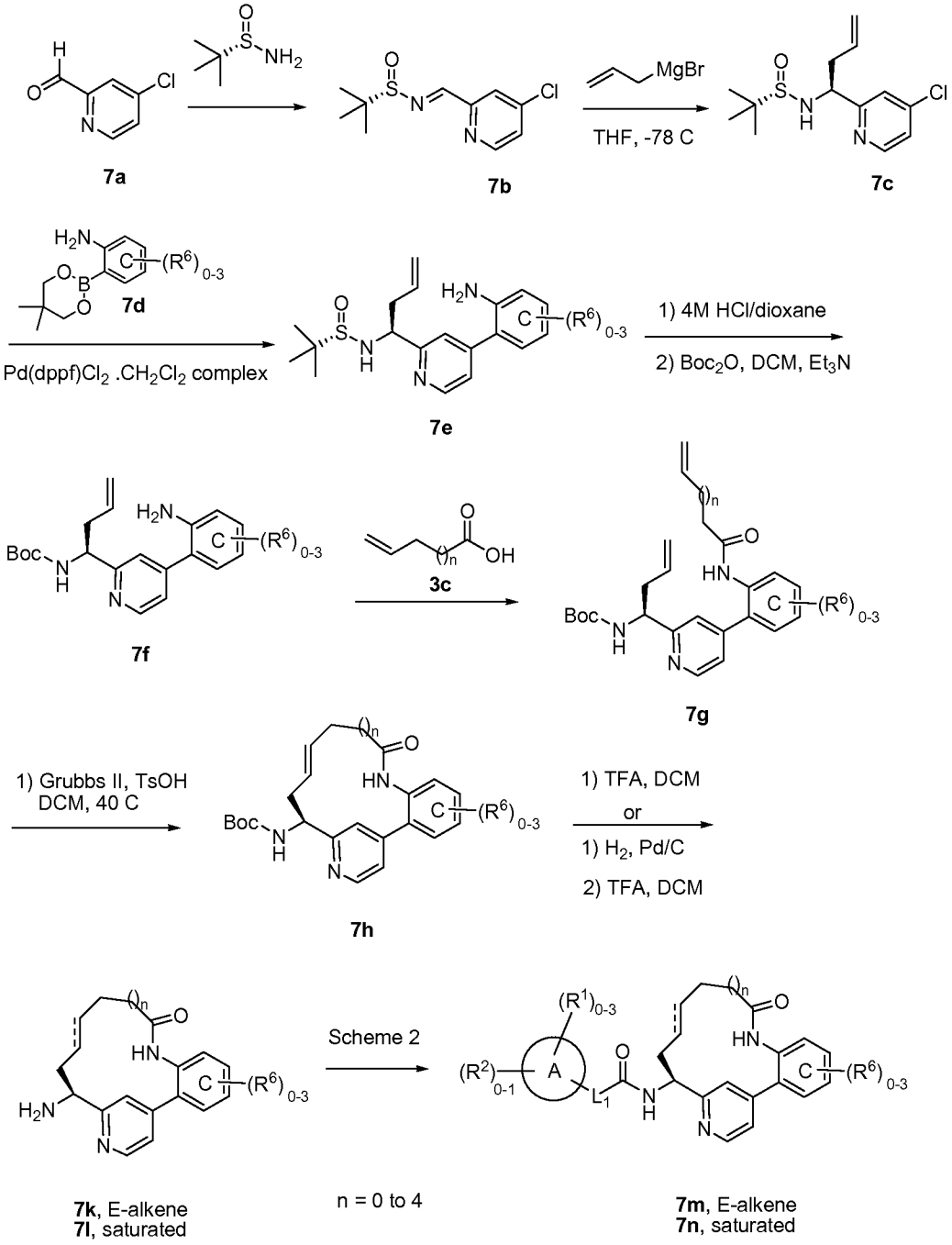
Scheme 6



[00194] The syntheses of appropriately substituted carboxylic acids of formulae 2k, where A = aryl and where L_1 = $-CH_2CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-OCH_2-$, $-S(O)_pCH_2-$, or $-CH_2NH-$, useful for the synthesis of amide compounds of this invention as outlined in Scheme 2 are described in PCT International Application No. WO 2009/114677 published 09/17/2009, which is incorporated in its entirety herein by reference. In addition, 1-amino-5,6,7,8-tetrahydroisoquinoline-6-carboxylic acid useful for the synthesis of amide compounds of this invention as outlined in Scheme 2 is described in U.S. Patent Application No. 2005/0282805 published 12/22/2005, which is incorporated in its entirety herein by reference.

[00195] Representative pyridine (ring B = pyridine) containing macrocycles of this invention wherein Y is NHCO can be prepared as shown in Scheme 7. Condensation of aldehyde 7a, prepared according to a modified procedure described by Negi (*Synthesis*, 991 (1996)), with (S)-2-methylpropane-2-sulfinamide in the presence of anhydrous copper sulfate in a solvent such as dichloromethane gives the sulfinimine 7b (Ellman, J., *J. Org. Chem.*, 64:1278 (1999).) Using a modified procedure described by Kuduk (*Tetrahedron Letters*, 45:6641 (2004)), suitably substituted Grignard reagents, for example allylmagnesium bromide, can be added to sulfinimine 7b to give a sulfinamide 7c, as a mixture of diastereomers which can be separated at various stages of the sequence. Suzuki-Miyaura coupling between 4-chloropyridine 7c and an appropriately substituted aryl or heteroaryl boronic acid or ester 7d in the presence of a base such as potassium phosphate in a solvent mixture, such dimethylsulfoxide and water, or dimethylformamide, using a precatalyst such as $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ complex provides 7e. Protecting group interconversion can be accomplished in two steps to give 7f. The aniline 7f can then be coupled with an appropriately substituted carboxylic acid 3c using propane phosphonic acid anhydride (T3P) to give the amide 7g. Ring closing metathesis, as described previously in Scheme 2, affords the pyridine containing macrocycle 7h, as the E-alkene. Boc deprotection on 7h with either TFA in dichloromethane or 4M hydrochloric acid in dioxane gives amine 7k. Alternatively, hydrogenation of 7h followed by Boc deprotection with TFA in dichloromethane provides amine 7l. Compounds 7k and 7l can be converted to compounds 3m and 3n according to Scheme 2.

Scheme 7



[00196] Additional pyridine (ring B = pyridine) containing macrocycles of this invention wherein Y is $NHCO_2$, NHC(O)NH, and $NHSO_2$ can be prepared according to Scheme 7 by replacing 3c with an appropriately substituted chloroformate 3d, isocyanate

3e, or sulfonyl chloride 3f. Additional macrocycles containing regioisomeric pyridine scaffolds to the one described in Scheme 7 can be prepared by an analogous sequence.

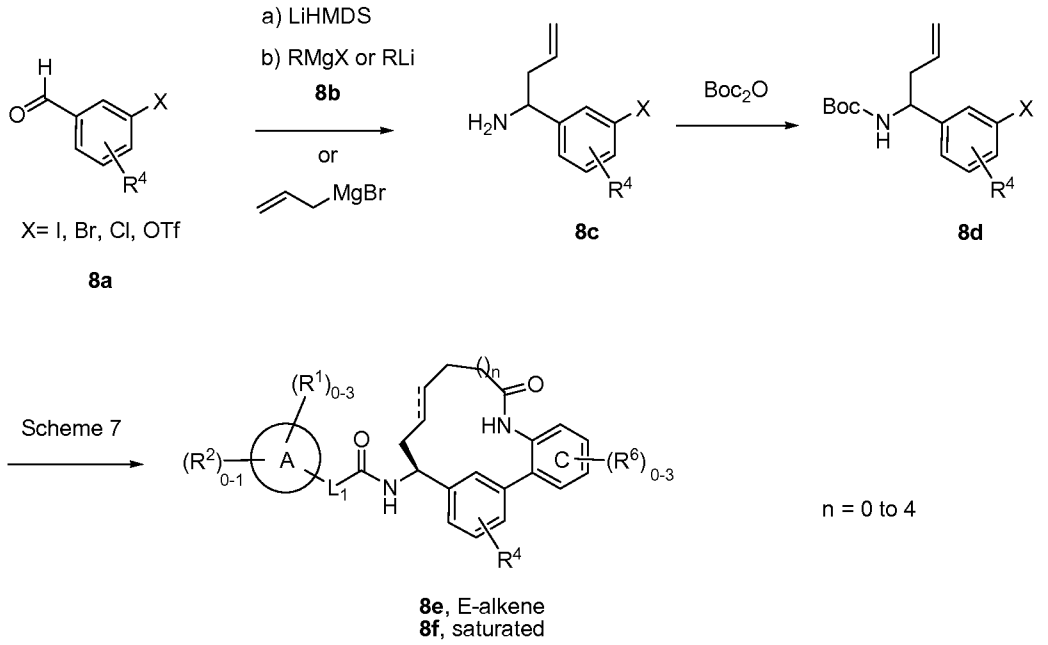
[00197] Methods for synthesis of a large variety of substituted pyridine compounds useful as starting materials for the preparation of compounds of the present invention are well known in the art and have been extensively reviewed. (For examples of methods useful for the preparation of pyridine starting materials see: Kroehnke, F., *Synthesis*, 1 (1976); "Pyridine and Its Derivatives", *The Chemistry of Heterocyclic Compounds*, 14(Suppl. 1-4), Abramovitch, R.A., ed., John Wiley & Sons, New York (1974); *Comprehensive Heterocyclic Chemistry*, 2:165-524, Boulton, A.J. et al., eds., Pergamon Press, New York (1984); *Comprehensive Heterocyclic Chemistry*, 5:1-300, McKillop, A., ed., Pergamon Press, New York (1996)).

[00198] In cases where suitably substituted boronic acids are not commercially available, a modification to this approach may be adopted wherein an aryl halide is subjected to a palladium mediated coupling with a diboron species such as bis(pinacolato) diboron or bis(neopentyl glycolato)diboron to provide the corresponding 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane or the 5,5-dimethyl-[1,3,2]dioxaborolane intermediates using the method of Ishiyama, T. et al. (*J. Org. Chem.*, 60(23):7508-7510 (1995)). Alternately, this same intermediate can be prepared by reaction of the intermediate halide with the corresponding dialkoxyhydroborane as described by Murata et al. (*J. Org. Chem.*, 62(19):6458-6459 (1997)). The boron pinacolate intermediates can be used in place of boronic acids for coupling to the aryl/heteroaryl halides or triflates or the boron pinacolate intermediate can be converted to the boronic acids. Alternately, the corresponding boronic acids can be prepared by metal-halogen exchange of the aryl/heteroaryl halide, quenching with a trialkoxyborate reagent, and aqueous workup to provide the boronic acids (Miyaura, N. et al., *Chem. Rev.*, 95:2457 (1995)).

[00199] It is also realized that the scope of intermediate synthesis can be further extended outside the use of Suzuki-Miyaura coupling methodology since the precursor aryl halides or triflates described above are also precursors for Stille, Negishi, Hiyama, and Kumada-type cross coupling methodologies (Tsuji, J., *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis,* John Wiley & Sons (2000); Tsuji, J., *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley & Sons (1996).)

[00200] Representative phenyl (ring B = phenyl) containing macrocycles of this invention wherein Y is NHCO can be prepared as shown in Scheme 8. Using a modification of the procedure described by Hart (*J. Org. Chem.*, 48(3):289-294 (1983)), *in situ* generation of N-trimethylsilylaldimines from a suitably substituted benzaldehyde 8a and lithium *bis*(trimethylsilyl)amide, followed by the addition of Grignard or alkyllithium reagents 8b, for instance allylmagnesium bromide, gives after aqueous work up the amine 8c. The amine can be protected as the Boc. Compounds of the formula 8e and 8f can be prepared following the sequence described in Scheme 7, by replacing 7c with 8d.

Scheme 8

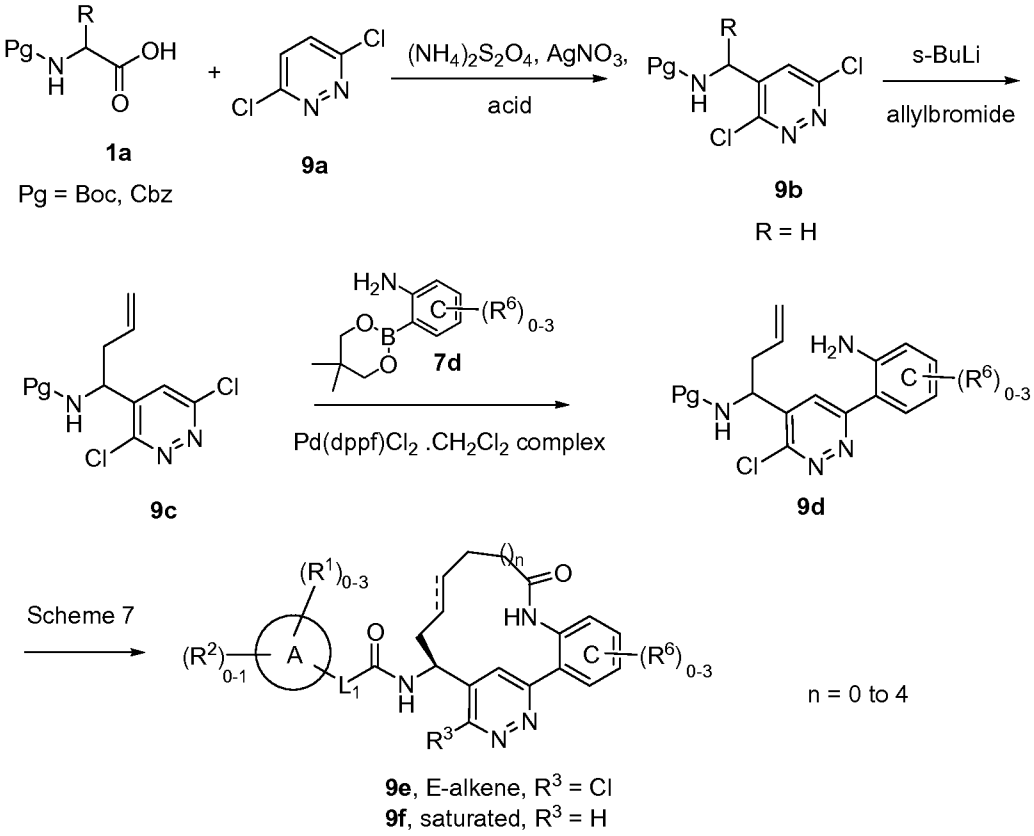


8e, E-alkene
8f, saturated

[00201] Representative pyridazine (ring B = pyridazine) containing macrocycles of this invention wherein Y is NHCO can be prepared as shown in Scheme 9. Using a modification of the Minisci reaction described by Cowden (*Org. Lett.*, 5:4497-4499 (2003)), an appropriately protected or derivatized alpha amino acid 1a and 3,6-dichloropyridazine 9a can be coupled at elevated temperature in the presence of silver nitrate, ammonium persulfate, and an acid, such as trifluoroacetic acid, in a solvent, such as water or a water/dimethylformamide mixture, to give compounds of the formulae 9b.

Compound 9b wherein R = H, prepared using an appropriately protected glycine derivative of 1a, can be further functionalized by deprotonation with sec-BuLi and subsequent alkylation with an appropriately substituted alkyl halide, for instance allyl bromide, to give compound 9c. Suzuki-Miyaura coupling between chloropyridazine 9c and an appropriately substituted aryl or heteroaryl boronic acid or ester 7d in the presence of a base such as potassium phosphate in a solvent mixture, such dimethylsulfoxide and water, or dimethylformamide, using a precatalyst such as $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ complex provides 9d. Compounds of the formula 9e and 9f can be prepared following the sequence described in Scheme 7, by replacing 7f with 9d.

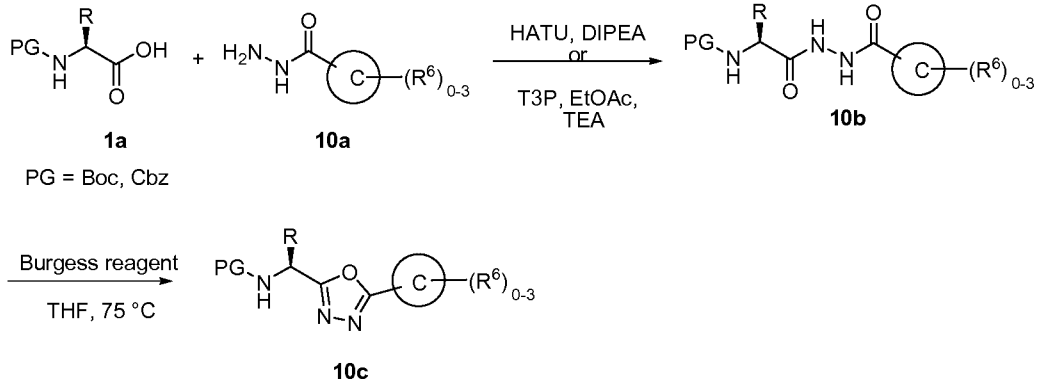
Scheme 9



[00202] Methods for the synthesis of a large variety of substituted pyridazines useful for the preparation of compounds of the present invention are well known in the art. (For examples of methods useful for the preparation of pyridazine starting materials see: "Pyridazines", *The Chemistry of Heterocyclic Compounds*, Vol. 28, Castle, R.N., ed.,

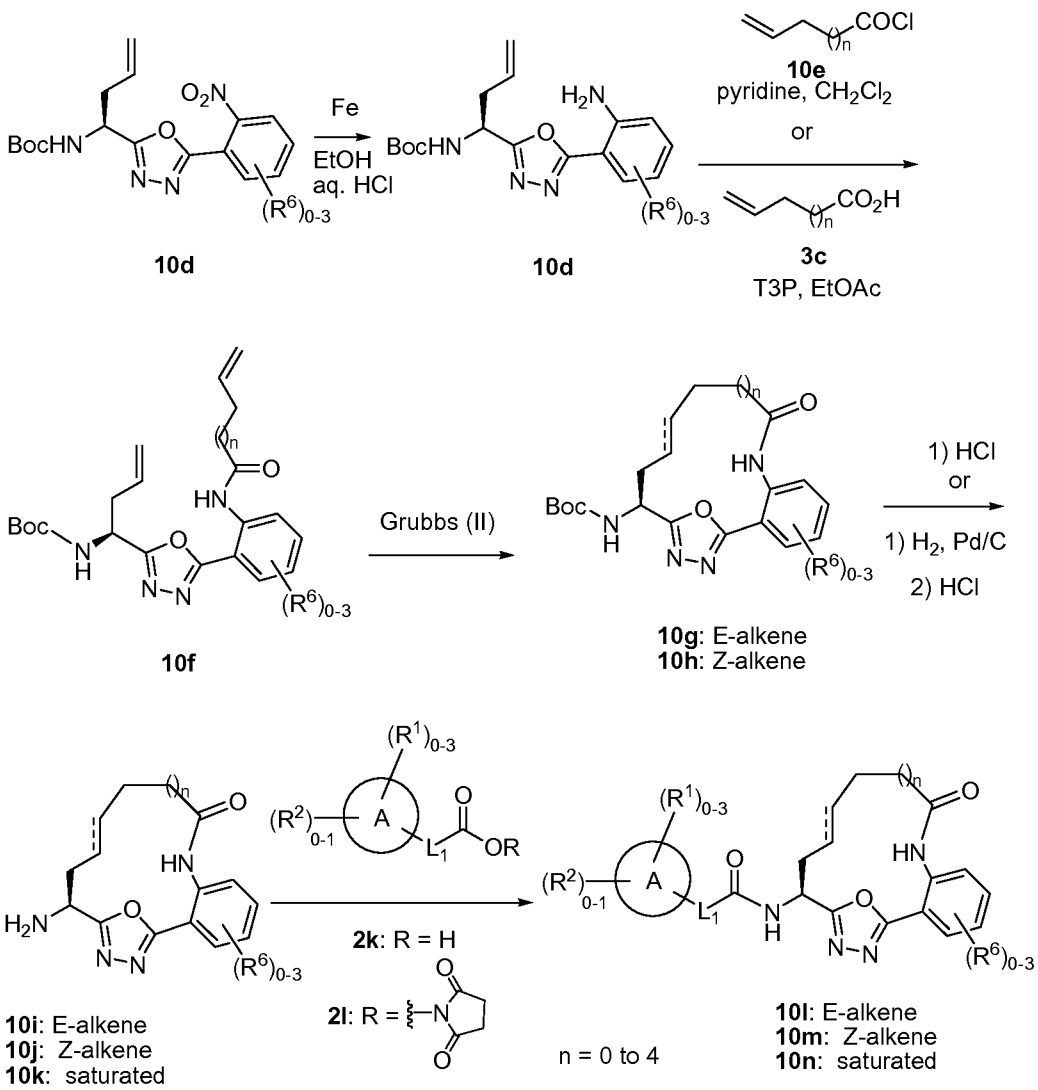
John Wiley & Sons, New York (1973); "The Pyridazines", *The Chemistry of Heterocyclic Compounds*, 57(Suppl. 1), Brown, D.J., ed., John Wiley & Sons, New York (2000); *Comprehensive Heterocyclic Chemistry II*, 6:1-93, Boulton, A.J., ed., Elsevier Science Inc., New York (1996)).

Scheme 10



[00203] Oxadiazole derivatives useful for the synthesis of the compounds of this invention may be synthesized according to the general method outlined in Scheme 10. A suitably protected amino acid 1a is coupled to a hydrazide of formula 10a in the presence of a coupling reagent such as HATU or T3P to provide acylhydrazide 10b which is cyclized to the corresponding oxadiazole 10c by heating in the presence of Burgess reagent in a suitable solvent such as THF.

Scheme 10a

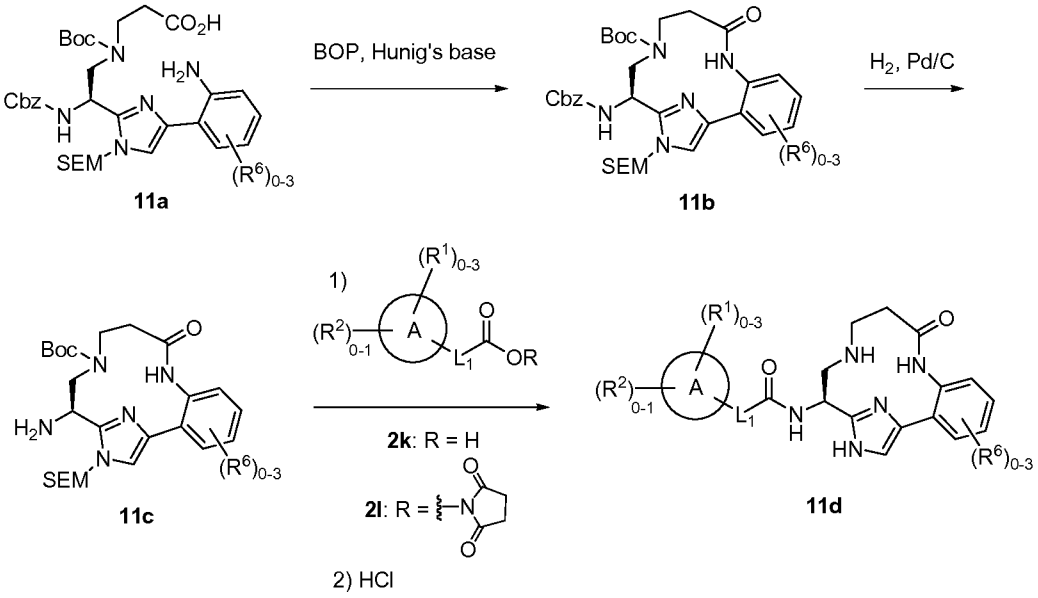


[00204] Representative oxadiazole (ring B = oxadiazole) containing macrocycles of this invention wherein Y is NHCO can be prepared as shown in Scheme 10a. Thus from N-Boc-allylglycine and a suitably substituted 2-nitrophenylhydrazine, compounds of formula 10d can be obtained and then converted into macrocyclic compounds of this invention using similar chemistry to that described above in Scheme 7.

[00205] It should be recognized to one skilled in the art of organic synthesis that additional macrocyclic compounds of this invention can be prepared by alternative cyclization strategies which are not limited to the ring-closing metathesis strategy described in Scheme 2. For instance, macrolactamization can also be used as described

in Scheme 11. Slow addition of a solution 11a and Hunig's base in DMF to a solution BOP reagent in a mixture dichloromethane and DMF, provides macrocycle 11b. Hydrogenolysis of the Cbz provides the amine 11c. Amide coupling of the amine 11c with 2k or 2l, as described in Scheme 2, and global deprotection gives 11d.

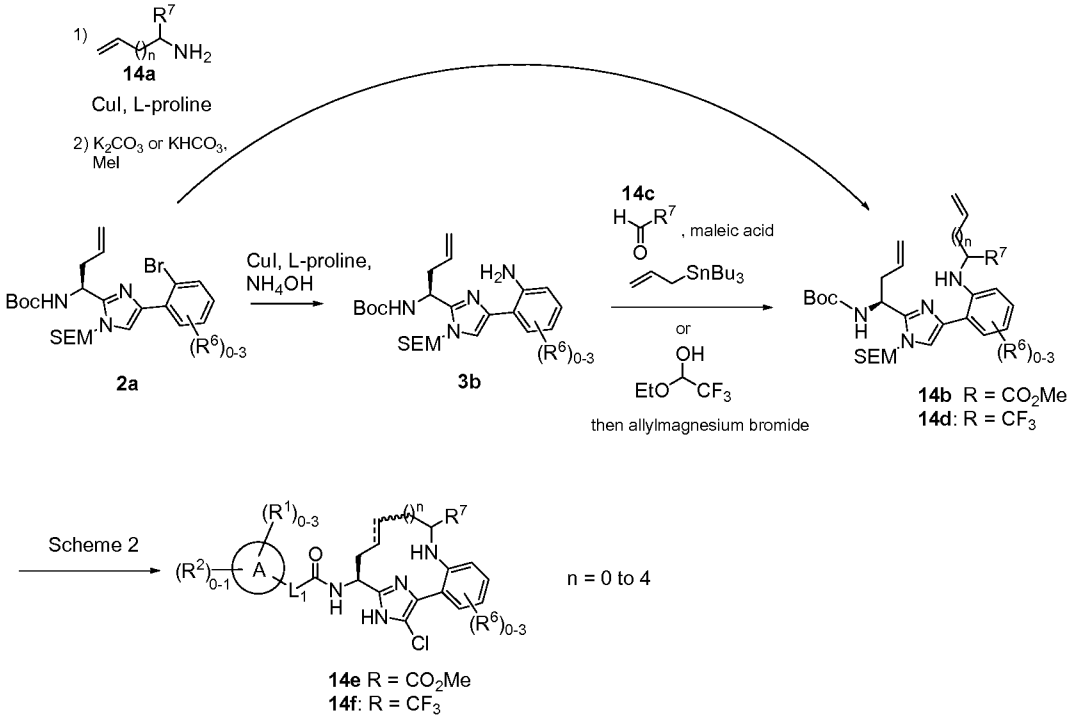
Scheme 11



[00206] Additional imidazole containing macrocycles of this invention wherein Y is NH can be prepared according to Scheme 14. Using a modified procedure described by Ma (*Synthesis*, 3:496 (2005)), bromide 2a can be coupled with an appropriately substituted amine or amino acid ($R^7 = CO_2H$) 14a employing copper (I) iodide and L-proline in the presence of a base such as potassium carbonate, in a solvent such as dimethylsulfoxide at elevated temperature, followed by alkylation of the carboxylic acid moiety with an alkyl iodide such as methyl iodide, gives the substituted aniline 14b. Alternatively, 14b can be prepared using a modified procedure described by Zhao (*Synthesis*, 19:3189 (2006)). Combining aniline 3b with appropriately substituted aldehdydes 14c in the presence of maleic acid and allyltributyltin provides 14b. Alternatively, aniline 3b can be condensed with trifluoroacealdehyde ethyl hemiacetal followed by the addition of Grignard reagents, such as allylmagnesium bromide, which gives 14d. Compounds of the formula 14b and 14d can be converted to compounds 14e

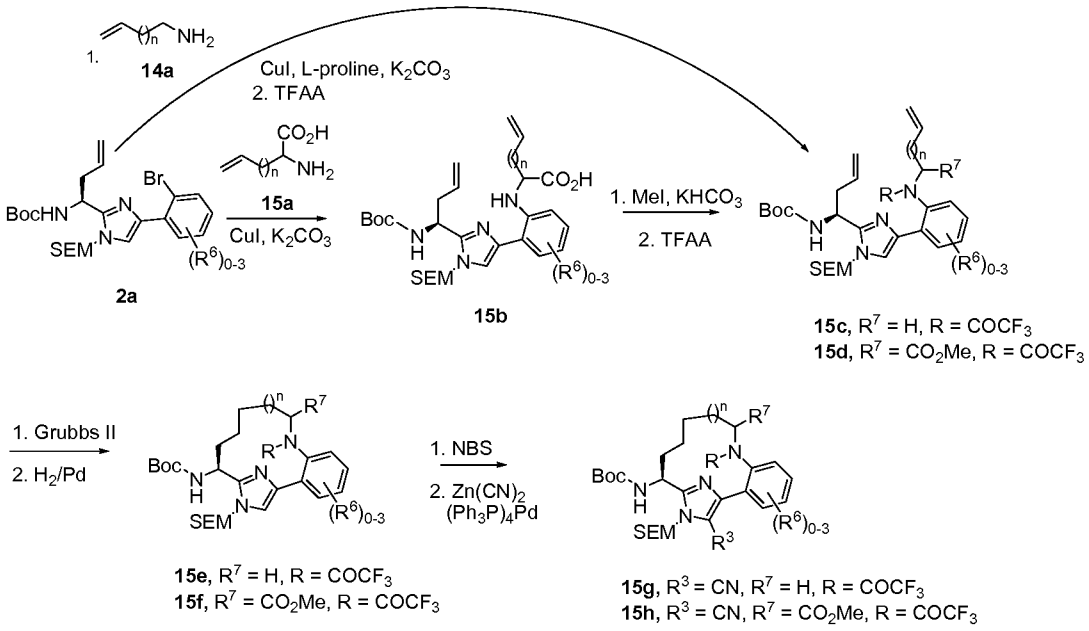
and 14f according to Scheme 2. For the preparation of compounds of the formulae 14e and 14f, the preferred method for removing both the Boc and SEM, as described in Scheme 2, employs anhydrous 4M hydrochloric acid in dioxane at elevated temperatures with either cysteine or O-methyl hydroxylamine as a formaldehyde scavenger. Further manipulation of functional groups on R^7 using methods known to one skilled in the art of organic synthesis will give additional compounds of the invention.

Scheme 14



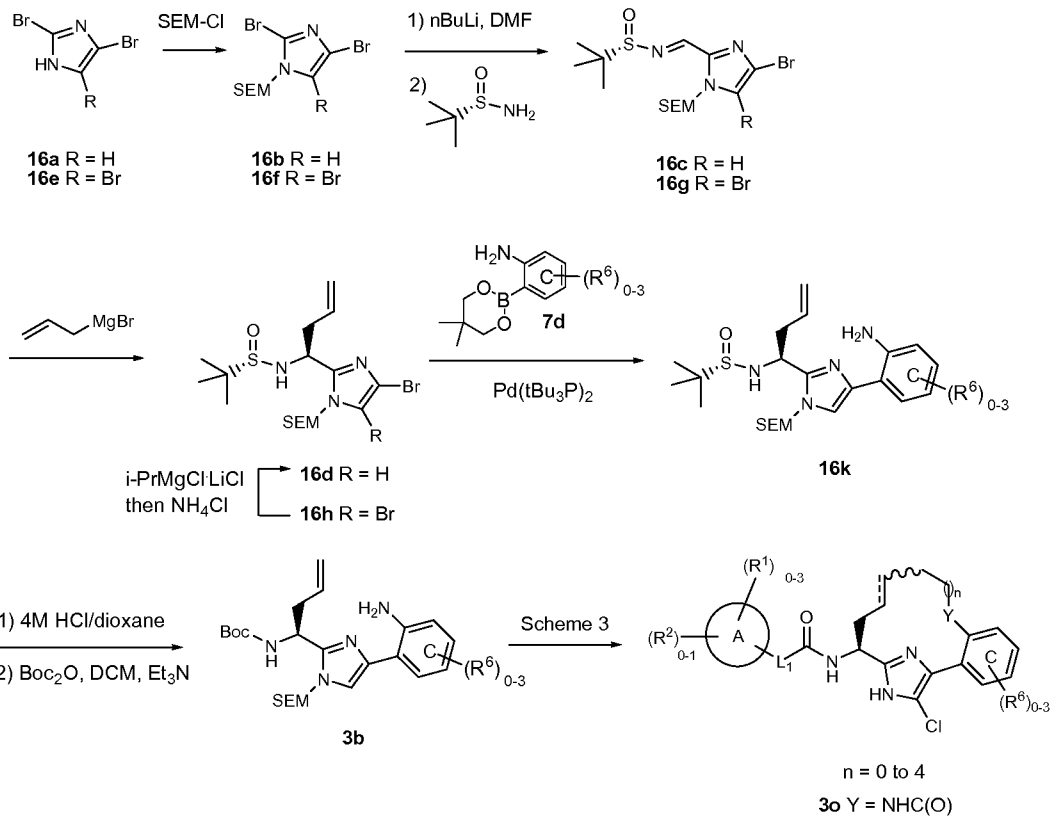
[00207] Additional imidazole macrocycles of this invention wherein R^3 is CN, can be prepared according to Scheme 15. Deprotection of intermediates 15g and 15h followed by amide coupling as described above will then provide additional compounds of this invention. Further manipulation of functional groups at R^7 and R^3 using methods known to one skilled in the art of organic synthesis and as exemplified in the specific examples given below will give additional compounds of the invention.

Scheme 15



[00208] Additional imidazole containing macrocycles of this invention can be prepared according to Scheme 16. Regioselective protection of the 2,4-dibromo imidazole with SEM-Cl provides 16b. Metal-halogen exchange of 16b with n-BuLi followed by quenching with dimethylformamide affords a mixture of the C2 and C4 aldehydes. Condensation of the C2-aldehyde with (S)-2-methylpropane-2-sulfinamide in the presence of anhydrous copper sulfate in a solvent such as dichloromethane gives the sulfinimine 16c. Appropriately substituted Grignard reagents, for example allylmagnesium bromide, can be added to sulfinimine 16c to give sulfinamine 16d, as a mixture of diastereomers which can be separated at various stages of the sequence. Alternatively, the 2, 4, 5-tribromo imidazole 16e can be converted to 16h according to the four step sequence described above. Regioselective halogen-magnesium exchange of 16h with isopropylmagnesium chloride, followed by quenching with saturated ammonium chloride, provides 16d. Suzuki-Miyaura coupling between bromoimidazole 16d and an appropriately substituted aryl or heteroaryl boronic acid or ester 7d in the presence of a base such as potassium carbonate in a solvent, such dioxane, using a catalyst such as $Pd(tBu_3P)_2$ provides 16k. Protecting group interconversion can be accomplished in two steps to give 3b. Compound 3b can be converted to compound 3o according to Scheme 3.

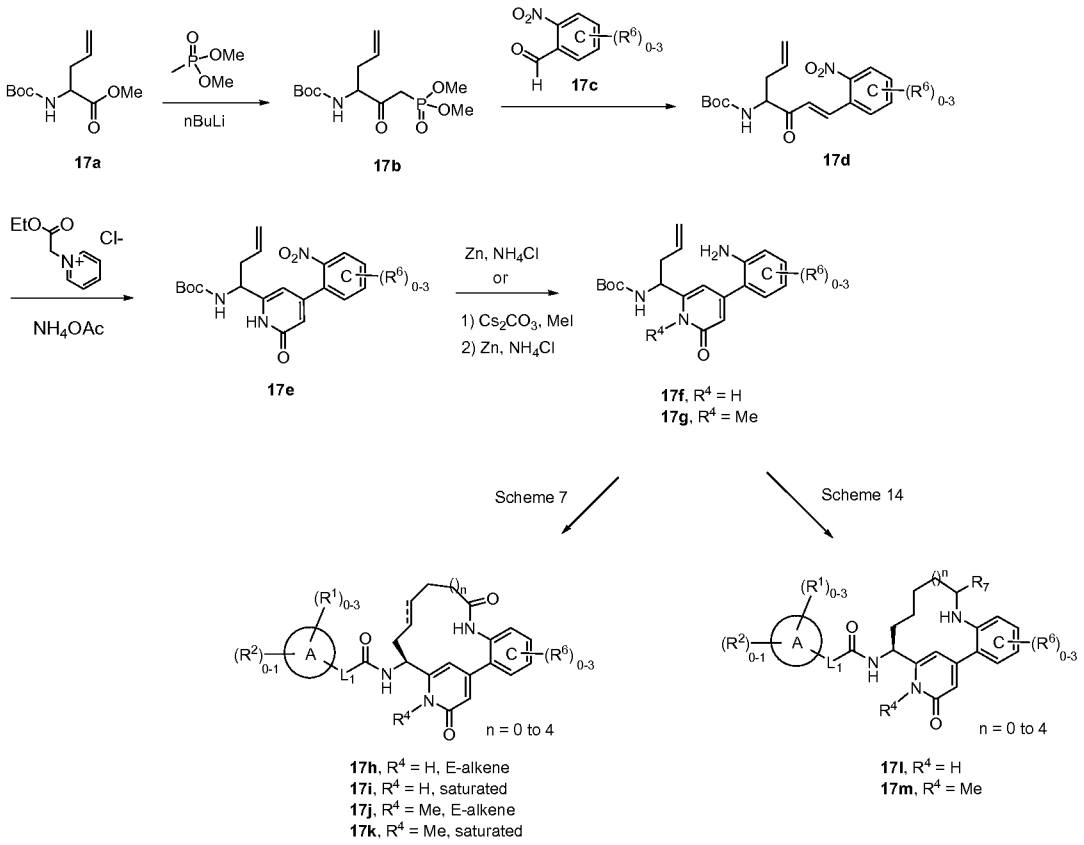
Scheme 16



[00209] Representative pyridone (ring B = pyridone) containing macrocycles of this invention can be prepared as shown in Scheme 17. Compound 17d can be prepared in two steps according to a modified procedure described by Resmini (Resmini, M. et al., *Tetrahedron Asymmetry*, 15:1847 (2004)). A suitably substituted amino ester 17a can be converted to the corresponding β-ketophosphonate 17b by treatment with lithium dimethylmethylphosphonate. Horner-Wadsworth-Emmons reaction of 17b and a suitably substituted aldehyde 17c in the presence of base such as potassium carbonate in a solvent such as ethanol or tetrahydrofuran gives the α,β-unsaturated ketone 17d. Condensation of 17d with 1-(ethoxycarbonylmethyl)-pyrdinium chloride or 1-(carbamoylmethyl)-pyridinium chloride in the presence of ammonium acetate in a solvent such as ethanol or glacial acetic acid generates the pyridone 17e. The nitro group can be reduced to the aniline17f with zinc and ammonium chloride in methanol. Alternatively, alkylation of the cesium salt of the pyridone 17e with methyl iodide, followed by reduction of the nitro as described above, can yield the N-Me pyridone derivative 17g. Compounds of the

formula 17f and 17g can be converted to compounds 17h-k, according to Scheme 7, or to compounds 17l-m, according to Scheme 14.

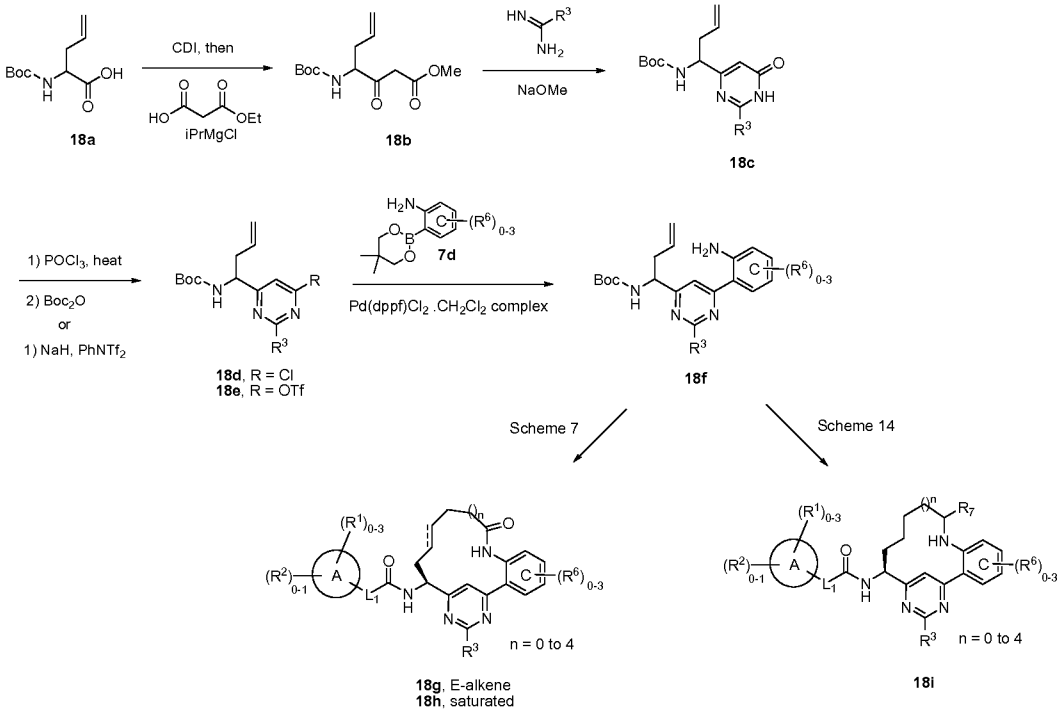
Scheme 17



[00210] Representative pyrimidine (ring B = pyrimidine) containing macrocycles of this invention can be prepared as shown in Scheme 18. Condensation of the β-ketoester 18b, prepared according to a modified procedure of Maibaum (*J. Org. Chem.*, 53:869 (1988)), with a suitably substituted amidine under basic conditions, such as formamidine and sodium methoxide in methanol, yields the pyrimidone 18c. The pyrimidone can be converted to the chloro pyrimidine 18d in two steps with phosphorus oxychloride and then reprotection of the amine with Boc-anhydride. Alternatively, the pyrimidone can be converted directly to the corresponding triflate 18e with sodium hydride and *N*-phenyltrifluoromethanesulfonimide. Suzuki-Miyaura coupling between 18d or 18e and an appropriately substituted aryl or heteroaryl boronic acid or ester 7d in the presence of a base such as potassium phosphate in a solvent mixture, such dimethylsulfoxide and

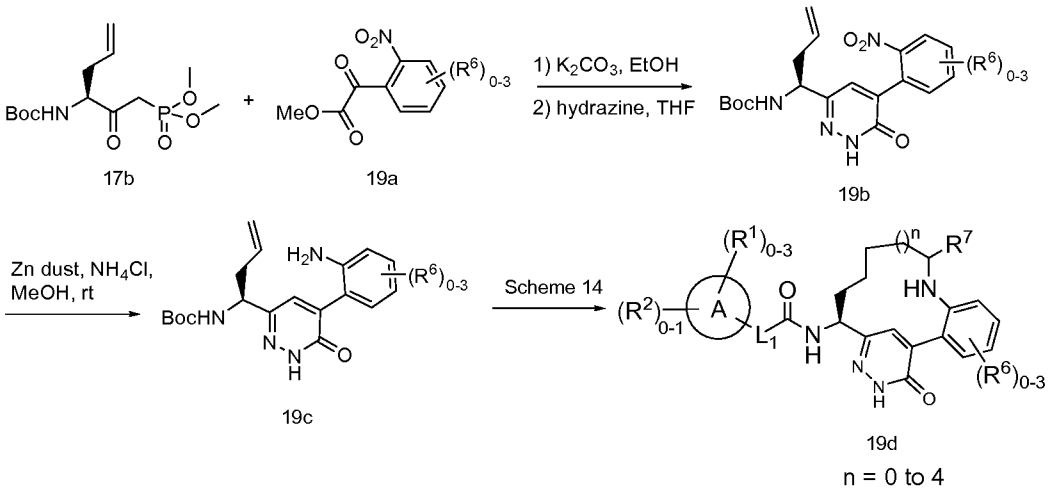
water, or dimethylformamide, using a precatalyst such as $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ complex provides 18f. Compounds of the formula 18f can be converted to compounds 18g-h, according to Scheme 7, or to compounds 18i, according to Scheme 14.

Scheme 18



[00211] Representative pyridazinone (ring B = pyridazinone) containing macrocycles of this invention can be prepared as shown in Scheme 19. Condensation of the potassium salt of 17b with a suitably substituted α-ketoester 19a, which is either commercially available or prepared using a modified procedure described by Domagala (*Tetrahedron Lett.*, 21:4997-5000), in a solvent such as tetrahydrofuran generates the α,β-unsaturated ketone derivative which can then be condensed with a suitably substituted hydrazine derivative to give pyridazinone 19b. The nitro group can be reduced to the aniline19c with zinc and ammonium chloride in methanol. Compounds of the formula 19c can be converted to compounds 19d according to Scheme 14.

Scheme 19



[00212] It should be recognized that additional deprotection steps and further functional group manipulations of compounds obtained via Schemes 1-19 using methods known in the art will then provide additional compounds of this invention.

[00213] Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out using prepacked SiO_2 cartridges eluting with either gradients of hexanes and ethyl acetate or dichloromethane and methanol unless otherwise indicated. Reverse phase preparative HPLC was carried out using C18 columns eluting with gradients of Solvent A (90% water, 10% methanol, 0.1% TFA) and Solvent B (10% water, 90% methanol, 0.1% TFA, UV 220 nm) or with gradients of Solvent A (90% water, 10% acetonitrile, 0.1% TFA) and Solvent B (10% water, 90% acetonitrile, 0.1% TFA, UV 220 nm) or with gradients of Solvent A (98% water, 2% acetonitrile, 0.05% TFA) and Solvent B (98% acetonitrile, 2% water, 0.05% TFA, UV 254 nm).

[00214] Unless otherwise stated, analysis of final products was carried out by reverse phase analytical HPLC using the Waters SunFire column (3.5 μm C18, 3.0 x 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B for 12 min and then 100% Solvent B for 3 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 254 nm). Method B: Agilent ZORBAX® (3.5 μm C18, 4.6 x 75 mm) eluted at 2.5 mL/min with an 8 min gradient from 100% A to 100% B (A: 10% methanol, 89.9% water, 0.1% H_3PO_4; B:

10% water, 89.9% methanol, 0.1% H_3PO_4, UV 220 nm). Method C: Waters SunFire column (3.5 μm C18, 4.6 x 150 mm) eluted at 1mL/min with a gradient from 10-100% Solvent B for 10 min and then 100% Solvent B for 5 min. (A: 0.01 M NH_4HCO_3 in water:methanol 95:5. B: 0.01 M NH_4HCO_3 in water:methanol 5:95. UV 254 nm). Method D: Waters SunFire column (3.5 μm C18, 3.0 x 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B for 10 min and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 254 nm).

IV. BIOLOGY

[00215] While blood coagulation is essential to the regulation of an organism's hemostasis, it is also involved in many pathological conditions. In thrombosis, a blood clot, or thrombus, may form and obstruct circulation locally, causing ischemia and organ damage. Alternatively, in a process known as embolism, the clot may dislodge and subsequently become trapped in a distal vessel, where it again causes ischemia and organ damage. Diseases arising from pathological thrombus formation are collectively referred to as thromboembolic disorders and include acute coronary syndrome, unstable angina, myocardial infarction, thrombosis in the cavity of the heart, ischemic stroke, deep vein thrombosis, peripheral occlusive arterial disease, transient ischemic attack, and pulmonary embolism. In addition, thrombosis occurs on artificial surfaces in contact with blood, including catheters, stents, artificial heart valves, and hemodialysis membranes.

[00216] Some conditions contribute to the risk of developing thrombosis. For example, alterations of the vessel wall, changes in the flow of blood, and alterations in the composition of the vascular compartment. These risk factors are collectively known as Virchow's triad. (*Hemostasis and Thrombosis, Basic Principles and Clinical Practice*, 5th Edition, p. 853, Colman, R.W. et al., eds., Lippincott Williams & Wilkins (2006))

[00217] Antithrombotic agents are frequently given to patients at risk of developing thromboembolic disease because of the presence of one or more predisposing risk factors from Virchow's triad to prevent formation of an occlusive thrombus (primary prevention). For example, in an orthopedic surgery setting (*e.g.*, hip and knee replacement), an antithrombotic agent is frequently administered prior to a surgical

procedure. The antithrombotic agent counterbalances the prothrombotic stimulus exerted by vascular flow alterations (stasis), potential surgical vessel wall injury, as well as changes in the composition of the blood due to the acute phase response related to surgery. Another example of the use of an antithrombotic agent for primary prevention is dosing with aspirin, a platelet activation inhibitor, in patients at risk for developing thrombotic cardiovascular disease. Well recognized risk factors in this setting include age, male gender, hypertension, diabetes mellitus, lipid alterations, and obesity.

[00218] Antithrombotic agents are also indicated for secondary prevention, following an initial thrombotic episode. For example, patients with mutations in Factor V (also known as Factor V Leiden) and additional risk factors (*e.g.*, pregnancy), are dosed with anticoagulants to prevent the reoccurrence of venous thrombosis. Another example entails secondary prevention of cardiovascular events in patients with a history of acute myocardial infarction or acute coronary syndrome. In a clinical setting, a combination of aspirin and clopidogrel (or other thienopyridines) may be used to prevent a second thrombotic event.

[00219] Antithrombotic agents are also given to treat the disease state (*i.e.*, by arresting its development) after it has already started. For example, patients presenting with deep vein thrombosis are treated with anticoagulants (*i.e.*, heparin, warfarin, or LMWH) to prevent further growth of the venous occlusion. Over time, these agents also cause a regression of the disease state because the balance between prothrombotic factors and anticoagulant/profibrinolytic pathways is changed in favor of the latter. Examples on the arterial vascular bed include the treatment of patients with acute myocardial infarction or acute coronary syndrome with aspirin and clopidogrel to prevent further growth of vascular occlusions and eventually leading to a regression of thrombotic occlusions.

[00220] Thus, antithrombotic agents are used widely for primary and secondary prevention (*i.e.*, prophylaxis or risk reduction) of thromboembolic disorders, as well as treatment of an already existing thrombotic process. Drugs that inhibit blood coagulation, or anticoagulants, are "pivotal agents for prevention and treatment of thromboembolic disorders" (Hirsh, J. et al., *Blood*, 105:453-463 (2005)).

[00221] An alternative way of initiation of coagulation is operative when blood is exposed to artificial surfaces (*e.g.*, during hemodialysis, "on-pump" cardiovascular surgery, vessel grafts, bacterial sepsis), on cell surfaces, cellular receptors, cell debris,

DNA, RNA, and extracellular matrices. This process is also termed contact activation. Surface absorption of Factor XII leads to a conformational change in the Factor XII molecule, thereby facilitating activation to proteolytic active Factor XII molecules (Factor XIIa and Factor XIIf). Factor XIIa (or XIIf) has a number of target proteins, including plasma prekallikrein and Factor XI. Active plasma kallikrein further activates Factor XII, leading to an amplification of contact activation. Alternatively, the serine protease prolylcarboxylpeptidase can activate plasma kallikrein complexed with high molecular weight kininogen in a multiprotein complex formed on the surface of cells and matrices (Shariat-Madar et al., *Blood*, 108:192-199 (2006)). Contact activation is a surface mediated process responsible in part for the regulation of thrombosis and inflammation, and is mediated, at least in part, by fibrinolytic-, complement-, kininogen/kinin-, and other humoral and cellular pathways (for review, Coleman, R., "Contact Activation Pathway", *Hemostasis and Thrombosis*, pp. 103-122, Lippincott Williams & Wilkins (2001); Schmaier, A.H., "Contact Activation", *Thrombosis and Hemorrhage*, pp. 105-128 (1998)). The biological relevance of the contact activation system for thromboembolic diseases is supported by the phenotype of Factor XII deficient mice. More specifically, Factor XII deficient mice were protected from thrombotic vascular occlusion in several thrombosis models as well as stroke models and the phenotype of the XII deficient mice was identical to XI deficient mice (Renne et al., *J. Exp. Med.*, 202:271-281 (2005); Kleinschmitz et al., *J. Exp. Med.*, 203:513-518 (2006)). The fact that Factor XI is down-stream from Factor XIIa, combined with the identical phenotype of the XII and XI deficient mice suggest that the contact activation system could play a major role in Factor XI activation *in vivo*.

[00222] Factor XI is a zymogen of a trypsin-like serine protease and is present in plasma at a relatively low concentration. Proteolytic activation at an internal R369-I370 bond yields a heavy chain (369 amino acids) and a light chain (238 amino acids). The latter contains a typical trypsin-like catalytic triad (H413, D464, and S557). Activation of Factor XI by thrombin is believed to occur on negatively charged surfaces, most likely on the surface of activated platelets. Platelets contain high affinity (0.8 nM) specific sites (130-500/platelet) for activated Factor XI. After activation, Factor XIa remains surface bound and recognizes Factor IX as its normal macromolecular substrate. (Galiani, D., *Trends Cardiovasc. Med.*, 10:198-204 (2000))

[00223] In addition to the feedback activation mechanisms described above, thrombin activates thrombin activated fibrinolysis inhibitor (TAFI), a plasma carboxypeptidase that cleaves C-terminal lysine and arginine residues on fibrin, reducing the ability of fibrin to enhance tissue-type plasminogen activator (tPA) dependent plasminogen activation. In the presence of antibodies to FXIa, clot lysis can occur more rapidly independent of plasma TAFI concentration. (Bouma, B.N. et al., *Thromb. Res.*, 101:329-354 (2001).) Thus, inhibitors of Factor XIa are expected to be anticoagulant and profibrinolytic.

[00224] Further evidence for the anti-thromboembolic effects of targeting Factor XI is derived from mice deficient in Factor XI. It has been demonstrated that complete fXI deficiency protected mice from ferric chloride ($FeCl_3$)-induced carotid artery thrombosis (Rosen et al., *Thromb. Haemost.*, 87:774-777 (2002); Wang et al., *J. Thromb. Haemost.*, 3:695-702 (2005)). Also, Factor XI deficiency rescues the perinatal lethal phenotype of complete protein C deficiency (Chan et al., *Amer. J. Pathology*, 158:469-479 (2001)). Furthermore, baboon cross-reactive, function blocking antibodies to human Factor XI protect against baboon arterial – venous shunt thrombosis (Gruber et al., *Blood*, 102:953-955 (2003)). Evidence for an antithrombotic effect of small molecule inhibitors of Factor XIa is also disclosed in published U.S. Patent Application No. 2004/0180855A1. Taken together, these studies suggest that targeting Factor XI will reduce the propensity for thrombotic and thromboembolic diseases.

[00225] Genetic evidence indicates that Factor XI is not required for normal homeostasis, implying a superior safety profile of the Factor XI mechanism compared to competing antithrombotic mechanisms. In contrast to hemophilia A (Factor VIII deficiency) or hemophilia B (Factor IX deficiency), mutations of the Factor XI gene causing Factor XI deficiency (hemophilia C) result in only a mild to moderate bleeding diathesis characterized primarily by postoperative or posttraumatic, but rarely spontaneous hemorrhage. Postoperative bleeding occurs mostly in tissue with high concentrations of endogenous fibrinolytic activity (*e.g.*, oral cavity, and urogenital system). The majority of the cases are fortuitously identified by preoperative prolongation of aPTT (intrinsic system) without any prior bleeding history.

[00226] The increased safety of inhibition of XIa as an anticoagulation therapy is further supported by the fact that Factor XI knock-out mice, which have no detectable Factor XI protein, undergo normal development, and have a normal life span. No

evidence for spontaneous bleeding has been noted. The aPTT (intrinsic system) is prolonged in a gene dose-dependent fashion. Interestingly, even after severe stimulation of the coagulation system (tail transection), the bleeding time is not significantly prolonged compared to wild-type and heterozygous litter mates. (Gailani, D., *Frontiers in Bioscience*, 6:201-207 (2001); Gailani, D. et al., *Blood Coagulation and Fibrinolysis*, 8:134-144 (1997).) Taken together, these observations suggest that high levels of inhibition of Factor XIa should be well tolerated. This is in contrast to gene targeting experiments with other coagulation factors, excluding Factor XII.

[00227] *In vivo* activation of Factor XI can be determined by complex formation with either C1 inhibitor or alpha 1 antitrypsin. In a study of 50 patients with acute myocardial infarction (AMI), approximately 25% of the patients had values above the upper normal range of the complex ELISA. This study can be viewed as evidence that at least in a subpopulation of patients with AMI, Factor XI activation contributes to thrombin formation (Minnema, M.C. et al., *Arterioscler. Thromb. Vasc. Biol.*, 20:2489-2493 (2000)). A second study establishes a positive correlation between the extent of coronary arteriosclerosis and Factor XIa in complex with alpha 1 antitrypsin (Murakami, T. et al., *Arterioscler. Thromb. Vasc. Biol.*, 15:1107-1113 (1995)). In another study, Factor XI levels above the 90th percentile in patients were associated with a 2.2-fold increased risk for venous thrombosis (Meijers, J.C.M. et al., *N. Engl. J. Med.*, 342:696-701 (2000)).

[00228] Plasma kallikrein is a zymogen of a trypsin-like serine protease and is present in plasma at 35 to 50 μg/mL. The gene structure is similar to that of Factor XI. Overall, the amino acid sequence of plasma kallikrein has 58% homology to Factor XI. Proteolytic activation by Factor XIIa at an internal I 389- R390 bond yields a heavy chain (371 amino acids) and a light chain (248 amino acids). The active site of plasma kallikrein is contained in the light chain. The light chain of plasma kallikrein reacts with protease inhibitors, including alpha 2 macroglobulin and C1- inhibitor. Interestingly, heparin significantly accelerates the inhibition of plasma kallikrein by antithrombin III in the presence of high molecular weight kininogen (HMWK). In blood, the majority of plasma kallikrein circulates in complex with HMWK. Plasma kallikrein cleaves HMWK to liberate bradykinin. Bradykinin release results in increase of vascular permeability and vasodilation (for review, Coleman, R., "Contact Activation Pathway", *Hemostasis and*

Thrombosis, pp. 103-122, Lippincott Williams & Wilkins (2001); Schmaier A.H., "Contact Activation", *Thrombosis and Hemorrhage*, pp. 105-128 (1998)).

[00229] Also, it is preferred to find new compounds with improved activity in *in vitro* clotting assays, compared with known serine protease inhibitors, such as the activated partial thromboplastin time (aPTT) or prothrombin time (PT) assay. (for a description of the aPTT and PT assays see, Goodnight, S.H. et al., "Screening Tests of Hemostasis", *Disorders of Thrombosis and Hemostasis: A Clinical Guide*, 2nd Edition, pp. 41-51, McGraw-Hill, New York (2001)).

[00230] It is also desirable and preferable to find compounds with advantageous and improved characteristics compared with known serine protease inhibitors, in one or more of the following categories that are given as examples, and are not intended to be limiting: (a) pharmacokinetic properties, including oral bioavailability, half life, and clearance; (b) pharmaceutical properties; (c) dosage requirements; (d) factors that decrease blood concentration peak-to-trough characteristics; (e) factors that increase the concentration of active drug at the receptor; (f) factors that decrease the liability for clinical drug-drug interactions; (g) factors that decrease the potential for adverse side-effects, including selectivity versus other biological targets; and (h) factors that improve manufacturing costs or feasibility.

[00231] Pre-clinical studies demonstrated significant antithrombotic effects of small molecule Factor XIa inhibitors in rabbit and rat model of arterial thrombosis, at doses that preserved hemostasis. (Wong P.C. et al., *American Heart Association Scientific Sessions*, Abstract No. 6118, November 12-15, 2006; Schumacher, W. et al., *J. Thromb. Haemost.*, 3(Suppl. 1):P1228 (2005); Schumacher, W.A. et al., *Eur. J. Pharmacol.*, 167-174 (2007)). Furthermore, it was observed that *in vitro* prolongation of the aPTT by specific XIa inhibitors is a good predictor of efficacy in our thrombosis models. Thus, the *in vitro* aPTT test can be used as a surrogate for efficacy *in vivo*.

[00232] As used herein, the term "patient" encompasses all mammalian species.

[00233] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting it development; and/or (b) relieving the disease-state, *i.e.*, causing regression of the disease state.

[00234] As used herein, "prophylaxis" or "prevention" cover the preventive treatment of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state.

[00235] As used herein, "risk reduction" covers therapies that lower the incidence of development of a clinical disease state. As such, primary and secondary prevention therapies are examples of risk reduction.

[00236] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit Factor XIa and/or plasma kallikrein and/or to prevent or treat the disorders listed herein. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

[00237] The term "thrombosis", as used herein, refers to formation or presence of a thrombus (pl. thrombi); clotting within a blood vessel that may cause ischemia or infarction of tissues supplied by the vessel. The term "embolism", as used herein, refers to sudden blocking of an artery by a clot or foreign material that has been brought to its site of lodgment by the blood current. The term "thromboembolism", as used herein, refers to obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel. The term "thromboembolic disorders" entails both "thrombotic" and "embolic" disorders (defined above).

[00238] The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular or cerebrovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart or in the peripheral circulation. The term "thromboembolic disorders" as used herein also includes specific disorders selected from, but not limited to, unstable angina or other acute coronary syndromes, atrial fibrillation, first or recurrent myocardial infarction,

ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis. The medical implants or devices include, but are not limited to: prosthetic valves, artificial valves, indwelling catheters, stents, blood oxygenators, shunts, vascular access ports, ventricular assist devices and artificial hearts or heart chambers, and vessel grafts. The procedures include, but are not limited to: cardiopulmonary bypass, percutaneous coronary intervention, and hemodialysis. In another embodiment, the term "thromboembolic disorders" includes acute coronary syndrome, stroke, deep vein thrombosis, and pulmonary embolism.

[00239] In another embodiment, the present invention provides a method for the treatment of a thromboembolic disorder, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, myocardial infarction, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis. In another embodiment, the present invention provides a method for the treatment of a thromboembolic disorder, wherein the thromboembolic disorder is selected from acute coronary syndrome, stroke, venous thrombosis, atrial fibrillation, and thrombosis resulting from medical implants and devices.

[00240] In another embodiment, the present invention provides a method for the primary prophylaxis of a thromboembolic disorder, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is

exposed to an artificial surface that promotes thrombosis. In another embodiment, the present invention provides a method for the primary prophylaxis of a thromboembolic disorder, wherein the thromboembolic disorder is selected from acute coronary syndrome, stroke, venous thrombosis, and thrombosis resulting from medical implants and devices.

[00241] In another embodiment, the present invention provides a method for the secondary prophylaxis of a thromboembolic disorder, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, recurrent myocardial infarction, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis. In another embodiment, the present invention provides a method for the secondary prophylaxis of a thromboembolic disorder, wherein the thromboembolic disorder is selected from acute coronary syndrome, stroke, atrial fibrillation and venous thrombosis.

[00242] The term "stroke", as used herein, refers to embolic stroke or atherothrombotic stroke arising from occlusive thrombosis in the carotid communis, carotid interna, or intracerebral arteries.

[00243] It is noted that thrombosis includes vessel occlusion (*e.g.*, after a bypass) and reocclusion (*e.g.*, during or after percutaneous transluminal coronary angioplasty). The thromboembolic disorders may result from conditions including but not limited to atherosclerosis, surgery or surgical complications, prolonged immobilization, arterial fibrillation, congenital thrombophilia, cancer, diabetes, effects of medications or hormones, and complications of pregnancy.

[00244] Thromboembolic disorders are frequently associated with patients with atherosclerosis. Risk factors for atherosclerosis include but are not limited to male gender, age, hypertension, lipid disorders, and diabetes mellitus. Risk factors for atherosclerosis are at the same time risk factors for complications of atherosclerosis, *i.e.*, thromboembolic disorders.

[00245] Similarly, arterial fibrillation is frequently associated with thromboembolic disorders. Risk factors for arterial fibrillation and subsequent thromboembolic disorders include cardiovascular disease, rheumatic heart disease, nonrheumatic mitral valve disease, hypertensive cardiovascular disease, chronic lung disease, and a variety of miscellaneous cardiac abnormalities as well as thyrotoxicosis.

[00246] Diabetes mellitus is frequently associated with atherosclerosis and thromboembolic disorders. Risk factors for the more common type 2 include but are not limited to are family history, obesity, physical inactivity, race / ethnicity, previously impaired fasting glucose or glucose tolerance test, history of gestational diabetes mellitus or delivery of a "big baby", hypertension, low HDL cholesterol, and polycystic ovary syndrome.

[00247] Risk factors for congenital thrombophilia include gain of function mutations in coagulation factors or loss of function mutations in the anticoagulant- or fibrinolytic pathways.

[00248] Thrombosis has been associated with a variety of tumor types, *e.g.*, pancreatic cancer, breast cancer, brain tumors, lung cancer, ovarian cancer, prostate cancer, gastrointestinal malignancies, and Hodgkins or non-Hodgkins lymphoma. Recent studies suggest that the frequency of cancer in patients with thrombosis reflects the frequency of a particular cancer type in the general population (Levitan, N. et al., *Medicine* (Baltimore), 78(5):285-291 (1999); Levine M. et al., *N. Engl. J. Med.,* 334(11):677-681 (1996); Blom, J.W. et al., *JAMA*, 293(6):715-722 (2005)). Hence, the most common cancers associated with thrombosis in men are prostate, colorectal, brain, and lung cancer, and in women are breast, ovary, and lung cancer. The observed rate of venous thromboembolism (VTE) in cancer patients is significant. The varying rates of VTE between different tumor types are most likely related to the selection of the patient population. Cancer patients at risk for thrombosis may possess any or all of the following risk factors: (i) the stage of the cancer (*i.e.*, presence of metastases), (ii) the presence of central vein catheters, (iii) surgery and anticancer therapies including chemotherapy, and (iv) hormones and antiangiogenic drugs. Thus, it is common clinical practice to dose patients having advanced tumors with heparin or low molecular heparin to prevent thromboembolic disorders. A number of low molecular heparin preparations have been approved by the FDA for these indications.

[00249] There are three main clinical situations when considering the prevention of VTE in a medical cancer patient: (i) the patient is bedridden for prolonged periods of time; (ii) the ambulatory patient is receiving chemotherapy or radiation; and (iii) the patient is with indwelling central vein catheters. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are effective antithrombotic agents in cancer patients undergoing surgery. (Mismetti, P. et al., *Brit. J. Surg.*, 88:913-930 (2001).)

A. *In Vitro* Assays

[00250] The effectiveness of compounds of the present invention as inhibitors of the coagulation Factors XIa, VIIa, IXa, Xa, XIIa, plasma kallikrein or thrombin, can be determined using a relevant purified serine protease, respectively, and an appropriate synthetic substrate. The rate of hydrolysis of the chromogenic or fluorogenic substrate by the relevant serine protease was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA (para nitroaniline), which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm, or the release of AMC (amino methylcoumarin), which was monitored spectrofluorometrically by measuring the increase in emission at 460 nm with excitation at 380 nm. A decrease in the rate of absorbance or fluorescence change in the presence of inhibitor is indicative of enzyme inhibition. Such methods are known to one skilled in the art. The results of this assay are expressed as the inhibitory constant, K_i.

[00251] Factor XIa determinations were made in 50 mM HEPES buffer at pH 7.4 containing 145 mM NaCl, 5 mM KCl, and 0.1% PEG 8000 (polyethylene glycol; JT Baker or Fisher Scientific). Determinations were made using purified human Factor XIa at a final concentration of 25-200 pM (Haematologic Technologies) and the synthetic substrate S-2366 (pyroGlu-Pro-Arg-pNA; CHROMOGENIX® or AnaSpec) at a concentration of 0.0002-0.001 M.

[00252] Factor VIIa determinations were made in 0.005 M calcium chloride, 0.15 M sodium chloride, 0.05 M HEPES buffer containing 0.1 % PEG 8000 at a pH of 7.5. Determinations were made using purified human Factor VIIa (Haematologic Technologies) or recombinant human Factor VIIa (Novo Nordisk) at a final assay concentration of 0.5-10 nM, recombinant soluble tissue factor at a concentration of 10-40

nM and the synthetic substrate H-D-Ile-Pro-Arg-pNA (S-2288; CHROMOGENIX® or BMPM-2; AnaSpec) at a concentration of 0.001-0.0075 M.

[00253] Factor IXa determinations were made in 0.005 M calcium chloride, 0.1 M sodium chloride, 0.0000001 M Refludan (Berlex), 0.05 M TRIS base and 0.5% PEG 8000 at a pH of 7.4. Refludan was added to inhibit small amounts of thrombin in the commercial preparations of human Factor IXa. Determinations were made using purified human Factor IXa (Haematologic Technologies) at a final assay concentration of 20-100 nM and the synthetic substrate PCIXA2100-B (CenterChem) or Pefafluor IXa 3688 (H-D-Leu-Ph'Gly-Arg-AMC; CenterChem) at a concentration of 0.0004-0.0005 M.

[00254] Factor Xa determinations were made in 0.1 M sodium phosphate buffer at a pH of 7.5 containing 0.2 M sodium chloride and 0.5% PEG 8000. Determinations were made using purified human Factor Xa (Haematologic Technologies) at a final assay concentration of 150-1000 pM and the synthetic substrate S-2222 (Bz-Ile-Glu (gamma-OMe, 50%)-Gly-Arg-pNA; CHROMOGENIX®) at a concentration of 0.0002-0.00035 M.

[00255] Factor XIIa determinations were made in 50 mM HEPES buffer at pH 7.4 containing 145 mM NaCl, 5 mM KCl, and 0.1% PEG 8000. Determinations were made using purified human Factor XIIa at a final concentration of 4 nM (American Diagnostica) and the synthetic substrate SPECTROZYME® #312 (H-D-CHT-Gly-L-Arg-pNA.2AcOH; American Diagnostica) at a concentration of 0.00015 M.

[00256] Plasma kallikrein determinations were made in 0.1 M sodium phosphate buffer at a pH of 7.5 containing 0.1-0.2 M sodium chloride and 0.5% PEG 8000. Determinations were made using purified human kallikrein (Enzyme Research Laboratories) at a final assay concentration of 200 pM and the synthetic substrate S-2302 (H-(D)-Pro-Phe-Arg-pNA; CHROMOGENIX®) at a concentration of 0.00008-0.0004 M. The K_m value used for calculation of K_i was 0.00005 to 0.00007 M.

[00257] Thrombin determinations were made in 0.1 M sodium phosphate buffer at a pH of 7.5 containing 0.2 M sodium chloride and 0.5% PEG 8000. Determinations were made using purified human alpha thrombin (Haematologic Technologies or Enzyme Research Laboratories) at a final assay concentration of 200-250 pM and the synthetic substrate S-2366 (pyroGlu-Pro-Arg-pNA; CHROMOGENIX® or AnaSpec) at a concentration of 0.0002-0.0004 M.

[00258] The Michaelis constant, K_m, for substrate hydrolysis by each protease, was determined at 25 °C using the method of Lineweaver and Burk. Values of K_i were determined by allowing the protease to react with the substrate in the presence of the inhibitor. Reactions were allowed to go for periods of 20-180 minutes (depending on the protease) and the velocities (rate of absorbance or fluorescence change versus time) were measured. The following relationships were used to calculate K_i values:

$(v_o-v_s)/v_s = I/(K_i(1 + S/K_m))$ for a competitive inhibitor with one binding site; or

$v_s/v_o = A + ((B-A)/1 + ((IC_{50}/(I)_n)))$; and

$K_i = IC_{50}/(1 + S/K_m)$ for a competitive inhibitor

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

A is the minimum activity remaining (usually locked at zero);

B is the maximum activity remaining (usually locked at 1.0);

n is the Hill coefficient, a measure of the number and cooperativity of potential inhibitor binding sites;

IC_{50} is the concentration of inhibitor that produces 50% inhibition under the assay conditions;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate; and

K_m is the Michaelis constant for the substrate.

[00259] The selectivity of a compound may be evaluated by taking the ratio of the K_i value for a given protease with the K_i value for the protease of interest (*i.e.*, selectivity for FXIa versus protease P = K_i for protease P/ K_i for FXIa). Compounds with selectivity ratios >20 are considered selective. Compounds with selectivity ratios >100 are preferred, and compounds with selectivity ratios > 500 are more preferred.

[00260] The effectiveness of compounds of the present invention as inhibitors of coagulation can be determined using a standard or modified clotting assay. An increase in the plasma clotting time in the presence of inhibitor is indicative of anticoagulation.

Relative clotting time is the clotting time in the presence of an inhibitor divided by the clotting time in the absence of an inhibitor. The results of this assay may be expressed as IC1.5x or IC2x, the inhibitor concentration required to increase the clotting time by 50 or 100 percent, respectively. The IC1.5x or IC2x is found by linear interpolation from relative clotting time versus inhibitor concentration plots using inhibitor concentration that spans the IC1.5x or IC2x.

[00261] Clotting times are determined using citrated normal human plasma as well as plasma obtained from a number of laboratory animal species (*e.g.*, rat, or rabbit). A compound is diluted into plasma beginning with a 10 mM DMSO stock solution. The final concentration of DMSO is less than 2%. Plasma clotting assays are performed in an automated coagulation analyzer (Sysmex, Dade-Behring, Illinois). Similarly, clotting times can be determined from laboratory animal species or humans dosed with compounds of the invention.

[00262] Activated Partial Thromboplastin Time (aPTT) is determined using ALEXIN® (Trinity Biotech, Ireland) or ACTIN® (Dade-Behring, Illinois) following the directions in the package insert. Plasma (0.05 mL) is warmed to 37 °C for 1 minute. ALEXIN® or ACTIN® (0.05 mL) is added to the plasma and incubated for an additional 2 to 5 minutes. Calcium chloride (25 mM, 0.05 mL) is added to the reaction to initiate coagulation. The clotting time is the time in seconds from the moment calcium chloride is added until a clot is detected.

[00263] Prothrombin Time (PT) is determined using thromboplastin (Thromboplastin C Plus, Dade-Behring, Illinois) following the directions in the package insert. Plasma (0.05 mL) is warmed to 37 °C for 1 minute. Thromboplastin (0.1 mL) is added to the plasma to initiate coagulation. The clotting time is the time in seconds from the moment thromboplastin is added until a clot is detected.

[00264] The exemplified Examples disclosed below were tested in the Factor XIa assay described above and found having Factor XIa inhibitory activity. A range of Factor XIa inhibitory activity (Ki values) of ≤ 10 μM (10000 nM) was observed. Table 1 below lists Factor XIa Ki values measured for the following examples.

TABLE 1

Example No.	Factor XIa Ki (nM)
1	2983
3	6174
4	636
6	34
9	249
10	< 5
11	6
19	96
21	4515
61	< 5
89	1057
90	< 5
93	< 5
121	< 5
122	25
136	962
137	192
138	20
167	157
I-4	< 5
I-5	< 5
I-9	1872
I-10	217
I-13	311
I-14	2920
I-17	351
I-21	< 5
I-57	6.6
I-59	< 5

Example No.	Factor XIa Ki (nM)
I-60	616
I-67	203
I-70	270
I-72	289
I-77	< 5
I-80	< 5
I-84	580
I-94	3851
I-99	1322
I-104	435
I-106	24
I-107	29
I-108	3869
I-114	296
I-115	< 5
I-121	736
I-124	< 5
I-134	< 5
I-136	183
I-137	2979
I-151	< 5
I-152	21
I-153	1652
I-183	4949
I-211	2171
I-227	< 5
I-242	456
I-251	< 5
I-258	947
I-262	675

Example No.	Factor XIa Ki (nM)
I-265	133
I-268	9
I-270	1745
I-278	< 5
I-284	102
I-299	19
I-309	9
I-311	< 5
II-3	< 5
II-4	111
II-10	23
II-13	< 5
II-15	4156
II-18	572
II-35	< 5
II-43	938
II-58	21
II-62	< 5

B. *In Vivo* Assays

[00265] The effectiveness of compounds of the present invention as antithrombotic agents can be determined using relevant *in vivo* thrombosis models, including *In Vivo* Electrically-induced Carotid Artery Thrombosis Models and *In Vivo* Rabbit Arterio-venous Shunt Thrombosis Models.

a. *In Vivo* Electrically-induced Carotid Artery Thrombosis (ECAT) Model

[00266] The rabbit ECAT model, described by Wong et al. (*J. Pharmacol. Exp. Ther.*, 295:212-218 (2000)), can be used in this study. Male New Zealand White rabbits are anesthetized with ketamine (50 mg/kg + 50 mg/kg/h IM) and xylazine (10 mg/kg + 10 mg/kg/h IM). These anesthetics are supplemented as needed. An electromagnetic flow

probe is placed on a segment of an isolated carotid artery to monitor blood flow. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to or after the initiation of thrombosis. Drug treatment prior to initiation of thrombosis is used to model the ability of test agents to prevent and reduce the risk of thrombus formation, whereas dosing after initiation is used to model the ability to treat existing thrombotic disease. Thrombus formation is induced by electrical stimulation of the carotid artery for 3 min at 4 mA using an external stainless-steel bipolar electrode. Carotid blood flow is measured continuously over a 90-min period to monitor thrombus-induced occlusion. Total carotid blood flow over 90 min is calculated by the trapezoidal rule. Average carotid flow over 90 min is then determined by converting total carotid blood flow over 90 min to percent of total control carotid blood flow, which would result if control blood flow had been maintained continuously for 90 min. The ED_{50} (dose that increased average carotid blood flow over 90 min to 50% of the control) of compounds are estimated by a nonlinear least square regression program using the Hill sigmoid E_{max} equation (DeltaGraph; SPSS Inc., Chicago, IL).

b. *In Vivo* Rabbit Arterio-venous (AV) Shunt Thrombosis Model

[00267] The rabbit AV shunt model, described by Wong et al. (Wong, P.C. et al., *J. Pharmacol. Exp. Ther.*, 292:351-357 (2000)), can be used in this study. Male New Zealand White rabbits are anesthetized with ketamine (50 mg/kg + 50 mg/kg/h IM) and xylazine (10 mg/kg + 10 mg/kg/h IM). These anesthetics are supplemented as needed. The femoral artery, jugular vein and femoral vein are isolated and catheterized. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of an outer piece of tygon tubing (length = 8 cm; internal diameter = 7.9 mm) and an inner piece of tubing (length = 2.5 cm; internal diameter = 4.8 mm). The AV shunt also contains an 8-cm-long 2-0 silk thread (Ethicon, Somerville, NJ). Blood flows from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread induces the formation of a significant thrombus. Forty minutes later, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID_{50} values (dose that produces

50% inhibition of thrombus formation) are estimated by a nonlinear least square regression program using the Hill sigmoid E_{max} equation (DeltaGraph; SPSS Inc., Chicago, IL).

[00268] The anti-inflammatory effect of these compounds can be demonstrated in an Evans Blue dye extravasation assay using C1-esterase inhibitor deficient mice. In this model, mice are dosed with a compound of the present invention, Evans Blue dye is injected via the tail vein, and extravasation of the blue dye is determined by spectrophotometric means from tissue extracts.

[00269] The ability of the compounds of the current invention to reduce or prevent the systemic inflammatory response syndrome, for example, as observed during on-pump cardiovascular procedures, can be tested in *in vitro* perfusion systems, or by on-pump surgical procedures in larger mammals, including dogs and baboons. Read-outs to assess the benefit of the compounds of the present invention include for example reduced platelet loss, reduced platelet / white blood cell complexes, reduced neutrophil elastase levels in plasma, reduced activation of complement factors, and reduced activation and/or consumption of contact activation proteins (plasma kallikrein, Factor XII, Factor XI, high molecular weight kininogen, C1-esterase inhibitors).

[00270] The compounds of the present invention may also be useful as inhibitors of additional serine proteases, notably human thrombin, human plasma kallikrein and human plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, including blood coagulation, fibrinolysis, blood pressure regulation and inflammation, and wound healing catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity of the aforementioned serine proteases, such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

[00271] The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release

formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00272] The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 18th Edition (1990).

[00273] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the

symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

[00274] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[00275] Compounds of this invention can also be administered by parenteral administration (*e.g.*, intra-venous, intra-arterial, intramuscularly, or subcutaneously. When administered intra-venous or intra-arterial, the dose can be given continuously or intermittent. Furthermore, formulation can be developed for intramuscularly and subcutaneous delivery that ensure a gradual release of the active pharmaceutical ingredient.

[00276] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[00277] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

[00278] 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 lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the

like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. 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, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[00279] The compounds of the present invention 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 phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[00280] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[00281] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 1000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

[00282] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the

like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00283] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00284] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

[00285] Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

[00286] Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to about 100 milligrams of the compound of the present invention and about 0.1 to about 100 milligrams per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to about 100 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to about 50 milligrams per dosage unit.

[00287] Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to about 25 milligrams of the compound of the present invention and about 50 to about 150 milligrams of the anti-platelet agent, preferably about 0.1 to about 1 milligrams of the compound of the present invention and about 1 to about 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

[00288] Where the compounds of the present invention are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to about

1 milligrams of the compound of the present invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 50-80% when administered with a compound of the present invention.

[00289] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00290] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

[00291] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from potassium channel openers, potassium channel blockers, calcium channel blockers, sodium hydrogen exchanger inhibitors, antiarrhythmic agents, antiatherosclerotic agents,

anticoagulants, antithrombotic agents, prothrombolytic agents, fibrinogen antagonists, diuretics, antihypertensive agents, ATPase inhibitors, mineralocorticoid receptor antagonists, phospodiesterase inhibitors, antidiabetic agents, anti-inflammatory agents, antioxidants, angiogenesis modulators, antiosteoporosis agents, hormone replacement therapies, hormone receptor modulators, oral contraceptives, antiobesity agents, antidepressants, antianxiety agents, antipsychotic agents, antiproliferative agents, antitumor agents, antiulcer and gastroesophageal reflux disease agents, growth hormone agents and/or growth hormone secretagogues, thyroid mimetics, anti-infective agents, antiviral agents, antibacterial agents, antifungal agents, cholesterol/lipid lowering agents and lipid profile therapies, and agents that mimic ischemic preconditioning and/or myocardial stunning, or a combination thereof.

[00292] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from an anti-arrhythmic agent, an anti-hypertensive agent, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, a fibrinolytic agent, a calcium channel blocker, a potassium channel blocker, a cholesterol/lipid lowering agent, or a combination thereof.

[00293] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, dipyridamol, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, ximelagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase, or a combination thereof.

[00294] In another embodiment, the present invention provides a pharmaceutical composition wherein the additional therapeutic agent is an antihypertensive agent selected from ACE inhibitors, AT-1 receptor antagonists, beta-adrenergic receptor antagonists, ETA receptor antagonists, dual ETA/AT-1 receptor antagonists, renin inhibitors (alliskerin) and vasopepsidase inhibitors, an antiarrythmic agent selected from IKur inhibitors, an anticoagulant selected from thrombin inhibitors, antithrombin-III activators, heparin co-Factor II activators, other Factor XIa inhibitors, other kallikrein

inhibitors, plasminogen activator inhibitor (PAI-1) antagonists, thrombin activatable fibrinolysis inhibitor (TAFI) inhibitors, Factor VIIa inhibitors, Factor IXa inhibitors, and Factor Xa inhibitors, or an antiplatelet agent selected from GPIIb/IIIa blockers, GP Ib/IX blockers, protease activated receptor 1 (PAR-1) antagonists, protease activated receptor4 (PAR-4) antagonists, prostaglandin E2 receptor EP3 antagonists, collagen receptor antagonists, phosphodiesterase-III inhibitors, $P2Y_1$ receptor antagonists, $P2Y_{12}$ antagonists, thromboxane receptor antagonists, cyclooxygense-1 inhibitors, and aspirin, or a combination thereof.

[00295] In another embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent(s) are an anti-platelet agent or a combination thereof.

[00296] In another embodiment, the present invention provides a pharmaceutical composition, wherein the additional therapeutic agent is the anti-platelet agent clopidogrel.

[00297] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[00298] Compounds that can be administered in combination with the compounds of the present invention include, but are not limited to, anticoagulants, anti-thrombin agents, anti-platelet agents, fibrinolytics, hypolipidemic agents, antihypertensive agents, and anti-ischemic agents.

[00299] Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin, heparin (either unfractionated heparin or any commercially available low molecular weight heparin, for example LOVENOX®), synthetic pentasaccharide, direct acting thrombin inhibitors including hirudin and argatroban, as well as other Factor VIIa inhibitors, Factor IXa inhibitors, Factor Xa inhibitors (*e.g.*, ARIXTRA®, apixaban, rivaroxaban, LY-517717,

DU-176b, DX-9065a, and those disclosed in WO 98/57951, WO 03/026652, WO 01/047919, and WO 00/076970), Factor XIa inhibitors, and inhibitors of activated TAFI and PAI-1 known in the art.

[00300] The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example, by inhibiting the aggregation, adhesion or granule-content secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDs) such as acetaminophen, aspirin, codeine, diclofenac, droxicam, fentaynl, ibuprofen, indomethacin, ketorolac, mefenamate, morphine, naproxen, phenacetin, piroxicam, sufentanyl, sulfinpyrazone, sulindac, and pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDs, aspirin (acetylsalicylic acid or ASA) and piroxicam are preferred. Other suitable platelet inhibitory agents include glycoprotein IIb/IIIa antagonists (*e.g.*, tirofiban, eptifibatide, abciximab, and integrelin), thromboxane-A2-receptor antagonists (*e.g.*, ifetroban), thromboxane-A-synthetase inhibitors, phosphodiesterase-III (PDE-III) inhibitors (*e.g.*, dipyridamole, cilostazol), and PDE-V inhibitors (such as sildenafil), protease-activated receptor 1 (PAR-1) antagonists (*e.g.*, E-5555, SCH-530348, SCH-203099, SCH-529153 and SCH-205831), and pharmaceutically acceptable salts or prodrugs thereof.

[00301] Other examples of suitable anti-platelet agents for use in combination with the compounds of the present invention, with or without aspirin, are ADP (adenosine diphosphate) receptor antagonists, preferably antagonists of the purinergic receptors $P2Y_1$ and $P2Y_{12}$, with $P2Y_{12}$ being even more preferred. Preferred $P2Y_{12}$ receptor antagonists include clopidogrel, ticlopidine, prasugrel, ticagrelor, and cangrelor, and pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine and clopidogrel are also preferred compounds since they are known to be more gentle than aspirin on the gastro-intestinal tract in use. Clopidogrel is an even more preferred agent.

[00302] A preferred example is a triple combination of a compound of the present invention, aspirin, and another anti-platelet agent. Preferably, the anti-platelet agent is clopidogrel or prasugrel, more preferably clopidogrel.

[00303] The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for

example, the aggregation of platelets, and/or the secretion of platelet granule contents including serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin, argatroban, dabigatran, AZD-0837, and those disclosed in WO 98/37075 and WO 02/044145, and pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

[00304] The term thrombolytic (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (TPA, natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK), lanoteplase (nPA), Factor VIIa inhibitors, thrombin inhibitors, inhibitors of Factors IXa, Xa, and XIa, PAI-I inhibitors (*i.e.*, inactivators of tissue plasminogen activator inhibitors), inhibitors of activated TAFI, alpha-2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

[00305] Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors (*e.g.*, pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, and other statins), low-density lipoprotein (LDL) receptor activity modulators (*e.g.*, HOE-402, PCSK9 inhibitors), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), nicotinic acid or derivatives thereof (*e.g.*, NIASPAN®), GPR109B (nicotinic acid receptor) modulators, fenofibric acid derivatives (*e.g.*,

gemfibrozil, clofibrate, fenofibrate and benzafibrate) and other peroxisome proliferator-activated receptors (PPAR) alpha modulators, PPARdelta modulators (*e.g.*, GW-501516), PPARgamma modulators (*e.g.*, rosiglitazone), compounds that have multiple functionality for modulating the activities of various combinations of PPARalpha, PPARgamma and PPARdelta, probucol or derivatives thereof (*e.g.*, AGI-1067), cholesterol absorption inhibitors and/or Niemann-Pick C1-like transporter inhibitors (*e.g.*, ezetimibe), cholesterol ester transfer protein inhibitors (*e.g.*, CP-529414), squalene synthase inhibitors and/or squalene epoxidase inhibitors or mixtures thereof, acyl coenzyme A: cholesteryl acyltransferase (ACAT) 1 inhibitors, ACAT2 inhibitors, dual ACAT1/2 inhibitors, ileal bile acid transport inhibitors (or apical sodium co-dependent bile acid transport inhibitors), microsomal triglyceride transfer protein inhibitors, liver-X-receptor (LXR) alpha modulators, LXRbeta modulators, LXR dual alpha/beta modulators, FXR modulators, omega 3 fatty acids (*e.g.*, 3-PUFA), plant stanols and/or fatty acid esters of plant stanols (*e.g.*, sitostanol ester used in BENECOL® margarine), endothelial lipase inhibitors, and HDL functional mimetics which activate reverse cholesterol transport (*e.g.*, apoAI derivatives or apoAI peptide mimetics).

[00306] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein. XIa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimentor that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

[00307] The compounds of the present invention may also be used in diagnostic assays involving thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein. For example, the presence of thrombin, Factor VIIa, IXa, Xa XIa, and/or plasma kallikrein in an unknown sample could be determined by addition of the relevant chromogenic substrate, for example S2366 for Factor XIa, to a series of solutions containing test sample and

optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude Factor XIa was present.

[00308] Extremely potent and selective compounds of the present invention, those having K_i values less than or equal to 0.001 μM against the target protease and greater than or equal to 0.1 μM against the other proteases, may also be used in diagnostic assays involving the quantitation of thrombin, Factor VIIa, IXa, Xa, XIa, and/or plasma kallikrein in serum samples. For example, the amount of Factor XIa in serum samples could be determined by careful titration of protease activity in the presence of the relevant chromogenic substrate, S2366, with a potent and selective Factor XIa inhibitor of the present invention.

[00309] The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic and/or inflammatory disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat a thromboembolic and/or inflammatory disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

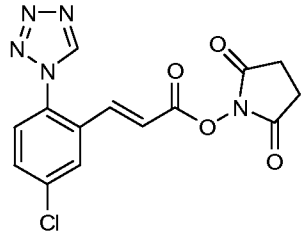
[00310] The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

[00311] The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

[00312] The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

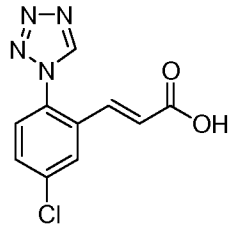
[00313] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof. The following Examples have been prepared, isolated and characterized using the methods disclosed herein.

Intermediate 1. (E)-2,5-Dioxopyrrolidin-1-yl 3-(5-chloro-2-(1H-tetrazol-1-yl)phenyl)acrylate



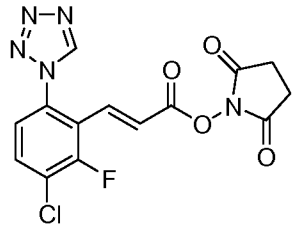
[00314] The synthesis was described as Intermediate 1 in PCT International Application No. WO 2009/114677 published 09/17/2009.

Intermediate 2. (E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acrylic acid



[00315] The synthesis was described as Intermediate 1B in PCT International Application No. WO 2009/114677 published 09/17/2009.

Intermediate 3. (E)-3-(3-Chloro-2-fluoro-6-tetrazol-1-yl-phenyl)-acrylic acid 2,5-dioxo-pyrrolidin-1-yl ester

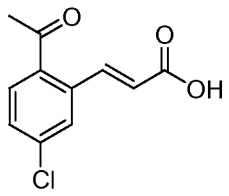


[00316] Intermediate 3A. (E)-3-(3-Chloro-2-fluoro-6-(1H-tetrazol-1-yl)phenyl)acrylic acid: The synthesis of Intermediate 3A was described as Intermediate 7 in PCT International Application No. WO 2009/114677 published 09/17/2009.

[00317] Intermediate 3. To a slightly turbid mixture of Intermediate 3A (1.0 g, 3.72 mmol) in THF (18.70 mL) and DMF (1.870 mL) was added 1-hydroxypyrrolidine-2,5-dione (0.471 g, 4.09 mmol) and DIC (0.638 mL, 4.09 mmol). The reaction was stirred at rt and a white precipitate formed overtime. The solid was collected by suction filtration

and washed with MeOH, water, MeOH, air-dried, and dried under vacuum to give Intermediate 3 (0.98 g, 72.0 % yield), as a white solid. MS (ESI) *m/z*: 366.2 $(M+H)^+$.

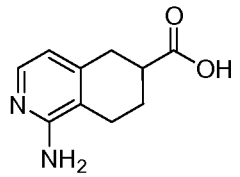
Intermediate 4. (E)-3-(2-Acetyl-5-chlorophenyl)acrylic acid



[00318] Intermediate 4A. (E)-*tert*-Butyl 3-(2-acetyl-5-chlorophenyl)acrylate: To a degassed solution of 1-(2-bromo-4-chlorophenyl)ethanone (1.0 g, 4.28 mmol), tributylamine (2.041 mL, 8.57 mmol), and *tert*-butyl acrylate (1.255 mL, 8.57 mmol) in DMF (10 mL) was added palladium on carbon (0.456 g, 0.428 mmol) and palladium(II) acetate (0.096 g, 0.428 mmol). The reaction mixture was warmed to 100°C. After 16 h, the reaction was cooled to rt. The reaction was filtered and the solid was rinsed with DMF. The filtrate was diluted with EtOAc, washed with water (2x), brine, dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography afforded Intermediate 4A (0.760 g, 63%), as a brown oil. MS (ESI) *m/z*: 225.0 $(M-C_4H_8+H)^+$.

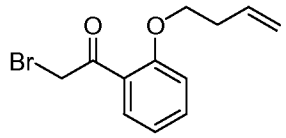
[00319] Intermediate 4. A solution of Intermediate 4A (0.048 g, 0.171 mmol) in 50% TFA/DCM (2 mL) was stirred at rt. After 1h, the reaction was concentrated to give Intermediate 4 (0.038 g, 100 % yield) as a yellow solid. The material was used without further purification. MS (ESI) *m/z*: 225.1 $(M+H)^+$.

Intermediate 5. 1-Amino-5,6,7,8-tetrahydroisoquinoline-6-carboxylic acid



[00320] The synthesis was described as Example 147, Part E in U.S. Patent Application No. 2005/0282805 published 12/22/2005.

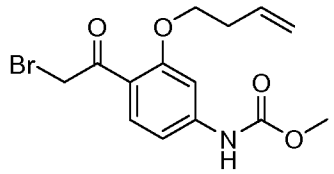
Intermediate 6. 2-Bromo-1-(2-(but-3-enyloxy)phenyl)ethanone



[00321] Intermediate 6A. 1-(2-But-3-enyloxy-phenyl)-ethanone: To a white suspension of potassium carbonate (15.2 g, 110 mmol) in acetone (29.4 mL) was added 5-bromobut-1-ene (3.73 mL, 36.7 mmol) and 1-(2-hydroxyphenyl)ethanone (4.42 mL, 36.7 mmol). The resulting off-white suspension was warmed to reflux and stirred overnight. The reaction was cooled to rt, filtered and the filtrate was concentrated. The residue was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave 1.12 g (15%) of Intermediate 6A, as a dark purple oil. MS (ESI) *m/z*: 205.2 $(M+H)^+$.

[00322] Intermediate 6. A suspension of Intermediate 6A (1.1153 g, 5.86 mmol) and copper (II) bromide (2.62 g, 11.73 mmol) in EtOAc (10.47 mL) was warmed to reflux. After 1 h, the suspension was cooled to rt, filtered, and the filtrate was concentrated to give a greenish-brown residue. The greenish-brown residue was taken up in EtOAc (100 mL) and washed with water (2 x 100mL). The organic layer was then washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by normal phase chromatography gave 0.773 g (44%) of Intermediate 6, as a yellow oil. MS (ESI) *m/z*: 271.1 $(M+H)^+$.

Intermediate 7. Methyl 4-(2-bromoacetyl)-3-(but-3-enyloxy)phenylcarbamate



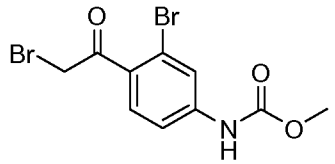
[00323] Intermediate 7A. 1-(4-Amino-2-(but-3-enyloxy)phenyl)ethanone: A suspension of 1-(4-amino-2-hydroxyphenyl)ethanone (3 g, 19.85 mmol), 4-bromobut-1-ene (6.04 mL, 59.5 mmol) and K_2CO_3 (16.46 g, 119 mmol) in acetone (30 mL) was heated in a sealed tube at 60 °C. After 18 h, another 2 eq. of 4-bromobut-1-ene was

added and the reaction was heated at 60 °C for 18 h. This process was repeated one more time, and the reaction was cooled to rt, diluted with EtOAc, washed with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography afforded 1.055 g (14.24 %) of Intermediate 7A, as a yellow solid. MS (ESI) *m/z*: 206.0 $(M+H)^+$.

[00324] Intermediate 7B. Methyl 4-acetyl-3-(but-3-enyloxy)phenylcarbamate: To a cooled (0 °C), clear yellow solution of Intermediate 7A (1.055 g) in DCM (9.42 mL) and pyridine (0.252 mL, 3.11 mmol) was added dropwise methyl chloroformate (0.230 mL, 2.97 mmol). The resulting yellow suspension was stirred at 0 °C for 2 h. The reaction was partitioned between EtOAc/sat. sodium bicarbonate and the layers were separated. The aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give a yellow solid. The solid was purified by trituration from DCM. The solid was collected via Buchner funnel filtration and rinsed with DCM (3 x 2 mL), air-dried, and dried under vacuum to give 0.91 g of Intermediate 7B as a white solid. MS (ESI) *m/z*: 264.0 $(M+H)^+$.

[00325] Intermediate 7 was prepared following the procedure described in Intermediate 6, by replacing Intermediate 6A with Intermediate 7B. The material was used without further purification. MS (ESI) *m/z*: 341.9 $(M+H)^+$ and 343.9 $(M+2+H)^+$.

Intermediate 8. [3-Bromo-4-(2-bromo-acetyl)-phenyl]-carbamic acid methyl ester



[00326] Intermediate 8A. 1-(4-Amino-2-bromophenyl)ethanone: (**Caution, possible explosion hazard!**) A clear, colorless solution of 1-(2-bromo-4-fluorophenyl)ethanone (22.8 g, 0.105 mol) in DMSO (105 mL) and ammonium hydroxide (68.2 mL, 0.526 mol) was divided into nineteen 20-mL microwave vials. The vials were sealed, microwaved at 150 °C for 1.5 h, and then cooled to rt. All the reactions were combined, partitioned between DCM and water (400 mL) and the layers were separated. The aqueous layer was extracted with DCM (2x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give 35g of Intermediate 8A as an

orange oil. The material was carried onto the next step without further purification. MS (ESI) *m/z*: 212.4 $(M+H)^+$ and 214.4 $(M+2+H)^+$.

[00327] Intermediate 8 was prepared following the procedures described in Intermediate 7, by replacing Intermediate 7A with Intermediate 8A. MS (ESI) *m/z*: 352.1 $(M+H)^+$ and 354.1 $(M+2+H)^+$.

An alternative preparation of Intermediate 8 is highlighted below:

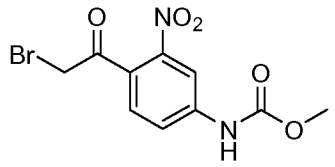
[00328] Alternative Intermediate 8A. 1-(4-Amino-2-bromophenyl)ethanone: To a solution of Intermediate 10C (19 g, 0.077 mol) in ethanol (400 mL) was added in portions tin(II) chloride (74 g, 0.39 mol). Following the addition, the reaction was heated to reflux overnight. The reaction was concentrated and the residue was dissolved in 10% aq. sodium hydroxide (200 mL). The solution was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine and concentrated to afford an oil. Petroleum ether (25 mL) was added to give a suspension. The petroleum ether was decanted and the solid was suspended in 20% ethyl acetate/petroleum ether. The solid was collected to afford 14 g of Intermediate 8A.

[00329] Alternative Intermediate 8B. (4-Acetyl-3-bromo-phenyl)-carbamic acid methyl ester: To a cooled (10 °C) mixture of alternative Intermediate 8A (14g, 0.065 mol) and Hunig's base (12.7 g, 0.098 mol) in dry dioxane (140 mL) was added dropwise methyl chloroformate (7.4 g, 0.078 m). After 3 h, the reaction was quenched with water (100 mL) and then extracted with ethyl acetate (2 x150 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification by trituration from isopropanol provided 14 g of the alternative Intermediate 8B. MS (ESI) *m/z*: 271.7 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.50 (s, 3H), 3.71 (s, 3H), 7.53 – 7.56 (m, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 10.14 (s, 1H).

[00330] Alternative Intermediate 8. To a cooled (10 °C) solution of alternative Intermediate 8B (90 g, 0.33 mol) in dry dioxane (900 mL) was added a solution of bromine (52.9 g, 0.33 mol) in dioxane (430 mL) dropwise over 1h. After 2h, ice cold water (500 mL) was added and the reaction was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to afford 110 g of crude product. A suspension of the crude

product in ethanol (1L) was warmed to 50 °C. After a clear solution formed, water (1.0 L) was added dropwise and the mixture was gradually cooled to 35 °C. The precipitated solid was collected by filtration, washed with ethanol (200 mL), air-dried, and then dried at 50 °C under vacuum for 30 min to yield 70 g of alternative Intermediate 8.

Intermediate 9. Methyl 4-(2-bromoacetyl)-3-nitrophenylcarbamate



[00331] Intermediate 9A. Methyl 4-iodo-3-nitrophenylcarbamate: To a cooled (0 °C), yellow suspension of 4-iodo-3-nitroaniline (8.46 g, 32.0 mmol) in DCM (320 mL) and pyridine (2.85 mL, 35.2 mmol) was added dropwise methyl chloroformate (2.61 mL, 33.6 mmol). The resulting clear, light yellow solution was stirred at 0 °C. After 1.5 h, the reaction was diluted with DCM, washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in a minimal amount of DCM (~100 mL) and then hexane (600mL) was added to give a yellow suspension. The suspension was filtered, and the solid was rinsed with hexane and then dried to give Intermediate 9A (10.3 g, 100 %), as yellow solid. MS (ESI) *m/z*: 321.3 $(M-H)^-$.

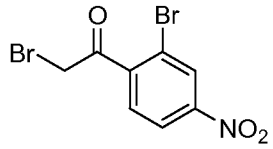
[00332] Intermediate 9B. Methyl 4-(1-ethoxyvinyl)-3-nitrophenylcarbamate: A solution of Intermediate 9A (6 g, 18.63 mmol), tributyl(1-ethoxyvinyl)stannane (7.55 mL, 22.36 mmol), and bis(triphenylphosphine)palladium(II) chloride (0.654 g, 0.932 mmol) in toluene (37.3 mL) was heated at 110 °C. After 2h, the reaction was cooled to rt. The reaction mixture was filtered through a 0.45 micron GMF, rinsing with EtOAc. The filtrate was concentrated. Purification by normal phase chromatography gave Intermediate 9B (3.59 g, 72.4 % yield), as a brown solid. MS (ESI) *m/z*: 267.4 $(M+H)^+$.

[00333] Intermediate 9. To a slightly cloudy orange mixture of Intermediate 9B (3.59 g, 13.48 mmol) in THF (20 mL) and water (7 mL) was added NBS (2.400 g, 13.48 mmol). The resulting clear, yellow solution was stirred at rt for 20 min and then the reaction was partitioned between EtOAc/brine. The layers were separated and the organic layer washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford

Intermediate 9 (4.28 g, 100 % yield), as a yellow foam. This material was used without further purification. MS (ESI) *m/z*: 317.3 $(M+H)^+$, 319.3 $(M+2+H)^+$.

[00334] Alternatively, Intermediate 9B can be hydrolyzed with aqueous 1N HCl to give the methyl ketone which can then be brominated with copper (II) bromide according to the procedure described in Intermediate 6.

Intermediate 10. 2-Bromo-1-(2-bromo-4-nitrophenyl)ethanone



[00335] Intermediate 10A. 2-Bromo-4-nitro-benzoic acid**:** To a warm (80 °C) solution of pyridine (500 mL) and water (1.0 L) was added 4-nitro-2-bromo toluene (100 g, 0.46 mol). The resulting suspension was stirred until it became a clear solution. Next, $KMnO_4$ (600 g, 3.8 mol) was added in portions over 1.5 h. The reaction was stirred overnight. The reaction mixture was cooled to RT and then 10% aq. sodium hydroxide (200 mL) was added. After 15 min, the reaction was filtered to remove the solid. The solid was rinsed with 10% aq. sodium hydroxide (5 x 100 mL). The filtrate was extracted with MTBE (3 x 250 mL). The clear aqueous layer was cooled to 10 °C and then it was acidified with concentrated HCl. The aqueous layer was extracted with MTBE (4 x 500 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated to afford 72 g of Intermediate 10A. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.96 (d, J = 8 Hz, 1H), 8.28 – 8.48 (m, 1H), 8.49 (d, J = 2.4 Hz, 1H), 14.1 (br. s, 1H).

[00336] Intermediate 10B. 2-(2-Bromo-4-nitro-benzoyl)-malonic acid diethyl ester: To a solution of Intermediate 10A (50 g, 0.2 mol) in toluene (500 mL) was added triethylamine (24.6 g, 0.24 mol). The reaction was cooled to 15 °C and ethyl chloroformate (24 g, 0.22 mol) was added. After 45 min, the mixed anhydride solution was cooled to 0 °C.

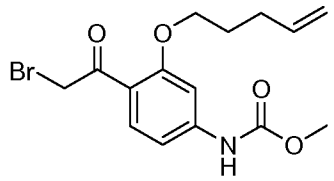
[00337] In a separate flask: To a suspension of Mg turnings (5.4 g) in dry ether (300 mL) was added ethanol (3.0 mL), carbon tetrachloride (2.0 mL), and diethyl malonate (34 mL, 0.22 mol). The mixture was stirred at 40 °C for an hour to ensure that the magnesium dissolved completely. After the reaction became a clear solution, it was

added to the cooled solution of the mixed anhydride. After 2 h, the reaction was quenched with 2N sulfuric acid (200 mL) and then extracted with ethyl acetate (4 X 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give 80 g of Intermediate 10B. This was used in the next step without further purification.

[00338] Intermediate 10C. 1-(2-Bromo-4-nitro-phenyl)-ethanone**:** A mixture of Intermediate 10B (80 g, 0.2 mol) in acetic acid (400 mL) and sulfuric acid (400 mL) was stirred at 105 °C. After 3h, the reaction was cooled to RT and then extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with 20% aq. sodium hydroxide, dried over sodium sulfate, filtered and concentrated to give 43.0 g of Intermediate 10C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.66 (s, 3H), 7.57 (d, J = 8 Hz, 1H), 8.21 – 8.24 (dd, 1H), 8.48 (d, J = 2.0 Hz, 1H).

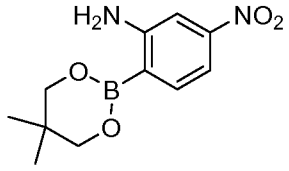
[00339] Intermediate 10. To a cooled (10 °C) solution of the Intermediate 10C (43 g, 0.17 mol) in dry dioxane (430 mL) was added a dropwise over 1.5 h a solution of bromine (31 g) in dioxane (430 mL). The reaction was stirred for 30 min and then ice cold water (150 mL) was added. The reaction was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography (petroleum ether/ethyl acetate) gave 30 g of Intermediate 10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H), 7.62 (d, J = 8.4 Hz, 1H), 8.25 – 8.27 (dd, 1H), 8.50 (d, J = 2.4 Hz, 1H).

Intermediate 11. Methyl 4-(2-bromoacetyl)-3-(pent-4-enyloxy)phenylcarbamate



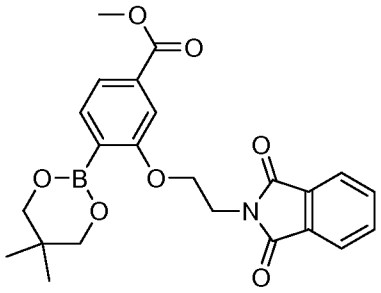
[00340] This compound was prepared following the procedures described in Intermediate 7, by replacing 4-bromobut-1-ene with 5-bromopent-1-ene. MS (ESI) *m/z*: 355.9 $(M+H)^+$, 357.9 $(M+2+H)^+$.

Intermediate 12. 2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-5-nitro-phenylamine



[00341] To a flame-dried flask, equipped with a reflux condensor, containing 2-bromo-5-nitroaniline (10.0 g, 46.1 mmol), bis(neopentyl glycolato)diboron (13.01 g, 57.6 mmol), potassium acetate (13.57 g, 138 mmol), and $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.941 g, 1.152 mmol) was added DMSO (132 mL). The resulting dark red-brown suspension was degassed with argon for 30 min. and then the reaction was warmed to 80 °C. After 4 h, the reaction was stopped and cooled to rt. The reaction was poured slowly into vigorously stirred ice-cold water (300 mL) to give a brown suspension. After stirring for 10 min, the suspension was filtered to collect the solid. The solid was rinsed with water (3 x 125 mL), air-dried, and then dried under a vacuum to give a brown solid. Purification by normal phase chromatography gave 4.36 g of Intermediate 12 as an orange solid. MS (ESI) *m/z*: 183.1 $(M\text{-}C_5H_8+H)^+$.

Intermediate 13. 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-benzoic acid methyl ester

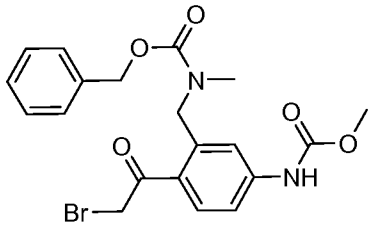


[00342] Intermediate 13A. 4-Bromo-3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-benzoic acid methyl ester: To a solution of methyl 4-bromo-3-hydroxybenzoate (2.0 g, 8.66 mmol) and 2-(2-bromoethyl)isoindoline-1,3-dione (2.419 g, 9.52 mmol) in DMF (10 mL) was added NaH (0.866 g, 21.64 mmol) in small portions at 0 °C. The reaction was stirred under argon at 0 °C for 2 h. The reaction was warmed to 60 °C and stirred for 4 h. After cooling to rt, the reaction mixture was diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave

Intermediate 13A (0.36 g, 10.3 % yield) as a white solid. MS (ESI) *m/z*: 404.0/406.0 $(M+H)^+$.

[00343] Intermediate 13 was prepared following the procedure described in Intermediate 12, by replacing 2-bromo-5-nitroaniline with Intermediate 13A and running the reaction in acetonitrile at 90 °C. MS (ESI) *m/z*: 352.1 $(M+H)^+$.

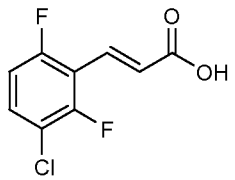
Intermediate 14. [3-[(Benzyloxycarbonyl-methyl-amino)-methyl]-4-(2-bromo-acetyl)-phenyl]-carbamic acid methyl ester



[00344] Intermediate 14A. Benzyl 5-amino-2-bromobenzyl(methyl)carbamate: To a mixture of benzyl 2-bromo-5-nitrobenzyl(methyl)carbamate (3.0 g, 7.91 mmol) in MeOH (60 mL) was added ammonium chloride (2.116 g, 39.6 mmol) and zinc (2.59 g, 39.6 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred under argon for 3 h. The solid was filtered off and the solvent was removed to give Intermediate 14A (2.72 g, 98 % yield) as a light tan solid. MS (ESI) *m/z*: 350.8 $(M+H)^+$.

[00345] Intermediate 14 was prepared following the procedures described in Intermediate 9, by replacing 4-iodo-3-nitroaniline with Intermediate 14A. MS (ESI) *m/z*: 449.0 $(M+H)^+$.

Intermediate 15. (E)-3-(3-Chloro-2,6-difluoro-phenyl)-acrylic acid



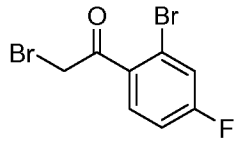
[00346] Intermediate 15A. 3-Chloro-2,6-difluorobenzaldehyde: To a solution of (3-chloro-2,6-difluorophenyl)methanol (1.07 g, 5.99 mmol) in CH_2Cl_2 (20 ml) was added Dess-Martin periodinane (3.05 g, 7.19 mmol). After 2h, the reaction was concentrated.

Purification by normal phase chromatography gave Intermediate 15A (0.94 g, 89 % yield), as a white solid. MS (ESI) *m/z*: 177.1 $(M+H)^+$.

[00347] Intermediate 15B. (E)-*tert*-Butyl 3-(3-chloro-2,6-difluorophenyl)acrylate: To a solution of Intermediate 15A (0.94 g, 5.32 mmol) in THF (30 ml) were added *tert*-butyl 2-(dimethoxyphosphoryl)acetate (1.194 g, 5.32 mmol) and KO^tBu (0.896 g, 7.99 mmol). After 2h, the reaction was diluted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography provided Intermediate 15B (0.866 g, 59.2 % yield), as a clear colorless oil. MS (ESI) *m/z*: 219.2 $(M-^tBu+H)^+$.

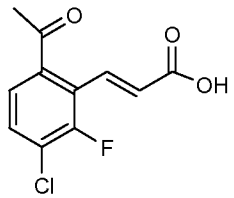
[00348] Intermediate 15. To a solution of Intermediate 15B (0.866 g, 3.15 mmol) in DCM (7.0 ml) was added TFA (3.0 mL, 38.9 mmol). After 1.5 h, the reaction was concentrated and the residue was dried *in vacuo* to give Intermediate 15 (0.689 g, 100 % yield) as an off-white solid. MS (ESI) *m/z*: 219.1 $(M+H)^+$.

Intermediate 17. 2-Bromo-1-(2-bromo-4-fluoro-phenyl)-ethanone



[00349] The synthesis was described as Method A-1, Page 92 in PCT International Application No. WO 2005/014566 published 02/17/2005.

Intermediate 18. (E)-3-(6-Acetyl-3-chloro-2-fluoro-phenyl)-acrylic acid



[00350] Intermediate 18A. 2-Bromo-4-chloro-3-fluorobenzoic acid: To a cooled (-78 °C) solution of DIEA (4.9 mL, 48 mmol) in THF was added dropwise n-BuLi (132 mL, 2.3 eq, 2.5 M solution). The mixture was stirred at -30 °C for 30 min. Again the reaction mixture was cooled to -78 °C, and a solution of 4-chloro-3-fluorobenzoic acid (25 g, 143 mmol) in THF was added over 1 h. The reaction was stirred at -78 °C overnight. The next

day a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (87 g, 267 mmol) in THF was added and the reaction was stirred at -78 °C for further 2 h and then RT for 4 h. The reaction mixture was quenched with water, the layers were separated, and the aqueous layer washed with Et_2O. The aqueous layer was acidified with 1.5N HCl and then extracted in EtOAc (2 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford Intermediate 18A (30 g, 83.3%). MS (ESI) *m/z*: 252.6 $(M-H)^+$.

[00351] Intermediate 18B. Diethyl 2-((2-bromo-4-chloro-3-fluorophenyl) (hydroxy)methylene)malonate: To a suspension of Intermediate 18A (14.6 g, 57 mmol) in DCM (200 mL) was added thionyl chloride (6.6 mL, 88 mmol). The mixture was stirred at reflux for 3 h. The solvent was removed and the residue was dried in vacuum to give the acid chloride as a light brown solid.

[00352] To a cooled (0 °C) suspension of sodium hydride (3.66 g (60%), 91.5 mmol) in THF was added a solution of diethyl malonate (0.612 g, 3.82 mmol) in THF (5 mL). After 10 min, a solution of the acid chloride (16.4 g, 60 mmol) in THF (160 mL) was added slowly. Following the addition, the reaction was warmed to RT. After 30 min, the solvent was removed and the residue was treated with cold (0 °C) 1.2 M HCl (150 mL). The mixture was extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give Intermediate 18B (20 g, 87%) as a solid. MS (ESI) *m/z*: 395/397 $(M+H)^+$.

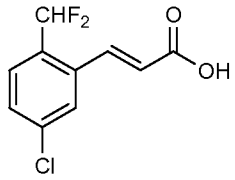
[00353] Intermediate 18C. 1-(2-Bromo-4-chloro-3-fluorophenyl)ethanone: A solution of Intermediate 18B (18.6 g, 47 mmol) in acetic acid (200 mL), H_2O (150 mL) and H_2SO_4 (2.0 mL) was stirred at 110 °C for 4 h. Most of the solvent was removed and the residue was diluted with EtOAc (400 mL), washed with water (5 x 20 mL), saturated $NaHCO_3$, 1N NaOH, and brine. The solvent was removed to give Intermediate 18C (10 g, 84%) as a low melting solid. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.42 (q, J = 6.8, 6.4 Hz, 1 H), 7.24 (q, J = 6.4, 5.2 Hz, 1 H), 2.5 (s, 3H).

[00354] Intermediate 18D. (E)-*tert*-Butyl 3-(6-acetyl-3-chloro-2-fluorophenyl)acrylate: To the mixture of Intermediate 18C (50 g, 198 mmol), *tert*-butyl acrylate (50.9 g, 397 mmol) and TEA (55 mL, 397 mmol) in DMF (500 mL) was added $Pd(OAc)_2$ (8.9 g, 39.7 mmol). The resulting mixture was stirred at 90 °C overnight. The

reaction was cooled to RT, filtered, and the filtrate was concentrated. Purification by normal phase chromatography gave Intermediate 18D (30 g, 50.8%) as a light yellow solid. MS (ESI) *m/z*: 242.7 $(M+H)^+$.

[00355] Intermediate 18. A solution of Intermediate 18D (25 g, 84 mmol) in DCM (330 mL) and TFA (330 mL) was stirred at RT. After 1.5 h, the solvent was concentrated to give Intermediate 18 (19.5 g, 97.0) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.69 (bs, 1 H), 7.80-7.76 (m, 2 H), 7.62 (d, J = 12.1 Hz, 1 H), 6.30 (dd, J =2.4, 2.0 Hz, 1 H), 2.6 (s, 3H). MS (ESI) *m/z*: 241 $(M-H)^+$.

Intermediate 19. (E)-3-(5-Chloro-2-(difluoromethyl)phenyl)acrylic acid



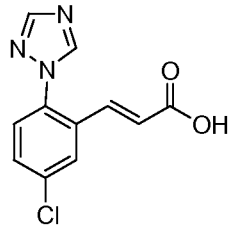
[00356] Intermediate 19A. 2-Bromo-4-chloro-1-(difluoromethyl)benzene: To a solution of 2-bromo-4-chlorobenzaldehyde (1 g, 4.56 mmol) in DCM (15 mL) was added DAST (0.903 mL, 6.83 mmol) at 0 °C. The reaction was allowed to warm to rt and stir overnight. The reaction mixture was diluted with EtOAc, washed with sat $NaHCO_3$ and brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to give Intermediate 19A (0.88g. 80% yield) as a clear oil. MS (ESI) *m/z*: 261.2 $(M+Na)^+$.

[00357] Intermediate 19B. (E)-*tert*-Butyl 3-(5-chloro-2-(difluoromethyl)phenyl)acrylate: To a solution of Intermediate 19A (0.88 g, 3.64 mmol) in DMF (10 mL) was added *tert*-butyl acrylate (1.401 g, 10.93 mmol), TEA (1.270 mL, 9.11 mmol) and palladium acetate (0.082 g, 0.364 mmol). The reaction was warmed to 90 °C. After 5h, the reaction was cooled to rt and then filtered to remove the solid. The filtrate was diluted with EtOAc, washed with 1M HCl, sat $NaHCO_3$ and brine. The organic phase was dried over magnesium sulfate, filtered and concentrated. Purification by normal phase chromatography gave Intermediate 19B (232 mg, 22 % yield) as a tan oil. MS (ESI) *m/z*: 233.1$(M-tBu)^+$.

[00358] Intermediate 19. A solution of Intermediate 19B (232 mg, 0.804 mmol) in DCM (2.0 mL) was added TFA (2.0 mL, 26.0 mmol). The reaction was stirred under

argon at rt. After 1h, the solvent was removed and the residue was dried to give Intermediate 19 (191mg, 100 % yield) as tan solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (dt, *J* = 15.8, 1.5 Hz, 1H), 7.83 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.55 - 7.48 (m, 1H), 7.01 (t, *J* = 54.6 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -111.67 (s, 2F). MS (ESI) *m/z*: 233.1$(M+H)^+$.

Intermediate 20. (E)-3-(5-Chloro-2-(1H-1,2,4-triazol-1-yl)phenyl)acrylic acid



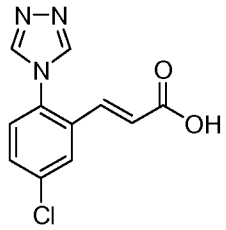
[00359] Intermediate 20A. 5-Chloro-2-(1H-1,2,4-triazol-1-yl)benzaldehyde: A mixture of 5-chloro-2-fluorobenzaldehyde (0.634 g, 4 mmol), 1H-1,2,4-triazole (0.290 g, 4.20 mmol), and cesium carbonate (1.564 g, 4.80 mmol) in DMF (6 mL) was stirred at 50 °C. After 20 h, the reaction was cooled to RT, partitioned between water and EtOAc and the layers were separated. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was suspended in DCM (5 mL) and then it was filtered. The solid was washed with hexane, air-dried, and dried under vacuum to give 0.22 g (26.5 %) of Intermediate 20A, as a yellow solid. MS (ESI) *m/z*: 208.1 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 8.2 Hz, 1 H), 7.72 (dd, J = 2.2 Hz, 8.2 Hz, 1 H), 8.06 (d, J = 2.2 Hz, 1 H), 8.20 (s, 1 H), 8.48 (s, 1 H), 9.99 (s, 1 H).

[00360] Intermediate 20B. (E)-*tert*-Butyl 3-(5-chloro-2-(1H-1,2,4-triazol-1-yl)phenyl)acrylate: To a suspension of NaH (60%, 0.100 g, 2.495 mmol) in THF (4 mL) was added dropwise *tert*-butyl 2-(dimethoxyphosphoryl)acetate (0.530 mL, 2.67 mmol). The cloudy reaction mixture was stirred at RT for 45 min and then cooled to 0 °C. Next a solution of Intermediate 20A (0.37 g, 1.78 mmol) in THF (14 mL) was added. The reaction mixture turned orange. After 30 min, the reaction was quenched with saturated NH_4Cl and then the reaction was diluted with EtOAc and water. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography afforded 0.178 g (26 %) of

Intermediate 20B, as a yellow gum. MS (ESI) *m/z*: 306.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 6.38 (d, *J*=15.9 Hz, 1 H), 7.34 - 7.42 (m, 2 H), 7.48 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.73 (d, *J*=2.2 Hz, 1 H), 8.17 (s, 1 H), 8.29 (s, 1 H).

[00361] Intermediate 20. To a solution of Intermediate 20B (0.178 g, 0.582 mmol) in DCM (1 ml) was added TFA (1 ml, 12.98 mmol). The reaction mixture was stirred at rt for 1 h and then it was concentrated to dryness. MeOH (3 mL) was added to give a white suspension. The solid was collected by filtration, rinsing with a small amount of methanol. The solid was air-dried and dried under vacuum to give 0.076 g (52%) of Intermediate 20 as a white solid. MS (ESI) *m/z*: 250.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 6.65 (d, 15.9 Hz, 1 H), 7.21 (d, 15.9 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.68 (dd, J = 2.2 Hz, 8.2 Hz, 1 H), 8.16 (d, J = 2.2 Hz, 1 H), 8.32 (s, 1 H), 8.93 (s, 1 H), 12.64 (s, 1 H).

Intermediate 21. (E)-3-(5-Chloro-2-(4H-1,2,4-triazol-4-yl)phenyl)acrylic acid



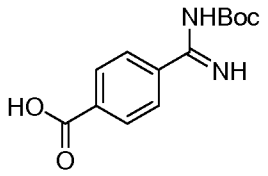
[00362] Intermediate 21A. 4-(4-Chloro-2-iodophenyl)-4H-1,2,4-triazole: To a suspension of 4-chloro-2-iodoaniline (0.760 g, 3 mmol) and N′-formylformohydrazide (0.793 g, 9 mmol) in pyridine (12 ml) was added dropwise chlorotrimethylsilane (5.71 ml, 45 mmol) followed by TEA (2.84 ml, 20.4 mmol). The reaction mixture was heated at 100 °C. After 4 h, the reaction was cooled to rt and the reaction was concentrated to give a solid. The solid was suspended in water and the solid was collected by filtration, washing with water. The solid was air-dried and dried under vacuum to give 0.8 g as an off-white solid. Purification by normal phase chromatography afforded 0.59 g (64 %) of Intermediate 21A, as a white solid. MS (ESI) *m/z*: 306.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.56 (d, J = 8.2 Hz, 1 H), 7.67 (dd, J = 2.2 Hz, 8.2 Hz, 1 H), 8.17 (d, J = 2.2 Hz, 1 H), 8.78 (s, 2 H).

[00363] Intermediate 21B. (E)-*tert*-Butyl 3-(5-chloro-2-(4H-1,2,4-triazol-4-yl)phenyl)acrylate: To a degassed solution of Intermediate 21A (0.48 g, 1.571 mmol),

tributylamine (0.749 mL, 3.14 mmol), and *tert*-butyl acrylate (1.151 mL, 7.86 mmol) in DMF (7.86 mL) was added palladium on carbon (10% w/w, 0.167 g, 0.157 mmol) and palladium(II) acetate (0.035 g, 0.157 mmol). The reaction was heated at 100 °C for 18 h. Additional *tert*-butyl acrylate (1.151 mL, 7.86 mmol) and palladium(II) acetate (0.035 g, 0.157 mmol) was added and the reaction was stirred at 100 °C for another 48 h. The reaction was cooled to RT, filtered through a 0.45 μm GMF, and rinsed with EtOAc. The filtrate was diluted with EtOAc, washed with water, brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography followed by reverse phase chromatography gave 0.122 g (25%) of Intermediate 21B, as a white solid. ^1H NMR (500 MHz, CD_3OD) δ ppm 1.47 (s, 9 H), 6.51 (d, *J*=16.0 Hz, 1 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.52 (d, *J*=8.5 Hz, 1 H), 7.62 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 8.86 (s, 2 H).

[00364] Intermediate 21. To the solution of Intermediate 21B (0.122 g, 0.399 mmol) in DCM (0.5 mL) was added TFA (0.5 mL, 6.49 mmol). The reaction was stirred at rt for 2 h, then it was concentrated to afford 0.100 g (100 %) of Intermediate 21, as a white solid. MS (ESI) *m/z*: 249.9 $(M+H)^+$.

Intermediate 22. 4-(N-(*tert*-Butoxycarbonyl)carbamimidoyl)benzoic acid, 2 NaOH salt



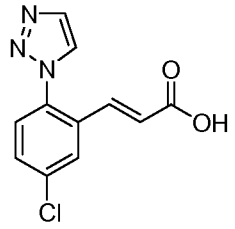
[00365] Intermediate 22A. Methyl 4-(N-hydroxycarbamimidoyl)benzoate: To a solution of methyl 4-cyanobenzoate (1.003 g, 6.22 mmol) in MeOH (15 mL) was added hydroxylamine hydrochloride (2.162 g, 31.1 mmol) and TEA (4.34 mL, 31.1 mmol). The reaction was stirred at rt for 24 h, then the reaction was concentrated to give a white solid. Water and DCM were added to give a suspension. The suspension was filtered and the solid was rinsed with water and then air-dried to give 1.14 g (94%) of Intermediate 22A, as a white solid. MS (ESI) *m/z*: 195.0 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ ppm 3.91 (s, 3 H), 7.74 - 7.77 (m, 2 H), 8.01 - 8.04 (m, 2 H). The material was carried onto the next step without further purification.

[00366] Intermediate 22B. Methyl 4-carbamimidoylbenzoate, 1 acetic acid salt: To a solution of Intermediate 22A (1.14 g, 5.87 mmol) in acetic acid (5 mL) was added acetic anhydride (2 mL, 21.20 mmol). The reaction turned to a white gel. After 10 min, MeOH (50 mL) was added followed by palladium on carbon (10% w/w, 0.625 g, 0.587 mmol). Hydrogen gas was bubbled through the reaction mixture for a few minutes, then the reaction was stirred under a H_2-balloon. After 24 h, the reaction was filtered through a 0.45μm GMF rinsing with MeOH. The filtrate was concentrated to give 1.32 g (94%) of Intermediate 22B as a white solid. MS (ESI) *m/z*: 179.0 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.90 (s, 3 H), 3.96 (s, 3 H), 7.89 (d, *J*=8.8 Hz, 2 H), 8.22 (d, *J*=8.8 Hz, 2 H).

[00367] Intermediate 22C. Methyl 4-(N-(*tert*-butoxycarbonyl)carbamimidoyl)benzoate: To a white suspension of Intermediate 22B (1.82 g, 7.64 mmol) in DCM (102 mL) was added di-*tert*-butyl dicarbonate (2.452 g, 11.24 mmol) and TEA (4.27 mL, 30.6 mmol). The reaction mixture was stirred at rt. Overtime, the reaction became a clear solution. After 72 h, additional di-*tert*-butyl dicarbonate (0.4 eq, 0.879 g) was added, and the reaction was stirred at rt. After an additional 24 h, the reaction was concentrated. Purification by normal phase chromatography afforded 0.84 g (30 %) of Intermediate 22C as a white solid. MS (ESI) *m/z*: 277.3 $(M-H)^-$. ^1H NMR (500 MHz, CD_3OD) δ ppm 1.52 (s, 9 H), 3.93 (s, 3 H), 7.86 - 7.91 (m, 2 H), 8.07 - 8.10 (m, 2 H).

[00368] Intermediate 22. To a solution of Intermediate 22C (0.84 g, 3.02 mmol) in MeOH (15.09 mL) was added 1N NaOH (6.04 mL, 6.04 mmol) to give a cloudy white mixture. Additional MeOH (15.09 mL) was added and the resulting clear solution was stirred at rt. After 24 h, the reaction was concentrated to give 0.895 g (86 %) of Intermediate 22, as a white solid. MS (ESI) *m/z*: 265.3 $(M+H)^+$. The material was used in the next step without further purification.

Intermediate 23. (E)-3-(5-Chloro-2-1,2,3-triazol-1-yl-phenyl)-acrylic acid

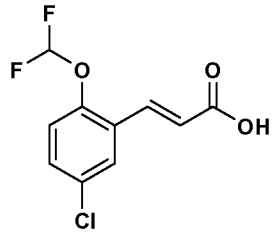


[00369] Intermediate 23A. 5-Chloro-2-1,2,3-triazol-1-yl-benzaldehyde and Intermediate 23B. 5-Chloro-2-1,2,3-triazol-2-yl-benzaldehyde: To a solution of 5-chloro-2-fluorobenzaldehyde (1 g, 6.31 mmol) in DMF (12.6 mL) was added 1H-1,2,3-triazole (0.365 ml, 6.31 mmol) and Cs_2CO_3 (4.11 g, 12.61 mmol). The reaction was stirred at rt for 18 h. Water was added to the reaction, and the resulting suspension was acidified with 1N HCl to pH<3, and then the reaction was filtered. The filtrate was extracted with EtOAc (3x). The organic layers were combined and washed with water, brine, dried over Na_2SO_4, filtered and concentrated. Trituration with DCM/hexane gave 0.35 g as a mixture of Intermediate 23A and Intermediate 23B as a yellow solid. The material was used in the next step without further purification.

[00370] Intermediate 23C. (E)-3-(5-Chloro-2-1,2,3-triazol-1-yl-phenyl)-acrylic acid *tert*-butyl ester and Intermediate 23D. (E)-3-(5-Chloro-2-1,2,3-triazol-2-yl-phenyl)-acrylic acid *tert*-butyl ester: The title compounds were prepared according to the procedure described in Intermediate 20B, by replacing Intermediate 20A with a mixture of Intermediate 23A and Intermediate 23B. The triazole regioisomers were separated by normal phase chromatography which gave 0.147 g (28.5 %) of Intermediate 23C. MS (ESI) *m/z*: 306.1 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.48 (s, 9 H), 6.36 (d, *J*=16.0 Hz, 1 H), 7.21 (d, *J*=16.0 Hz, 1 H), 7.44 (d, *J*=8.5 Hz, 1 H), 7.48 - 7.52 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.74 (d, *J*=2.2 Hz, 1 H), 7.79 (d, *J*=1.1 Hz, 1 H), 7.89 (d, *J*=1.1 Hz, 1 H).

[00371] Intermediate 23. The title compound was prepared according to the procedure described in Intermediate 20, by replacing Intermediate 20B with Intermediate 23C. MS (ESI) *m/z*: 250.0 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ ppm 6.51 (d, *J*=15.7 Hz, 1 H), 7.22 (d, *J*=16.0 Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.63 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.96 (d, *J*=0.83 Hz, 1 H), 8.00 (d, *J*=2.2 Hz, 1 H), 8.30 (d, *J*=0.83 Hz, 1 H).

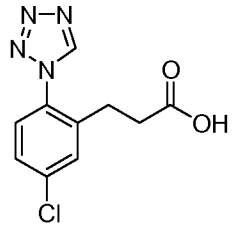
Intermediate 24. (E)-3-(5-Chloro-2-difluoromethoxy-phenyl)-acrylic acid



[00372] Intermediate 24A. (E)-3-(5-Chloro-2-difluoromethoxy-phenyl)-acrylic acid *tert*-butyl ester: To a cooled (0 °C) solution of potassium *tert*-butoxide (0.407 g, 3.63 mmol) in THF (10 mL) was added *tert*-butyl 2-(dimethoxyphosphoryl)acetate (0.528 mL, 2.66 mmol) and 5-chloro-2-(difluoromethoxy)benzaldehyde (0.50g, 2.420 mmol). The reaction was allowed to warm to RT. After 4h, the reaction was quenched with the addition of sat. ammonium chloride. The reaction was diluted with EtOAc, washed with sat. ammonium chloride, sat $NaHCO_3$ and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography gave 550 mg (74%) of Intermediate 24A as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (1 H, d, J=16.31 Hz), 7.58 (1 H, d, J=2.51 Hz), 7.31 (1 H, dd, J=8.66, 2.64 Hz), 7.12 (1 H, d, J=8.78 Hz), 6.52 (1 H, t, J=72.78 Hz) 6.40 (1 H, d, J=16.31 Hz), 1.53 (9 H, s). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.11. MS (ESI) *m/z*: 327.0 $(M+Na)^+$.

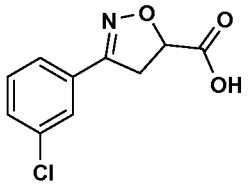
[00373] Intermediate 24. To a solution of Intermediate 24A (458 mg, 1.503 mmol) in DCM (4.0 mL) was added TFA (2.0 mL, 26.0 mmol). The reaction was stirred under argon at RT for 1h. The solvent was removed to give Intermediate 24 as a white solid. MS (ESI) *m/z*: 249.0 $(M+H)^+$.

Intermediate 25. 3-(5-Chloro-2-tetrazol-1-yl-phenyl)-propionic acid



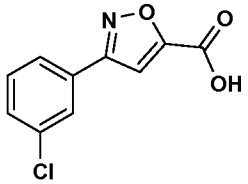
[00374] The synthesis was described as Example 63A in PCT International Application No. WO 2007/070826 published 06/21/2007.

Intermediate 26: 3-(3-Chlorophenyl)-4,5-dihydroisoxazole-5-carboxylic acid



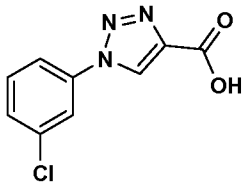
[00375] Intermediate 26 was obtained via the procedure described in U.S. Patent No. 4,889,551 A1 (1989).

Intermediate 27: 3-(3-Chlorophenyl)isoxazole-5-carboxylic acid



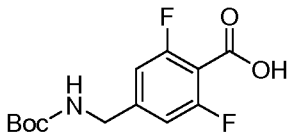
[00376] Intermediate 27 was obtained via the procedure described by Gruenanger, F., *Gazz. Chim. Ital.*, 89:598-609 (1959).

Intermediate 28: 1-(3-Chlorophenyl)-1H-1,2,3-triazole-4-carboxylic acid



[00377] Intermediate 28 was obtained via the procedure described by Sader Al, B.H. et al., *Tetrahedron Letters*, 4661-4664 (1985).

Intermediate 29. 4-(*tert*-Butoxycarbonylamino-methyl)-2,6-difluoro-benzoic acid



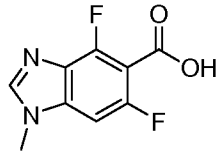
[00378] Intermediate 29A. 4-Cyano-2,6-difluoro-benzoic acid: To a cooled (-78 °C) clear, colorless solution of 3,5-difluorobenzonitrile (1 g, 7.19 mmol) in THF (28.8 mL) was added dropwise 1.6M n-butyllithium in hexane (4.49 ml, 7.19 mmol) to give a red-orange solution. After 45 min, carbon dioxide (sublimation of dry ice passing through a drierite tower) was bubbled through the reaction to eventually give a thick off-white

suspension. After 25 min, the reaction was quenched with 1M HCl (aq) and the reaction was allowed to warm to RT. The reaction was extracted with EtOAc(2x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to a white residue. The crude residue was partitioned between EtOAc and 1M NaOH (aq) and the layers were separated. The organic layer was extracted with 1N NaOH (aq) (2x). The aqueous layers were combined and then washed with EtOAc (2x). The aqueous layer was then acidified to pH ~2 to give a cloudy white suspension. The aqueous layer was then extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to a give 922.5mg (65.3 %) of Intermediate 29A as a white solid. MS (ESI) *m/z*: 184.0 $(M+H)^+$.

[00379] Intermediate 29B. 4-Aminomethyl-2,6-difluoro-benzoic acid: A black suspension of Intermediate 29A (922.5mg, 5.04 mmol) and Pd/C (268 mg, 0.126 mmol) in EtOH (50.4 mL) was degassed with hydrogen (balloon) for several minutes. The reaction was stirred under hydrogen atmosphere for 24 h. The reaction was filtered through CELITE® eluting with 1M HCl (aq) and MeOH. The filtrate was concentrated to a pale yellow solid. The solid was dissolved in (1:1) 1N HCl and EtOAc and the layers were separated. The aqueous layer was neutralized to pH 7 and extracted with 15% isopropanol/chloroform. The aqueous layer still contained some product, so both the organic and aqueous layers were concentrated and combined to give Intermediate 29B as an off-white solid. MS (ESI) *m/z*: 188.0 $(M+H)^+$. The product was used as is without further purification.

[00380] Intermediate 29. To a suspension of Intermediate 29B (943mg, 4.22 mmol) in DCM (14.1 mL) was added triethylamine (2.351 mL, 16.87 mmol) followed by BOC_2O (1.077 mL, 4.64 mmol). DMF (5mL) was added to facilitate mixing. After stirring for 1.5 h, the slightly purple suspension was diluted with water and DCM and the layers were separated. The aqueous layer was neutralized to pH~7 using 1N HCl (aq) and then extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to give a viscous, pink oil. Purification by normal phase chromatography (0-10% DCM:MeOH) gave 803.2 mg (55.0 %) of Intermediate 29, as a clear oil. MS (ESI) *m/z*: 232.2 $(M - C_4H_8 + H)^+$. ^1H NMR (500 MHz, CD_3OD) δ: 1.46 (s, 9 H), 4.24 (s, 2 H), 6.95 (d, *J*=9.3 Hz, 2 H).

Intermediate 30. 4,6-Difluoro-1-methyl-1H-benzo[d]imidazole-5-carboxylic

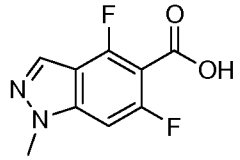


[00381] Intermediate 30A. 3,5-Difluoro-N-methyl-2-nitroaniline: To a solution of 1,3,5-trifluoro-2-nitrobenzene (1.0 g, 5.65 mmol) and methanamine (8.47 mL, 16.94 mmol) in MeOH (10 mL) was stirred for 4 h at 80 °C. Reaction mixture was concentrated *in vacuo*, yielding oil, which was subjected to the following reaction w/o any further purification. MS (ESI) *m/z*: 189.2 $(M+H)^+$.

[00382] Intermediate 30B. 4,6-Difluoro-1-methyl-1H-benzo[d]imidazole: Solution of Intermediate 30A (1.063 g, 5.65 mmol) in formic acid (5 mL) was heated at 80 °C for 12h. Rxn mixture after concentration was diluted in EtOAc (100 mL) and washed with 1N aq NaOH. Organic solution was dried over Na_2SO_4 and concentrated *in vacuo*, yielding oily mixture. It was purified on normal phase column chromatography to yield Intermediate 30B (0.39 g, 41.1%).

[00383] Intermediate 30. (Reference: WO 2009/083526) To a solution of Intermediate 30B (227 mg, 1.35 mmol) in THF (10 mL) was added BuLi (0.74 mL, 1.485 mmol) dropwise and the resulting solution was stirred for 0.5h at -78 °C. To the solution was added bromotrimethylsilane (0.175 mL, 1.350 mmol) dropwise and solution was stirred for 15 min. To the solution was added sec-butyllithium (1.298 mL, 1.688 mmol) dropwise and solution was stirred for 0.5h. The solution was then poured into THF solution of dry ice (2 pieces). The solution was stirred for 1h at -78 °C. The reaction was then quenched by adding 1N HCl and the reaction was warmed to RT. The reaction was concentrated and then it was purified by reverse phase chromatography which gave Intermediate 30 (121 mg, 41.0 %). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.80 (s, 1 H), 7.51 (d, *J*=9.0 Hz, 1 H), 3.99 (s, 3 H). MS(ESI) *m/z*: 213.0 $(M+H)^+$.

Intermediate 31. 4,6-Difluoro-1-methyl-1H-indazole-5-carboxylic acid

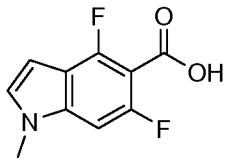


[00384] Intermediate 31A. (E)-1-Methyl-2-(2,4,6-trifluorobenzylidene)hydrazine: A solution of monomethyl hydrazine (2.158 g, 46.8 mmol) and 2,4,6-trifluorobenzaldehyde (2.5g, 15.6 mmol) in THF (20 mL) was stirred at RT for 5h. The reaction mixture was concentrated *in vacuo*, yielding oily residue, which was subjected to the following reaction w/o further purification. MS (ESI) *m/z*: 189.4 $(M+H)^+$.

[00385] Intermediate 31B. 4,6-Difluoro-1-methyl-1H-indazole: A solution of Intermediate 31A (8.84 g, 47 mmol) in DMF (5 mL) and pyridine (5.00 mL) was stirred at 90 °C for 12h. The reaction mixture was concentrated *in vacuo*, yielding an oily mixture, which was purified on normal phase chromatography to provide Intermediate 31B (2.3 g, 29.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (s, 1 H), 6.78 (d, *J*=8.5 Hz, 1 H), 6.55 (td, *J*=9.7, 1.8 Hz, 1 H), 3.95 (s, 3 H). MS (ESI) *m/z*: 169.0 $(M+H)^+$.

[00386] Intermediate 31. To a solution of Intermediate 31B (250 mg, 1.48 mmol) in THF (15 mL) was added LDA (0.89 µL, 1.78 mmol) in several portions and the resulting dark solution was stirred for 0.5h at -78 °C. To the solution was added a few pieces of dry ice. The resulting solution was stirred at -78 °C for 0.5h and at 25 °C for 0.5h. It was diluted with EtOAc (40 mL) and washed with 1N HCl. Organic solution was dried over $MgSO_4$ and concentrated *in vacuo*, yielding oil, which was then purified on reverse phase chromatography to yield Intermediate 31 (0.26g, 82%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.15 (s, 1 H), 7.27 (d, *J*=10.0 Hz, 1 H), 4.04 (s, 3 H). MS (ESI) *m/z*: 212.9 $(M+H)^+$.

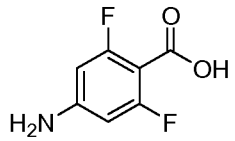
Intermediate 32: 4,6-Difluoro-1-methyl-1H-indole-5-carboxylic acid



[00387] Intermediate 32A. 4,6-Difluoro-1-methyl-1H-indole: The synthesis is described in WO 2009/050235.

[00388] Intermediate 32. In a flame-dried 25 ml RBF, diisopropylamine (0.352 ml, 2.51 mmol) in 10 ml dry THF was cooled down to 0 °C under Ar, butyllithium (1.6M in Hexane) (1.571 ml, 2.51 mmol) was added, stirred at 0 °C for 30 mins, before cooling down to -78 °C. Intermediate 32A (382 mg, 2.285 mmol) in 2 ml dry THF was added dropwise, stirred at -78 °C for 1 hrs, before dry ice was added to the reaction. The reaction was stirred at -78 °C for 30 mins and then warmed up to rt and stirred at rt overnight. The reaction was concentrated, diluted with EtOAc, washed with H_2O, washed again with EtOAc. The aqueous layer was acidified with 1N HCl, white precipitate formed immediately. It was extracted with EtOAc twice. EtOAc layers washed with brine, dried over $MgSO_4$, filtered off solid, concentrated to give Intermediate 32 as a pale yellow solid (177 mg, 38%). MS (ESI) *m/z*: 212.1 $(M+H)^+$.

Intermediate 33: 4-Amino-2,6-difluoro-benzoic acid



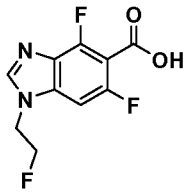
[00389] Intermediate 33A. 4-Bromo-2,6-difluorobenzoic acid methyl ester: To a solution of 4-bromo-2,6-difluorobenzoic acid (1.00 g, 4.22 mmol) in 30 mL methanol was added TMS-Cl (1.1 ml, 8.61 mmol), and the mixture was heated at 60 °C under N_2 over night. An additional 1 mL TMS-Cl was added and heating continued at 60 °C for an additional 4 h. Reaction mixture was cooled to RT and diluted with aq. NaOH, then extracted with EtOAc. The combined organic extracts were washed with dilute aq. NaOH to remove unreacted starting material, then dried over Na_2SO_4, filtered and evaporated to obtain Intermediate 33A as a pale pink solid (0.86g, 81%) MS (ESI) *m/z*: 251.05 $(M+H)^+$.

[00390] Intermediate 33B. 4-(Benzhydrylidene-amino)-2,6-difluoro-benzoic acid methyl ester: Intermediate 33A (0.600 g, 2.390 mmol) and cesium carbonate (1.324 g, 4.06 mmol) were weighed into a 50 mL 3-necked rbf and flushed with N_2. Palladium(II) acetate (10.73 mg, 0.048 mmol) and rac-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.045 g, 0.072 mmol) were added, followed by 7.5 mL toluene. Benzophenone imine (0.521 ml, 3.11 mmol) was then added to the above mixture, and the reaction was heated

with stirring at 100 °C overnight. The reaction mixture was diluted with ~50 mL Et_2O, and filtered. The filtrate was evaporated and the residue was purified by flash chromatography to provide Intermediate 33B as a yellow oil which was used without further purification in the next step. MS (ESI) *m/z*: 352.2 $(M+H)^+$.

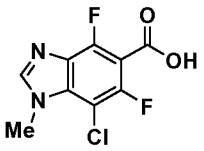
[00391] Intermediate 33. Intermediate 33B (0.840 g, 2.39 mmol) was dissolved in MeOH (16 mL), and hydroxylamine hydrochloride (0.332 g, 4.78 mmol) and sodium acetate (0.490 g, 5.98 mmol) were added. The mixture was stirred for ~ 1h and then diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, then dried over Na_2SO_4, filtered and evaporated. The crude product was dissolved in EtOH (~12 mL) and 1M NaOH (6 mL, 6.0 mmol) was added. The mixture was stirred for 3 days at room temperature. Reaction mixture was neutralized with 1M HCl and then evaporated to remove ethanol. The residue was redissolved in MeOH, filtered and evaporated (2X) to remove the bulk of the inorganic salts. The filtrate was evaporated and the residue was purified by reverse phase HPLC to provide Intermediate 33 (0.36g, 88%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 5.99 (s, 2 H) 6.10 (d, *J*=10.99 Hz, 2 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -111.82 (s, 2 F).

Intermediate 34. 4,6-Difluoro-1-(2-fluoro-ethyl)-1*H*-benzoimidazole-5-carboxylic acid



[00392] Intermediate 34 was prepared following the procedures described in Intermediate 30, by replacing methylamine with 2-fluoroethanamine, HCl. MS (ESI) *m/z*: 245.1 $(M+H)^+$.

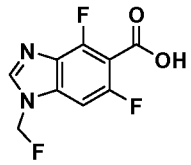
Intermediate 35. 7-Chloro-4,6-difluoro-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid



[00393] Intermediate 35A. 2-Chloro-3,5-difluoro-N-methyl-6-nitroaniline: Solution of Intermediate 30A (1.1 g, 5.85 mmol) and NCS (0.781 g, 5.85 mmol) in acetonitrile (25 mL) was stirred for 12h at 70 °C. The reaction mixture was concentrated *in vacuo*, yielding yellow solid, which was redissolved in EtOAc and washed with aq. $NaHCO_3$ and brine. Concentration of organic solution provided oily residue, which was purified on normal phase chromatography to provide Intermediate 35A (0.78g, 60%). MS (ESI) *m/z*: 222.9/224.8 $(M+H)^+$.

[00394] Intermediate 35. Intermediate 35 was prepared following the procedures described in Intermediate 30, by replacing Intermediate 30A with Intermediate 35A. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.18 (s, 1 H), 4.16 (s, 3 H). MS (ESI) *m/z*: 246.9/248.8 $(M+H)^+$.

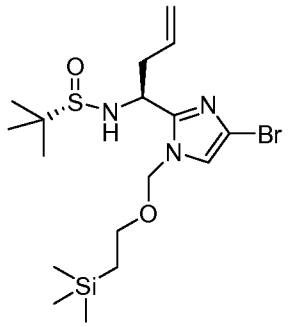
Intermediate 36. 4,6-Difluoro-1-fluoromethyl-1*H*-benzoimidazole-5-carboxylic acid



[00395] Intermediate 36A. 4,6-Difluoro-1-(fluoromethyl)-1H-benzo[d]imidazole: (Reference: *Tetrahedron*, 63:10569-10575 (2007).) To a solution of 4,6-difluoro-1H-benzo[d]imidazole (100 mg, 0.649 mmol) in DMF (5 mL) was added NaH (57.1 mg, 1.43 mmol) and the resulting solution was stirred for 0.5h at rt. The solution was cooled down to -78 °C and FCH_2Cl was bubbled in for 10 min. The reaction mixture was then sealed in the microwave vial and stirred at 80 °C for 2h. The reaction mixture was diluted with EtOAc (30 ml) and washed with 1N HCl (20 mL), then aq NH_4Cl. Organic solution was concentrated and purified on reverse phase chromatography to provide Intermediate 36A (52 mg, 43 %). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.02 (d, 2 H), 7.29 - 7.40 (m, 1 H), 7.00 - 7.13 (m, 1 H), 6.82 - 6.98 (m, 2 H), 6.29 (s, 1 H), 6.18 (d, *J*=5.5 Hz, 2 H), 6.07 (s, 1 H), 1.59 (s, 2 H). MS (ESI) *m/z*: 187.0 $(M+H)^+$.

[00396] Intermediate 36. Intermediate 36 was prepared following the procedure described in Intermediate 30, by replacing Intermediate 30B with Intermediate 36A. MS (ESI) *m/z*: 231.1 $(M+H)^+$.

Intermediate 37. 2-Methyl-propane-2-sulfinic acid {(S)-1-[4-bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-but-3-enyl}-amide



[00397] Intermediate 37A. 2,4,5-Tribromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole: To a cooled (0 °C) suspension of sodium hydride (0.9 g, 0.03 mole) in THF (50 mL) was added dropwise a solution of 2, 4, 5-tribromo imidazole (5 g, 0.016 mol) in THF (50 mL). After 1h, a solution of trimethylsilylethoxymethyl chloride (SEMCl) (3 mL, 0.017 mol) in THF (30 mL) was added dropwise. The reaction mixture was quenched with saturated ammonium chloride solution and then the reaction was extracted with ethyl acetate [3 x 100 mL]. The organic layers were combined and washed with 10 % sodium bicarbonate solution, water, brine, dried over sodium sulfate, filtered and concentrated to yield 7.2 g of Intermediate 37A as pale, yellow oil which solidified on standing. The material was used in the next step without further purification. MS (ESI) *m/z*: 435 $(M+2+H)^+$.

[00398] Intermediate 37B. 4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carbaldehyde: To a cooled (-78 °C) solution of Intermediate 37A (16 g, 0.03 mol) in THF (160 mL) was added a solution of n-BuLi (13.5 mL, 3M in hexane; 0.04 mol) dropwise. After 1h, DMF (14 mL, 0.2 mol) was added dropwise. After 1h, the reaction was quenched with saturated ammonium chloride solution and then the reaction was allowed to warm to RT. The reaction was extracted with ethyl acetate [2 x 100 mL]. The organic layers were combined and washed with 10 % sodium bicarbonate solution, water, brine and then concentrated. Purification by normal phase chromatography

(gradient elution pet ether: ethyl acetate) gave 11.5 g (40%) of Intermediate 37B. MS (ESI) *m/z*: 384.1 $(M)^+$.

[00399] Intermediate 37C. (S,E)-N-((4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methylene)-2-methylpropane-2-sulfinamide: To a solution of Intermediate 37B (35 g, 0.09 mol) in methylene chloride (350 mL) was added (*S*)-(−)-2-Methyl-2-propanesulfinamide (22 g, 0.18 mole) and anhydrous copper sulfate (72 gc 0.45 mol). The resulting suspension was stirred at RT. After 20 h, the reaction was filtered through CELITE®. The filtrate was concentrated and purification by normal phase chromatography (gradient elution pet ether:ethyl acetate) gave 42 g (94%) of Intermediate 37C as a pale yellow oil which solidified on standing. MS (ESI) *m/z*: 487.3 $(M+H)^+$.

[00400] Intermediate 37D. 2-Methyl-propane-2-sulfinic acid {(S)-1-[4,5-dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-but-3-enyl}-amide: To a cooled (-78 °C) solution of Intermediate 37C (17 g, 0.03 mole) in THF (170 mL) was added allylmagnesium bromide (1M in diethylether, 52.3 mL, 0.05 mol) dropwise. After 1 h, the reaction was quenched with saturated ammonium chloride solution and then the reaction was allowed to warm to RT. The reaction mixture was extracted with ethyl acetate (2 x 250 mL). The organic layers were combined and washed with sodium bicarbonate solution, brine, water, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by normal phase chromatography (gradient elution; hexane:ethyl acetate) gave 25 g (67%) of Intermediate 37D, as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.71 (m, 1H), 5.60 (d, 1H, J = 11.6 Hz), 5.28 (m, 1H), 5.06 (m, 2H), 4.57 (q, 1H, J = 7.2 Hz), 3.98 (d, 1H, J = 8.4Hz), 3.55 (m, 2H), 2.70 (t, 2H, 7.2 Hz), 1.2 (s, 9H), 0.92 (m, 2H), -0.01 (s, 9H). MS (ESI) *m/z*: 529.4 $(M+H)^+$.

[00401] Intermediate 37. A solution of Intermediate 37D (5.25 g, 9.92 mmol) in THF (33.1 mL) was degassed with argon for 15 min. The solution was cooled to -3 °C (ice/brine) and isopropylmagnesium chloride, lithium chloride complex in THF (8.00 mL, 10.4 mmol) was added dropwise over 20 min, keeping the temperature below 0 °C during the addition. After 30 min, the second equivalent of isopropylmagnesium chloride, lithium chloride complex in THF (8.00 mL, 10.4 mmol) was added dropwise over 20 min, keeping the temperature below 0 °C during the addition. After 30 min, the reaction was quenched with sat. ammonium chloride (30 mL) and the reaction was allowed to

warm to RT. The reaction was partitioned between EtOAc and sat. ammonium chloride and the layers were separated. The aqueous layer was extracted with EtOAc (1x). The organic layers were combined and washed with sat. $NaHCO_3$, brine, dried over sodium sulfate, filtered and concentrated to give clear, yellow viscous oil weighing 4.67 g. Purification by normal phase chromatography gave 3.98 g (89%) of Intermediate 37, as a white solid. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.20 (s, 1 H), 5.69 - 5.82 (m, 1 H), 5.49 (d, J=11.3 Hz, 1 H), 5.30 (d, J=11.3 Hz, 1 H), 5.09 (dd, J=17.1, 1.7 Hz, 1 H), 5.04 (d, J=10.5 Hz, 1 H), 4.62 (t, J=7.3 Hz, 1 H), 3.51 - 3.67 (m, 2 H), 2.69 (t, J=7.3 Hz, 2 H), 1.20 (s, 9 H), 0.85 - 1.04 (m, 2 H), 0.00 (s, 9 H). MS (ESI) *m/z*: 450.1 $(M+H)^+$. $[\alpha]_D^{23.6}$ = + 70.13 (c = 1.70; chloroform).

Alternatively, Intermediate 37 can be prepared by the following sequence:

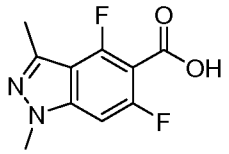
[00402] Intermediate 37E. 2,4-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole: To a cooled (0 °C) suspension of NaH (1.062 g, 26.6 mmol) in THF (44.3 mL) was added dropwise over 20 min. a clear, pale yellow solution of 2,4-dibromo-1H-imidazole (5.00 g, 22.14 mmol) in THF (20 mL). The resulting purple-gray suspension was stirred at 0 °C for 1h. Next, SEMCl (4.71 mL, 26.6 mmol) was added dropwise. The reaction was maintained at 0 °C for 1h and then it was quenched with the slow addition of sat. ammonium chloride. The reaction was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried over sulfate, filtered and concentrated to give a clear liquid weighing 9.06 g. Purification by normal phase chromatography gave 5.97 g (76%) of Intermediate 37E, as a clear, colorless liquid. Ratio of regioisomers by HPLC was 14.7:1. MS (ESI) *m/z*: 357.0 $(M+2+H)^+$.

[00403] Intermediate 37F. 4-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole-2-carbaldehyde: To a cooled (-78 °C) clear, colorless solution of Intermediate 37E (1.0 g, 2.81 mmol) in THF (9.36 mL) was added dropwise over 10 min. n-BuLi (1.930 mL, 3.09 mmol). The resulting clear, golden yellow solution was stirred at -78 °C for 1 h and then DMF (1.087 mL, 14.04 mmol) was added. The reaction was stirred at -78 °C for 1 h and then the reaction was quenched with sat. ammonium chloride and the reaction was allowed to warm to RT. The reaction was partitioned between EtOAc and

water and the layers were separated. The organic layer was washed with sat. $NaHCO_3$, brine, dried over sodium sulfate, filtered, and concentrated. Purification by normal phase chromatography gave 0.130 g (16%) of Intermediate 37F, as a white solid. MS (ESI) *m/z*: 339.1 $(M+CH_4O+2+H)^+$, consistent with hemiacetal of methanol addition to the aldehyde.

[00404] Intermediate 37. Intermediate 37 was prepared by following the procedures described in Intermediate 37C, by replacing Intermediate 37B with Intermediate 37F; followed by procedure described in Intermediate 37D which gave a 9:1 mixture of diastereomers.

Intermediate 38. 4,6-Difluoro-1,3-dimethyl-1*H*-indazole-5-carboxylic acid

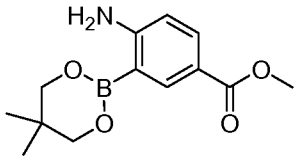


[00405] Intermediate 38A. 4,6-Difluoro-1,3-dimethyl-1*H*-indazole: K_2CO_3 (1.191 g, 8.61 mmol) and copper(II) oxide (0.023 g, 0.287 mmol) were weighed into a microwave tube. Vacuum and filled with Ar for several times. Methylhydrazine (0.363 ml, 6.89 mmol) was added. The reaction was cooled down to 0 °C. 1-(2,4,6-trifluorophenyl)ethanone (0.767 ml, 5.74 mmol) was added dropwise. The tube was placed in an oil bath and heated at 100 °C for 4hrs, then cooled down to rt overnight. The reaction mixture was diluted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$. Purification by normal phase chromatography gave 877 mg (84%) of Intermediate 38A as a white solid. MS (ESI) *m/z*: 183.0 $(M+H)^+$.

[00406] Intermediate 38. In a flame-dried 25 ml RBF, diisopropylamine (0.494 ml, 3.52 mmol) in THF (14.68 ml) was cooled down to 0 °C under Ar. Butyllithium (1.6M in Hexane) (1.571 ml, 2.51 mmol) was added. The reaction was stirred at 0 °C for 1hr, before cooling down to -78 °C. 4,6-difluoro-1,3-dimethyl-1H-indazole (535 mg, 2.94 mmol) in 4 ml dry THF was added dropwise. The reaction was stirred at -78 °C for 1 hrs, before dry ice was added to the reaction. The reaction was stirred at -78 °C for 30 mins and then warmed up to rt and stirred at rt overnight. The reaction was concentrated, diluted with EtOAc, washed with H_2O. The aqueous layer was acidified with 1N HCl. It

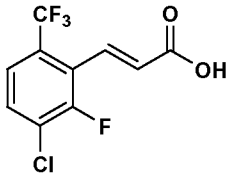
was filtered and the white solid was dried in a vacuum oven to give 160 mg (24%) of Intermediate 38 as a white solid. MS (ESI) *m/z*: 227.0 $(M+H)^+$.

Intermediate 39. 4-Amino-3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-benzoic acid methyl ester



[00407] A flame-dried flask, equipped with a reflux condensor, containing methyl 4-amino-3-bromobenzoate (2.5 g, 10.87 mmol), bis(neopentyl glycolato)diboron (3.07 g, 13.58 mmol), potassium acetate (3.20 g, 32.6 mmol), and $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.222 g, 0.272 mmol) was added degassed DMSO (31.0 mL). The resulting dark red-brown suspension was warmed to 85 °C. After 2.5 h, the resulting dark black reaction was cooled to RT and poured into cold water (100 mL) to give a suspension. The suspension was extracted with EtOAc (3x). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried over sodium sulfate, filtered and concentrated to give a brown solid weighing 3.1 g. Purification by normal phase chromatography gave 1.64 g (55%) of Intermediate 39 as a pale, yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.35 (d, J=2.20 Hz, 1 H), 7.84 (dd, J=8.53, 2.20 Hz, 1 H), 6.52 (d, J=8.53 Hz, 1 H), 5.25 (br. s., 2 H), 3.84 (s, 3 H), 3.79 (s, 4 H), 1.03 (s, 6 H). MS (ESI) *m/z*: 196.0 $(M-C_5H_8+H)^+$.

Intermediate 40. (E)-3-(3-Chloro-2-fluoro-6-(trifluoromethyl)phenyl)acrylic acid

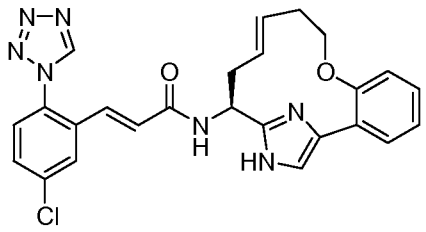


[00408] Intermediate 40 was prepared following the procedures described in Intermediate 24, by replacing 5-chloro-2-(difluoromethoxy) benzaldehyde with 3-chloro-2-fluoro-6-(trifluoromethyl)benzaldehyde. MS (ESI) *m/z:* 292 $(M+Na)^+$. ^1H NMR (400

MHz, $CDCl_3$) δ ppm 7.87 (1 H, dd, *J*=16.17, 2.02 Hz), 7.49 - 7.62 (2 H, m), 6.67 (1 H, dd, *J*=16.30, 1.39 Hz).

Example 1.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-(E)-(S)-8-oxa-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl-acrylamide, 1 TFA salt



[00409] 1A. (S)-2-*tert*-Butoxycarbonylamino-pent-4-enoic acid 2-(2-but-3-enyloxy-phenyl)-2-oxo-ethyl ester: A suspension of (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid (515 mg, 2.394 mmol) and potassium hydrogen carbonate (0.288 g, 2.87 mmol) in DMF (12.00 mL) was stirred at rt for 20 min. The reaction was then cooled to 0 °C and Intermediate 6 (0.773g, 2.87 mmol) was added. The resulting yellow solution was allowed to warm to rt. After stirring overnight, the reaction was cooled to 0 °C and then poured into cold water to give a white suspension. The white suspension was then extracted with EtOAc (3 x 75mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 1.072 g of 1A as a yellow oil. This was used without further purification. MS (ESI) *m/z*: 304.3 $(M-C_5H_8O_2+H)^+$.

[00410] 1B. {(S)-1-[4-(2-But-3-enyloxy-phenyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: Compound 1A (1.07 g, 2.66 mmol) was dissolved in xylene (26.6 mL) and divided evenly between two 20-mL microwave vials. Next ammonium acetate (2.047 g, 26.6 mmol) was added to each vial. The vials were microwaved at 140 °C for 30 min. The resulting bright orange solutions were combined, partitioned between EtOAc and sat. $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a peach residue. Purification by normal phase chromatography gave 0.626g (62%) of 1B as a sticky, yellow solid. MS (ESI) *m/z*: 384.4$(M+H)^+$.

[00411] 1C. {(S)-1-[4-(2-But-3-enyloxy-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a cooled (0 °C) suspension of NaH (58.7mg, 1.468mmol) in DMF (2.06mL) was added dropwise a solution of 1B (536.2mg, 1.40mmol) in DMF (1.3mL). The resulting orange solution was allowed to warm to rt. After 1 h, the reaction was cooled to 0 °C and SEMCl (0.27 mL, 1.52mmol) was added dropwise. The resulting peach solution was allowed to warm to rt. After 1h and 45min, the cloudy yellow mixture was cooled to 0 °C and quenched with water (20mL). The reaction was extracted with EtOAc (3 x 20mL). The combined organic layers were washed with water (3 x 6 mL), dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave 462.5mg (64%) of 1C as a pale yellow oil. MS (ESI) *m/z*: 514.3$(M+H)^+$.

[00412] 1D. [(E)-(S)-16-(2-Trimethylsilanyl-ethoxymethyl)-8-oxa-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt; and 1E. [(Z)-(S)-16-(2-Trimethylsilanyl-ethoxymethyl)-8-oxa-16,18-diaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt: (Flask 1): To a flame-dried RBF was added Grubbs (II) (681mg, 0.802mmol). The flask was degassed with argon for several minutes and then degassed DCM (10mL) was added to give a clear, burgundy solution. (Flask 2): To a separate flame-dried RBF was added 1C (412mg, 0.802mmol), pTsOH monohydrate (168mg, 0.882mmol) and DCM (779 mL). The flask was equipped with a reflux condenser and the solution was degassed with argon for 30 min. Next, the reaction was warmed to 40 °C. After 1h, the solution of Grubbs (II) was added dropwise. After 1 h, the reaction was cooled to rt and washed with $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave a pale, brown oil. Further purification by reverse phase chromatography gave 78.6mg (20%) of 1D (E-alkene) as a pale brown oil and 33.2 mg (9%) of 1E (Z-alkene) as a pale, brown oil. For 1D: MS (ESI) *m/z*: 486.5 $(M+H)^+$. For 1E: MS (ESI) *m/z*: 486.5 $(M+H)^+$.

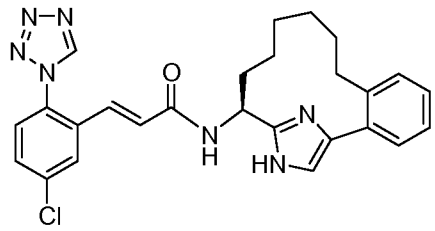
[00413] 1F. (E)-(S)-(8-Pxa-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl)amine, 2 TFA: A yellow solution of 1D (59.2 mg, 0.122 mmol) in 5M HCl (2.50 mL, 82 mmol) and EtOH (2.44mL) was heated to 50 °C. After stirring overnight, the reaction was concentrated to remove EtOH and the remaining

aqueous layer was adjusted to pH > 10 with sat. K_2CO_3. The reaction was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give a brown residue. Purification by reverse phase chromatography gave 0.0246 g (42%) of 1F as a clear, colorless oil. MS (ESI) *m/z*: 256.3 $(M+H)^+$.

[00414] 1G. Example 1: To a solution of Intermediate 1 (33.5 mg, 0.096 mmol) and 1F (24.6mg, 0.096mmol) in DMF (0.321 mL) was added Hunig's Base (0.084mL, 0.482mmol). After 45 min, water was added to give a suspension. The solid was collected by filtration. Purification by reverse phase chromatography gave after concentration and lyophilization 0.0195 g (33%) of Example 1 as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.40 - 2.71 (m, 3 H), 2.76 - 2.88 (m, 1 H), 3.68 - 3.84 (m, 1 H), 4.21 - 4.42 (m, 1 H), 5.13 - 5.28 (m, 2 H), 5.77 - 5.91 (m, 1 H), 6.81 (d, *J*=15.9 Hz, 1 H), 7.14 - 7.23 (m, 2 H), 7.29 (dd, *J*=8.2, 1.1 Hz, 1 H), 7.47 (td, *J*=7.7, 1.6 Hz, 1 H), 7.55 (s, 1 H), 7.57 - 7.62 (m, 2 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 8.00 (d, *J*=2.2 Hz, 1 H), 9.54 (s, 1 H). MS (ESI) *m/z*: 488.3$(M+H)^+$. Analytical HPLC: RT = 5.35 min.

Example 2.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-(S)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl-acrylamide, 1 TFA salt



[00415] 2A. (S)-2-(2-Bromophenyl)-2-oxoethyl 2-(*tert*-butoxycarbonylamino)pent-4-enoate: To a clear, colorless solution of (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid (3.33 g, 15.47 mmol) in DMF (38.7 mL) was added potassium hydrogen carbonate (1.859 g, 18.57 mmol). The reaction was stirred for 20 min at rt and then it was cooled to 0 °C. Next a solution of 2-bromo-1-(2-bromophenyl)ethanone (4.3 g, 15.47 mmol) in DMF (38.7 mL) was added dropwise and the reaction was allowed to warm to rt. After 3 h, the reaction was cooled to 0 °C, poured into ice-cold water, and then extracted with EtOAc (3x). The combined organic layers were washed with water (1x), brine (1x), dried

over sodium sulfate, filtered and concentrated to give 2A (6.37 g) as a yellow oil which solidified on storage in the freezer. MS (ESI) *m/z*: 410.2 $(M-H)^-$, 412.2 $(M+2-H)^-$. The material was used in the next step without further purification.

[00416] 2B. (S)-*tert*-Butyl 1-(5-(2-bromophenyl)-1H-imidazol-2-yl)but-3-enylcarbamate: To the clear, yellow solution of 2A (6.37 g, 15.45 mmol) in xylene (155 mL) was added ammonium acetate (11.91 g, 155 mmol). The reaction mixture was heated to reflux with a Dean-Stark trap to remove water azeotropically. After 4 h, the reaction was cooled to rt, diluted with EtOAc (500 mL) and then washed with sat. sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated to give a brown residue. Purification by normal phase chromatography afforded 2B (2.768 g, 45.7 %) as a yellow solid. MS (ESI) *m/z*: 392.3 $(M+H)^+$, 394.3 $(M+2+H)^+$.

[00417] 2C. (S)-*tert*-Butyl 1-(4-(2-bromophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)but-3-enylcarbamate: To a cooled (0 °C), suspension of NaH (60% dispersion in mineral oil, 0.299 g, 7.48 mmol) in THF (10.0 mL) was added dropwise a solution of 2B (2.668 g, 6.80 mmol) in THF (15.0 mL). Gas evolution was observed. The flask containing 2B was rinsed with THF (2.2 mL) and then this solution was added to the reaction mixture. The resulting clear orange solution was stirred at 0 °C for 30 min, then SEM-Cl (1.206 mL, 6.80 mmol) was added dropwise. The resulting orange solution was maintained at 0 °C. After 3 h, the reaction was quenched with sat. ammonium chloride and diluted with EtOAc (200 mL) and water. The layers were separated and the aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give clear orange oil. Purification by normal phase chromatography gave 2C (2.76 g, 78 %) as a yellow oil. MS (ESI) *m/z*: 522.5 $(M+H)^+$, 524.5 $(M+2+H)^+$.

[00418] 2D. (S)-*tert*-Butyl 1-(4-(2-(pent-4-enyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)but-3-enylcarbamate: To a flame-dried, thick-walled vial was placed 2C (1.085 g, 2.076 mmol), pent-4-enylboronic acid (0.757 g, 6.64 mmol), silver oxide (1.203 g, 5.19 mmol), potassium carbonate (1.722 g, 12.46 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.170 g, 0.208 mmol). The vial was purged with argon for several minutes and then degassed THF (8.3 mL) was added. The vial was sealed with a teflon-coated screw cap and the black suspension was warmed to 80 °C. After 16 h the reaction was cooled to rt. The reaction mixture was diluted with EtOAc,

washed with water, sat. sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated to give an orange-brown residue. Purification by normal phase chromatography yielded a clear, colorless oil which was a mixture of 2D and starting material. The material was purified further by reverse phase chromatography. The pure fractions were neutralized with sat. sodium bicarbonate and then concentrated to remove the organic solvent. The remaining residue was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to afford 2D (0.21 g, 20%) as a clear, colorless oil. MS (ESI) *m/z*: 512.6 $(M+H)^+$.

[00419] 2E. [(E)-(S)-16-(2-Trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl]-carbamic acid *tert*-butyl ester and 2F. [(Z)-(S)-16-(2-Trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl]-carbamic acid *tert*-butyl ester: (Flask 1): To a flame-dried flask was added Grubbs (II) (0.139 g, 0.164 mmol). The flask was degassed with argon for several minutes and then degassed DCM (2 mL) was added to give a clear, burgundy solution. (Flask 2): To a separate flame-dried RBF was added 2D (0.21 g, 0.410 mmol), p-toluenesulfonic acid monohydrate (0.086 g, 0.451 mmol) and DCM (420 mL). The flask was equipped with a reflux condenser and the solution was degassed with argon for 30 min. The reaction was heated to 40 °C. After 1 h, the solution of Grubbs (II) was added dropwise. After 1 h, the reaction was cooled to rt, washed with sat. sodium bicarbonate, brine, dried over $MgSO_4$, filtered and concentrated to give a brown foam. Purification by reverse phase chromatography gave, after neutralization and extractive workup as described in 2D**,** 2E (0.09 g, 45.3 %, E-alkene) as a yellow solid and 2F (0.035 g, 17.6 %, Z-alkene) as a yellow solid. For 2E: MS (ESI) *m/z*: 484.6 $(M+H)^+$. For 2F: MS (ESI) *m/z*: 484.6 $(M+H)^+$.

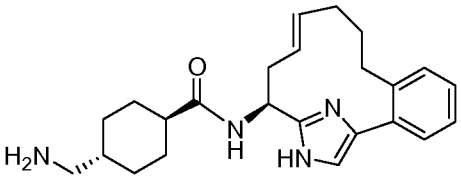
[00420] 2G. [(S)-16-(2-Trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To the solution of 2E and 2F (mixture of E/Z isomers) (0.049 g, 0.101 mmol) in MeOH (3 mL) was added 10% palladium on carbon (10.78 mg, 10.13 μmol). The reaction mixture was stirred under H_2-balloon. After 2 h, the reaction was filtered

through a 0.45 μm glass microfiber filter (GMF) and the Pd/C was rinsed with MeOH. The filtrate was concentrated to give 2G (0.046 g, 93 %) as a clear, colorless residue. MS (ESI) *m/z*: 486.7 $(M+H)^+$. The material was used in the next step without further purification.

[00421] 2H. Example 2 was prepared by following the procedures described in step 1F, by replacing 1D with 2G; followed by step 1G. ^1H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.47 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.57 (d, *J*=8.8 Hz, 1 H), 7.43 - 7.49 (m, 3 H), 7.32 - 7.39 (m, 2 H), 7.18 (d, *J*=16.0 Hz, 1 H), 6.76 (dd, *J*=15.7, 3.6 Hz, 1 H), 4.99 - 5.04 (m, 1 H), 2.52 - 2.60 (m, 1 H), 2.40 - 2.48 (m, 1 H), 2.18 - 2.26 (m, 1 H), 1.84-1.90 (m, 1 H), 1.31 - 1.58 (m, 4 H), 1.21 - 1.29 (m, 2 H), 0.87-1.01 (m, 1 H), 0.40-0.54 (m, 1 H). MS (ESI) *m/z*: 488.0 $(M+H)^+$. Analytical HPLC: RT = 5.78 min.

Example 3.

2 TFA salt



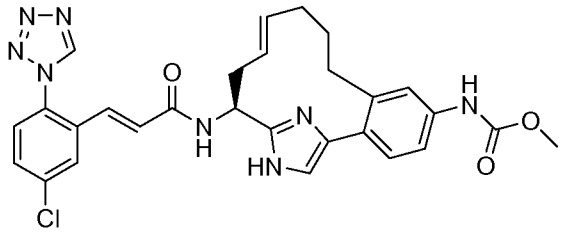
[00422] 3A. (E)-(S)-(16,18-Diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl)amine, 2 TFA salt: This compound was prepared following the procedures described in 1F, by replacing 1D with 2E. MS (ESI) *m/z*: 254.5 $(M+H)^+$.

[00423] 3B. {4-[(E)-(S)-(16,18-Diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl)carbamoyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester: To a solution of 3A (0.014 g, 0.029 mmol) in DMF (0.5 mL) was added (1r,4r)-4-((*tert*-butoxycarbonylamino)methyl)cyclohexanecarboxylic acid (8.23 mg, 0.032 mmol), EDC (0.011 g, 0.058 mmol), HOBt (8.91 mg, 0.058 mmol) and Hunig's base (0.015 g, 0.116 mmol). The reaction was stirred at rt for 16 h and then quenched with water to give a suspension. The solid was collected by filtration and then the solid was rinsed with water, air-dried, and then dried in a vacuum oven (50 °C) for 2 h to afford 3B (0.010 g, 69.8 %) as white solid. MS (ESI) *m/z*: 293.7 $(M+H)^+$. The material was used in the next step without further purification.

[00424] 3C. Example 3: To a solution of 3B (0.01 g, 0.020 mmol) in DCM (0.3 mL) was added TFA (0.3 mL, 3.89 mmol). The reaction was stirred at rt for 1 h, and then concentrated. Purification by reverse phase chromatography afforded Example 3 (0.0095 g, 73.7 %) as a white solid. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 7.40 - 7.45 (m, 2 H), 7.38 (s, 1 H), 7.29 - 7.37 (m, 2 H), 5.48 - 5.56 (m, 1 H), 5.07 - 5.15 (m, 1 H), 5.01 (dd, *J*=10.4, 4.9 Hz, 1 H), 2.75 - 2.84 (m, 3 H), 2.58 - 2.66 (m, 1 H), 2.43 - 2.51 (m, 2 H), 2.35-2.45 (m, 1 H), 1.82 - 2.03 (m, 6 H), 1.44 - 1.69 (m, 4 H), 1.20 - 1.30 (m, 1 H), 1.06 - 1.18 (m, 2 H). MS (ESI) *m/z*: 393.6 $(M+H)^+$. Analytical HPLC: RT = 3.70 min.

Example 4.

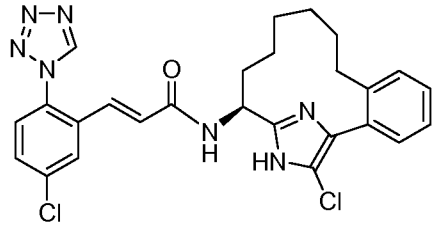
{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00425] Example 4 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 8; followed by steps 2B-2E; 1F; and 1G. ^{1}H NMR (50 °C, 500 MHz, CD_3OD) δ ppm 9.47 (s, 1 H), 7.96 (d, *J*=1.6 Hz, 1 H), 7.67 (d, *J*=8.8 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.46 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.29 - 7.37 (m, 2 H), 7.19 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.50 - 5.60 (m, 1 H), 5.09 - 5.19 (m, 1 H), 5.02 - 5.09 (m, 1 H), 3.75 (s, 3 H), 2.77 - 2.86 (m, 1 H), 2.40 - 2.60 (m, 3 H), 1.95 - 2.05 (m, 1 H), 1.85 - 1.95 (m, 1 H), 1.49 - 1.62 (m, 1 H), 1.25 - 1.38 (m, 1 H). MS (ESI) *m/z*: 559.1 $(M+H)^+$ and 561.1 $(M+2+H)^+$. Analytical HPLC (Method D): RT = 5.42 min.

Example 5.

(E)-*N*-((S)-17-Chloro-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt

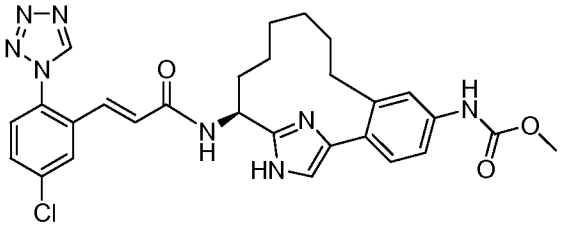


[00426] 5A. [(S)-17-Chloro-16-(2-trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To a solution of 2G (0.068 g, 0.140 mmol) in acetonitrile (0.5 mL)/$CHCl_3$ (0.5 mL) was added NCS (0.022 g, 0.168 mmol). The vial was sealed with a teflon-coated screw cap and the reaction was warmed to 65 °C. After 3 h, the reaction was cooled to rt. The reaction was diluted with EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by reverse phase chromatography gave, after neutralization of pure fractions and workup as described in step 2D, 0.020 g (27.5 %) of 5A as a white solid. MS (ESI) *m/z*: 520.7 $(M+H)^+$.

[00427] 5B. Example 5 was prepared by following the procedures described in step 1F, by replacing 1D with 5A; followed by step 1G. ^1H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.65 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.56 (d, *J*=8.8 Hz, 1 H), 7.35 - 7.39 (m, 2 H), 7.32 (s, 1 H), 7.26 - 7.31 (m, 2 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 4.86 (dd, *J*=10.4, 5.5 Hz, 1 H), 2.48 - 2.56 (m, 1 H), 2.36 - 2.43 (m, 1 H), 2.08 - 2.16 (m, 1 H), 1.60 - 1.70 (m, 1 H), 1.33 - 1.55 (m, 3 H), 1.11 - 1.31 (m, 3 H), 0.97 - 1.08 (m, 1 H), 0.28-0.41 (m, 1 H). MS (ESI) *m/z*: 522.4 $(M+H)^+$. Analytical HPLC: RT = 8.48 min.

Example 6.

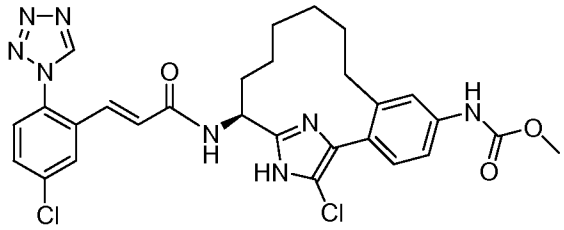
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00428] Example 6 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 8; followed by steps 2B-2G; 1F, by replacing ethanol with methanol and by running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.47 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.46 (d, *J*=2.2 Hz, 1 H), 7.41 - 7.44 (m, 2 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.17 (d, *J*=15.9 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 5.01 (dd, *J*=9.1, 5.8 Hz, 1 H), 3.75 (s, 3 H), 2.47 - 2.56 (m, 1 H), 2.36 - 2.44 (m, 1 H), 2.17 - 2.25 (m, 1 H), 1.82 - 1.91 (m, 1 H), 1.31 - 1.56 (m, 4 H), 1.23-1.26 (m, 2 H), 0.87 - 0.98 (m, 1 H), 0.38-0.53 (m, 1 H). MS (ESI) *m/z*: 561.1 $(M+H)^+$. Analytical HPLC: RT = 5.45 min.

Example 7.

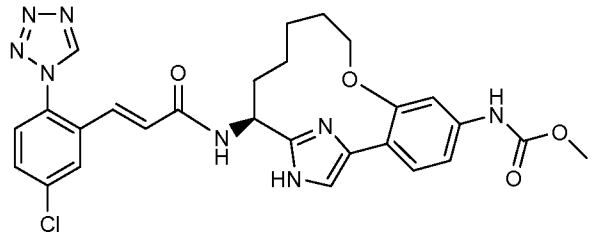
{(S)-17-Chloro-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00429] To the solution of Example 6 (0.012 g, 0.018 mmol) in acetonitrile (0.3 mL)/chloroform (0.300 mL) was added NCS (2.85 mg, 0.021 mmol). The vial was sealed with a teflon-coated screw cap and the reaction was warmed to 65 °C. After 4 h, additional NCS (2.85 mg, 0.021 mmol) was added. After another 1 h, the reaction was cooled to rt, and then concentrated. Purification by reverse phase chromatography afforded 0.0040 g (30.9 %) of Example 7 as a yellow solid. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.65 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 7.40 (d, *J*=2.2 Hz, 1 H), 7.36 (dd, *J*=8.3, 1.6 Hz, 1 H), 7.27 (d, *J*=8.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 4.85 (dd, *J*=10.4, 5.5 Hz, 1 H), 3.75 (s, 3 H), 2.43 - 2.52 (m, 1 H), 2.31 - 2.40 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.57 - 1.68 (m, 1 H), 1.10 - 1.53 (m, 6 H), 0.95 - 1.07 (m, 1 H), 0.26-0.38 (m, 1 H). MS (ESI) *m/z*: 561.1 $(M+H)^+$. Analytical HPLC: RT = 7.48 min.

Example 8.

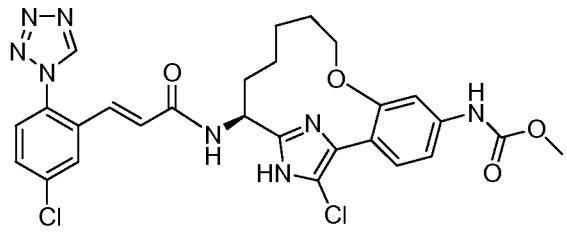
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00430] Example 8 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 7; followed by steps 2B-2C; 2E/2F-2G; 1F, by replacing ethanol with methanol and by running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.48 - 7.52 (m, 2 H), 7.46 (d, *J*=8.2 Hz, 1 H), 7.21 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.16 (d, *J*=15.9 Hz, 1 H), 6.78 (d, *J*=15.9 Hz, 1 H), 5.14 (dd, *J*=10.4, 6.0 Hz, 1 H), 3.82 - 3.88 (m, 1 H), 3.75 (s, 3 H), 3.67 - 3.72 (m, 1 H), 2.19 - 2.28 (m, 1 H), 1.84 - 1.99 (m, 2 H), 1.46 - 1.62 (m, 2 H), 1.35 - 1.45 (m, 1 H), 1.11 - 1.21 (m, 1 H), 0.88 - 0.99 (m, 1 H). MS (ESI) *m/z*: 562.9 $(M+H)^+$. Analytical HPLC: RT = 5.65 min.

Example 9.

{(S)-17-Chloro-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

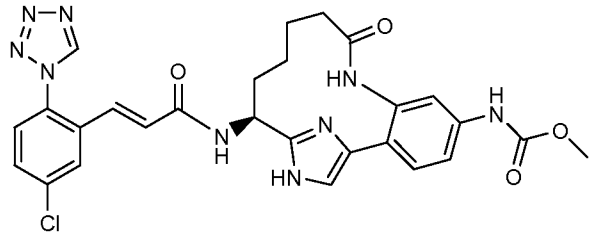


[00431] To a solution of Example 8 (0.013 g, 0.019 mmol) in acetonitrile (0.5 mL)/chloroform (0.500 mL) was added Hunig's base (6.69 µL, 0.038 mmol). The

reaction was stirred at rt for 10 min, then NCS (3.08 mg, 0.023 mmol) was added. The vial was sealed with a teflon-coated screw cap and the reaction was warmed to 65 °C. After 4 h, additional NCS (3.08 mg, 0.023 mmol) was added. After another 2 h, the reaction was cooled to rt and then concentrated. Purification by reverse phase chromatography afforded 0.0050 g (35.5 %) of Example 9 as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.3 Hz, 1 H), 7.47 - 7.51 (m, 2 H), 7.20 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.05 (dd, *J*=10.4, 6.0 Hz, 1 H), 3.80 - 3.85 (m, 1 H), 3.75 (s, 3 H), 3.64 - 3.70 (m, 1 H), 2.13 - 2.22 (m, 1 H), 1.81 - 1.92 (m, 2 H), 1.49 - 1.61 (m, 2 H), 1.30 - 1.41 (m, 1 H), 1.10 - 1.20 (m, 1 H), 0.89 - 1.01 (m, 1 H). MS (ESI) *m/z*: 597.0 $(M+H)^+$. Analytical HPLC: RT = 8.09 min.

Example 10.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00432] 10A. {3-Bromo-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-3*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: This compound was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 8; followed by step 2B. MS (ESI) *m/z*: 467.1 $(M+2+H)^+$.

[00433] 10B. {3-Bromo-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: (The following is an alternative procedure to procedure 2C). To a cooled (0 °C) solution of 10A (15 g, 32.2 mmol) in THF (77 mL) was added N,N-dicyclohexylmethylamine (7.52 mL, 35.5 mmol) followed by the dropwise addition of SEM-Cl (6.29 mL, 35.5 mmol). The reaction was stirred at 0 °C for 2h and then it was allowed to warm slowly to

rt. After 18 h, the yellow suspension was diluted with EtOAc, washed with sat. sodium bicarbonate, brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave 12.24 g (63.8%) of 10B as an off-white solid. MS (ESI) *m/z*: 595.1 $(M+H)^+$ and 597.2 $(M+2+H)^+$.

[00434] 10C. {3-Amino-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: A thick-walled vial containing 10B (2 g, 3.36 mmol), copper(I) iodide (0.128 g, 0.672 mmol), L-proline (0.155 g, 1.343 mmol) and potassium carbonate (1.392 g, 10.07 mmol) in DMSO (6.72 mL) was vacuumed and back-filled with argon three times. Then 28% aq. ammonium hydroxide (0.607 mL, 4.37 mmol) was added. The vial was sealed with a teflon-coated screw cap and the reaction was warmed to 85 °C. After 20 h, the reaction was cooled to rt, diluted with EtOAc, washed with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography afforded 1.05 g (58.8%) of 10C as a yellow solid. MS (ESI) *m/z*: 532.5 $(M+H)^+$.

[00435] 10C (Alternative route). Compound 10B (1.0 g, 1.679 mmol), copper(I) iodide (0.032 g, 0.168 mmol), L-proline (0.058 g, 0.504 mmol) and sodium azide (0.131 g, 2.015 mmol) were added to a 35 mL pressure tube. Next, EtOH (2.52 mL), water (0.839 mL), and 1N NaOH (0.504 mL, 0.504 mmol) were added. The reaction vessel was vacuumed and back-filled with argon three times. The pressure tube was sealed with a teflon screw cap, containing a viton O-ring, and then the reaction was warmed to 95 °C. After 20 h, the reaction was cooled to rt, and additional sodium azide (0.131 g, 2.015 mmol), L-proline (0.058 g, 0.504 mmol), copper(I) iodide (0.032 g, 0.168 mmol), NaOH (0.504 mL, 0.504 mmol) and EtOH (2.52 mL) were added. The vessel was sealed and the reaction was warmed to 95 °C. After another 24 h, the reaction was cooled to rt, diluted with EtOAc, washed with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography gave 0.475 g (53.2%) of 10C as an orange solid. MS (ESI) *m/z*: 532.4 $(M+H)^+$.

[00436] 10D. {3-But-3-enoylamino-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: To a cooled (-10 °C) solution of Hunig's base (0.300 mL, 1.715 mmol), but-3-enoic acid (0.049 g, 0.572 mmol) and 10C (0.304 g, 0.572 mmol) in ethyl acetate (16.34 mL) was added 1-propanephosphonic acid cyclic anhydride (T3P) (50% in EtOAc,

0.674 mL, 1.143 mmol). After 5 min, the reaction was allowed to warm to rt. After 1 h at rt, the reaction was concentrated. Purification by normal phase chromatography gave 0.30 g (87%) of 10D as a yellow solid. MS (ESI) *m/z*: 600.3 $(M+H)^+$.

[00437] 10E. [(E)-(S)-14-*tert*-Butoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-yl]-carbamic acid methyl ester; and 10F. [(Z)-(S)-14-*tert*-Butoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-yl]-carbamic acid methyl ester: Compound 10E, the E-alkene, and compound 10F, the Z-alkene, were prepared following the procedure described in 2E/2F, by replacing 2D with 10D. MS (ESI) *m/z*: 572.2 $(M+H)^+$.

[00438] 10G. [(S)-14-*tert*-Butoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl]-carbamic acid methyl ester: To a suspension of 10E (0.25 g, 0.437 mmol) in MeOH (10 mL)/EtOAc (5 mL) was added 10% palladium on carbon (0.047 g, 0.044 mmol). Hydrogen was bubbled through the reaction mixture for 5 min and then the reaction was stirred vigorously under a hydrogen atmosphere (balloon). After 24 h, the reaction was filtered through a 0.45 μm GMF, rinsing with MeOH, DCM and EtOAc. The filtrate was concentrated and purification by reverse phase chromatography afforded 0.220 g (88%) of 10G, as an off-white solid. MS (ESI) *m/z*: 574.4 $(M+H)^+$.

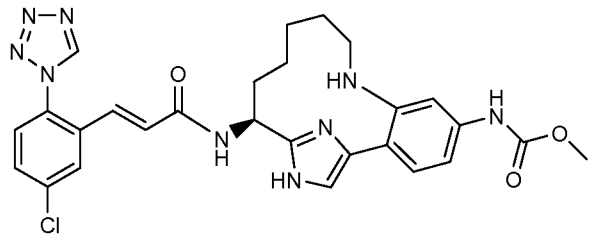
[00439] 10H. ((S)-14-Amino-9-oxo-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester, 2 HCl salt: A mixture of 10G (0.099 g, 0.173 mmol) and 4M HCl in dioxane (2 mL, 8.00 mmol) in a sealed tube was heated at 50 °C. After 2 h, the yellow suspension was cooled to rt and then concentrated. The residue was suspended in MeOH (0.2 mL) and Et_2O. The solid was collected by filtration. The solid was rinsed with Et_2O, air-dried (very hygroscopic) to afford 0.053 g (73.8 %) of 10H as a yellow solid. MS (ESI) *m/z*: 344.2 $(M+H)^+$.

[00440] 10I. Example 10 was prepared following the procedure described in 1G, by replacing 1F with 10H. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.50 (d, *J*=8.2 Hz, 1 H), 7.44 (s, 1 H), 7.42 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.9 Hz, 1 H), 5.13 (dd, *J*=10.2, 6.3 Hz, 1 H), 3.75 (s, 3 H), 2.42 - 2.52 (m, 1 H), 2.17 - 2.29 (m, 1

H), 2.05 - 2.15 (m, 1 H), 1.96 (m, 1 H), 1.51 - 1.71 (m, 2 H), 1.36 - 1.49 (m, 1 H), 0.92 - 1.07 (m, 1 H). MS (ESI) *m/z*: 576.3 $(M+H)^+$. Analytical HPLC: RT = 4.60 min.

Example 11.

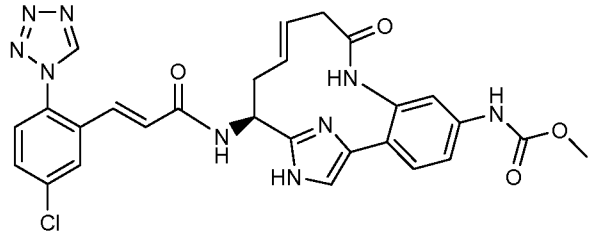
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00441] Example 11 was prepared following the procedures described in step 10C, by replacing ammonium hydroxide with but-3-enylamine and running the reaction at 90 °C; followed by steps 10E/F; 10G, by replacing the methanol/EtOAc mixture with EtOAc; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 8.01 (d, *J*=2.2 Hz, 1 H), 7.82 (s, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.61 (d, *J*=8.8 Hz, 1 H), 7.55 (d, *J*=8.2 Hz, 1 H), 7.40 (s, 1 H), 7.28 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.24 (d, *J*=15.9 Hz, 1 H), 6.81 (d, *J*=15.4 Hz, 1 H), 5.29 (dd, *J*=10.7, 6.3 Hz, 1 H), 3.72 (s, 3 H), 3.16 - 3.24 (m, 1 H), 2.93 (t, *J*=11.5 Hz, 1 H), 2.00 - 2.20 (m, 3 H), 1.82 - 1.92 (m, 1 H), 1.62 - 1.76 (m, 2 H), 1.27 - 1.41 (m, 1 H), 0.78-0.87 (m, 1 H). MS (ESI) *m/z*: 562.2 $(M+H)^+$. Analytical HPLC: RT = 5.59 min.

Example 12.

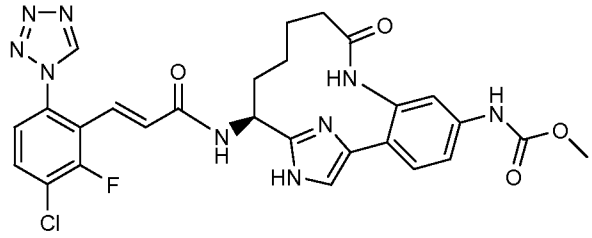
{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00442] Example 12 was prepared following the procedures described in step 10H, by replacing 10G with 10E; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.66 - 7.72 (m, 2 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.45 (s, 2 H), 7.35 (s, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.73 - 5.82 (m, 1 H), 5.21 - 5.29 (m, 1 H), 5.10 (dd, *J*=9.1, 5.2 Hz, 1 H), 3.75 (s, 3 H), 2.91 - 3.03 (m, 2 H), 2.81 - 2.89 (m, 1 H), 2.48-2.59 (m, 1 H). MS (ESI) *m/z*: 574.1 $(M+H)^+$. Analytical HPLC: RT = 4.78 min.

Example 13.

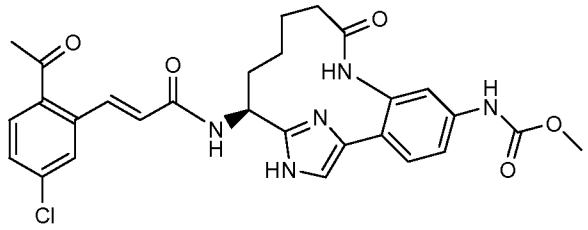
{(S)-14-[(E)-3-(3-Chloro-2-fluoro-6-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00443] Example 13 was prepared following the procedure described in 1G, by replacing 1F with 10H and by replacing Intermediate 1 with Intermediate 3. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.78 (t, *J*=8.2 Hz, 1 H), 7.56 (s, 1 H), 7.40 - 7.52 (m, 4 H), 7.00 (d, *J*=15.9 Hz, 1 H), 6.81 (d, *J*=15.9 Hz, 1 H), 5.12 (dd, *J*=9.9, 6.6 Hz, 1 H), 3.75 (s, 3 H), 2.42 - 2.51 (m, 1 H), 2.16 - 2.26 (m, 1 H), 2.04 - 2.13 (m, 1 H), 1.89 - 2.00 (m, 1 H), 1.51 - 1.69 (m, 2 H), 1.36 - 1.48 (m, 1 H), 0.90 - 1.03 (m, 1 H). MS (ESI) *m/z*: 594.3 $(M+H)^+$. Analytical HPLC: RT = 4.79 min.

Example 14.

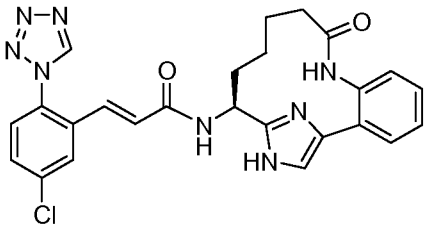
{(S)-14-[(E)-3-(2-Acetyl-5-chloro-phenyl)-acryloylamino]-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00444] Example 14 was prepared following the procedure described in step 1G, by replacing 1F with 10H, by replacing Intermediate 1 with Intermediate 4, and by using EDC, HOBt, and triethylamine. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.97 (d, *J*=15.4 Hz, 1 H), 7.91 (d, *J*=8.2 Hz, 1 H), 7.65 (d, *J*=1.6 Hz, 1 H), 7.58 (d, *J*=2.2 Hz, 1 H), 7.50 - 7.55 (m, 2 H), 7.47 (s, 1 H), 7.43 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.54 (d, *J*=15.9 Hz, 1 H), 5.17 (dd, *J*=10.2, 6.3 Hz, 1 H), 3.76 (s, 3 H), 2.59 (s, 3 H), 2.45 - 2.53 (m, 1 H), 2.20 - 2.31 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.92 - 2.02 (m, 1 H), 1.55 - 1.72 (m, 2 H), 1.40 - 1.52 (m, 1 H), 0.94 - 1.07 (m, 1 H). MS (ESI) *m/z*: 550.2 $(M+H)^+$. Analytical HPLC: RT = 5.01 min.

Example 15.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl)-acrylamide, 1 TFA salt



[00445] 15A. {(S)-1-[4-(2-Nitro-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: This compound was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with 2-bromo-1-(2-nitrophenyl)ethanone; followed by steps 2B, by replacing xylene with toluene; and 2C. MS (ESI) *m/z*: 489.4$(M+H)^+$.

[00446] 15B. {(S)-1-[4-(2-Amino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a yellow solution of 15A

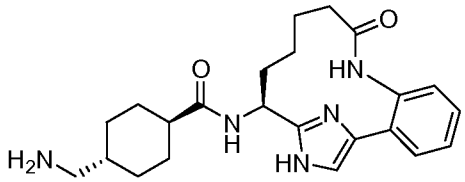
(1.0441 g, 2.137 mmol) in MeOH (14.15 mL) was added zinc dust (1.397 g, 21.37 mmol) and ammonium chloride (1.143 g, 21.37 mmol). The gray suspension was stirred vigorously at rt. After 1h, the flask was equipped with a reflux condenser and the reaction was warmed to 60 °C. After 1h, the reaction was cooled to rt and allowed to stir overnight. The reaction was filtered through a 0.45 μm GMF, eluting with methanol. The filtrate was concentrated to give a yellow solid. The solid was partitioned between EtOAc and 0.5M HCl (aq). The layers were separated and the aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give an orange oil. Purification by normal phase chromatography gave 0.818g (83%) of 15B as a yellow foam. MS (ESI) *m/z*: 459.4$(M+H)^+$.

[00447] 15C. (S)-14-Amino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-9-one, 2HCl: This compound was prepared following the procedures in step 10D, by replacing 10C with 15B; followed by steps 2E/2F; 2G, by replacing the hydrogen balloon with hydrogen (50-55 psi); and 10H. MS (ESI) *m/z*: 489.4$(M+H)^+$.

[00448] 15D. Example 15: A suspension of Intermediate 2 (0.074g, 0.296 mmol), 15C (0.113g, 0.329 mmol), EDC (0.095g, 0.494 mmol), and HOBT (0.076g, 0.494 mmol) in DMF (1.65mL) and Hunig's Base (0.172mL, 0.988 mmol) was stirred at rt overnight. Water was added to the brown solution to give a suspension. The mixture was extracted with EtOAc (2x). The organic layers were combined and washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. Purification by reverse phase chromatography gave 0.0964g (47%) of Example 15 as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.96 - 1.13 (m, 1 H), 1.37 - 1.50 (m, 1 H), 1.51 - 1.72 (m, 2 H), 1.90 - 2.01 (m, 1 H), 2.05 - 2.15 (m, 1 H), 2.18 - 2.28 (m, 1 H), 2.44 - 2.50 (m, 1 H), 5.13 (dd, *J*=10.2, 6.3 Hz, 1 H), 6.75 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.31 (dd, *J*=7.8, 0.7 Hz, 1 H), 7.44 (td, *J*=7.6, 1.1 Hz, 1 H), 7.49 (s, 1 H), 7.53 (td, *J*=7.7, 1.4 Hz, 1 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.61 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). MS (ESI) *m/z*: 503.3$(M+H)^+$. Analytical HPLC: RT = 4.72 min.

Example 16.

4-Aminomethyl-cyclohexanecarboxylic acid ((S)-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl)-amide, 2 TFA salt

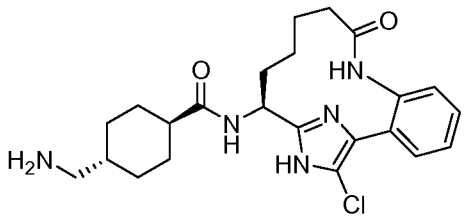


[00449] 16A. [4-((S)-9-Oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-ylcarbamoyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester: This compound was prepared following the procedure described in 3B, by replacing 3A with 15C. MS (ESI) *m/z*: 510.4(M+H)$^+$.

[00450] 16B. Example 16 was prepared following the procedure described in 3C, by replacing 3B with 16A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.91 - 1.18 (m, 3 H), 1.28 - 1.75 (m, 6 H), 1.84 - 1.98 (m, 5 H), 2.07 - 2.23 (m, 2 H), 2.33 (tt, *J*=12.1, 3.3 Hz, 1 H), 2.43 - 2.53 (m, 1 H), 2.79 (d, *J*=6.9 Hz, 2 H), 5.05 (dd, *J*=10.7, 6.3 Hz, 1 H), 7.32 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.44 (td, *J*=7.7, 1.3 Hz, 1 H), 7.49 (s, 1 H), 7.53 (td, *J*=7.7, 1.5 Hz, 1 H), 7.60 (dd, *J*=7.7, 1.4 Hz, 1 H). MS (ESI) *m/z*: 410.4(M+H)$^+$. Analytical HPLC: RT = 1.56, 2.10 min.

Example 17.

4-Aminomethyl-cyclohexanecarboxylic acid ((S)-17-chloro-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl)-amide, 2 TFA salt



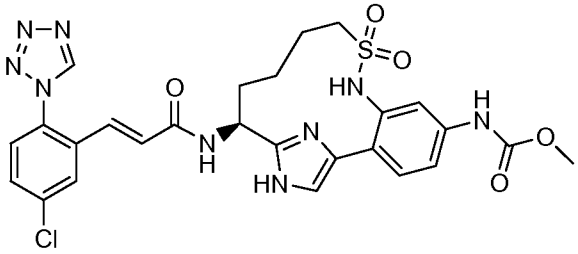
[00451] 17A. [4-((S)-17-Chloro-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-ylcarbamoyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester: Compound 16A was dissolved in EtOAc and washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give the free base of 16A. To a suspension of the free base of 16A (0.067g, 0.131 mmol) in acetonitrile (1.32mL) and

chloroform (1.32mL) was added NCS (0.018 mg, 0.131 mmol). The thick-walled vial was sealed with a teflon coated screw cap and the reaction was heated to 65 °C. After 1h and 35min, the reaction was cooled to rt and partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc (1x). The organic layers were combined, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. Purification by reverse phase chromatography gave 0.018 g (17%) of 17A as a white solid. MS (ESI) *m/z*: 544.3$(M+H)^+$.

[00452] 17B. Example 17 was prepared following the procedure described in 3C, by replacing 3B with 17A. ^1H NMR (500 MHz, CD_3OD) δ ppm 0.93 - 1.17 (m, 3 H), 1.34 - 1.80 (m, 7 H), 1.86 - 2.10 (m, 6 H), 2.25 - 2.34 (m, 1 H), 2.36 - 2.43 (m, 1 H), 2.80 (d, *J*=7.2 Hz, 2 H), 4.93 (dd, *J*=10.7, 6.1 Hz, 1 H), 7.27 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.41 (td, *J*=7.6, 1.3 Hz, 1 H), 7.46 (td, *J*=7.6, 1.6 Hz, 1 H), 7.60 (dd, *J*=7.4, 1.4 Hz, 1 H). MS (ESI) *m/z*: 444.2$(M+H)^+$. Analytical HPLC: RT = 3.36 min.

Example 18.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9,9-dioxo-9λ^6-thia-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

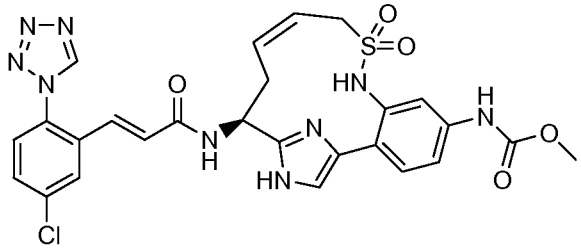


[00453] 18A. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(prop-2-ene-1-sulfonylamino)-phenyl]-carbamic acid methyl ester: To a solution of 10C (178 mg, 0.335 mmol) in CH_2Cl_2 (2 mL) was added DIEA (0.117 mL, 0.670 mmol). The reaction was cooled to 0 °C. Next, a solution of prop-2-ene-1-sulfonyl chloride (54.5 mg, 0.368 mmol) in DCM (1 ml) was added dropwise. The resulting mixture was stirred at 0 °C for 2 h. The reaction was concentrated and purification by normal phase chromatography gave 18A as a pale yellow solid (124 mg, 58%). MS (ESI) *m/z*: 636.4 $(M+H)^+$.

[00454] 18B. Example 18 was prepared following the procedures described in step 2E/2F, by replacing 2D with 18A; followed by steps 2G; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.64 - 7.75 (m, 2 H), 7.54 - 7.64 (m, 2 H), 7.43 - 7.54 (m, 2 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.78 (d, *J*=15.4 Hz, 1 H), 5.04 (dd, *J*=9.3, 4.9 Hz, 1 H), 3.75 (s, 3 H), 2.92 - 3.01 (m, 2 H), 2.16 - 2.27 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.69 - 1.81 (m, 1 H), 1.52 - 1.66 (m, 1 H), 1.08 - 1.25 (m, 1 H), 0.72 - 0.93 (m, 1 H). MS (ESI) *m/z*: 612.3 $(M+H)^+$. Analytical HPLC: RT = 3.92 min (Method B).

Example 19.

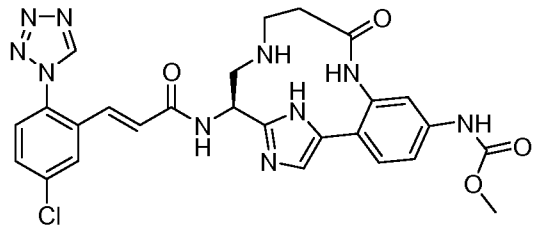
{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9,9-dioxo-9 λ^6-thia-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00455] Example 19 was prepared following the procedures described in step 2E, by replacing 2D with 18A; followed by steps 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.98 (d, *J*=2.3 Hz, 1 H), 7.74 (s, 1 H), 7.68 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.54 - 7.62 (m, 1 H), 7.46 - 7.54 (m, 2 H), 7.43 (s, 1 H), 7.17 (d, *J*=15.7 Hz, 1 H), 6.78 (d, *J*=15.7 Hz, 1 H), 5.88 - 6.06 (m, 1 H), 5.07 - 5.22 (m, 2 H), 3.85 - 4.08 (m, 2 H), 3.76 (s, 3 H), 2.81 - 2.95 (m, 1 H), 2.47 - 2.64 (m, 1 H). MS (ESI) *m/z*: 610.3 $(M+H)^+$. Analytical HPLC: RT = 3.49 min (Method B).

Example 20.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,12,16,18-tetraaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00456] 20A. {(S)-2-Benzyloxycarbonylamino-2-[4-(2-bromo-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-ethyl}-carbamic acid *tert*-butyl ester: This compound was prepared following the procedures described in step 2A, by replacing (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid with (S)-2-benzyloxycarbonylamino-3-*tert*-butoxycarbonylamino-propionic acid and by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 8; followed by steps 2B; and 10B. MS (ESI) *m/z*: 720.5$(M+H)^+$.

[00457] 20B. {4-[2-((S)-2-Amino-1-benzyloxycarbonylamino-ethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-bromo-phenyl}-carbamic acid methyl ester: This compound was prepared following the procedure described in 3C, by replacing 3B with 20A. MS (ESI) *m/z*: 620.3$(M+H)^+$.

[00458] 20C. 3-{(S)-2-Benzyloxycarbonylamino-2-[4-(2-bromo-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-ethylamino}-propionic acid methyl ester: To a mixture of 20B (204 mg, 0.330 mmol), methyl acrylate (0.089 mL, 0.989 mmol) and triethylamine (0.230 mL, 1.649 mmol) was added isopropyl alcohol (3 mL) in a sealed microwave tube. The reaction was stirred at 80 °C overnight. The reaction mixture was concentrated to give 20C (208 mg, 90 % yield) as a beige solid. MS (ESI) *m/z*: 706.4$(M+H)^+$.

[00459] 20D. 3-({(S)-2-Benzyloxycarbonylamino-2-[4-(2-bromo-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-ethyl}-*tert*-butoxycarbonyl-amino)-propionic acid methyl ester: To a solution of 20C (208 mg, 0.295 mmol) in CH_2Cl_2 (2952 μL) at 0 °C was added di-*tert*-butyl dicarbonate (64.4 mg, 0.295 mmol) and DMAP (3.61 mg, 0.030 mmol). The reaction mixture was stirred at 0 °C and allowed to warm slowly to rt. After 4 h, the reaction mixture was concentrated and purified by normal phase chromatography to give 20D (180 mg, 0.224 mmol, 76 % yield) as a pale yellow solid. MS (ESI) *m/z*: 806.2$(M+H)^+$.

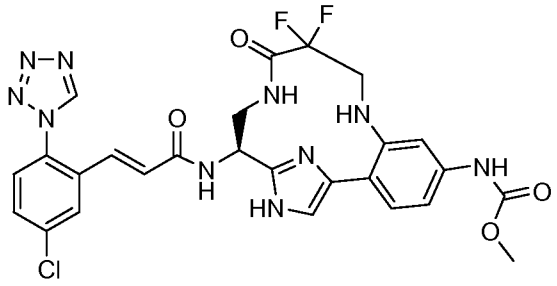
[00460] 20E. 3-({(S)-2-[4-(2-Amino-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-2-benzyloxycarbonylamino-ethyl}-*tert*-butoxycarbonyl-amino)-propionic acid: This compound was prepared following the procedure described in 10C (alternative route), by replacing 10B with 20D. MS (ESI) *m/z*: 727.6$(M+H)^+$.

[00461] 20F. (S)-14-Benzyloxycarbonylamino-5-methoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,12,16,18-tetraaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-12-carboxylic acid *tert*-butyl ester: To a solution of BOP (50.2 mg, 0.113 mmol) in DCM (44.900 ml) and DMF (0.449 ml) at rt was added a solution of 20E (33 mg, 0.045 mmol) and DIEA (0.079 ml, 0.454 mmol) in DMF (3 mL) *via* a syringe pump over 5 h. The reaction mixture was concentrated to remove DCM, then diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered, and concentrated. Normal phase chromatography gave 20F (28 mg, 87 % yield) as an off-white solid. MS (ESI) *m/z*: 709.3$(M+H)^+$.

[00462] 20G. Example 20 was prepared following the procedures described in step 2G, by replacing 2E/2F with 20F; followed by steps 1G; and 3C. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 9.49 (s, 1 H) 7.93 (d, *J*=2.2 Hz, 1 H) 7.66 (dd, *J*=8.79, 2.2 Hz, 1 H) 7.57 (d, *J*=8.24 Hz, 2 H) 7.42 (m, 3 H) 7.22 (d, *J*=15.94 Hz, 1 H) 6.62 (d, *J*=15.39 Hz, 1 H) 5.40 (dd, *J*=6.05, 2.75 Hz, 1 H) 3.74 (s, 3 H) 3.51-3.69 (m, 2 H) 3.25-3.39 (m, 2 H) 2.89-2.98 (m, 2 H). MS (ESI) *m/z*: 577.3$(M+H)^+$. Analytical HPLC: RT = 4.72min.

Example 21.

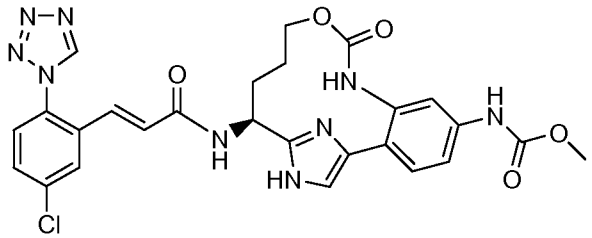
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10,10-difluoro-11-oxo-8,12,16,18-tetraaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00463] Example 21 was prepared following the procedures described in step10C (alternative route), by replacing sodium azide with 3-amino-2,2-difluoropropanoic acid and by replacing 10B with 20A; followed by steps 3C; 20F; 2G; 1G; and 3C. MS (ESI) *m/z*: 613.3$(M+H)^+$. Analytical HPLC: RT = 5.24 min.

Example 22.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-10-oxa-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00464] 22A. (S)-2-(2-Bromo-4-nitrophenyl)-2-oxoethyl 5-(benzyloxy)-2-(*tert*-butoxycarbonylamino)pentanoate: This compound was prepared following the procedure described in 2A, by replacing (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid with (S)-5-(benzyloxy)-2-(*tert*-butoxycarbonylamino)pentenoic acid and replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 10. MS (ESI) *m/z*: 565.4 $(M+2-H)^-$.

[00465] 22B. (S)-2-(4-Amino-2-bromophenyl)-2-oxoethyl 5-(benzyloxy)-2-(*tert*-butoxycarbonylamino)pentanoate: To a solution of 22A (2.6 g, 4.60 mmol) in ethanol (30 mL) was added iron powder (2.57 g, 46.0 mmol). The suspension was mixed briefly and then 1.0 M aqueous hydrochloric acid (2.299 mL, 2.299 mmol) was added. The reaction mixture was heated to 50 °C. After 2 h, the reaction was cooled to rt, diluted with ethyl acetate, and filtered through a pad of CELITE®, eluting with ethyl acetate. The filtrate was concentrated, re-dissolved in ethyl acetate, washed with sat. $NaHCO_3$,

brine, dried over sodium sulfate and concentrated to give 22B (1.954 g, 79 % yield) as a yellow solid. The material was used in the next step without further purification. MS (ESI) *m/z*: 537.4 $(M+2+H)^+$.

[00466] 22C. {3-Amino-4-[2-((S)-4-benzyloxy-1-*tert*-butoxycarbonylamino-butyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: This compound was prepared following the procedures described in step Intermediate 7B, by replacing Intermediate 7A with 22B; followed by steps 1B; 10B; and 10C (alternate). MS (ESI) *m/z*: 640.5 $(M+H)^+$.

[00467] 22D. {3-Amino-4-[2-((S)-1-*tert*-butoxycarbonylamino-4-hydroxy-butyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: To a solution of 22C (0.446 g, 0.697 mmol) in EtOAc (10 mL) was added TFA (0.081 mL, 1.046 mmol). The reaction was stirred at rt for 5 min, then 10% palladium on carbon (0.074 g, 0.070 mmol) was added. Hydrogen was bubbled through the reaction for a few minutes, then the reaction was stirred vigorously under a hydrogen atmosphere (balloon). After 17 h, the reaction was filtered through a 0.45 micron GMF, rinsing with EtOAc and MeOH. The filtrate was concentrated, redissolved in EtOAc, washed with sat. sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated to afford 22D (0.35 g, 91 %) as a yellow solid. MS (ESI) *m/z*: 550.4 $(M+H)^+$. The material was used in the next step without further purification.

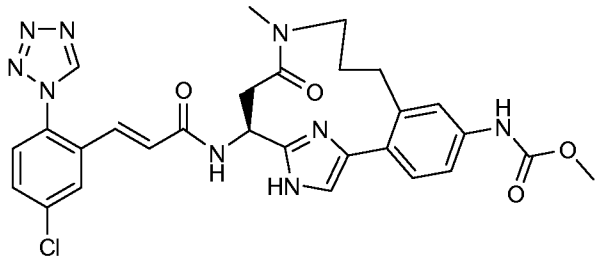
[00468] 22E. [(S)-5-Methoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-10-oxa-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To a solution of 22D (0.19 g, 0.346 mmol) in DCM (15.03 mL) at 0 °C was added TEA (0.096 mL, 0.691 mmol) followed by 4-nitrophenyl carbonochloridate (0.077 g, 0.380 mmol). After 1 h, the reaction was warmed to rt. After 18 h, the reaction was concentrated. Purification by reverse phase chromatography afforded 22E (0.049 g, 24.63 %), as a yellow solid. MS (ESI) *m/z*: 576.5 $(M+H)^+$.

[00469] 22F. Example 22 was prepared following the procedures described in step 1F, by replacing 1E with 22E, by replacing ethanol with methanol, and by running the reaction at 75 °C; followed by step 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.42 (s, 1 H), 7.76 (d, *J*=2.2 Hz, 1 H), 7.59 - 7.68 (m, 2 H), 7.46 - 7.55 (m, 2 H), 7.22 (d, *J*=8.3 Hz, 1 H), 7.16 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.88 (d, *J*=15.4 Hz, 1 H), 6.65 (d, *J*=15.4 Hz, 1 H),

5.26 (t, *J*=7.7 Hz, 1 H), 3.71 (s, 3 H), 3.61 (t, *J*=6.0 Hz, 2 H), 2.08 - 2.22 (m, 2 H), 1.54 - 1.74 (m, 2 H). MS (ESI) *m/z*: 578.3 $(M+H)^+$. Analytical HPLC: RT = 4.70 min.

Example 23.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-methyl-12-oxo-11,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00470] 23A. (S)-3-[4-(2-Bromo-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-3-*tert*-butoxycarbonylamino-propionic acid benzyl ester: This compound was prepared following the procedures described in 2A, by replacing (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid with (S)-2-*tert*-butoxycarbonylamino-succinic acid 4-benzyl ester, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 8 and by replacing potassium hydrogen carbonate with potassium carbonate; followed by steps 2B, by replacing xylene with toluene; and 10B. MS (ESI) *m/z*: 703.3, 705.3 $(M+H)^+$.

[00471] 23B. Methyl-prop-2-ynyl-carbamic acid benzyl ester: To a solution of N-methylprop-2-yn-1-amine (3.50 g, 50.6 mmol) in DCM (50 mL) were added TEA (8.47 mL, 60.8 mmol) and Cbz-Cl (7.95 mL, 55.7 mmol) dropwise at 0 °C. The reaction was stirred under argon at 0 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2, washed with 1M HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give 23B (10.02 g, 97% yield) as a clear oil. MS (ESI) *m/z*: 204.1 $(M+H)^+$.

[00472] 23C. (S)-3-[4-{2-[3-(Benzyloxycarbonyl-methyl-amino)-prop-1-ynyl]-4-methoxycarbonylamino-phenyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-3-*tert*-butoxycarbonylamino-propionic acid benzyl ester: To a solution of 23A (200 mg, 0.284 mmol) in DMF (5 mL) was added 23B (69.3 mg, 0.341 mmol), CuI (10.83 mg,

0.057 mmol), TEA (0.119 mL, 0.853 mmol) and $Pd(Ph_3P)_4$ (32.8 mg, 0.028 mmol). The reaction was purged with argon for 3 min and then stirred under argon at 90 °C for 6 h. The reaction was cooled to rt and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase chromatography to give 23C (205 mg, 87% yield) as a solid. LC-MS (ESI) *m/z*: 826.5 $(M+H)^+$.

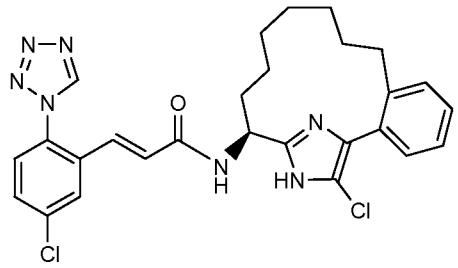
[00473] 23D. (S)-3-(*tert*-Butoxycarbonylamino)-3-(4-(4-(methoxycarbonylamino)-2-(3-(methylamino)propyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)propanoic acid, TFA salt: This compound was prepared following the procedure described in 2G, by replacing 2E with 23C. MS (ESI) *m/z*: 606.4 $(M+H)^+$.

[00474] 23E. [(S)-5-Methoxycarbonylamino-11-methyl-12-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-11,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To a solution of DMAP (23.19 mg, 0.190 mmol), DIEA (0.166 mL, 0.949 mmol) and BOP (168 mg, 0.380 mmol) in DCM (20 mL) was added a solution of 23D (115 mg, 0.190 mmol) in DMF (2 mL) at rt through a syringe pump over 1.5 h. Upon addition, the reaction was stirred for another 30 min and the solvent was removed. The crude product was purified by reverse phase chromatography to give 23E (44 mg, 39.4% yield) as a solid. MS (ESI) *m/z*: 588.4 $(M+H)^+$.

[00475] 23F. Example 23 was prepared following the procedures described in step 1F, by replacing 1D with 23E and by replacing ethanol with methanol; followed by step 1G. ^1H NMR (400 MHz, CD_3OD, rotamers) δ ppm 9.52 (two singlets, 1H), 9.36 (s, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.68 (ddd, J = 8.6, 6.3, 2.3 Hz, 1H), 7.59 (dd, J = 8.5, 5.5 Hz, 1H), 7.49 - 7.43 (m, 1H), 7.41 - 7.33 (m, 3H), 7.19 (two doublets, J = 16.0 Hz, 1H), 6.81 (two doublets, J = 15.6 Hz, 1H), 5.49 (dd, J = 8.7, 4.8 Hz, 1H), 4.12 (ddd, J = 7.3, 6.0, 3.7 Hz, 1H), 3.75 (two singlets, 3H), 3.55 - 3.43 (m, J = 9.2, 7.6, 5.9 Hz, 1H), 3.00 (two singlets, 3H), 2.81 (dd, J = 13.9, 4.8 Hz, 1H), 2.69 - 2.57 (m, 2H), 2.48 - 2.28 (m, 1H), 1.91 - 1.76 (m, 1H), 1.64 - 1.44 (m, 1H). LC-MS (ESI) *m/z*: 590.2 $(M+H)^+$. Analytical HPLC: RT = 5.328 min.

Example 24.

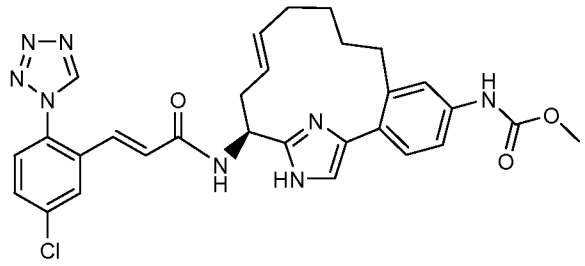
(E)-*N*-((S)-18-Chloro-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00476] Example 24 was prepared following the procedures described in step 2D, by replacing pent-4-enylboronic acid with hex-5-enylboronic acid; followed by steps 2E/2F; 2G; 1F; 1G; and 7. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.45 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.64 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 7.24 - 7.35 (m, 4 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.9 Hz, 1 H), 4.91 (dd, *J*=9.6, 4.1 Hz, 1 H), 2.68 - 2.76 (m, 1 H), 2.39 - 2.48 (m, 1 H), 2.06 - 2.14 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.56 - 1.65 (m, 1 H), 1.23 - 1.45 (m, 7 H), 0.76 - 0.86 (m, 1 H), 0.49 - 0.59 (m, 1 H). MS (ESI) *m/z*: 536.4 $(M+H)^+$. Analytical HPLC: RT = 8.84 min.

Example 25.

{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

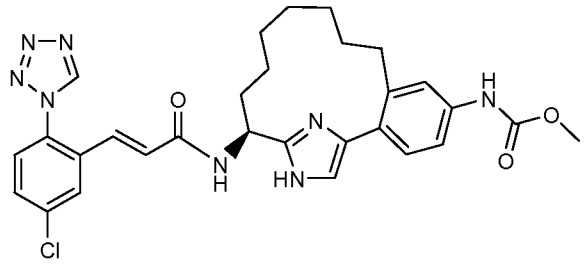


[00477] Example 25 was prepared following the procedures described in step 2D, by replacing 2C with 10B and by replacing pent-4-enylboronic acid with hex-5-enylboronic acid; followed by steps 2E; 1F, by replacing ethanol with methanol and by running the reaction at 50-75 °C; and 1G. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.96 (d, *J*=2.7 Hz, 1 H), 7.64 - 7.70 (m, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.37 - 7.46 (m, 2

H), 7.32 - 7.35 (m, 1 H), 7.28 (d, *J*=8.2 Hz, 1 H), 7.19 (d, *J*=15.9 Hz, 1 H), 6.74 (d, *J*=15.9 Hz, 1 H), 5.48 - 5.58 (m, 1 H), 5.22 - 5.31 (m, 1 H), 5.09 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.81 - 2.89 (m, 1 H), 2.69 - 2.78 (m, 1 H), 2.52 - 2.62 (m, 1 H), 2.38 - 2.48 (m, 1 H), 2.06 - 2.23 (m, 2 H), 1.38 - 1.59 (m, 2 H), 1.09 - 1.19 (m, 2 H). MS (ESI) *m/z*: 573.4 $(M+H)^+$. Analytical HPLC: RT = 5.63 min.

Example 26.

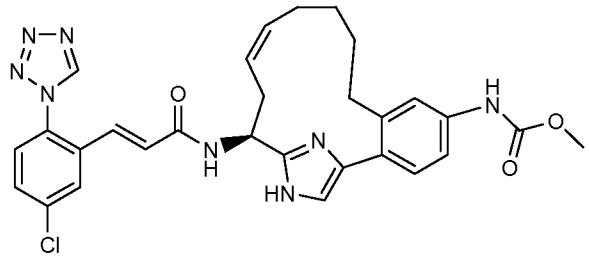
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00478] Example 26 was prepared following the procedures described in step 2D, by replacing 2C with 10B and by replacing pent-4-enylboronic acid with hex-5-enylboronic acid; followed by steps 2E/2F; 2G; 1F, by replacing ethanol with methanol and running the reaction at 50-75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.43 - 7.46 (m, 2 H), 7.41 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.31 (d, *J*=8.2 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.00 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.56 - 2.67 (m, 2 H), 2.21 - 2.30 (m, 1 H), 2.03 - 2.13 (m, 1 H), 1.66 - 1.76 (m, 1 H), 1.25 - 1.57 (m, 7 H), 0.47-0.60 (m, 2 H). MS (ESI) *m/z*: 575.5 $(M+H)^+$. Analytical HPLC: RT = 5.73 min.

Example 27.

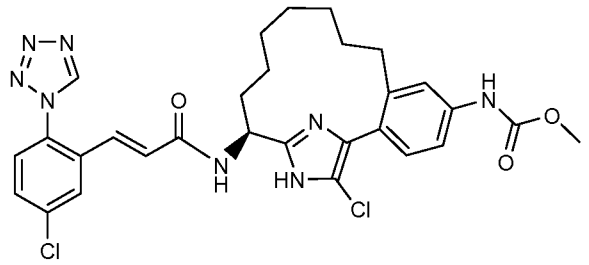
{(Z)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00479] Example 27 was prepared following the procedures described in step 2D, by replacing 2C with 10B and by replacing pent-4-enylboronic acid with hex-5-enylboronic acid; followed by steps 2F; 1F, by replacing ethanol with methanol and running the reaction at 50-75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.44 (s, 1 H), 7.41 (dd, *J*=8.3, 4.7 Hz, 1 H), 7.32 (s, 1 H), 7.30 (d, *J*=8.2 Hz, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.78 (d, *J*=15.4 Hz, 1 H), 5.33 - 5.48 (m, 2 H), 5.10 - 5.17 (m, 1 H), 3.74 (s, 3 H), 2.71 - 2.97 (m, 3 H), 2.44 - 2.61 (m, 1 H), 1.99 - 2.23 (m, 2 H), 1.48 - 1.58 (m, 2 H), 0.99 - 1.25 (m, 2 H). MS (ESI) *m/z*: 573.5 $(M+H)^+$. Analytical HPLC: RT = 5.67 min.

Example 28.

{(S)-18-Chloro-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

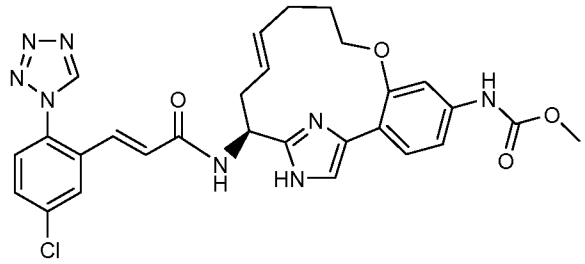


[00480] Example 28 was prepared following the procedure described in 7, by replacing Example 6 with Example 26. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.45 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.64 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 (d, *J*=8.2 Hz, 1 H), 7.40 (d, *J*=2.2 Hz, 1 H), 7.35 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.25 (d, *J*=8.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.75 (d, *J*=15.9 Hz, 1 H), 4.90 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.62 - 2.73 (m, 1 H), 2.35 - 2.45 (m, 1 H), 2.07 - 2.16 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.56

- 1.67 (m, 1 H), 1.22 - 1.45 (m, 7 H), 0.72 - 0.86 (m, 1 H), 0.47-0.58 (d, 1 H). MS (ESI) *m/z*: 609.1 $(M+H)^+$. Analytical HPLC: RT = 7.81 min.

Example 29.

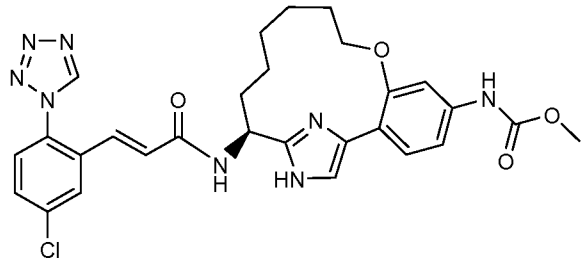
{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00481] Example 29 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 11; followed by steps 2B; 2C; 2E; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.46 (s, 1 H), 7.42 (s, 1 H), 7.37 (d, *J*=8.2 Hz, 1 H), 7.17 (d, *J*=15.4 Hz, 1 H), 7.05 (dd, *J*=8.3, 1.6 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.66 - 5.74 (m, 1 H), 5.48 - 5.56 (m, 1 H), 5.11 (dd, *J*=10.2, 3.6 Hz, 1 H), 4.09 - 4.16 (m, 2 H), 3.75 (s, 3 H), 2.69 - 2.77 (m, 1 H), 2.52 - 2.61 (m, 1 H), 2.33 - 2.47 (m, 2 H), 2.01 - 2.09 (m, 1 H), 1.91 - 2.00 (m, 1 H). MS (ESI) *m/z*: 575.0 $(M+H)^+$. Analytical HPLC: RT = 6.15 min.

Example 30.

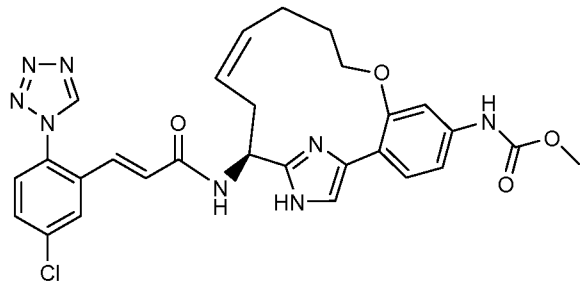
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00482] Example 30 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 11; followed by steps 2B; 2C; 2E/2F; 2G; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.40 (s, 1 H), 7.33 - 7.38 (m, 2 H), 7.14 (d, *J*=15.4 Hz, 1 H), 7.06 (d, *J*=8.2 Hz, 1 H), 6.78 (d, *J*=15.9 Hz, 1 H), 5.04 (dd, *J*=9.9, 4.4 Hz, 1 H), 4.05 - 4.10 (m, 1 H), 3.93 (td, *J*=8.2, 2.7 Hz, 1 H), 3.75 (s, 3 H), 2.19 - 2.27 (m, 1 H), 1.94 - 2.03 (m, 1 H), 1.69 - 1.83 (m, 2 H), 1.49 - 1.63 (m, 4 H), 0.91 - 1.09 (m, 2 H). MS (ESI) *m/z*: 577.1 $(M+H)^+$. Analytical HPLC: RT = 6.16 min.

Example 31.

{(Z)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

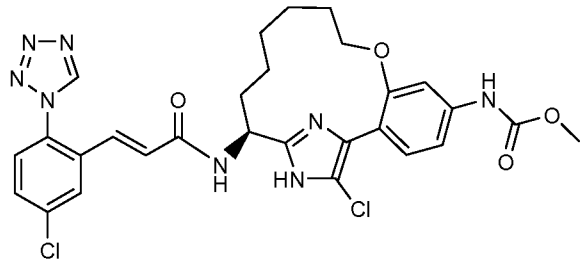


[00483] Example 31 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 11; followed by steps 2B; 2C; 2F; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.50 (d, *J*=1.6 Hz, 1 H), 7.44 (s, 1 H), 7.38 (d, *J*=8.2 Hz, 1 H), 7.15 - 7.21 (m, 2 H), 6.74 (d, *J*=15.9 Hz, 1 H), 5.41 - 5.51 (m, 2

H), 5.20 - 5.25 (m, 1 H), 3.74 - 3.82 (m, 4 H), 3.66 - 3.72 (m, 1 H), 2.95 - 3.06 (m, 1 H), 2.79 - 2.89 (m, 1 H), 2.47 - 2.58 (m, 1 H), 2.23 - 2.34 (m, 1 H), 1.89 - 2.03 (m, 1 H), 1.65-1.77 (m, 1 H). MS (ESI) *m/z*: 575.1 $(M+H)^+$. Analytical HPLC: RT = 5.94 min.

Example 32.

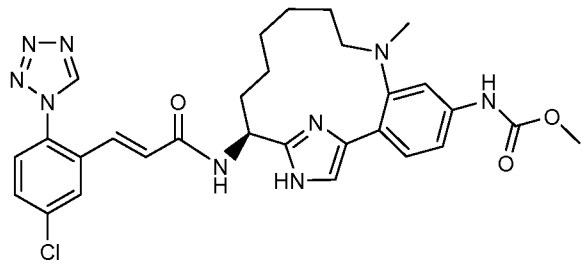
{(S)-18-Chloro-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-17,19-diaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00484] Example 32 was prepared following the procedure described in 9, by replacing Example 8 with Example 30. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.46 (s, 1 H), 7.94 (d, *J*=2.2 Hz, 1 H), 7.64 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.55 (d, *J*=8.8 Hz, 1 H), 7.32 - 7.37 (m, 2 H), 7.15 (d, *J*=15.9 Hz, 1 H), 7.05 (d, *J*=8.2 Hz, 1 H), 6.74 (d, *J*=15.4 Hz, 1 H), 4.94 (dd, *J*=9.6, 3.6 Hz, 1 H), 4.00 - 4.06 (m, 1 H), 3.88 - 3.94 (m, 1 H), 3.76 (s, 3 H), 2.12 - 2.20 (m, 1 H), 1.75 - 1.93 (m, 2 H), 1.65 - 1.74 (m, 1 H), 1.46 - 1.60 (m, 4 H), 1.0 - 1.12 (m, 1 H), 0.92 - 1.02 (m, 1 H). MS (ESI) *m/z*: 610.9 $(M+H)^+$. Analytical HPLC: RT = 7.74 min.

Example 33.

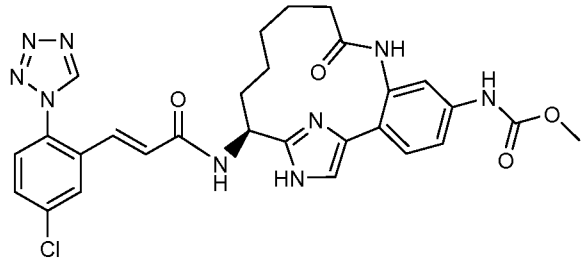
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-methyl-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00485] Example 33 was prepared following the procedures described in step 10C, by replacing ammonium hydroxide with pent-4-enylamine and running the reaction at 90 °C; followed by steps 2E/2F; 2G (N-methylation occurred during the hydrogenation step in the presence of methanol); 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.52 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.63 - 7.71 (m, 2 H), 7.55 - 7.60 (m, 2 H), 7.46 (d, *J*=8.2 Hz, 1 H), 7.28 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.73 (d, *J*=15.4 Hz, 1 H), 5.08 (t, *J*=6.9 Hz, 1 H), 3.76 (s, 3 H), 2.94 (s, 3 H), 2.87 - 2.92 (m, 2 H), 2.15 - 2.22 (m, 2 H), 1.66 - 1.85 (m, 2 H), 1.39 - 1.65 (m, 4 H), 0.75 - 0.87 (m, 2 H). MS (ESI) *m/z*: 590.3 $(M+H)^+$. Analytical HPLC: RT = 6.26 min.

Example 34.

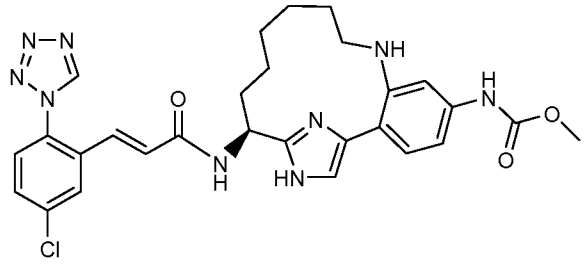
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00486] Example 34 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with pent-4-enoic acid; followed by steps 2E/2F; 2G; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.61 (s, 1 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.38 - 7.45 (m, 3 H), 7.12 (d, *J*=15.9 Hz, 1 H), 6.74 (d, *J*=15.9 Hz, 1 H), 5.01 (dd, *J*=10.2, 4.7 Hz, 1 H), 3.75 (s, 3 H), 2.28 - 2.41 (m, 2 H), 2.15 - 2.25 (m, 1 H), 1.95 - 2.07 (m, 1 H), 1.41 - 1.76 (m, 4 H), 0.71 - 0.98 (m, 2 H). MS (ESI) *m/z*: 590.1 $(M+H)^+$. Analytical HPLC: RT = 4.96 min.

Example 35.

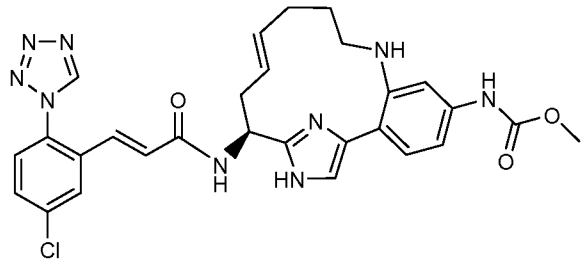
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00487] Example 35 was prepared following the procedures described in step 10C, by replacing ammonium hydroxide with pent-4-enylamine and running the reaction at 90 °C; followed by steps 2E/2F; 2G by replacing MeOH with EtOAc; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.82 (s, 1 H), 7.66 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.60 (d, *J*=8.8 Hz, 1 H), 7.56 - 7.59 (m, 2 H), 7.26 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.68 (d, *J*=15.9 Hz, 1 H), 5.12 (dd, *J*=9.9, 3.3 Hz, 1 H), 3.76 (s, 3 H), 3.09 - 3.24 (m, 2 H), 2.31 - 2.43 (m, 1 H), 1.89 - 2.10 (m, 2 H), 1.53 - 1.85 (m, 5 H), 1.07 - 1.27 (m, 2 H). MS (ESI) *m/z*: 576.3 $(M+H)^+$. Analytical HPLC: RT = 5.91 min.

Example 36.

{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt

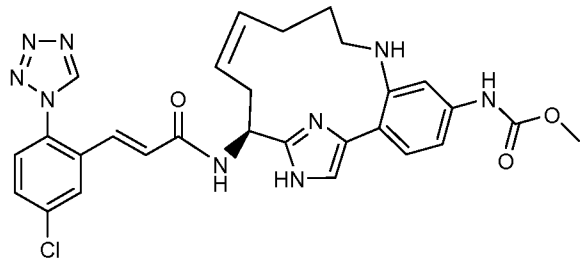


[00488] Example 36 was prepared following the procedures described in step 10C, by replacing ammonium hydroxide with pent-4-enylamine and running the reaction at 90 °C; followed by steps 2E; 1F, by replacing ethanol with methanol and running the reaction at

75 °C; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.59 (d, *J*=8.8 Hz, 1 H), 7.43 (s, 1 H), 7.28 - 7.32 (m, 2 H), 7.18 (d, *J*=15.4 Hz, 1 H), 6.98 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.76 (d, *J*=15.9 Hz, 1 H), 5.69 - 5.79 (m, 1 H), 5.45 - 5.54 (m, 1 H), 5.15 (dd, *J*=9.3, 4.4 Hz, 1 H), 3.74 (s, 3 H), 3.03 - 3.20 (m, 2 H), 2.72 - 2.82 (m, 1 H), 2.56 - 2.68 (m, 1 H), 2.28 - 2.48 (m, 2 H), 1.82 - 2.03 (m, 2 H). MS (ESI) *m/z*: 574.2 $(M+H)^+$. Analytical HPLC: RT = 5.85 min.

Example 37.

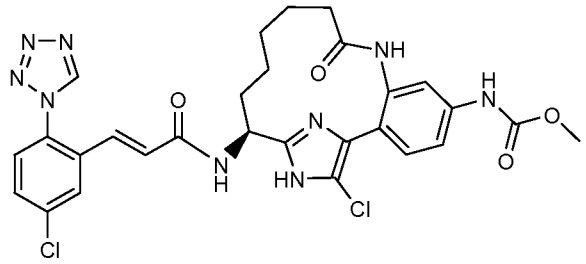
{(Z)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00489] Example 37 was prepared following the procedures described in step 10C, by replacing ammonium hydroxide with pent-4-enylamine and running the reaction at 90 °C; followed by steps 2F; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.48 (s, 1 H), 7.86 - 7.95 (m, 2 H), 7.69 (d, *J*=8.2 Hz, 1 H), 7.65 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.54 - 7.58 (m, 2 H), 7.33 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.21 (d, *J*=15.9 Hz, 1 H), 6.65 (d, *J*=15.9 Hz, 1 H), 5.52 - 5.60 (m, 1 H), 5.36 - 5.44 (m, 1 H), 5.30 (dd, *J*=9.9, 3.3 Hz, 1 H), 3.78 (s, 3 H), 3.10 - 3.28 (m, 3 H), 2.60 - 2.76 (m, 2 H), 2.36 - 2.47 (m, 1 H), 2.15 - 2.25 (m, 1 H), 1.96 - 2.07 (m, 1 H). MS (ESI) *m/z*: 574.2 $(M+H)^+$. Analytical HPLC: RT = 5.88 min.

Example 38.

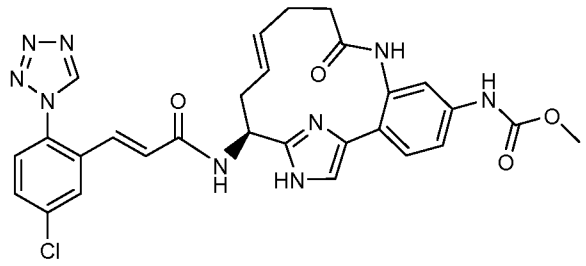
{(S)-18-Chloro-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00490] Example 38 was prepared following the procedure described in 7, by replacing Example 6 with Example 34. ^{1}H NMR (500 MHz, DMSO-d_6+2 drops of D_2O) δ ppm 9.76 (s, 1 H), 7.90 (d, *J*=1.6 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.63 (d, *J*=8.3 Hz, 1 H), 7.38 (s, 1 H), 7.30 - 7.36 (m, 2 H), 6.77 - 6.84 (m, 2 H), 4.76 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.62 (s, 3 H), 2.07 - 2.21 (m, 2 H), 1.83 - 1.91 (m, 1 H), 1.56 - 1.66 (m, 1 H), 1.44 - 1.54 (m, 1 H), 1.34 - 1.44 (m, 1 H), 1.19 - 1.31 (m, 2 H), 0.85 - 0.96 (m, 1 H), 0.38 - 0.49 (m, 1 H). MS (ESI) *m/z*: 624.3 $(M+H)^+$. Analytical HPLC: RT = 6.32 min.

Example 39.

{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



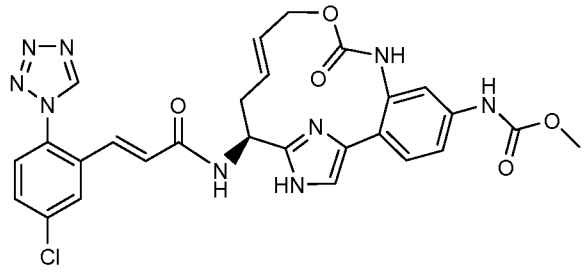
[00491] 39A. ((E)-(S)-15-*tert*-Butoxycarbonylamino-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl)-carbamic acid methyl ester: This compound was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with pent-4-enoic acid; followed by step 2E. MS (ESI) *m/z*: 586.4 $(M+H)^+$.

[00492] 39B. Example 39 was prepared following the procedures described step 10H, by replacing 10G with 39A; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 2

H), 7.37 - 7.41 (m, 3 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.50 - 5.59 (m, 1 H), 5.37 - 5.45 (m, 1 H), 5.08 (dd, *J*=10.2, 4.7 Hz, 1 H), 3.75 (s, 3 H), 2.76 - 2.84 (m, 1 H), 2.32 - 2.60 (m, 5 H). MS (ESI) *m/z*: 588.1 $(M+H)^+$. Analytical HPLC: RT = 4.79 min

Example 40.

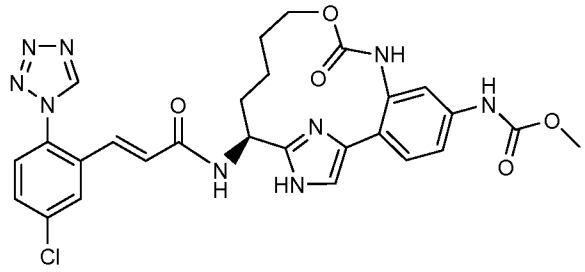
{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-10-oxa-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00493] Example 40 was prepared following the procedures described in Intermediate 7B, by replacing Intermediate 7A with 10C and by replacing methyl chloroformate with allyl chloroformate; followed by steps 2E; 10H; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.50 (br. s., 1 H), 7.34 - 7.43 (m, 3 H), 7.14 (d, *J*=15.7 Hz, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 5.83 - 5.93 (m, 1 H), 5.68 - 5.76 (m, 1 H), 5.13 (dd, *J*=10.2, 5.2 Hz, 1 H), 4.28 - 4.43 (m, 2 H), 3.75 (s, 3 H), 2.88 - 2.97 (m, 1 H), 2.53 - 2.65 (m, 1 H). MS (ESI) *m/z*: 590.2 $(M+H)^+$. Analytical HPLC: RT = 4.90 min.

Example 41.

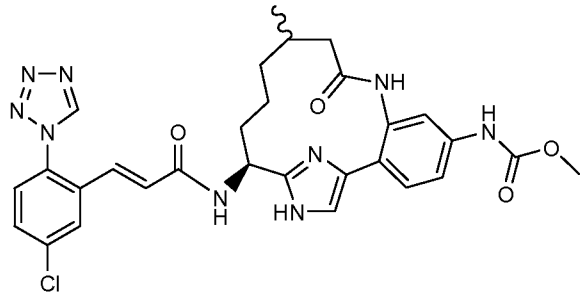
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-10-oxa-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00494] Example 41 was prepared following the procedures described in Intermediate 7B, by replacing Intermediate 7A with 10C and by replacing methyl chloroformate with allyl chloroformate; followed by steps 2E/2F; 2G, by replacing methanol with EtOAc; 1F, by replacing ethanol with methanol and running the reaction at 75 °C for 2 h; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.55 (d, *J*=1.6 Hz, 1 H), 7.43 - 7.47 (m, 2 H), 7.39 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.12 (d, *J*=15.4 Hz, 1 H), 6.74 (d, *J*=15.4 Hz, 1 H), 4.98 (dd, *J*=10.4, 4.9 Hz, 1 H), 4.13 - 4.26 (m, 1 H), 3.89 - 4.03 (m, 1 H), 3.75 (s, 3 H), 2.18 - 2.31 (m, 1 H), 1.84 - 1.98 (m, 1 H), 1.42 - 1.65 (m, 3 H), 1.19 - 1.35 (m, 1 H). MS (ESI) *m/z*: 592.2 $(M+H)^+$. Analytical HPLC: RT = 5.11 min.

Example 42.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt. Mixture of diastereomers



[00495] Example 42 (mixture of diastereomers) was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 3-methylpent-4-enoic acid; followed by steps 2E/2F; 2G; 10H; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50, 9.51 (s, 1 H), 7.94 - 7.98 (m, 1 H), 7.64 - 7.69 (m, 1 H), 7.55 - 7.60 (m, 2 H), 7.37 - 7.44 (m, 3 H), 7.08 - 7.15 (m, 1 H), 6.70 - 6.82 (m, 1 H), 4.96 - 5.02 (m, 1 H), 3.75 (s, 3 H),

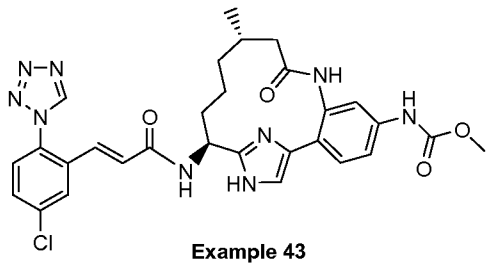
2.38 - 2.47 (m, 1 H), 2.19 - 2.26 (m, 0.5 H), 2.10 - 2.18 (m, 0.5 H), 1.87 - 2.07 (m, 3 H), 1.54 - 1.70 (m, 1 H), 1.36 - 1.52 (m, 1 H), 0.95 - 1.02 (m, 3.5 H), 0.80 - 0.89 (m, 0.5 H), 0.67 - 0.77 (m, 0.5 H), 0.46 - 0.55 (m, 0.5 H). MS (ESI) *m/z*: 604.3 $(M+H)^+$. Analytical HPLC: RT = 5.11 min.

Example 43.

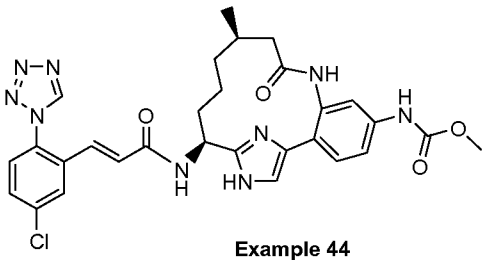
{(11S,15S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt; and

Example 44.

{(11R,15S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



Example 43



Example 44

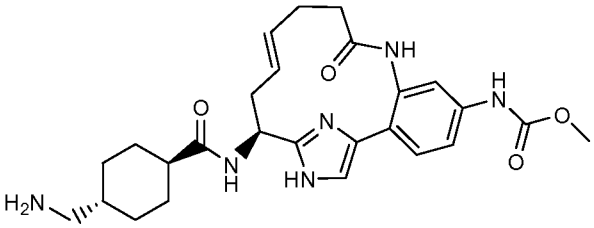
[00496] The diastereomers of Example 42 were separated on CHIRALCEL® OD-H column (isocratic; 30% 1:1 MeOH:EtOH/Heptane; 20 mL/min; 254 nm detection). The pure fractions were concentrated, dissolved in methanol containing two drops of TFA, concentrated and then lyophilized to give 0.0047 g of Example 43, as a white solid and 0.0042 g of Example 44, as a white solid.

[00497] Example 43: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.37 - 7.44 (m, 3 H), 7.14 (d, *J*=15.9 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 5.00 (dd, *J*=9.3, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.43 (d, *J*=10.4 Hz, 1 H), 2.18 - 2.30 (m, 1 H), 1.84 - 1.98 (m, 3 H), 1.61 - 1.74 (m, 1 H), 1.34 - 1.49 (m, 1 H), 0.93 - 1.05 (m, 4 H), 0.46 - 0.58 (m, 1 H). MS (ESI) *m/z*: 604.3 $(M+H)^+$ and 606.2 $(M+2+H)^+$. Analytical HPLC (Method D): RT = 4.63 min. CHIRALCEL® OD (40% 1:1 MeOH:EtOH/Heptane; 4.6 x 250 mm; 1mL/min.; 220 nm): 10.08 min. (>99% de).

[00498] Example 44: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.60 (s, 1 H, exchangeable), 9.50 (s, 1 H), 7.95 (d, *J*=1.6 Hz, 1 H), 7.66 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.59 (br. s., 1 H), 7.57 (d, *J*=8.8 Hz, 1 H), 7.36 - 7.45 (m, 3 H), 7.11 (d, *J*=15.9 Hz, 1 H), 6.71 (d, *J*=15.9 Hz, 1 H), 4.98 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.42 (d, *J*=11.0 Hz, 1 H), 2.08 - 2.19 (m, 1 H), 1.91 - 2.08 (m, 3 H), 1.56 - 1.65 (m, 1 H), 1.41 - 1.52 (m, 1 H), 0.99 (d, *J*=6.6 Hz, 3 H), 0.81 - 0.94 (m, 1 H), 0.69 - 0.79 (m, 1 H). MS (ESI) *m/z*: 604.3 $(M+H)^+$ and 606.2 $(M+2+H)^+$. Analytical HPLC (Method D): RT = 4.69 min. CHIRALCEL® OD (40% 1:1 MeOH:EtOH/Heptane; 4.6 x 250 mm; 1mL/min.; 220 nm): 13.74 min. (>99% de).

Example 45.

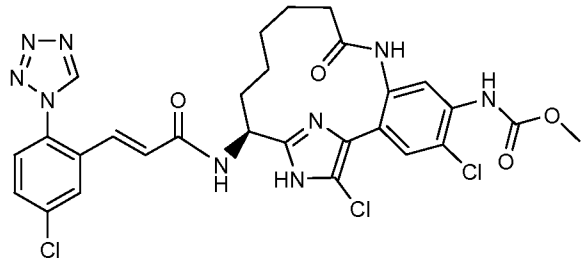
{(E)-(S)-15-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00499] Example 45 was prepared following the procedures described in step 10H, by replacing 10G with 39A; followed by steps 3B, by replacing Hunig's base with triethylamine and running the reaction at 50 °C; and 3C. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.55 (d, *J*=1.6 Hz, 1 H), 7.43 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.37 - 7.40 (m, 2 H), 5.46 - 5.56 (m, 1 H), 5.34 - 5.43 (m, 1 H), 4.98 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.71 - 2.82 (m, 3 H), 2.27 - 2.55 (m, 6 H), 1.83 - 1.99 (m, 4 H), 1.56 - 1.67 (m, 1 H), 1.39 - 1.53 (m, 2 H), 1.01 - 1.17 (m, 2 H). MS (ESI) *m/z*: 495.3 $(M+H)^+$. Analytical HPLC: RT = 1.8, 2.4 min.

Example 46.

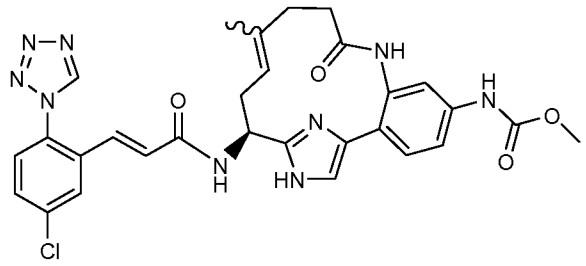
{(S)-4,18-Dichloro-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00500] To a solution of Example 34 (0.023 g, 0.033 mmol) in acetonitrile (1 mL)/chloroform (1.000 mL) was added NCS (5.23 mg, 0.039 mmol). The thick-walled vial was sealed with a teflon coated screw cap and the reaction was warmed to 65 °C. After 6 h, additional NCS (5.23 mg, 0.039 mmol) was added. After another 4 h, the reaction was cooled to rt and concentrated. Purification by reverse phase chromatography afforded Example 46 (0.006 g, 23.2 %) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.93 - 8.02 (m, 2 H), 7.62 - 7.68 (m, 1 H), 7.53 - 7.59 (m, 2 H), 7.10 (d, *J*=15.4 Hz, 1 H), 6.75 (d, *J*=15.4 Hz, 1 H), 4.79 - 4.98 (m, 1 H), 3.78 (s, 3 H), 2.26 - 2.37 (m, 2 H), 2.01 - 2.12 (m, 1 H), 1.84 - 1.95 (m, 1 H), 1.59 - 1.72 (m, 2 H), 1.32 - 1.50 (m, 2 H), 1.05 - 1.19 (m, 1 H), 0.73 - 0.86 (m, 1 H). MS (ESI) *m/z*: 656.4 $(M-H)^-$. Analytical HPLC: RT = 7.49 min.

Example 47.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

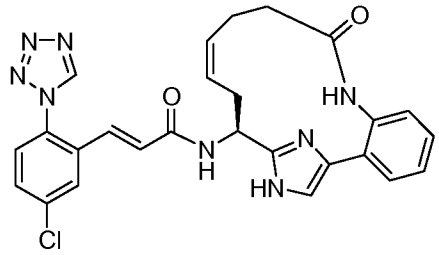


[00501] Example 47 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 4-methylpent-4-enoic acid; followed by steps 2E/2F; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 - 7.62 (m, 2 H), 7.33 - 7.44 (m, 3 H), 7.15 (d,

J=15.9 Hz, 1 H), 6.78 (d, *J*=15.9 Hz, 1 H), 5.14 - 5.21 (m, 1 H), 5.06 (dd, *J*=10.2, 5.2 Hz, 1 H), 3.76 (s, 3 H), 2.75 - 2.83 (m, 1 H), 2.48 - 2.69 (m, 3 H), 2.34 - 2.42 (m, 2 H), 1.56 (s, 3 H). MS (ESI) *m/z*: 602.3 $(M+H)^+$. Analytical HPLC: RT = 5.09 min.

Example 48.

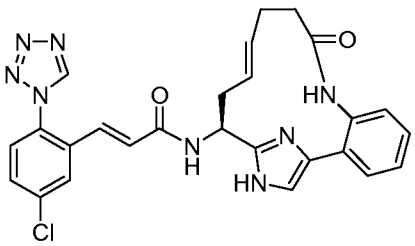
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((Z)-(S)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt



[00502] Example 48 was prepared following the procedures described in step 10D, by replacing 10C with 15B and by replacing but-3-enoic acid with pent-4-enoic acid; followed by 2F; 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.25 - 3.00 (m, 6 H), 5.14 - 5.24 (m, 1 H), 5.41 - 5.54 (m, 1 H), 5.57 - 5.70 (m, 1 H), 6.75 (d, *J*=15.7 Hz, 1 H), 7.17 (d, *J*=15.7 Hz, 1 H), 7.33 - 7.40 (m, 3 H), 7.48 - 7.54 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 515.3$(M+H)^+$. Analytical HPLC: RT = 5.06 min.

Example 49.

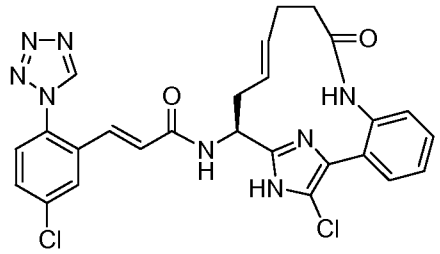
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt



[00503] Example 49 was prepared following the procedures described in step 10D, by replacing 10C with 15B and by replacing but-3-enoic acid with pent-4-enoic acid; followed by steps 2E; 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.32 - 2.62 (m, 5 H), 2.77 - 2.86 (m, 1 H), 5.09 (dd, *J*=10.2, 4.7 Hz, 1 H), 5.38 - 5.47 (m, 1 H), 5.52 - 5.61 (m, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 7.34 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.41 (td, *J*=7.6, 1.2 Hz, 1 H), 7.44 (s, 1 H), 7.52 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.55 (td, *J*=7.7, 1.6 Hz, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 515.3$(M+H)^+$. Analytical HPLC: RT = 5.00min.

Example 50.

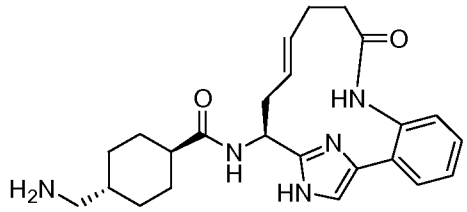
(E)-*N*-((E)-(S)-18-Chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00504] Example 50 was prepared following the procedure described in 17A, by replacing 16A with Example 49. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.30 - 2.53 (m, 5 H), 2.66 - 2.76 (m, 1 H), 4.97 (dd, *J*=10.3, 4.3 Hz, 1 H), 5.32 - 5.42 (m, 1 H), 5.49 - 5.59 (m, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.32 (dd, *J*=7.7, 1.2 Hz, 1 H), 7.40 (td, *J*=7.6, 1.3 Hz, 1 H), 7.48 - 7.53 (m, 2 H), 7.58 (d, *J*=8.3 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 549.2$(M+H)^+$. Analytical HPLC: RT = 6.87min.

Example 51.

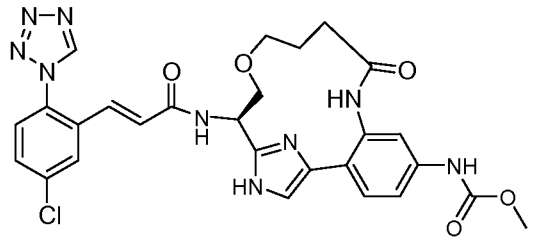
4-Aminomethyl-cyclohexanecarboxylic acid ((E)-(S)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-amide, 2 TFA salt



[00505] Example 51 was prepared following the procedures described in step 10D, by replacing 10C with 15B and by replacing but-3-enoic acid with pent-4-enoic acid; followed by steps 2E; 10H; 3B; and 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.03 - 1.17 (m, 2 H), 1.40 - 1.53 (m, 2 H), 1.56 - 1.67 (m, 1 H), 1.83 - 2.00 (m, 4 H), 2.29 - 2.45 (m, 4 H), 2.45 - 2.55 (m, 2 H), 2.72 - 2.81 (m, 3 H), 5.00 (dd, *J*=10.6, 4.8 Hz, 1 H), 5.35 - 5.44 (m, 1 H), 5.47 - 5.56 (m, 1 H), 7.33 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.42 (td, *J*=7.6, 1.3 Hz, 1 H), 7.44 (s, 1 H), 7.50 (dd, *J*=7.7, 1.7 Hz, 1 H), 7.55 (td, *J*=7.7, 1.7 Hz, 1 H). MS (ESI) *m/z*: 422.3(M+H)$^+$. Analytical HPLC: RT = 1.62min.

Example 52.

{(R)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-13-oxa-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00506] 52A. (S)-3-Allyloxy-2-*tert*-butoxycarbonylamino-propionic acid methyl ester: This compound was prepared following a procedure described in *Organic Letters*, 10(17):3883 (2008). To a solution of N-(*tert*-butoxycarbonyl)-L-serine methyl ester (0.781 mL, 3.85 mmol) in THF (15 mL) was added allyl methyl carbonate (0.524 mL, 4.61 mmol). The solution was purged with N_2, followed by the addition of *tetrakis*(triphenylphosphine)palladium(0) (444 mg, 0.385 mmol). The vessel was sealed and heated at 60 °C overnight. The reaction mixture was diluted with ethyl acetate, washed with sat $NaHCO_3$, and brine. The organic layer was concentrated. Purification by normal phase chromatography provided 52A (550 mg, 55.2 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.75 - 5.94 (m, 1 H) 5.32 - 5.47 (m, 1 H) 5.11 - 5.29 (m, 2 H) 4.35 - 4.53 (m, 1 H) 3.92 - 4.03 (m, 2 H) 3.80 - 3.89 (m, 1 H) 3.76 (m, 3 H) 3.61 - 3.70 (m, 1 H) 1.46 (m, 9 H).

[00507] 52B. (S)-3-Allyloxy-2-*tert*-butoxycarbonylamino-propionic acid: A solution of 52A (1000 mg, 3.86 mmol) and lithium hydroxide (486 mg, 11.57 mmol) in THF, water and MeOH was stirred at rt for 4 h. The solution was acidified using 5M HCl in water (pH ~3). The mixture was extracted with EtOAc. The combined organic layers were concentrated to give 52B (0.96 g, 100 % yield) as a yellow oil. MS (ESI) *m/z*: 146.0 $(M+H\text{-boc})^+$.

[00508] 52C. (S)-3-Allyloxy-2-*tert*-butoxycarbonylamino-propionic acid 2-(2-bromo-4-nitro-phenyl)-2-oxo-ethyl ester: To a solution of 52B (0.95 g, 3.87 mmol) and Intermediate 10 (1.376 g, 4.26 mmol) in DMF (20 mL) was added potassium bicarbonate (0.465 g, 4.65 mmol). After 1.5 h at rt, the reaction was diluted with EtOAc, washed with water, saturated sodium bicarbonate solution, then brine, dried over magnesium sulfate, filtered, and concentrated to give 52C (1.82 g, 96 % yield) as a thick orange oil. MS (ESI) *m/z*: 389.0$(M+H\text{-boc})^+$.

[00509] 52D. (S)-3-Allyloxy-2-*tert*-butoxycarbonylamino-propionic acid 2-(4-amino-2-bromo-phenyl)-2-oxo-ethyl ester: To a mixture of 52C (1700 mg, 3.49 mmol) and iron (3896 mg, 69.8 mmol) in ethanol (15 mL) and water (15.00 mL) was added 12M conc. HCl (0.204 mL, 2.442 mmol). The suspension was heated at 50° for 2 hr. The dark suspension was filtered, washed with methanol and concentrated to give 52D (1.7 g, 100%). MS (ESI) *m/z*: 359.0$(M+H\text{-boc})^+$.

[00510] 52E. (S)-3-Allyloxy-2-*tert*-butoxycarbonylamino-propionic acid 2-(2-bromo-4-methoxycarbonylamino-phenyl)-2-oxo-ethyl ester: To a cooled (ice bath) solution 52D (1670 mg, 3.65 mmol) and pyridine (0.325 mL, 4.02 mmol) in dichloromethane (50 mL) was added methyl chloroformate (0.297 mL, 3.83 mmol). The reaction mixture was stirred for 10 min, washed with brine, dried ($MgSO_4$) and concentrated to give 52E (1.8 g, 96 % yield) as a yellow foam. MS (ESI) *m/z*: 417.1$(M+H\text{-boc})^+$.

[00511] 52F. {4-[2-((R)-2-Allyloxy-1-*tert*-butoxycarbonylamino-ethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-amino-phenyl}-carbamic acid methyl ester: This compound was prepared following the procedures described in step

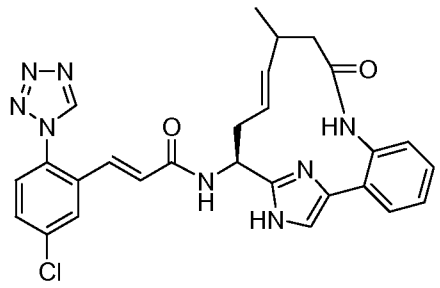
1B, by replacing 1A with 52E; followed by steps 10B; and 10C (alternative). MS (ESI) *m/z*: 562.3$(M+H)^+$.

[00512] 52G. {3-Acryloylamino-4-[2-((R)-2-allyloxy-1-*tert*-butoxycarbonylamino-ethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: A solution of 52F (50 mg, 0.089 mmol), and DIEA (50 µL, 0.286 mmol) in THF (2 mL) was cooled in ice bath. Acryloyl chloride (10µL, 0.123 mmol) was added into the solution in a portion. Then, the ice bath was removed and reaction mixture was stirred for 1 hr at rt. To the reaction mixture was added sat. $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layer were washed with brine and concentrated to provide an oily residue, which has gel like material insoluble in CH_2Cl_2. The soluble portion of the residue was purified by normal phase chromatography to give 52G (43 mg, 78 % yield). MS(ESI) *m/z*: 616.4 $(M+H)^+$.

[00513] 52H. Example 52 was prepared following the procedures described in step 2E/2F, by replacing 2D with 52G; followed by steps 2G; 10H; and 1G. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 (s, 1 H) 7.79 (s, 1 H) 7.50 - 7.62 (m, 1 H) 7.42 (t, *J*=7.91 Hz, 2 H) 7.10 (br. s., 1 H) 6.60 (d, *J*=15.31 Hz, 1 H) 5.22 (br. s., 1 H) 4.04 - 4.18 (m, 1 H) 3.92 - 4.02 (m, 1 H) 3.78 (s, 4 H) 3.60 (d, *J*=6.27 Hz, 2 H) 3.28 - 3.49 (m, 1 H) 2.81 (t, *J*=7.28 Hz, 1 H) 2.34 (s, 1 H) 2.05 (d, *J*=5.02 Hz, 2 H) 1.63 (br. s., 1 H) 0.88 (t, *J*=6.90 Hz, 2 H). MS(ESI) *m/z*: 592.3$(M+H)^+$. Analytical HPLC: RT = 5.16 min.

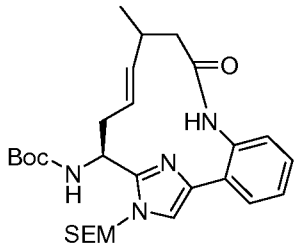
Example 53.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt

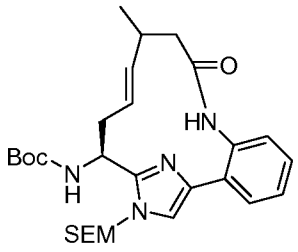


[00514] 53A. {(S)-1-[4-[2-(3-Methyl-pent-4-enoylamino)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: This compound was prepared following the procedure described in 10D, by replacing 10C with 15B and by replacing but-3-enoic acid with 3-methyl-4-pentenoic acid. MS (ESI) *m/z*: 555.5$(M+H)^+$.

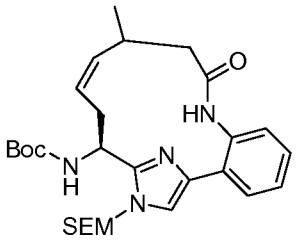
[00515] 53B. [(E)-(S)-11-Methyl-9-oxo-17-(2-trimethylsilanyl-ethoxymethyl)-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt, diastereomer A; 53C. [(E)-(S)-11-Methyl-9-oxo-17-(2-trimethylsilanyl-ethoxymethyl)-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt, diastereomer B; and 53D. [(Z)-(S)-11-Methyl-9-oxo-17-(2-trimethylsilanyl-ethoxymethyl)-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt



53B, diastereomer A



53C, diastereomer B



53D

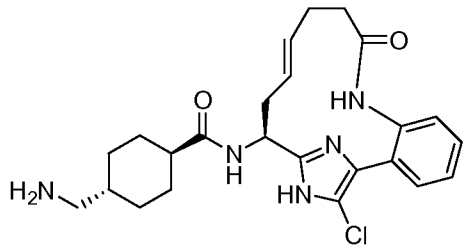
[00516] These compounds were prepared following the procedure described in 2E/2F, by replacing 2D with 53A. Purification by reverse phase chromatography gave 53B, diastereomer A (16.3 mg, 2.291 % yield) as a pale, purple foam; 53C, diastereomer B (180.6 mg, 25.4 % yield) as a pale, purple foam; and 53D (90.5 mg, 12.72 % yield) as a pale, purple foam.

[00517] 53E. Example 53 was prepared following the procedures described in step 10H, by replacing 10G with 53C; followed by step 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.06 (d, *J*=6.9 Hz, 3 H), 2.13 (dd, *J*=13.9, 11.7 Hz, 1 H), 2.43 - 2.53 (m, 2 H), 2.65 - 2.77 (m, 1 H), 2.83 - 2.91 (m, 1 H), 5.05 (dd, *J*=11.8, 4.7 Hz, 1 H), 5.28 (ddd, *J*=15.1, 9.4, 1.1 Hz, 1 H), 5.53 (ddd, *J*=15.1, 10.5, 4.1 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.17 (d, *J*=15.7 Hz, 1 H), 7.34 (d, *J*=8.0 Hz, 1 H), 7.39 - 7.44 (m, 2 H), 7.51 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.56 (td, *J*=7.7, 1.4 Hz, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.69 (dd, *J*=8.5, 2.2 Hz, 1 H),

7.99 (d, *J*=2.2 Hz, 1 H), 9.52 (s, 1 H). MS (ESI) *m/z*: 529.3(M+H)$^+$. Analytical HPLC: RT = 5.39 min.

Example 54.

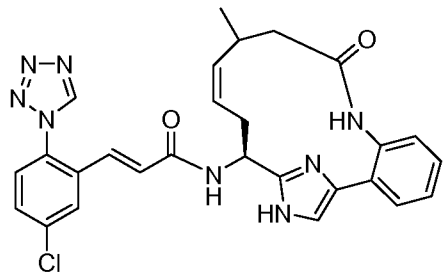
4-Aminomethyl-cyclohexanecarboxylic acid ((E)-(S)-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-amide, 2 TFA salt



[00518] Example 54 was prepared following the procedures described in step 10D, by replacing 10C with 15B and by replacing but-3-enoic acid with pent-4-enoic acid; followed by steps 2E; 10H; 3B; 17A; and 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.02 - 1.18 (m, 2 H), 1.40 - 1.55 (m, 2 H), 1.56 - 1.68 (m, 1 H), 1.84 - 1.98 (m, 4 H), 2.26 - 2.53 (m, 6 H), 2.68 - 2.76 (m, 1 H), 2.79 (d, *J*=7.2 Hz, 2 H), 4.88 - 4.92 (m, 1 H), 5.33 - 5.43 (m, 1 H), 5.46 - 5.55 (m, 1 H), 7.33 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.43 (td, *J*=7.6, 1.1 Hz, 1 H), 7.51 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.55 (td, *J*=7.7, 1.6 Hz, 1 H). MS (ESI) *m/z*: 456.2(M+H)$^+$. Analytical HPLC: RT = 3.36min.

Example 55.

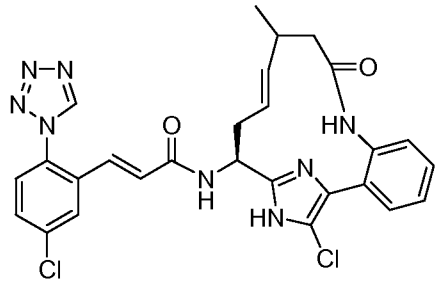
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((Z)-(S)-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt



[00519] Example 55 was prepared following the procedures described in step 10H, by replacing 10G with 53D; followed by step 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.06 (d, *J*=6.6 Hz, 3 H), 2.08 (t, *J*=12.0 Hz, 1 H), 2.47 (dd, *J*=12.4, 2.5 Hz, 1 H), 2.58 - 2.67 (m, 1 H), 2.83 - 2.96 (m, 1 H), 2.99 - 3.08 (m, 1 H), 5.14 (dd, *J*=12.4, 4.4 Hz, 1 H), 5.33 (td, *J*=11.5, 3.4 Hz, 1 H), 5.46 - 5.54 (m, 1 H), 6.74 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 7.27 (d, *J*=8.0 Hz, 1 H), 7.36 - 7.42 (m, 2 H), 7.47 - 7.53 (m, 2 H), 7.56 (d, *J*=8.5 Hz, 1 H), 7.65 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). MS (ESI) *m/z*: 529.3(M+H)$^+$. Analytical HPLC: RT = 5.35 min.

Example 56.

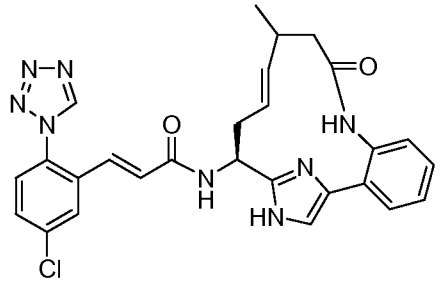
(E)-N-((E)-(S)-18-Chloro-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00520] Example 56 was prepared following the procedure described in 17A, by replacing 16A with Example 53. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.05 (d, *J*=6.9 Hz, 3 H), 2.16 (dd, *J*=13.9, 11.7 Hz, 1 H), 2.30 - 2.39 (m, 1 H), 2.42 (dd, *J*=13.9, 3.2 Hz, 1 H), 2.64 - 2.79 (m, 2 H), 4.92 (dd, *J*=11.8, 4.1 Hz, 1 H), 5.19 (ddd, *J*=15.1, 9.4, 1.1 Hz, 1 H), 5.52 (ddd, *J*=14.9, 10.7, 4.1 Hz, 1 H), 6.79 (d, *J*=15.7 Hz, 1 H), 7.15 (d, *J*=15.7 Hz, 1 H), 7.32 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.40 (td, *J*=7.6, 1.2 Hz, 1 H), 7.47 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.51 (td, *J*=7.7, 1.5 Hz, 1 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 8.01 (d, *J*=2.5 Hz, 1 H), 9.52 (s, 1 H). MS (ESI) *m/z*: 563.3(M+H)$^+$. Analytical HPLC: RT = 7.22 min.

Example 57.

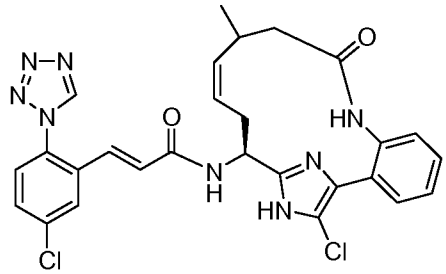
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt



[00521] Example 57 was prepared following the procedures described in step 10H, by replacing 10G with 53B; followed by step 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.08 (d, *J*=6.9 Hz, 3 H), 2.26 (dd, *J*=14.3, 11.6 Hz, 1 H), 2.49 (dd, *J*=14.4, 3.7 Hz, 1 H), 2.63 - 2.75 (m, 3 H), 5.18 (dd, *J*=6.7, 5.4 Hz, 1 H), 5.44 (dd, *J*=15.5, 8.7 Hz, 1 H), 5.55 - 5.64 (m, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.31 (d, *J*=8.0 Hz, 1 H), 7.40 (td, *J*=7.6, 1.1 Hz, 1 H), 7.48 (s, 1 H), 7.50 - 7.56 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). MS (ESI) *m/z*: 529.3(M+H)$^+$. Analytical HPLC: RT = 6.03 min.

Example 58.

(E)-*N*-((Z)-(S)-18-Chloro-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt

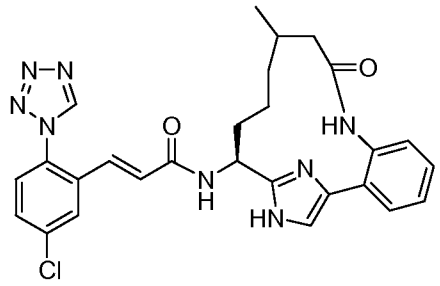


[00522] Example 58 was prepared following the procedure described in 17A, by replacing 16A with Example 55. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.06 (d, *J*=6.9 Hz, 3 H), 2.16 (t, *J*=12.1 Hz, 1 H), 2.40 (dd, *J*=12.8, 2.3 Hz, 1 H), 2.54 - 2.63 (m, 1 H), 2.81 - 2.96 (m, 2 H), 4.97 (dd, *J*=12.0, 4.3 Hz, 1 H), 5.35 (td, *J*=11.5, 3.4 Hz, 1 H), 5.50 (td,

J=10.6, 1.7 Hz, 1 H), 6.71 (d, *J*=15.7 Hz, 1 H), 7.16 (d, *J*=15.7 Hz, 1 H), 7.30 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.39 (td, *J*=7.6, 1.3 Hz, 1 H), 7.50 (td, *J*=7.8, 1.5 Hz, 1 H), 7.54 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 563.3(M+H)$^+$. Analytical HPLC: RT = 6.93 min.

Example 59.

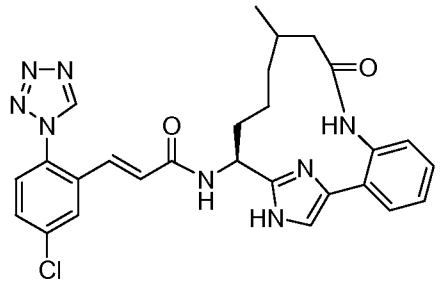
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-acrylamide, 1 TFA salt



[00523] Example 59 was prepared following the procedures described in step 2G, by replacing 2E/2F with a mixture of 53B and 53C and by replacing the hydrogen balloon with hydrogen (50 psi); followed by steps 10H; and 15D. MS (ESI) *m/z*: 531.3(M+H)$^+$. Analytical HPLC: RT = 5.79 min.

Example 60.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-acrylamide, 1 TFA salt



[00524] Example 60 was prepared following the procedures described in step 2G, by replacing 2E/2F with 53C and by replacing the hydrogen balloon with hydrogen (50 psi); followed by steps 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.48 - 0.60 (m, 1 H), 0.98 - 1.02 (m, 4 H), 1.34 - 1.49 (m, 1 H), 1.58 - 1.74 (m, 1 H), 1.86 - 2.02 (m, 3 H),

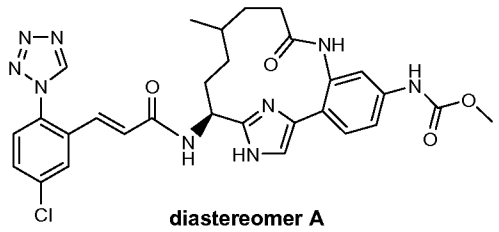
2.22 - 2.29 (m, 1 H), 2.40 - 2.47 (m, 1 H), 5.00 (dd, *J*=9.6, 4.4 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.33 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.41 - 7.47 (m, 2 H), 7.51 - 7.60 (m, 3 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). MS (ESI) *m/z*: 531.3(M+H)$^+$. Analytical HPLC: RT = 5.01min.

Example 61.

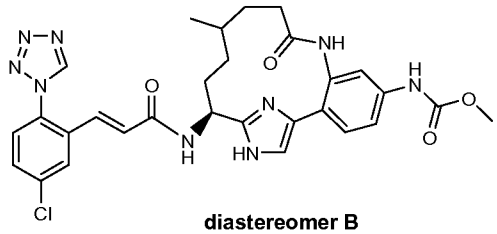
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt, diastereomer A; and

Example 62.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt, diastereomer B



diastereomer A



diastereomer B

[00525] 61A. (S)-Methyl N-4-(2-(1-(*tert*-butoxycarbonylamino)but-3-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)-3-(4-methylpent-4-enamido)phenylmethanimidoperoxoate: This compound was prepared following the procedure described in 10D, by replacing but-3-enoic acid with 4-methylpent-4-enoic acid. MS (ESI) *m/z*: 628.2 (M+H)$^+$.

[00526] 61B. To a solution of 61A (0.066 g, 0.105 mmol) in DCE (1 mL) was added Grubbs (II) (0.018 g, 0.021 mmol). The reaction mixture was vacuumed and back-filled with argon three times, and then the microwave vial was capped. The reaction was microwaved at 120 °C for 20 min, cooled to rt and concentrated. Purification by reverse phase chromatography afforded 61B (mixture of E/Z isomers) (0.026 g, 34.6 %) as a brown solid. MS (ESI) *m/z*: 600.5 (M+H)$^+$ for both peaks.

[00527] 61C. Example 61 and Example 62 were prepared following the procedures described in step 2G, by replacing 2E/2F with 61B (mixture of E/Z-isomers); followed by

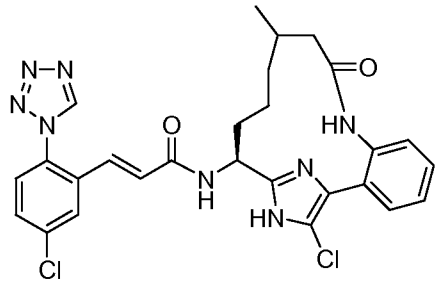
steps 10H; and 1G. The diastereomers were then separated by reverse phase chromatography to give Example 61 (diastereomer A) and Example 62 (diastereomer B).

[00528] Example 61: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.57 - 7.60 (m, 2 H), 7.38 - 7.44 (m, 3 H), 7.14 (d, *J*=15.7 Hz, 1 H), 6.75 (d, *J*=15.7 Hz, 1 H), 4.95 (dd, *J*=10.6, 4.5 Hz, 1 H), 3.76 (s, 3 H), 2.47 - 2.54 (m, 1 H), 2.23 - 2.33 (m, 2 H), 1.91 - 2.00 (m, 1 H), 1.53 - 1.61 (m, 1 H), 1.37 - 1.51 (m, 3 H), 0.86 (d, *J*=6.3 Hz, 3 H), 0.27 - 0.36 (m, 1 H). MS (ESI) *m/z*: 604.3 $(M+H)^+$. Analytical HPLC: RT = 5.28 min.

[00529] Example 62: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.49 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.40 - 7.45 (m, 3 H), 7.12 (d, *J*=15.7 Hz, 1 H), 6.71 (d, *J*=15.4 Hz, 1 H), 5.00 (dd, *J*=9.5, 5.4 Hz, 1 H), 3.75 (s, 3 H), 2.41 - 2.48 (m, 1 H), 2.24 - 2.32 (m, 1 H), 2.11 - 2.21 (m, 2 H), 1.60 - 1.69 (m, 1 H), 1.44 - 1.53 (m, 1 H), 1.27 - 1.42 (m, 2 H), 0.90 (d, *J*=6.3 Hz, 3 H), 0.68 - 0.78 (m, 1 H). MS (ESI) *m/z*: 604.3 $(M+H)^+$. Analytical HPLC: RT = 5.36 min.

Example 63.

(E)-*N*-((S)-18-Chloro-11-methyl-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt

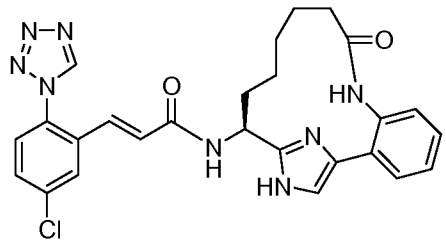


[00530] Example 63 was prepared following the procedure described in 17A, by replacing 16A with Example 60. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.65 - 0.76 (m, 1 H), 0.99 (d, *J*=6.3 Hz, 3 H), 1.08 - 1.18 (m, 1 H), 1.31 - 1.45 (m, 1 H), 1.47 - 1.61 (m, 1 H), 1.80 - 1.91 (m, 1 H), 1.93 - 2.01 (m, 2 H), 2.06 - 2.15 (m, 1 H), 2.35 - 2.38 (m, 1 H), 4.90 (dd, *J*=10.2, 4.4 Hz, 1 H), 6.79 (d, *J*=15.7 Hz, 1 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.33 (d, *J*=8.0 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.48 - 7.53 (m, 2 H), 7.57 (d, *J*=8.5 Hz, 1 H),

7.66 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.99 (d, *J*=2.5 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 565.3(M+H)$^+$. Analytical HPLC: RT = 7.41 min.

Example 64.

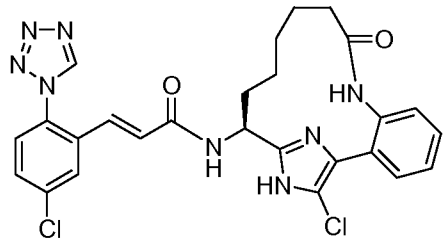
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-acrylamide, 1 TFA salt



[00531] Example 64 was prepared following the procedures described in step 10D, by replacing 10C with 15B and by replacing but-3-enoic acid with pent-4-enoic acid; followed by steps 2F; 2G, by replacing the hydrogen balloon with hydrogen (50 psi); 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.72 - 0.82 (m, 1 H), 0.83 - 0.94 (m, 1 H), 1.42 - 1.59 (m, 2 H), 1.59 - 1.77 (m, 2 H), 1.98 - 2.10 (m, 1 H), 2.16 - 2.25 (m, 1 H), 2.29 - 2.44 (m, 2 H), 5.05 (dd, *J*=10.0, 4.8 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.11 (d, *J*=15.7 Hz, 1 H), 7.33 (d, *J*=8.0 Hz, 1 H), 7.40 - 7.45 (m, 1 H), 7.49 (s, 1 H), 7.52 - 7.58 (m, 3 H), 7.65 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 9.49 (s, 1 H). MS (ESI) *m/z*: 517.3(M+H)$^+$. Analytical HPLC: RT = 5.02 min.

Example 65.

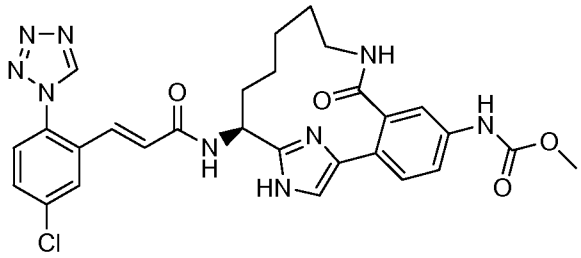
(E)-*N*-((S)-18-Chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00532] Example 65 was prepared following the procedure described in 17A, by replacing 16A with Example 64. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.75 - 0.94 (m, 1 H), 1.07 - 1.21 (m, 1 H), 1.33 - 1.54 (m, 2 H), 1.62 - 1.72 (m, 2 H), 1.86 - 1.99 (m, 1 H), 2.05 - 2.16 (m, 1 H), 2.30 - 2.36 (m, 2 H), 4.90 (dd, *J*=10.6, 4.5 Hz, 1 H), 6.75 (d, *J*=15.4 Hz, 1 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.34 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.41 (td, *J*=7.7, 1.4 Hz, 1 H), 7.50 (td, *J*=7.7, 1.6 Hz, 1 H), 7.54 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). MS (ESI) *m/z*: 551.3$(M+H)^+$. Analytical HPLC: RT = 6.98 min.

Example 66.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxo-9,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



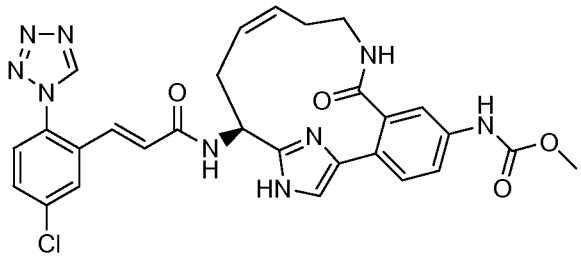
[00533] 66A. 2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-5-methoxycarbonylamino-benzoic acid: To a solution of 10B (230 mg, 0.386 mmol) in dry THF(2 ml) at -78 °C under Ar was added methyllithium in THF (0.515 mL, 0.772 mmol). The reaction was stirred at -78 °C for 30 min after which butyllithium in THF (0.232 mL, 0.579 mmol) was added dropwise. After 30 min, solid dry ice was added to the reaction mixture and the mixture was stirred at -78 °C for 30 min. The reaction mixture was quenched with conc. NH_4Cl (aq). It was extracted with ether and the ether layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to yield 66A as a white solid. This was a mixture of product and starting material. The mixture was used in the next step without further purification. MS (ESI) *m/z*: 561.2 $(M+H)^+$.

[00534] 66B. Example 66 was prepared following the procedures described in step 3B, by replacing (1R,4R)-4-((*tert*-butoxycarbonylamino)methyl) cyclohexanecarboxylic

acid with 66A and by replacing 3A with but-3-en-1-amine; followed by steps 2E/2F; 2G; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.63 - 7.70 (m, 2 H), 7.54 - 7.63 (m, 2 H), 7.51 (s, 1 H), 7.30 (d, *J*=8.2 Hz, 1 H), 7.14 - 7.24 (d, *J*=15.7 Hz, 1 H), 6.70 - 6.81 (d, J=15.7 Hz, 1 H) 4.99 - 5.13 (m, 1 H), 3.68 (s, 3 H), 3.25 – 3.35 (m, 2 H), 2.24 - 2.44 (m, 1 H), 1.87 - 2.09 (m, 1 H), 1.42 - 1.82 (m, 4 H), 0.60 - 0.89 (m, 1 H), 0.30 - 0.60 (m, 1 H) MS (ESI) *m/z*: 590.3 $(M+H)^+$. Analytical HPLC: RT = 4.28 min (Method B).

Example 67.

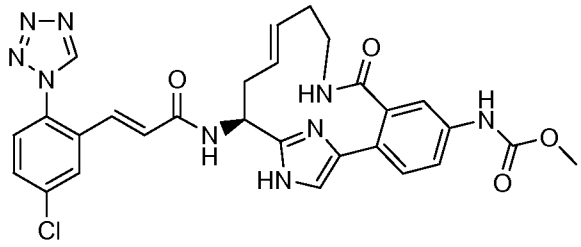
{(Z)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxo-9,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00535] Example 67 was prepared following the procedures described in step 3B, by replacing (1r,4r)-4-((*tert*-butoxycarbonylamino)methyl)cyclohexanecarboxylic acid with 66A and by replacing 3A with but-3-en-1-amine; followed by steps 2F;10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.53 - 7.71 (m, 4 H), 7.41 (s, 1 H), 7.35 (d, *J*=8.8 Hz, 1 H), 7.17 (d, *J*=15.4 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.59 - 5.73 (m, 1 H), 5.29 - 5.41 (m, 1 H), 5.05 - 5.14 (m, 1 H), 3.73 (s, 3 H), 3.33 - 3.46 (m, 2 H), 2.72 - 2.87 (m, 1 H), 2.51 - 2.65 (m, 1 H), 2.41 - 2.51 (m, 1 H), 2.34 (none, 1 H) MS (ESI) *m/z*: 588.3 $(M+H)^+$. Analytical HPLC: RT = 3.60 min (Method B).

Example 68.

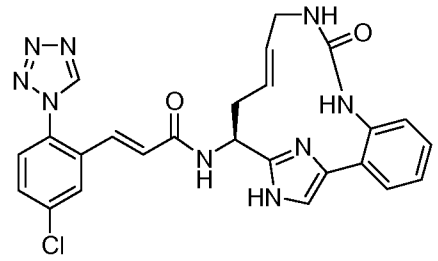
{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxo-9,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00536] Example 68 was prepared following the procedures described in step 3B, by replacing (1r,4r)-4-((*tert*-butoxycarbonylamino)methyl)cyclohexanecarboxylic acid with 66A and by replacing 3A with but-3-en-1-amine; followed by steps 2E;10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.95 (d, J=2.2 Hz, 1 H), 7.65 – 7.70 (m, 1 H), 7.57 (d, J=8.8 Hz, 2 H), 7.46 - 7.54 (m, 1 H), 7.41 (s, 1 H), 7.24 - 7.36 (m, 1 H), 7.13 – 7.17 (m, 1 H), 6.71 - 6.85 (m, 1 H), 5.50 - 5.62 (m, 1 H), 5.10 - 5.29 (m, 1 H), 3.69 (s, 3 H), 2.95 - 3.21 (m, 1 H), 2.63 - 2.87 (m, 1 H), 2.29 - 2.51 (m, 1 H), 2.06 - 2.29 (m, 1 H). MS (ESI) *m/z*: 588.3 $(M+H)^+$. Analytical HPLC: RT = 3.62 min. (Method B).

Example 69.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-9-oxo-8,10,17,19-tetraaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt



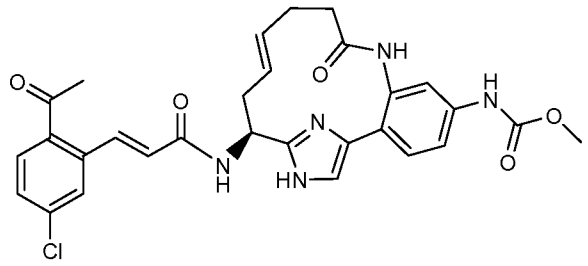
[00537] 69A. {(S)-1-[4-[2-(3-Allyl-ureido)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a cooled (0 °C), orange solution of 15B (150 mg, 0.327 mmol) and pyridine (26.5 µL, 0.327 mmol) in DCM (1308 µL) was added dropwise allyl isocyanate (28.9 µL, 0.327 mmol). After 35 min, additional allyl isocyanate (28.9 µL, 0.327 mmol) was added. After an additional 30 min, sat. $NaHCO_3$(aq) (1.31 mL) was added and the reaction was stirred vigorously. The reaction was allowed to warm to rt and stir overnight. The reaction was partitioned between 1:1 mixture of DCM and sat. $NaHCO_3$(aq) and the

layers were separated. The aqueous layer was extracted with DCM (2x). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to give an orange residue. Purification by normal phase chromatography gave 69A (109.8 mg, 59.5 % yield) as a yellow foam. MS (ESI) *m/z*: 542.5$(M+H)^+$.

[00538] 69B. Example 69 was prepared following the procedures described in step 2E, by replacing 2D with 69A; followed by steps 10H; and 15D. ^1H NMR (500 MHz, CD_3OD) δ ppm 2.52 - 2.70 (m, 1 H), 2.81 - 2.93 (m, 1 H), 3.48 - 3.59 (m, 2 H), 5.15 (dd, *J*=10.0, 5.4 Hz, 1 H), 5.56 - 5.73 (m, 2 H), 6.77 (d, *J*=15.4 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 7.28 (d, *J*=8.0 Hz, 1 H), 7.33 (td, *J*=7.6, 1.1 Hz, 1 H), 7.39 (s, 1 H), 7.46 - 7.50 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 516.2$(M+H)^+$. Analytical HPLC: RT = 4.77min.

Example 70.

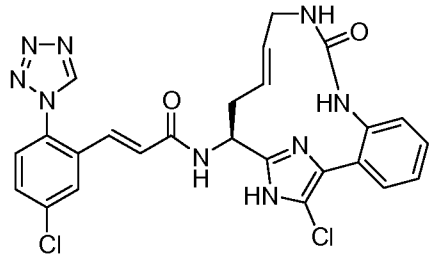
{(E)-(S)-15-[(E)-3-(2-Acetyl-5-chloro-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00539] Example 70 was prepared following the procedures described in step 10H, by replacing 10G with 39A; followed by step 15D, by replacing Intermediate 2 with Intermediate 4 and by replacing Hunig's base with triethylamine. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.98 (d, *J*=15.9 Hz, 1 H), 7.91 (d, *J*=8.2 Hz, 1 H), 7.66 (d, *J*=2.2 Hz, 1 H), 7.59 (s, 1 H), 7.54 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.41 - 7.43 (m, 3 H), 6.55 (d, *J*=15.9 Hz, 1 H), 5.54 - 5.62 (m, 1 H), 5.38 - 5.46 (m, 1 H), 5.13 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.79 - 2.87 (m, 1 H), 2.34 - 2.63 (m, 8 H). MS (ESI) *m/z*: 562.5 $(M+H)^+$. Analytical HPLC: RT = 5.36 min.

Example 71.

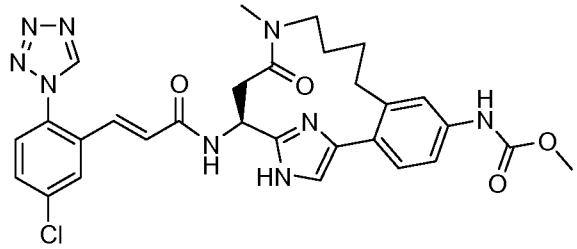
(E)-*N*-((E)-(S)-18-Chloro-9-oxo-8,10,17,19-tetraaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00540] Example 71 was prepared following the procedure described in 17A, by replacing 16A with Example 69. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.40 - 2.57 (m, 1 H), 2.72 - 2.84 (m, 1 H), 3.45 - 3.68 (m, 2 H), 5.03 (dd, *J*=9.9, 4.9 Hz, 1 H), 5.37 - 5.53 (m, 1 H), 5.54 - 5.67 (m, 1 H), 6.78 (d, *J*=15.4 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 7.28 - 7.34 (m, 2 H), 7.43 - 7.48 (m, 2 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.97 - 8.00 (m, 1 H), 9.52 (s, 1 H). MS (ESI) *m/z*: 550.2 $(M+H)^+$. Analytical HPLC: RT = 6.48 min.

Example 72.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-methyl-13-oxo-12,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00541] 72A. (S)-3-[4-(2-Allyl-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-3-*tert*-butoxycarbonylamino-propionic acid benzyl ester: 23A (0.30 g, 0.426 mmol), allyltributylstannane (0.282 g, 0.853 mmol), CsF (0.162 g, 1.065 mmol), Pd_2dba_3 (0.020 g, 0.021 mmol), and tri-(*tert*-butyl)phosphine (0.173 g, 0.085 mmol) were added together with dioxane (10 mL). The mixture was heated to 90 °C under argon. After 2.5 h, an additional two equivalents of

allyltributylstannane and CsF, and a catalytic amount of Pd_2dba_3 and tri-(*tert*-butyl)phosphine were added. The mixture was stirred at 90 °C under argon for 3 h. The solvent was removed and the residue was partitioned between EtOAc and water. The EtOAc solution was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by normal phase chromatography to give 72A (0.26 g, 92% yield). MS (ESI) *m/z*: 665.3 $(M+H)^+$.

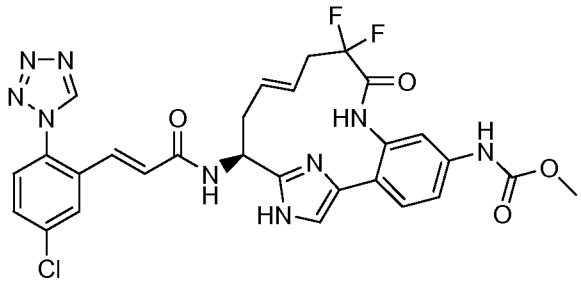
[00542] 72B. (S)-3-(4-(2-Allyl-4-(methoxycarbonylamino)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(*tert*-butoxycarbonylamino)propanoic acid: 72A (0.26 g, 0.39 mmol) was dissolved in THF (6 mL) and 2N LiOH (2 mL) was added. The mixture was stirred at rt under argon for 20 h. The solvent was removed and the residue was diluted with water and acidified to pH about 5 with 1N HCl. The mixture was extracted with EtOAc. The combined EtOAc solution was washed with brine, dried over Na_2SO_4 and concentrated to give 72B (0.24 g, 100% yield). MS (ESI) *m/z*: 575.3 $(M+H)^+$.

[00543] 72C. {3-Allyl-4-[2-[(S)-2-(allyl-methyl-carbamoyl)-1-*tert*-butoxycarbonylamino-ethyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: To a solution of 72B in DMF (4 mL) were added PyBOP (0.26 g, 0.47 mmol), Et_3N (0.22 mL, 1.56 mmol), and methylallylamine (0.71 g, 0.998 mmol). The mixture was stirred at rt under argon for 1.5 h. Water was added and the mixture was extracted with EtOAc. The combined EtOAc solution was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by normal phase chromatography to give 72C (0.16 g, 64% yield). MS (ESI) *m/z*: 628.4 $(M+H)^+$.

[00544] 72D. Example 72 was prepared following the procedures described in step 2E/2F, by replacing 2D with 72C; followed by steps 2G; 1F, by replacing ethanol with methanol; and 1G. ^1H NMR (400 MHz, CD_3OD, rotamers) δ ppm 9.52 (s, 1H), 9.30 (s, 1H), 8.00 (dd, *J* = 14.56 and 2.26 Hz, 1H), 7.64 - 7.77 (m, 1 H), 7.55 - 7.63 (m, 1 H), 7.46 (dd, *J* = 10.42 and 2.13 Hz, 1H), 7.36 - 7.43 (m, 1 H), 7.35 (d, *J* = 1.25 Hz, 1H), 7.30 (d, *J* = 8.03 Hz, 1H), 7.21 (dd, *J* = 15.69 and 5.14 Hz, 1H), 5.67 (m, 1H), 5.53 (m, 1H), 4.46 (m, 1H), 3.75 (two singlets, 3H), 3.47 (m, 1H), 3.28 (m, 2H), 3.25(m, 1H), 2.92 (two singlets, 3H), 2.68 (m, 2H), 2.29 (m, 1H), 1.29 (m, 1H). LC-MS (ESI) *m/z*: 604.3 $(M+H)^+$. Analytical HPLC: RT = 6.22/6.49 min (two rotational isomers).

Example 73.

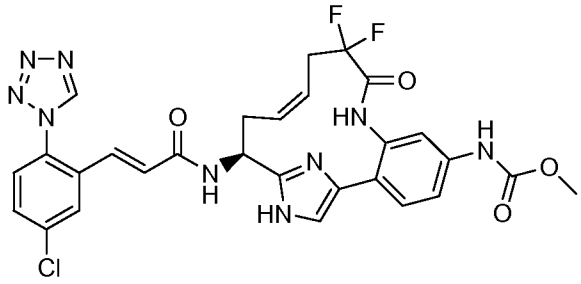
{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10,10-difluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00545] Example 73 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 2,2-difluoropent-4-enoic acid; followed by steps 2E; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (s, 1 H), 7.67 (s, 1 H), 7.54 - 7.62 (m, 2 H), 7.49 (s, 1 H), 7.38 - 7.47 (m, 2 H), 7.12 – 7.16 (d, *J*=15.4 Hz, 1 H), 6.74 - 6.78 (d, *J*=15.4 Hz, 1 H), 5.69 - 5.81 (m, 1 H), 5.23 - 5.35 (m, 1 H), 5.06 - 5.14 (m, 1 H), 3.76 (s, 3 H), 2.75 - 3.00 (m, 3 H), 2.53 - 2.68 (m, 1 H) MS (ESI) *m/z*: 624.3 $(M+H)^+$. Analytical HPLC: RT = 4.31 min. (Method B).

Example 74.

{(Z)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10,10-difluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

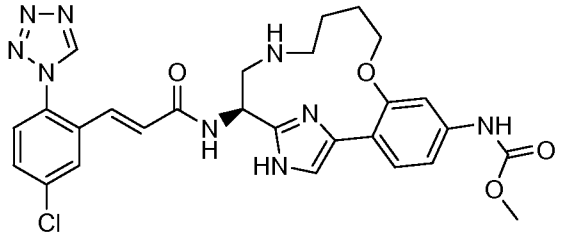


[00546] Example 74 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 2,2-difluoropent-4-enoic acid; followed by steps 2F; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (s, 1 H), 7.52 - 7.76 (m,

3 H), 7.27 - 7.52 (m, 3 H), 7.04 - 7.27 (m, 1 H), 6.66 - 6.87 (m, 1 H), 5.50 - 5.75 (m, 2 H), 5.09 - 5.29 (m, 1 H), 3.76 (s, 3 H), 2.52 - 3.18 (m, 4 H). MS (ESI) *m/z*: 624.2 $(M+H)^+$. Analytical HPLC: RT = 4.24 min. (Method B).

Example 75.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8-oxa-13,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00547] 75A. (S)-2-Benzyloxycarbonylamino-3-*tert*-butoxycarbonylamino-propionic acid 2-(2-hydroxy-4-methoxycarbonylamino-phenyl)-2-oxo-ethyl ester: This compound was prepared following the procedures described in 2A, by replacing (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid with (S)-2-Benzyloxycarbonylamino-3-*tert*-butoxycarbonylamino-propionic acid and by replacing 2-bromo-1-(2-bromophenyl)ethanone with methyl 4-(2-bromoacetyl)-3-hydroxyphenylcarbamate. MS (ESI) *m/z*: 546.3 $(M+H)^+$.

[00548] 75B. (S)-2-Benzyloxycarbonylamino-3-*tert*-butoxycarbonylamino-propionic acid 2-(2-allyloxy-4-methoxycarbonylamino-phenyl)-2-oxo-ethyl ester**:** To a solution of 75A (3.3 g, 6.05 mmol) in DMF (8.5 mL) was added potassium carbonate (1.254 g, 9.07 mmol), followed by addition of 3-bromoprop-1-ene (0.580 mL, 6.65 mmol). The reaction was heated at 70 °C for 2 hr. The reaction mixture turned dark red. It was cooled down, partitioned between water and EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered off solid and concentrated. Purification by normal phase chromatography gave 75B as a pale yellow foam (2.05 g, 58%). MS (ESI) *m/z*: 586.4 $(M+H)^+$.

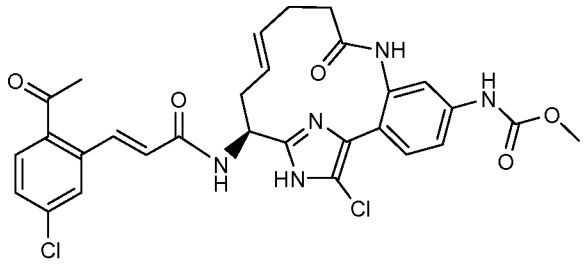
[00549] 75C. {4-[2-((S)-2-Allylamino-1-benzyloxycarbonylamino-ethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-allyloxy-phenyl}-carbamic acid methyl ester: This compound was prepared following the procedures described in step

2B, by replacing 2A with 75B; followed by steps 3C; and 75B. MS (ESI) *m/z*: 636.5 $(M+H)^+$.

[00550] 75D. Example 75 was prepared following the procedures described in step 20D, by replacing 20C with 75C; followed by steps 2E/2F; 2G; 1G; and 10H. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.5, 2.5 Hz, 1 H), 7.60 (d, J=8.3 Hz, 1 H), 7.45 (d, J=8.2 Hz, 1 H), 7.40 (s, 1 H), 7.34 (s, 1 H), 7.23 (d, J=15.9 Hz, 1 H), 6.98 - 7.02 (m, 1 H), 6.68 (d, J=15.9 Hz, 1 H), 5.42 (dd, J=7.1, 3.3 Hz, 1 H), 4.14 (s, 2 H), 3.75 (s, 3 H), 3.51 - 3.59 (m, 1 H), 3.42 - 3.49 (m, 1 H), 3.10 - 3.22 (m, 2 H), 1.95 - 2.09 (m, 4 H). MS (ESI) *m/z*: 578.3 $(M+H)^+$. Analytical HPLC: RT = 3.63 min. (Method B).

Example 76.

{(E)-(S)-15-[(E)-3-(2-Acetyl-5-chloro-phenyl)-acryloylamino]-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00551] 76A. [(E)-(S)-18-Chloro-5-methoxycarbonylamino-9-oxo-17-(2-trimethylsilanylethoxymethyl)-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl]-carbamic acid *tert*-butyl ester: To a solution of 39A (0.37 g, 0.632 mmol) in acetonitrile (3 mL)/chloroform (3 mL) was added NCS (0.101 g, 0.758 mmol). The reaction was heated at 65 °C for 3 h, cooled to rt and concentrated. Purification by reverse phase chromatography gave 76A (0.205 g, 0.331 mmol, 52.3 %) as a white solid. MS (ESI) *m/z*: 620.1 $(M+H)^+$.

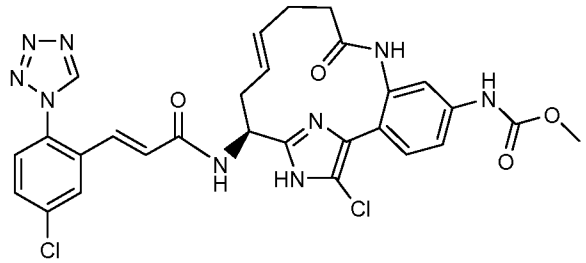
[00552] 76B. ((E)-(S)-15-Amino-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl)-carbamic acid methyl ester, 2 HCl salt: The mixture of 76A (0.205 g, 0.279 mmol) and 4M HCl in dioxane (2 mL, 8.00 mmol) in a sealed tube was heated at 75 °C. After 2h, the reaction was cooled

to rt. The solid was collected by filtration, rinsed with hexane, and then dried to afford 76B (0.12 g, 93 %) as a white solid. MS (ESI) *m/z*: 390.1 $(M+H)^+$.

[00553] 76C. Example 76 was prepared following the procedure described in step 15D, by replacing 15C with 76B, by replacing Intermediate 2 with Intermediate 4 and by replacing Hunig's base with triethylamine. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.97 (d, *J*=15.4 Hz, 1 H), 7.89 (d, *J*=8.2 Hz, 1 H), 7.67 (d, *J*=2.2 Hz, 1 H), 7.59 (s, 1 H), 7.52 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.41 (s, 2 H), 6.55 (d, *J*=15.9 Hz, 1 H), 5.52 - 5.60 (m, 1 H), 5.34 - 5.42 (m, 1 H), 5.02 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.72 - 2.79 (m, 1 H), 2.59 (s, 3 H), 2.32 - 2.53 (m, 5 H). MS (ESI) *m/z*: 596.0 $(M+H)^+$. Analytical HPLC: RT = 6.86 min.

Example 77.

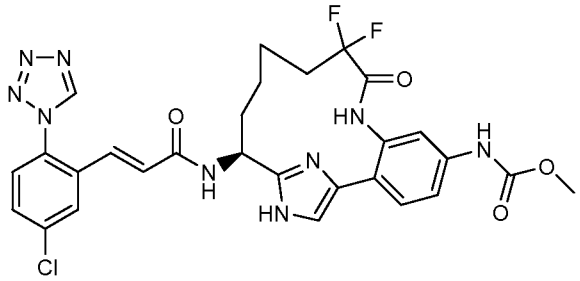
{(E)-(S)-18-Chloro-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00554] Example 77 was prepared following the procedure described in 1G, by replacing 1F with 76B. ^1H NMR (400 MHz, DMSO-d_6 +2 drops D_2O) δ ppm 9.76 (s, 1 H), 7.92 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.64 (d, *J*=8.2 Hz, 1 H), 7.38 (s, 1 H), 7.31 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.26 (d, *J*=8.3 Hz, 1 H), 6.77 - 6.87 (m, 2 H), 5.37 - 5.47 (m, 1 H), 5.12 - 5.21 (m, 1 H), 4.87 (dd, *J*=10.2, 4.1 Hz, 1 H), 3.61 (s, 3 H), 2.12 - 2.33 (m, 6 H). MS (ESI) *m/z*: 622.0 $(M+H)^+$. Analytical HPLC: RT = 6.46 min.

Example 78.

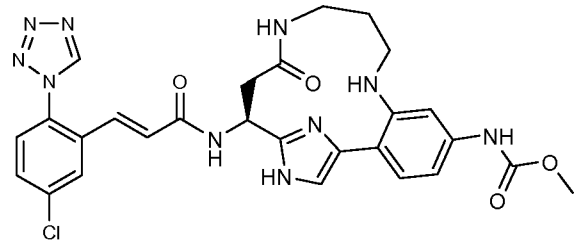
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10,10-difluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester 1 TFA salt



[00555] Example 78 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 2,2-difluoropent-4-enoic acid; followed by steps 2E/2F; 2G; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.96 (d, J=2.2 Hz, 1 H), 7.67 (d, J=2.2 Hz, 1 H), 7.65 (d, J=2.2 Hz, 1 H), 7.61 (s, 1 H), 7.57 (d, J=8.8 Hz, 1 H), 7.51 (s, 1 H), 7.47 - 7.50 (m, 1 H), 7.11 (d, J=15.9 Hz, 1 H), 6.75 (d, J=15.4 Hz, 1 H), 5.53 - 5.65 (m, 1 H), 3.76 (s, 3 H), 1.95 - 2.29 (m, 4 H), 1.56 (d, J=4.9 Hz, 2 H), 0.68 - 0.94 (m, 2 H). MS (ESI) *m/z*: 626.3 $(M+H)^+$. Analytical HPLC: RT = 4.27 min. (Method B).

Example 79.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-13-oxo-8,12,17,19-tetraaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



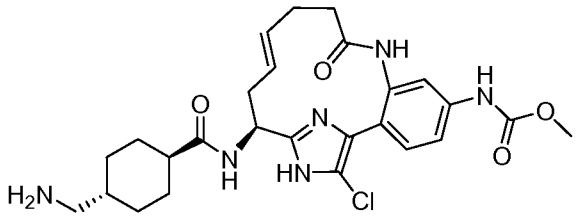
[00556] 79A. (S)-Benzyl 3-(4-(2-(3-(benzyloxycarbonylamino)propylamino)-4-(methoxycarbonylamino)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(*tert*-butoxycarbonylamino)propanoate: To a solution of 23A (200 mg, 0.284 mmol) in DMSO were added benzyl 3-aminopropylcarbamate, HCl salt (83 mg, 0.341 mmol), L-proline (6.54 mg, 0.057 mmol), CuI (5.41 mg, 0.028 mmol) and K_2CO_3 (118 mg, 0.853 mmol). The reaction was purged with argon for 3 min. The reaction was stirred at 80 °C for 16 h. The reaction was cooled to rt and then was diluted with EtOAc, washed with H_2O, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$,

filtered and concentrated. The crude product was purified by normal phase chromatography to give 79A (47 mg, 20% yield) as a light tan solid. LC-MS (ESI) *m/z*: 831.4 $(M+H)^+$.

[00557] 79B. Example 79 was prepared following the procedures described in step 2G, by replacing 2E with 79A; followed by steps 23E;1F, by replacing ethanol with methanol; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.99 (1 H, d, *J*=2.26 Hz), 7.83 (1 H, s), 7.64 - 7.71 (2 H, m), 7.55 - 7.62 (2 H, m), 7.25 (1 H, dd, *J*=8.53, 2.01 Hz), 7.21 (1 H, d, *J*=15.56 Hz), 6.74 (1 H, d, *J*=15.56 Hz), 5.60 (1 H, dd, *J*=9.29, 4.27 Hz), 3.77 (3 H, s), 3.61 - 3.71 (1 H, m), 3.43 - 3.51 (1 H, m), 3.34 - 3.40 (2 H, m), 2.85 - 2.94 (1 H, m), 2.75 - 2.84 (1 H, m), 2.13 - 2.27 (2 H, m). LC-MS (ESI) *m/z*: 591.2 $(M+H)^+$. Analytical HPLC: RT = 4.836 min.

Example 80.

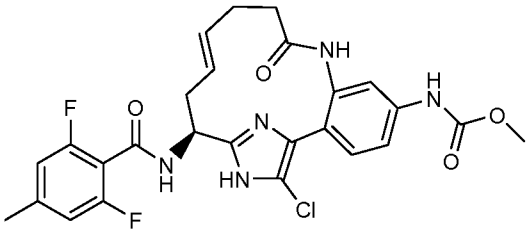
{(E)-(S)-15-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00558] Example 80 was prepared following the procedures described in step 3B, by replacing 3A with 76B and by running the reaction at 55 °C; followed by step 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.53 (d, *J*=1.4 Hz, 1 H), 7.42 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.36 (d, *J*=8.5 Hz, 1 H), 5.46 - 5.54 (m, 1 H), 5.27 - 5.36 (m, 1 H), 4.79 - 4.90 (m, 1 H), 3.75 (s, 3 H), 2.79 (d, *J*=6.9 Hz, 2 H), 2.58 - 2.66 (m, 1 H), 2.26 - 2.48 (m, 6 H), 1.85 - 1.98 (m, 4 H), 1.57 - 1.67 (m, 1 H), 1.42 - 1.55 (m, 2 H), 1.03 - 1.16 (m, 2 H). MS (ESI) *m/z*: 529.1 $(M+H)^+$. Analytical HPLC: RT = 3.31 min.

Example 82.

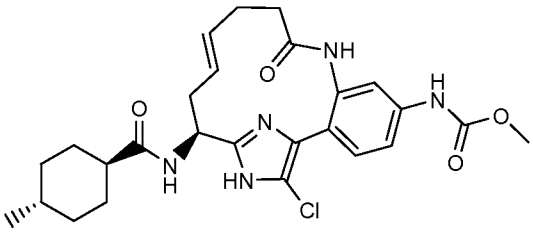
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid methyl ester, 1 TFA salt



[00559] Example 82 was prepared following the procedure described in step 15D, by replacing 15C with 76B, by replacing Intermediate 2 with 2,6-difluoro-4-methyl benzoic acid, by replacing Hunig's base with triethylamine and running the reaction at 55 °C. ^{1}H NMR (500 MHz, DMSO-d_6+2 drops D_2O) δ ppm 7.39 (d, *J*=1.6 Hz, 1 H), 7.33 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.29 (d, *J*=8.3 Hz, 1 H), 6.93 (d, *J*=8.8 Hz, 2 H), 5.40 - 5.48 (m, 1 H), 5.17 - 5.24 (m, 1 H), 5.06 (dd, *J*=9.1, 4.1 Hz, 1 H), 3.62 (s, 3 H), 2.37 - 2.43 (m, 1 H), 2.24 - 2.36 (m, 6 H), 2.15 - 2.22 (m, 2 H). MS (ESI) *m/z*: 544.2 $(M+H)^+$. Analytical HPLC: RT = 6.67 min.

Example 83.

{(E)-(S)-18-Chloro-15-[(4-methyl-cyclohexanecarbonyl)-amino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

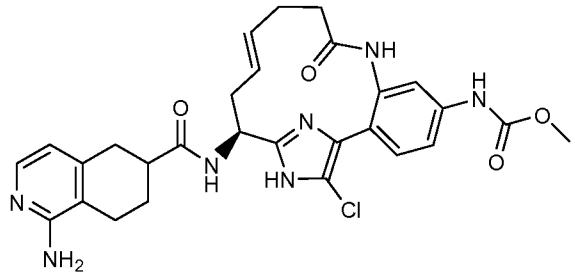


[00560] Example 83 was prepared following the procedure described in step 15D, by replacing 15C with 76B, by replacing Intermediate 2 with 4-methylcyclohexanecarboxylic acid, by replacing Hunig's base with triethylamine and running the reaction at 55 °C. ^{1}H NMR (500 MHz, DMSO-d_6+2 drops D_2O) δ ppm 7.40 (d, *J*=2.2 Hz, 1 H), 7.32 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.27 (d, *J*=8.8 Hz, 1 H), 5.37 - 5.45 (m, 1 H), 5.13 - 5.21 (m, 1 H), 4.81 (dd, *J*=9.6, 4.1 Hz, 1 H), 3.62 (s, 3 H), 2.14 - 2.38 (m, 6

H), 2.03 - 2.11 (m, 1 H), 1.56 - 1.70 (m, 4 H), 1.16 - 1.32 (m, 3 H), 0.75 - 0.89 (m, 5 H). MS (ESI) *m/z*: 514.2 $(M+H)^+$. Analytical HPLC: RT = 6.84 min.

Example 84.

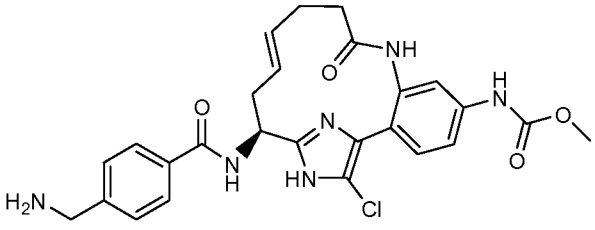
{(E)-(S)-15-[(1-Amino-5,6,7,8-tetrahydro-isoquinoline-6-carbonyl)-amino]-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt (mixture of diastereomers)



[00561] Example 84 was prepared following the procedure described in 15D, by replacing 15C with 76B, by replacing Intermediate 2 with Intermediate 5, by replacing Hunig's base with triethylamine and running the reaction at 55 °C. ^{1}H NMR (500 MHz, DMSO-d_6+2 drops D_2O) δ ppm 7.65 - 7.70 (m, 1 H), 7.42 (s, 1 H), 7.35 - 7.39 (m, 1 H), 7.28 - 7.33 (m, 1 H), 6.69 - 6.74 (m, 1 H), 5.42 - 5.51 (m, 1 H), 5.16 - 5.26 (m, 1 H), 4.86 - 4.92 (m, 1 H), 3.65 (s, 3 H), 2.77 - 2.85 (m, 2 H), 2.63 - 2.72 (m, 1 H), 2.45 - 2.53 (m, 1 H), 2.18 - 2.44 (m, 7 H), 2.00 - 2.09 (m, 1 H), 1.63 - 1.78 (m, 1 H). MS (ESI) *m/z*: 564.2 $(M+H)^+$. Analytical HPLC: RT = 3.56 min.

Example 85.

[(E)-(S)-15-(4-Aminomethyl-benzoylamino)-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid methyl ester, 2 TFA salt

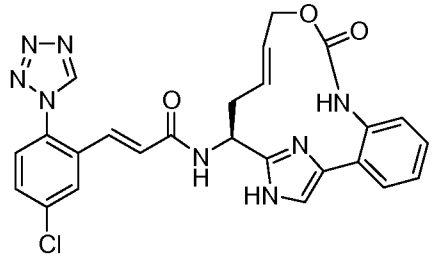


[00562] 85A. {(E)-(S)-15-[4-(*tert*-Butoxycarbonylamino-methyl)-benzoylamino]-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt: This compound was prepared following the procedure described in 15D, by replacing 15C with 76B, by replacing Intermediate 2 with 4-((*tert*-butoxycarbonylamino)methyl)benzoic acid, by replacing Hunig's base with triethylamine and running the reaction at 55 °C. MS (ESI) *m/z*: 623.3 $(M+H)^+$.

[00563] 85B. Example 85 was prepared following the procedure described in 3C, by replacing 3B with 85A. ^{1}H NMR (500 MHz, DMSO-d_6+2 drops D_2O) δ ppm 7.93 (d, *J*=8.5 Hz, 2 H), 7.54 (d, *J*=8.3 Hz, 2 H), 7.46 (s, 1 H), 7.39 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.32 (d, *J*=8.5 Hz, 1 H), 5.52 - 5.60 (m, 1 H), 5.24 - 5.32 (m, 1 H), 5.15 (dd, *J*=9.4, 4.7 Hz, 1 H), 4.09 (s, 2 H), 3.68 (s, 3 H), 2.23 - 2.54 (m, 6 H). MS (ESI) *m/z*: 523.1 $(M+H)^+$. Analytical HPLC: RT = 3.44 min.

Example 87.

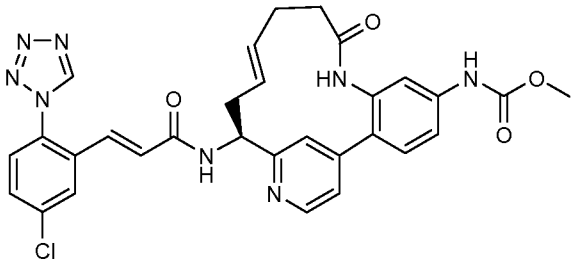
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-9-oxo-10-oxa-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt



[00564] Example 87 was prepared following the procedures described in step 69A, by replacing allyl isocyanate with allyl chloroformate; followed by steps 2E; 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.53 - 2.69 (m, 1 H), 2.88 - 2.98 (m, 1 H), 4.28 - 4.43 (m, 2 H), 5.16 (dd, *J*=10.5, 5.2 Hz, 1 H), 5.63 - 5.79 (m, 1 H), 5.84 - 5.94 (m, 1 H), 6.78 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.25 (d, *J*=7.7 Hz, 1 H), 7.39 (t, *J*=7.4 Hz, 1 H), 7.44 (s, 1 H), 7.48 - 7.54 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). MS (ESI) *m/z*: 517.2$(M+H)^+$. Analytical HPLC: RT = 5.12 min.

Example 88.

{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17-diaza-tricyclo[14.3.1.0^{2,7}]icosa-1(20),2(7),3,5,12,16,18-heptaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00565] 88A. (S,E)-N-((4-Chloropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide: Reference: Liu, G. et al., *J. Org. Chem.*, 64:1278 (1999). To a solution of S-(-)-*t*-butyl-sulfinamide (0.856 g, 7.06 mmol) in dichloromethane (14.13 mL) was added sequentially copper(II) sulfate (2.481 g, 15.54 mmol) and 4-chloropicolinaldehyde [1.0 g, 7.06 mmol, prepared according to a modified described by Negi (*Synthesis*, 991 (1996))]. The white suspension was stirred at rt. After 3h, the brown suspension was filtered through CELITE®, eluting with DCM, to give a clear brown filtrate. Concentration gave a brown oil weighing 1.85 g. Purification by normal phase chromatography gave 1.31 g of 88A as a clear, yellow oil. MS (ESI) *m/z*: 245.0 $(M+H)^+$.

[00566] 88B. (S)-N-((S)-1-(4-Chloropyridin-2-yl)but-3-enyl)-2-methylpropane-2-sulfinamide: Using a modified procedure described by Kuduk (*Tetrahedron Letters*, 45:6641 (2004)). To a cooled (-78 °C), clear, yellow solution of 88A (2.50 g, 10.21 mmol) in THF (34.0 mL) was added dropwise allylmagnesium bromide (1.0 M in diethyl ether, 14.30 mL, 14.30 mmol) over 25 min. The resulting orange-brown suspension was stirred at -78 °C. After 30 min, additional allylmagnesium bromide (1.40 mL) was added. After 1h, the reaction was stopped by quenching with sat. NH_4Cl. The resulting orange-brown suspension was allowed to warm to rt. The reaction was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give a blue oil weighing 3.22 g. Purification by normal phase chromatography gave 2.55 g (87%) of 88B as an

orange-brown solid. The diastereomeric excess based on HPLC of the reaction mixture was 1:5.7 diastereomer A:diastereomer B. MS (ESI) *m/z*: 287.1 $(M+H)^+$.

[00567] 88C. (S)-N-((S)-1-(4-(2-Amino-4-nitrophenyl)pyridin-2-yl)but-3-enyl)-2-methylpropane-2-sulfinamide: To a RBF was added 88B (1.40 g, 4.88 mmol), Intermediate 12 (2.441 g, 9.76 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.399 g, 0.488 mmol), and potassium phosphate, tribasic (2.072 g, 9.76 mmol). The RBF was equipped with a reflux condensor then the apparatus was purged with argon for several minutes. Next, degassed DMSO (24.41 mL) was added followed by degassed water (0.440 mL, 24.41 mmol). The bright orange suspension was warmed to 90 °C. After 5 h, the reaction was stopped and cooled to rt. The black mixture was filtered to remove the solid, rinsing with EtOAc. The filtrate was then partitioned between EtOAc and water and the layers were separated. The aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give a thick black oil weighing 3.8 g. Purification by normal phase chromatography gave 1.70 g as a mixture of diastereomers. The diastereomers were separated by reverse phase chromatography. Pure fractions of diastereomer A were neutralized and worked up as described in 2D to give 0.139 g of diastereomer A as an orange foam. Pure fractions of diastereomer B were neutralized and worked up as described in 2D to give 0.996 g of 88C, as an orange foam. Diastereomer B: MS (ESI) *m/z*: 389.2 $(M+H)^+$.

[00568] 88D. {(S)-1-[4-(2-Amino-4-nitro-phenyl)-pyridin-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a clear, orange solution of 88C (1.22 g, 3.14 mmol) in methanol (31.4 mL) was added 4 M HCl in dioxane (15.70 mL, 62.8 mmol). The reaction was slightly exothermic to the touch, so a water bath was used. After 1 h, the orange solution was concentrated to give an orange residue. The residue was suspended in DCM and concentrated. The residue was again suspended in DCM and then concentrated to give the amine as an orange solid. MS (ESI) *m/z*: 285.2 $(M+H)^+$. The orange solid was suspended in DCM (10.46 mL) and then BOC_2O (0.802 mL, 3.45 mmol) was added. Next, triethylamine (1.750 mL, 12.56 mmol) was added and the reaction became an orange-brown suspension. The reaction was stirred at rt. After 2 h, the reaction was diluted with EtOAc and washed with sat. $NaHCO_3$. The aqueous layer was extracted

with EtOAc (1x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give a dark brown foam weighing 1.53 g. Purification by normal phase chromatography gave 1.15 g (95%) of 88D as a yellow foam. MS (ESI) *m/z*: $(M+H)^+$.

[00569] 88E. {(S)-1-[4-(4-Nitro-2-pent-4-enoylamino-phenyl)-pyridin-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a cooled (-5 °C) clear, yellow solution of 88D (0.413 g, 1.074 mmol) and pent-4-enoic acid (0.220 mL, 2.149 mmol) in ethyl acetate (10.74 mL) was added Hunig's Base (0.563 mL, 3.22 mmol) and propane phosphonic acid anhydride (1.266 mL, 2.149 mmol). Following the addition, the reaction was allowed to warm to rt and stir overnight. After 17.5 h, additional pent-4-enoic acid (2 x 0.220 mL, 2.149 mmol), Hunig's Base (2 x 0.563 mL, 3.22 mmol) and propane phosphonic acid anhydride (2 x 1.266 mL, 2.149 mmol) were added. After an additional 24 h, the reaction was stopped, partitioned between EtOAc and sat. $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give an orange oil weighing 0.739 g. Purification by normal phase chromatography gave 0.448 g (88%) of 88E as a pale, yellow foam. MS (ESI) *m/z*: 467.3 $(M+H)^+$.

[00570] 88F. {4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-3-pent-4-enoylamino-phenyl}-carbamic acid methyl ester: To a clear, yellow solution of 88E (0.330 g, 0.707 mmol) in MeOH (14.15 mL) was added zinc dust (0.463 g, 7.07 mmol) and ammonium chloride (0.378 g, 7.07 mmol). The gray suspension was stirred vigorously at rt. After 2 h, the reaction was stopped and then filtered through a 0.45 micron nylon filter, eluting with methanol. The filtrate was concentrated to give a clear, pale yellow residue. The residue was partitioned between EtOAc and 0.25 M HCl (20 mL) and the layers were separated. The organic layer was extracted with 0.25 M HCl (2 x 10 mL). The acid layer was basified with 1.5 M K_2HPO_4 and then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give the aniline as a pale, yellow foam weighing 0.3047 g. MS (ESI) *m/z*: 437.3 $(M+H)^+$. To a cooled (-5 °C) clear, pale yellow solution of the aniline (0.3047 g, 0.698 mmol) in dichloromethane (6.98 mL) was added pyridine (0.056 mL, 0.698 mmol) and methyl chloroformate (0.054 mL, 0.698 mmol). The

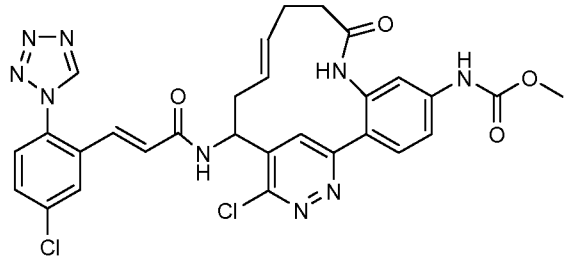
resulting bright yellow solution was stirred at -5 °C for 1h. The reaction was diluted with EtOAc and washed with sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give a white foam weighing 0.345 g. Purification by normal phase chromatography gave 0.312 g (90%) of 88F, as a white foam. MS (ESI) *m/z*: 495.3 $(M+H)^+$.

[00571] 88G. ((E)-(S)-15-*tert*-Butoxycarbonylamino-9-oxo-8,17-diaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2(7),3,5,12,16,18-heptaen-5-yl)-carbamic acid methyl ester, 1 TFA salt: To a flame-dried 500 mL RBF was added 88F (0.116 g, 0.235 mmol), pTsOH monohydrate (0.049 g, 0.258 mmol), and DCM (235 mL). The flask was equipped with a reflux condensor and the clear, colorless solution was degassed with argon for 30 min. The reaction was then warmed to 40 °C for 1 h. In a separate, flame-dried RBF was added Grubbs (II) (0.020 g, 0.023 mmol) and the flask was purged with argon for several minutes. Degassed DCM (2 mL) was added to give a clear, burgundy solution. The solution of Grubbs (II) was added dropwise over 5 min to the above reaction. The resulting clear yellow solution was stirred at 40 °C. The reaction was stopped after a total of 1.5 h. Upon cooling to rt, the reaction was washed with sat. $NaHCO_3$, brine, dried over sodium sulfate, filtered, and concentrated to give dark brown solid weighing 0.134 g. Purification by reverse phase chromatography gave 0.102 g (75%) of 88 G, as an off-white solid. MS (ESI) *m/z*: 467.3 $(M+H)^+$.

[00572] 88H. Example 88 was prepared following the procedures described in step 3C, by replacing 3B with 88G; followed by step 1G. ^1H NMR (500 MHz, DMSO-d_6 and D_2O) δ ppm 9.89 (s, 1 H), 9.81 (s, 1 H), 8.63 (d, *J*=5.5 Hz, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.73 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.69 (d, *J*=8.2 Hz, 1 H), 7.38 - 7.48 (m, 3 H), 7.31 (d, *J*=8.2 Hz, 1 H), 7.18 (s, 1 H), 6.98 (d, *J*=15.4 Hz, 1 H), 6.80 (d, *J*=15.4 Hz, 1 H), 5.37 - 5.48 (m, 1 H), 5.18 - 5.28 (m, 1 H), 4.93 (dd, *J*=9.1, 3.6 Hz, 1 H), 3.67 (s, 3 H), 2.50 - 2.55 (m, 1 H), 2.17 - 2.37 (m, 5 H). MS (ESI) *m/z*: 599.3 $(M+H)^+$. Analytical HPLC (Method D): RT = 4.57 min.

Example 89.

{(E)-17-Chloro-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,18,19-triaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2,4,6,12,16,18-heptaen-5-yl}-carbamic acid methyl ester



[00573] 89A. *tert*-Butyl 1-(3,6-dichloropyridazin-4-yl)but-3-enylcarbamate: To a cooled (-78 °C) solution of *tert*-butyl (3,6-dichloropyridazin-4-yl)methylcarbamate (3.28 g, 11.79 mmol) prepared by following a literature procedure (Cowden, C.J., *Org. Lett.*, 4497-4499 (2003)) in THF (15 mL) was added TMEDA (1.780 mL, 11.79 mmol). Then *sec*-butyllithium (1.4M in cyclohexane, 21.06 mL, 29.5 mmol) was added dropwise at -78 °C. The reaction was warmed to - 40 °C over 30 min before it was cooled to -78 °C. Allyl bromide (1.496 mL, 17.69 mmol) was added at -78 °C. The reaction was stirred under argon at -78 °C for 30 min and then was quenched with NH_4Cl solution. The reaction mixture was diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase chromatography to give 89A (1.49 g, 40% yield) as a solid. LC-MS (ESI) *m/z*: 318.1 $(M+H)^+$.

[00574] 89B. *tert*-Butyl 1-(6-(2-amino-4-nitrophenyl)-3-chloropyridazin-4-yl)but-3-enylcarbamate: A flask containing 89A (1.49 g, 4.68 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-nitroaniline (1.756 g, 7.02 mmol) and Cs_2CO_3 (3.81 g, 11.71 mmol) was purged with argon. To it were added dioxane (40 mL), tri-*tert*-butylphosphine tetrafluoroborate (0.204 g, 0.702 mmol) and Pd_2dba_3 (0.429 g, 0.468 mmol) at rt. The reaction was stirred under argon at 90 °C for 3 h. The reaction was cooled to rt. The solid was filtered off and the solvent was removed to give a dark solid. The crude product was purified by normal phase chromatography to give 89B (0.66 g, 34% yield) as a dark brown solid. LC-MS (ESI) *m/z*: 420.2 $(M+H)^+$.

[00575] 89C. *tert*-Butyl 1-(3-chloro-6-(4-nitro-2-pent-4-enamidophenyl)pyridazin-4-yl)but-3-enylcarbamate: To a solution of 89B (0.66 g, 1.572 mmol) in DCM (20 mL)

were added TEA (0.438 mL, 3.14 mmol) and pent-4-enoyl chloride (0.208 mL, 1.886 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 1.5 h. The reaction mixture was diluted with DCM, washed with 1M HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over sodium sulfate, filtered and concentrated to give 89C (0.79 g, 100% yield) as a brown solid. LC-MS (ESI) *m/z*: 502.2 $(M+H)^+$.

[00576] 89D. *tert*-Butyl 1-(6-(4-amino-2-pent-4-enamidophenyl)-3-chloropyridazin-4-yl)but-3-enylcarbamate: To a solution of 89C (0.79 g, 1.574 mmol) in methanol (30 mL) were added zinc powder (0.515 g, 7.87 mmol) and ammonium chloride (0.842 g, 15.74 mmol) at 0 °C. The reaction was stirred under argon at rt for 4 h. The solid was filtered through a pad of CELITE® and the filtrate was concentrated to give 89D (0.74 g, 100% yield) as a dark brown solid. LC-MS (ESI) *m/z*: 472.4 $(M+H)^+$.

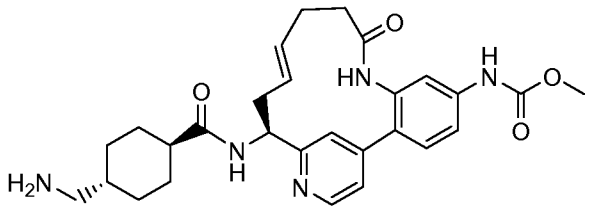
[00577] 89E. {4-[5-(1-*tert*-Butoxycarbonylamino-but-3-enyl)-6-chloro-pyridazin-3-yl]-3-pent-4-enoylamino-phenyl}-carbamic acid methyl ester: To a solution of 89D (0.74 g, 1.568 mmol) in DCM (20 mL) and DMF (2 mL)(to make it more soluble) were added pyridine (0.254 mL, 3.14 mmol) and methyl chloroformate (0.121 mL, 1.568 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 30 min. Water was added to quench the reaction. Most DCM was evaporated. The reaction mixture was diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase chromatography to give 89E (501 mg, 60% yield) as a brown solid. LC-MS (ESI) *m/z*: 530.3^+.

[00578] 89F. ((E)-17-Chloro-5-methoxycarbonylamino-9-oxo-8,18,19-triaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2,4,6,12,16,18-heptaen-15-yl)-carbamic acid *tert*-butyl ester: To a solution of 89E (350 mg, 0.660 mmol) in DCM (100 mL) was added Grubbs (II) (168 mg, 0.198 mmol) at rt. The solution was purged with argon for 3 min and then was stirred under argon at reflux for 1 h. Solvent was removed. The residue was dissolved in EtOAc, which was washed with water and brine. Organic phase was dried over $MgSO_4$, filtered and concentrated to give a dark solid. The crude product was purified by normal phase chromatography to give 89F (185 mg, 56% yield) as a brown solid. LC-MS (ESI) *m/z*: 502.3 $(M+H)^+$.

[00579] 89G. Example 89 was prepared following the procedures described in step 3C, by replacing 3B with 89F; followed by step1G. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.48 (s, 1H), 8.67 (d, *J* = 4.3 Hz, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.92 (s, 1H), 7.64 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.45 (dd, *J* = 14.0, 7.6 Hz, 1H), 7.07 (d, *J* = 15.6 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 5.34 - 5.11 (m, 2H), 4.58 - 4.36 (m, 1H), 3.76 (s, 3H), 3.10 - 2.96 (m, 1H), 2.64 - 2.51 (m, 1H), 2.19 (dd, *J* = 17.9, 11.0 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 1H). LC-MS (ESI) *m/z*: 634.3 $(M+H)^+$. Analytical HPLC: RT = 7.596 min.

Example 90.

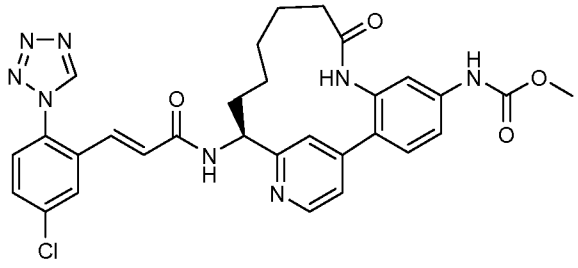
{(E)-(S)-15-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-9-oxo-8,17-diaza-tricyclo[14.3.1.0^{2,7}]icosa-1(20),2(7),3,5,12,16,18-heptaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00580] Example 90 was prepared following the procedures described in step 3C, by replacing 3B with 88G; followed by steps 3B; and 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.70 (d, *J*=6.0 Hz, 1 H), 7.75 (dd, *J*=6.0, 1.6 Hz, 1 H), 7.53 - 7.63 (m, 2 H), 7.49 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.39 (d, *J*=8.2 Hz, 1 H), 5.46 - 5.59 (m, 1 H), 5.36 (dd, *J*=15.7, 5.5 Hz, 1 H), 4.97 (dd, *J*=9.3, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.77 (d, *J*=7.1 Hz, 2 H), 2.67 - 2.75 (m, 1 H), 2.44 - 2.58 (m, 2 H), 2.30 - 2.44 (m, 4 H), 1.79 - 1.97 (m, 4 H), 1.51 - 1.65 (m, 1 H), 1.32 - 1.50 (m, 2 H), 0.99 - 1.15 (m, 2 H). MS (ESI) *m/z*: 506.4 $(M+H)^+$. Analytical HPLC (Method C): RT = 6.97 min.

Example 91.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17-diaza-tricyclo[14.3.1.0^{2,7}]icosa-1(20),2(7),3,5,16,18-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

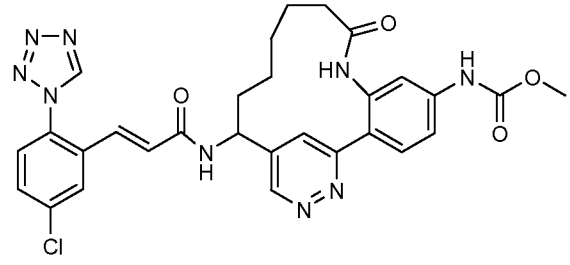


[00581] 91A. ((S)-15-Amino-9-oxo-8,17-diaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2(7),3,5,16,18-hexaen-5-yl)-carbamic acid methyl ester, 2 TFA salt: Compound 91A was prepared following the procedures described in step 2G, by replacing 2E/2F with 88G; followed by step 3C. MS (ESI) *m/z*: 369.1 $(M+H)^+$.

[00582] 91B. Example 91 was prepared following the procedure described in step1G, by replacing 1F with 91A. ^{1}H NMR (500 MHz, DMSO-d_6)) δ ppm 9.81 (s, 1 H), 9.78 (s, 1 H), 9.36 (s, 1 H), 8.56 (d, *J*=4.9 Hz, 1 H), 8.53 (d, *J*=7.7 Hz, 1 H), 7.87 (d, *J*=1.6 Hz, 1 H), 7.66 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.64 (d, *J*=8.8 Hz, 1 H), 7.37 - 7.43 (m, 2 H), 7.28 (d, *J*=8.2 Hz, 1 H), 7.21 (dd, *J*=4.9, 1.1 Hz, 1 H), 7.11 (s, 1 H), 6.93 (d, *J*=15.4 Hz, 1 H), 6.73 (d, *J*=15.9 Hz, 1 H), 4.76 - 4.83 (m, 1 H), 3.62 (s, 3 H), 2.09 - 2.20 (m, 2 H), 1.76 - 1.88 (m, 1 H), 1.56 - 1.68 (m, 2 H), 1.30 - 1.42 (m, 1 H), 1.07 - 1.26 (m, 3 H), 0.70 - 0.82 (m, 1 H). MS (ESI) *m/z*: 601.3 $(M+H)^+$ and 603.2 $(M+2+H)^+$. Analytical HPLC (Method D): RT = 4.56 min.

Example 92.

{15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,18,19-triaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2,4,6,16,18-hexaen-5-yl}-carbamic acid methyl ester

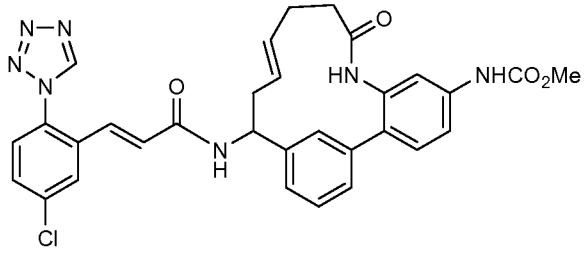


[00583] Example 92 was prepared by following the procedures described in step 2G, by replacing 2E with 89F; followed by steps 3C; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.44 (s, 1H), 9.27 (d, *J* = 5.4 Hz, 1H), 8.32 (d, *J* = 1.5 Hz, 1H), 7.99 (d, *J* = 5.4 Hz, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.55 - 7.48 (m, 2H), 7.23 (d, *J* = 8.5

Hz, 1H), 6.91 (d, J = 15.6 Hz, 1H), 6.41 (d, J = 15.7 Hz, 1H), 4.76 - 4.64 (m, 1H), 3.76 (s, 3H), 2.37 - 2.23 (m, 2H), 2.04 - 1.91 (m, 1H), 1.82 - 1.70 (m, 1H), 1.58 - 1.17 (m, 6H). LC-MS (ESI) *m/z*: 602.3 $(M+H)^+$. Analytical HPLC: RT = 6.253 min.

Example 93.

{(E)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8-aza-tricyclo[14.3.1.02,7]icosa-1(20),2,4,6,12,16,18-heptaen-5-yl}-carbamic acid methyl ester



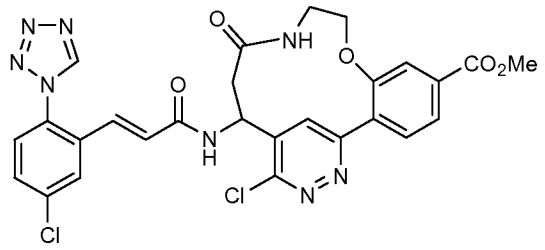
[00584] 93A. [1-(3-Bromo-phenyl)-but-3-enyl]-carbamic acid *tert*-butyl ester: Lithium hexamethyldisilazne solution (1M in THF, 7.30 mL, 7.3 mmol) was added to a cold (0 °C) THF (25 mL) solution of the 3-bromobenzaldehyde (1.33 g, 7.3 mmol) and stirred cold for 0.5 h. The reaction mixture was cooled to -78 °C, followed by the addition of allyl MgBr (1M, 7.30 mL, 7.3 mmol) dropwise. The cold reaction mixture was stirred at this temperature for 1.5 h, than quenched with sat. NH_4Cl and gradually allowed to warm up to room temperature. Extracted the organic materials with EtOAc (2x100 mL), dried ($MgSO_4$) and evaporated to an oil (1.1 g). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.52(s, 1H), 7.45-7.2(m, 3H), 5.77-5.68(m, 1H), 5.15-5.09(m, 2H), 3.99-3.95(m, 1H), 2.49-2.30(m, 2H). MS (ESI) *m/z*: 326.0 $(M+H)^+$. The crude reaction mixture was dissolved in dioxane (50 mL), and, to this was added Boc_2O (0.74g, 3.4 mmol) followed by the addition of TEA (1 mL) and subsequently stirred at room temperature overnight. Quenched the reaction mixture with water (100 mL) and the desired product was extracted with EtOAc (2x100 mL), dried ($MgSO_4$) and evaporated to a semi-solid mass which gradually solidified (1.25 g, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.45-7.18(m, 4H), 5.66-5.61(m, 1H), 5.17-5.08(m, 2H), 4.89(bs, 1H), 4.68(bs, 1H), 2.48(bm, 2H), 1.41(bs, 9H)ppm. MS (ESI) *m/z*: 3499 $(M+Na)^+$.

[00585] 93B. Example 93 was prepared following the procedures described in step 88C, by replacing 88B with 93A; followed by steps 88E; 88F, by replacing methanol

with acetone and by replacing solid ammonium chloride with a saturated aqueous solution of ammonium chloride; 88G, by running the reaction without pTsOH; 3C; and 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.77(s, 1H), 9.68(bs, 1H), 9.12(s, 1H), 8.61(d, J = 7.7Hz, 1H), 7.98(s, 1H), 7.66(m, 2H), 7.40-7.10(m, 4H), 6.95(s, 1H), 6.81(q, 2H), 5.40-5.20, m, 2H), 4.78(m, 1H), 3.62(s, 3H), 2.25(m, 4H), 1.16(m, 2H)ppm. MS (ESI) *m/z*: 598.4 $(M+H)^+$. Analytical HPLC: RT = 7.851 min.

Example 94.

16-Chloro-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-oxo-8-oxa-11,17,18-triaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2,4,6,15,17-hexaene-5-carboxylic acid methyl ester



[00586] 94A. 4-[5-(2-Benzyloxycarbonyl-1-*tert*-butoxycarbonylamino-ethyl)-6-chloro-pyridazin-3-yl]-3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-benzoic acid methyl ester: To a solution of benzyl 3-(*tert*-butoxycarbonylamino)-3-(3,6-dichloropyridazin-4-yl)propanoate (200 mg, 0.469 mmol) prepared by following a literature procedure (Cowden, C.J., *Org. Lett.*, 4497-4499 (2003)) in dioxane (10 mL) were added Intermediate 13 (308 mg, 0.704 mmol), Cs_2CO_3 (382 mg, 1.173 mmol) and tri-*tert*-butylphosphine tetrafluoroborate (13.61 mg, 0.047 mmol). The solution was purged with argon for 2 min and then Pd_2dba_3 (21.48 mg, 0.023 mmol) was added. The reaction was stirred under argon at 90 °C for 2 h. The solid was filtered-off and the solvent was removed. The crude mixture was purified by normal phase chromatography to give 94A (128 mg, 38% yield) as a yellow solid. LC-MS (ESI) *m/z*: 715.2 $(M+H)^+$.

[00587] 94B. 4-[5-(1-*tert*-Butoxycarbonylamino-2-carboxy-ethyl)-6-chloro-pyridazin-3-yl]-3-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-benzoic acid methyl ester: To a solution of 94A (128 mg, 0.179 mmol) in MeOH (5 mL) and ethyl acetate (5 mL) (more soluble in EtOAc) was added catalytic amount of 10% Pd/C. The reaction was stirred

under a hydrogen balloon at rt for 3 h. The catalyst was filtered off and the solvent was removed to give 94B (102 mg, 91% yield) as a yellow solid. LC-MS (ESI) *m/z*: 625.2 $(M+H)^+$.

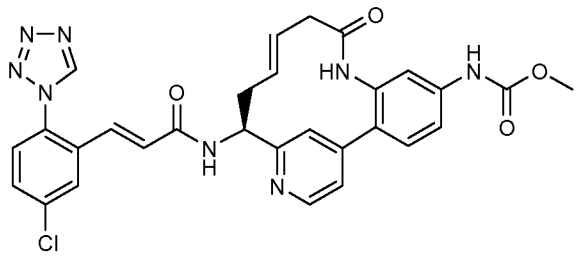
[00588] 94C. 3-(2-Amino-ethoxy)-4-[5-(1-*tert*-butoxycarbonylamino-2-carboxy-ethyl)-6-chloro-pyridazin-3-yl]-benzoic acid methyl ester, TFA salt: To a solution of 94B (102 mg, 0.163 mmol) in EtOH (5 mL) was added hydrazine (0.1 mL, 3.19 mmol) at rt. The reaction was stirred under argon at reflux for 30 min. the solvent was removed. Purification by reverse phase chromatography gave 94C (25 mg, 25.2 % yield) as a solid. LC-MS (ESI) *m/z*: 495.1 $(M+H)^+$.

[00589] 94D. 14-*tert*-Butoxycarbonylamino-16-chloro-12-oxo-8-oxa-11,17,18-triaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-5-carboxylic acid methyl ester: To a solution of BOP reagent (36.3 mg, 0.082 mmol), DIEA (0.036 mL, 0.205 mmol) and DMAP (5.02 mg, 0.041 mmol) in DCM (30 mL) was added a solution of 94C (25 mg, 0.041 mmol) in DMF (2.0 mL) through a syringe pump over 2 h at rt. Upon addition, the reaction was stirred for another 30 min and the solvent was removed. The crude product was purified by reverse phase chromatography to give 94D (3.0 mg, 15.32 % yield) as a tan solid. LC-MS (ESI) *m/z*: 477.1 $(M+H)^+$.

[00590] 94E. Example 94 was prepared by following the procedures described in step 3C, by replacing 3B with 94D; followed by step 1G. ^{1}H NMR (400 MHz, DMF-d_7) δ ppm 9.84 (1 H, s), 8.80 (1 H, d, *J*=8.03 Hz), 8.33 (1 H, s), 8.19 - 8.28 (1 H, m), 8.11 (1 H, s), 7.83 (1 H, d, *J*=8.28 Hz), 7.73 - 7.80 (4 H, m), 7.00 - 7.09 (1 H, m), 6.90 - 6.99 (1 H, m), 5.47 - 5.63 (1 H, m), 4.24 (2 H, dd, *J*=5.65, 1.88 Hz), 3.94 (3 H, s), 3.61 (2 H, t, *J*=5.90 Hz), 3.03 - 3.14 (2 H, m). LC-MS (ESI) *m/z*: 609.2 $(M+H)^+$. Analytical HPLC: RT = 7.620 min.

Example 95.

{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-yl}-carbamic acid methyl ester, 1 TFA salt

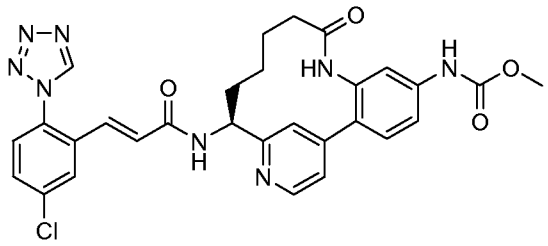


[00591] 95A. ((E)-(S)-14-*tert*-Butoxycarbonylamino-9-oxo-8,16-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-yl)-carbamic acid methyl ester, 1 TFA salt: This compound was prepared following the procedures described in step 88E, by replacing pent-4-enoic acid with but-3-enoic acid; followed by steps 88F; and 88G. MS (ESI) *m/z*: 453.3 $(M+H)^+$.

[00592] 95B. Example 95 was prepared following the procedures described in step 3C, by replacing 3B with 95A; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.65 (s, 1 H), 9.49 (s, 1 H), 8.64 (d, *J*=6.0 Hz, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.71 (dd, *J*=6.0, 1.6 Hz, 1 H), 7.66 (dd, *J*=8.8, 2.7 Hz, 1 H), 7.63 (br. s., 1 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.46 - 7.52 (m, 2 H), 7.38 (s, 1 H), 7.10 (d, *J*=15.4 Hz, 1 H), 6.83 (d, *J*=15.4 Hz, 1 H), 5.79 - 5.90 (m, 1 H), 5.08 (dd, *J*=9.6, 4.1 Hz, 1 H), 4.89 - 4.99 (m, 1 H), 3.76 (s, 3 H), 2.98 (dd, *J*=11.5, 8.8 Hz, 1 H), 2.75 - 2.89 (m, 2 H), 2.40 - 2.53 (m, 1 H). MS (ESI) *m/z*: 585.3 $(M+H)^+$. Analytical HPLC (Method D): RT = 5.07 min.

Example 96.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



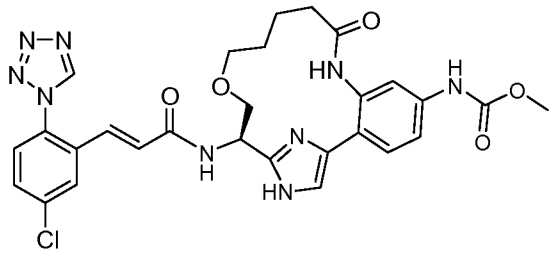
[00593] 96A. ((S)-14-Amino-9-oxo-8,16-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-yl)-carbamic acid methyl ester, 2 TFA salt: Compound

96A was prepared following the procedures described in step 2G, by replacing 2E/2F with 95A; followed by step 3C. MS (ESI) *m/z*: 355.2 $(M+H)^+$.

[00594] 96B. Example 96 was prepared following the procedures described in step1G, by replacing 1F with 96A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.66 (s, 1 H), 9.49 (s, 1 H), 8.68 (d, *J*=6.0 Hz, 1 H), 8.04 (s, 1 H), 7.97 (d, *J*=1.6 Hz, 1 H), 7.80 (d, *J*=5.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.61 (d, *J*=8.2 Hz, 1 H), 7.54 - 7.58 (m, 2 H), 7.50 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.10 (d, *J*=15.4 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.06 - 5.15 (m, 1 H), 3.76 (s, 3 H), 2.47 - 2.56 (m, 1 H), 2.08 - 2.19 (m, 1 H), 1.63 - 2.02 (m, 4 H), 1.33 - 1.44 (m, 1 H), 0.66 - 0.81 (m, 1 H). MS (ESI) *m/z*: 587.3 $(M+H)^+$. Analytical HPLC (Method D): RT = 4.37 min.

Example 113.

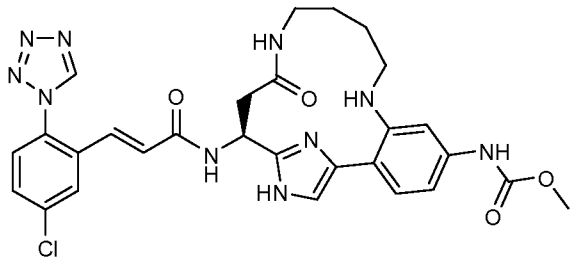
{(R)-16-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-14-oxa-8,18,20-triaza-tricyclo[15.2.1.0^{2,7}]icosa-1(19),2,4,6,17(20)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00595] Example 113 was prepared following the procedures described in step 10D, by replacing 10C with 52F; followed by steps 2E/2F; 2G; 10H; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.59 (s, 1 H) 9.52 (s, 1 H) 7.97 (d, *J*=2.26 Hz, 1 H) 7.77 (d, *J*=1.76 Hz, 1 H) 7.66 - 7.70 (m, 1 H) 7.56 - 7.61 (m, 1 H) 7.45 - 7.48 (m, 1 H) 7.44 (d, *J*=2.01 Hz, 1 H) 7.36 - 7.42 (m, 1 H) 7.16 (d, *J*=15.81 Hz, 1 H) 6.80 (d, *J*=15.56 Hz, 1 H) 5.29 (t, *J*=4.14 Hz, 1 H) 3.84 - 3.97 (m, 2 H) 3.75 (s, 3 H) 3.58 - 3.69 (m, 1 H) 3.43 - 3.55 (m, 1 H) 2.26 - 2.44 (m, 2 H) 1.54 - 1.75 (m, 4 H). MS(ESI) *m/z*: 606.3$(M+H)^+$. Analytical HPLC: RT = 5.28min.

Example 115.

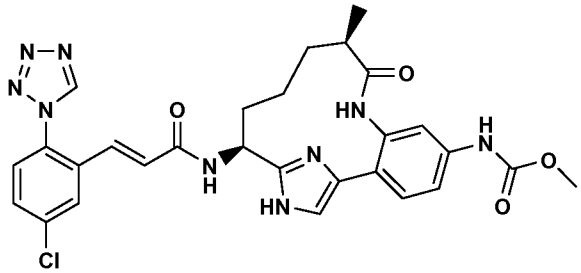
{(S)-16-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-14-oxo-8,13,18,20-tetraaza-tricyclo[15.2.1.0^{2,7}]icosa-1(19),2,4,6,17(20)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00596] Example 115 was prepared following the procedures described in Example 79 by replacing benzyl 3-aminopropylcarbamate HCl salt with benzyl 4-aminobutylcarbamate HCl salt in 79A. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.52 (1 H, s), 8.00 (1 H, d, *J*=2.26 Hz), 7.68 (1 H, dd, *J*=8.53, 2.26 Hz), 7.57 - 7.62 (2 H, m), 7.54 (1 H, d, *J*=8.53 Hz), 7.51 (1 H, s), 7.19 (1 H, d, *J*=15.56 Hz), 7.15 (1 H, dd, *J*=8.53, 2.01 Hz), 6.77 (1 H, d, *J*=15.81 Hz), 5.54 (1 H, dd, *J*=8.53, 5.02 Hz), 3.75 (3 H, s), 3.19 - 3.43 (4 H, m), 2.80 - 2.93 (1 H, m), 1.56 - 1.81 (4 H, m). LC-MS (ESI) *m/z*: 605.2 $(M+H)^+$. Analytical HPLC, RT = 4.950 min.

Example 116.

{(10R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10-methyl-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester,1TFA salt, diastereomer A



[00597] 116A. A solution of Example 10C (5 g, 9.40 mmol) and triethylamine (1.564 ml, 11.28 mmol) in EtOAc (Volume: 30 ml) was cooled down to 0 °C under Ar, 2,2,2-trifluoroacetic anhydride (1.458 ml, 10.34 mmol) was added dropwise. After 1hr, the reaction mixture was washed with water and brine, dried over Na_2SO_4, filtered off solid,

concentrated. Purification by normal phase chromatography gave 5.26 g (97%) of 116A as a pale yellow solid. MS (ESI) *m/z*: 628.1 $(M+H)^+$.

[00598] 116B. Benzyl 2-methylbut-3-enoate: To a solution of 2-methylbut-3-enoic acid (2 g, 18.98 mmol) in CH_2Cl_2 (38.0 ml) was added phenylmethanol (1.966 ml, 18.98 mmol), DCC (3.92 g, 18.98 mmol) and DMAP (0.232 g, 1.898 mmol) (slight exotherm). The reaction was stirred at rt for four hours. The reaction was filtered off solid, rinsed with hexane, concentrated. Purification by normal phase chromatography gave 3.55 g (98%) of 116B as a colorless oil.

[00599] 116C. (6S,E)-Benzyl 6-(*tert*-butoxycarbonylamino)-6-(4-(4-(methoxycarbonylamino)-2-(2,2,2-trifluoroacetamido)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-2-methylhex-3-enoate: A solution of 116A (0.841 g, 1.340 mmol) in DCM (Volume: 26.8 ml) was added pTsOH (0.255 g, 1.340 mmol) . The reaction mixture was degassed by bubbling into Ar for 30 mins, then the mixture was stirred under Ar at 40 °C for 40 mins, 116B (1.53 g, 8.04 mmol) was added, followed by Grubbs(II) (0.341 g, 0.402 mmol) in 2 ml degassed DCM dropwise. The reaction was stirred at 40 °C overnight. The reaction was quenched with sat. aq. $NaHCO_3$, extracted with DCM, washed with brine, and dried the organic layer over $MgSO_4$, filtered off solid, concentrated. Purification by normal phase chromatography gave 522 mg (49%) of 116C as a light brownish oil. MS (ESI) *m/z*: 790.4 $(M+H)^+$.

[00600] 116D. (6S)-6-(*tert*-Butoxycarbonylamino)-6-(4-(4-(methoxycarbonylamino)-2-(2,2,2-trifluoroacetamido)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-2-methylhexanoic acid: A solution of 116C (810 mg, 1.025 mmol) in MeOH (20.5 ml) was vacuumed and refilled with Ar, then Pd/C 10%wt (109 mg, 0.103 mmol) was added, vacuumed and refilled with H_2, stirred under H_2 balloon at rt overnight. The reaction mixture was filtered, rinsed and concentrated to give 116D as light greenish foam (709 mg, 99%) without further purification. MS (ESI) *m/z*: 702.5 $(M+H)^+$.

[00601] 116E. (6S)-6-(4-(2-Amino-4-(methoxycarbonylamino)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(*tert*-butoxycarbonylamino)-2-methylhexanoic acid: To a solution of 116D (709 mg, 1.010 mmol) in MeOH (10.100 ml) was added lithium hydroxide (2N aq) (3.54 ml, 7.07 mmol), sealed and heated at 60 °C for 5 hr. The reaction was cooled down and concentrated. The residue was adjusted with

1N HCl in aq to pH ~6, extracted with EtOAc until no more product in aqueous layer. EtOAc layer washed with brine, dried over $MgSO_4$, filtered off solid, concentrated to give 116E as a dark black foam (640 mg, 100%) and used in next step without further purification. MS (ESI) *m/z*: 606.4 $(M+H)^+$.

[00602] 116F. To a solution of BOP (1.117 g, 2.53 mmol) and DMAP (0.518 g, 4.24 mmol) in CH_2Cl_2 (Ratio: 25, Volume: 324 ml) and DMF (Ratio: 1.000, Volume: 12.95 ml) was added dropwise via syringe pump a solution of 116E (0.612 g, 1.010 mmol) and DIEA (1.235 ml, 7.07 mmol) in 8 ml DMF over 8 hrs. Stirred at rt overnight. The reaction was transferred to a sealed bottle and heated at 60 °C for 5 hrs then cooled down to rt and stirred at rt over the weekend. MeOH was added to quench the reaction. The reaction was concentrated, diluted with EtOAc, washed with H_2O (2x), brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave 116F (287 mg, 48%) as a light yellow solid. Separation of 116F by reverse phase chromatography provided two diastereomers.

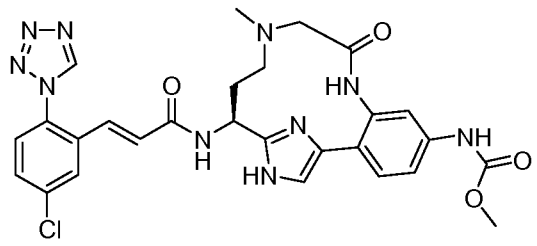
[00603] 116G. [(10R,14S)-5-Methoxycarbonylamino-10-methyl-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: fast eluting isomer. MS (ESI) *m/z*: 588.3 $(M+H)^+$.

[00604] 116H. [(10S,14S)-5-Methoxycarbonylamino-10-methyl-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: slow eluting isomer. MS (ESI) *m/z*: 588.3 $(M+H)^+$.

[00605] 116I. Example 116 was prepared following the procedures described in 1F, by replacing 1D with 116G; followed by 1G. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.96 (d, J=2.2 Hz, 1 H), 7.67 (dd, J=8.8, 2.2 Hz, 1 H), 7.58 (d, J=8.8 Hz, 2 H), 7.48 - 7.54 (m, 1 H), 7.41 - 7.48 (m, 2 H), 7.13 (d, J=15.4 Hz, 1 H), 6.74 (d, J=15.9 Hz, 1 H), 5.02 (dd, J=10.4, 6.0 Hz, 1 H), 3.75 (s, 3 H), 2.43 - 2.56 (m, 1 H), 2.16 - 2.29 (m, 1 H), 1.83 - 1.97 (m, 1 H), 1.57 (d, J=9.3 Hz, 1 H), 1.21 - 1.36 (m, 2 H), 1.18 (d, J=7.1 Hz, 3 H), 1.05 - 1.18 (m, 1 H). MS (ESI) *m/z*: 590.3 $(M+H)^+$. Analytical HPLC: RT = 4.16 min. (Method B).

Example 117.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-methyl-9-oxo-8,11,16,18-tetraaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00606] 117A. {3-Bromo-4-[2-((S)-1-*tert*-butoxycarbonylamino-3-oxo-propyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: To a solution of 10B(100 mg, 0.168 mmol) in acetonitrile (4.00 ml) were added water (1 ml), sodium periodate (144 mg, 0.672 mmol) and osmium tetroxide (0.105 ml, 8.39 μmol) at 0 °C. The reaction mixture was stirred and allowed to warm slowly to rt, then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered and concentrated to a brown solid. Normal phase chromatography gave 117A as a brown solid (50 mg, 49.8 % yield). MS (ESI) *m/z*: 631.5$(M+H)^+$.

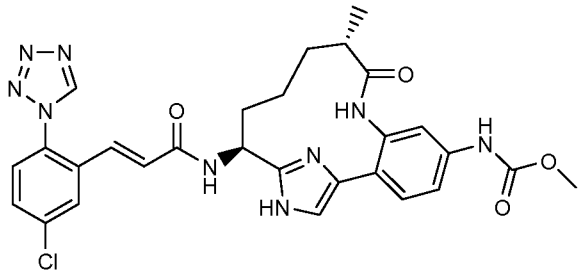
[00607] 117B. ({(S)-3-[4-(2-Bromo-4-methoxycarbonylamino-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-3-*tert*-butoxycarbonylamino-propyl}-methyl-amino)-acetic acid: To a solution of 117A (300 mg, 0.502 mmol) in DCE (6 mL) was added 2-(methylamino)acetic acid (67.1 mg, 0.753 mmol) and 1 drop of acetic acid (0.01 mL, 0.175 mmol). The reaction mixture was sonicated and stirred at room temperature for 2 hours. Sodium triacetoxyborohydride (319 mg, 1.506 mmol) was added and the reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered and concentrated to yield 117B. MS (ESI) *m/z*: 672.3$(M+H)^+$.

[00608] 117C. Example 117 was prepared following the procedure described in step 10C alternate), by replacing 10B with 117B; followed by steps 20F; 10H; and 1G. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 9.52 (s, 1 H) 7.97 (d, *J*=2.2 Hz, 1 H) 7.67 (dd, *J*=8.53, 2.2 Hz, 1 H) 7.59 (m, 2 H) 7.55 (s, 1 H) 7.46 (s, 1 H) 7.37 (dd, *J*=8.52, 2.2 Hz, 1

H) 7.19 (d, *J*=15.68 Hz, 1H) 6.69 (d, *J*=15.41 Hz, 1 H) 5.26 (br s, 1 H) 3.93 (m, 1 H) 3.75 (m, 4 H) 3.27 (m, 1 H) 3.00 (m, 1 H) 2.82 (s, 3 H) 2.44 (br s, 1 H) 2.37 (br s, 1 H). MS (ESI) *m/z*: 591.3(M+H)$^+$. Analytical HPLC: RT = 4.48min.

Example 118.

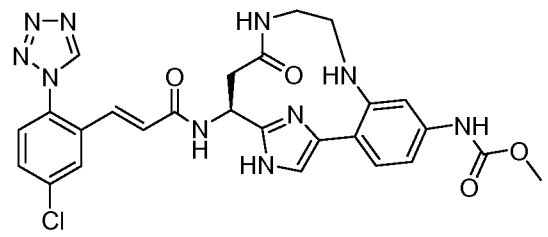
{(10S,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10-methyl-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester 1 TFA salt



[00609] Example 118 was prepared following the procedures described in step 1F, by replacing 1D with 116H; followed by step 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.50 (d, *J*=8.2 Hz, 1 H), 7.45 (s, 1 H), 7.35 - 7.42 (m, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.75 (d, *J*=15.4 Hz, 1 H), 5.14 (dd, *J*=9.9, 6.6 Hz, 1 H), 3.76 (s, 3 H), 2.68 - 2.80 (m, 1 H), 2.12 - 2.26 (m, 1 H), 1.90 - 2.05 (m, 1 H), 1.51 - 1.72 (m, 3 H), 1.03 (d, *J*=7.1 Hz, 3 H), 0.70 (br. s., 1 H). MS (ESI) *m/z*: 590.3 (M+H)$^+$. Analytical HPLC: RT = 4.08 min. (Method B).

Example 119.

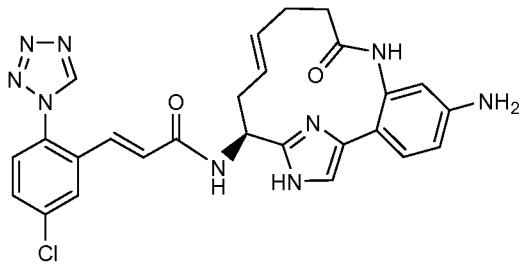
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-oxo-8,11,16,18-tetraaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00610] Example 119 was prepared following the procedures described in Example 79 by replacing benzyl 3-aminopropylcarbamate HCl salt with benzyl 2-aminoethylcarbamate in 79A. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.99 (1 H, d, *J*=2.26 Hz), 7.92 (1 H, d, *J*=1.51 Hz), 7.75 (1 H, d, *J*=8.53 Hz), 7.67 (1 H, dd, *J*=8.53, 2.26 Hz), 7.55 - 7.61 (2 H, m), 7.34 (1 H, dd, *J*=8.53, 2.01 Hz), 7.21 (1 H, d, *J*=15.81 Hz), 6.76 (1 H, d, *J*=15.56 Hz), 5.48 - 5.64 (1 H, m), 3.78 - 3.93 (1 H, m), 3.77 (3 H, s), 3.33 - 3.72 (3 H, m), 2.81 (2 H, d, *J*=7.03 Hz). LC-MS (ESI) *m/z*: 577.2 $(M+H)^+$. Analytical HPLC: RT = 4.621 min.

Example 120.

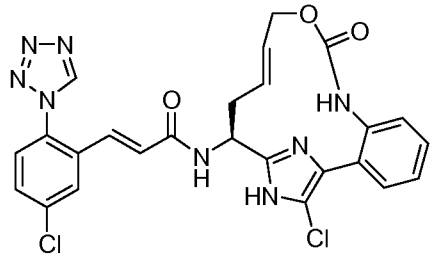
(E)-*N*-((E)-(S)-5-Amino-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 2 TFA salt



[00611] Example 120 was prepared following the procedure described in step 10H, by replacing 10G with 39A and by running the reaction at 75 °C for 20 h; followed by step 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.31 (s, 1 H), 7.24 (d, *J*=8.2 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.71 - 6.80 (m, 3 H), 5.50 - 5.60 (m, 1 H), 5.35 - 5.44 (m, 1 H), 5.08 (dd, *J*=9.9, 4.9 Hz, 1 H), 2.74 - 2.83 (m, 1 H), 2.31 - 2.61 (m, 5 H). MS (ESI) *m/z*: 530.2 $(M+H)^+$. Analytical HPLC: RT = 4.24 min.

Example 121.

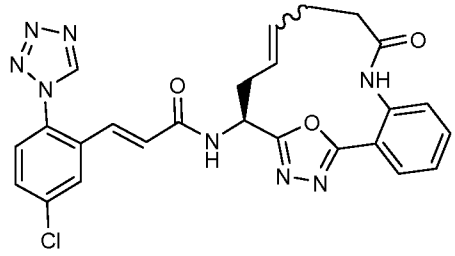
(E)-*N*-((E)-(S)-18-Chloro-9-oxo-10-oxa-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00612] Example 121 was prepared following the procedure described in 17A, by replacing 16A with Example 87. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.48 - 2.60 (m, 1 H), 2.81 - 2.93 (m, 1 H), 4.37 (br. s., 2 H), 5.05 (dd, *J*=10.5, 5.0 Hz, 1 H), 5.60 - 5.73 (m, 1 H), 5.76 - 5.89 (m, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 7.24 (d, *J*=8.0 Hz, 1 H), 7.40 (td, *J*=7.4, 1.2 Hz, 1 H), 7.49 (td, *J*=7.8, 1.2 Hz, 1 H), 7.52 - 7.56 (m, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.99 (d, *J*=1.9 Hz, 1 H), 9.52 (s, 1 H) MS (ESI) *m/z*: 551.2 $(M+H)^+$. Analytical HPLC: RT = 7.25 min.

Example 122.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-9-oxo-19-oxa-8,17,18-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16-hexaen-15-yl)-acrylamide, and (Z)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-9-oxo-19-oxa-8,17,18-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16-hexaen-15-yl)-acrylamide



[00613] 122A. (S)-*tert*-Butyl 1-(2-(2-nitrobenzoyl)hydrazinyl)-1-oxopent-4-en-2-ylcarbamate: A mixture of [(S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid (0.500 g, 2.323 mmol), HATU (1.060 g, 2.79 mmol), and DIPEA (1.623 mL, 9.29 mmol) in DCM (15 mL) was stirred at rt under nitrogen for 3 d. Reaction mixture was diluted with additional DCM, then washed with water, 5% aq. citric acid, sat'd aq. $NaHCO_3$ and brine, then dried over anhydrous Mg_2SO_4, filtered and evaporated. Residue was purified by normal phase chromatography to provide the acylhydrazide (0.7 g,, 79.6.0 % yield). MS (ESI) *m/z*: 379.3 $(M+H)^+$; 323.3 $(M+H\text{-}tBu)^+$; 279.3 $(M+H\text{-}Boc)^+$.

[00614] 122B. (S)-*tert*-Butyl 1-(5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl)but-3-enylcarbamate: Into a 150mL pressure vessel was charged a solution of 122A (0.57 g, 1.506 mmol) in anhydrous THF (30 mL), and Burgess reagent (1.077 g, 4.52 mmol) was added. The vessel was sealed under Ar, and the mixture was heated in a 75 °C oil bath with stirring behind a blast shield for 2 hrs. Reaction was cooled to room temperature, vented and then left standing at room temperature overnight. Reaction mixture was transferred to a round bottom flask with the aid of a little MeOH and evaporated to dryness. Residue was purified by silica gel chromatography to provide the oxadiazole product (0.327 g, 0.907 mmol, 60.2 % yield) MS (ESI) *m/z* 383.3 $(M+Na)^+$ 305.3 $(M+H-tBu)^+$.

[00615] 122C. (S)-*tert*-Butyl 1-(5-(2-aminophenyl)-1,3,4-oxadiazol-2-yl)but-3-enylcarbamate: 122B (0.325 g, 0.902 mmol) was dissolved in ethanol (4.5 mL) and iron powder (1.007 g, 18.04 mmol) was added. The mixture was stirred at room temperature for 1-2 min then 0.1 M HCl (4.51 mL, 0.451 mmol) was added, and the reaction was heated with stirring under nitrogen in a 50 °C oil bath for 1.5 h. Reaction was cooled to room temperature and then filtered twice through a pad of CELITE® and solids washed with water, EtOH and EtOAc then discarded. Filtrate was evaporated and remaining aqueous was diluted with $NaHCO_3$ (to pH 8), and extracted 3x with EtOAc. Combined extracts were washed with saturated aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and evaporated to provide the amine as a white crystalline solid, (0.216 g, 0.654 mmol, 72.5 % yield). MS (ESI) *m/z*: 331.4 $(M+H)^+$; 275.3 $(M+H-tBu)^+$; 231.3 $(M+H-Boc)^+$.

[00616] 122D. (S)-*tert*-Butyl 1-(5-(2-pent-4-enamidophenyl)-1,3,4-oxadiazol-2-yl)but-3-enylcarbamate: 122C was dissolved in DCM (3.5 mL) and pyridine (0.105 mL, 1.302 mmol) was added. The solution was cooled in an ice/salt water bath to ~ 0 °C, then 4-pentenoyl chloride (0.072 mL, 0.651 mmol) was added dropwise with stirring under nitrogen. The resulting mixture was stirred at 0-5 °C for 1 h then allowed to warm to room temperature. After 2h, the reaction was diluted with EtOAc and washed with water, 1M HCl, saturated aq. $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4, filtered and evaporated. Residue was purified by silica gel chromatography to provide the amide

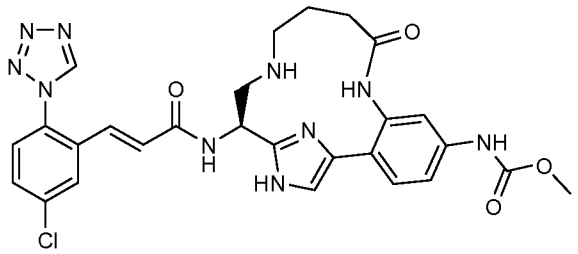
(0.242 g, 0.587 mmol, 90 % yield). MS (ESI) *m/z*: 413.4 $(M+H)^+$; 357.3 $(M+H\text{-}tBu)^+$; 313,4 $(M+H\text{-}Boc)^+$.

[00617] 122E. ((E)-(S)-9-Oxo-19-oxa-8,17,18-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16-hexaen-15-yl)-carbamic acid *tert*-butyl ester; and ((Z)-(S)-9-Oxo-19-oxa-8,17,18-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16-hexaen-15-yl)-carbamic acid *tert*-butyl ester: 122D (135 mg, 0.327 mmol) was divided between five-20mL microwave vials. The vials were then flushed with argon for 10-15 min followed by addition of anhydrous DCM (4.8 mM) and Grubbs (II) (36 mol%). All operations were carried out under argon and the fully charged vials were flushed for an additional few minutes with argon, then capped, sealed, and heated for 90 min at 75 °C in the microwave then left standing overnight. Contents of the five vials were combined and concentrated to remove DCM, redissolved in MeOH, filtered and purified by reverse phase HPLC to provide the macrocyclic alkene as a mixture of trans/cis isomers (34 mg, 27%). MS (ESI) *m/z*: 385.2 $(M+H)^+$; 329.1 $(M+H\text{-}tBu)^+$.

[00618] 122E. Example 122: 122E (34 mg, 0.088 mmol) was dissolved in DCM (2 mL) and TFA (0.5 mL, 6.49 mmol) was added. The resulting mixture was stirred at room temperature under N2 for ~ 5 h, then stripped to dryness. Residue was taken up in MeOH and stripped (2X) then dried on vacuum pump. The crude trifluoroacetic acid salt of the amine (MS (ESI) *m/z*: 285.2 $(M+H)^+$; 33 mg, 0.116 mmol) was dissolved in DMF (1 mL) and (E)-2,5-dioxopyrrolidin-1-yl 3-(5-chloro-2-(1H-tetrazol-1-yl)phenyl)acrylate (46 mg, 0.132 mmol) and DIPEA (0.1 mL, 0.573 mmol) were added. The resulting dark solution was stirred under a blanket of argon overnight. Reaction mixture was diluted with water and extracted 3X with EtOAc. Combined extracts were washed with 5% aq. citric acid soln, saturated aq. $NaHCO_3$ soln and brine, then dried over anhydrous sodium sulfate, filtered and evaporated. Residue was suspended in MeOH, sonicated and filtered. Solid was dissolved in a 1:1 mixture of DMSO/MeOH, filtered and purified by reverse phase HPLC to provide the title compound (14 mg, 23%). MS (ESI) *m/z*: 517.3 $(M+H)^+$ as an ~ 5:1 mixture of the trans/cis double bond isomers as determined by nmr and HPLC. Analytical HPLC: major trans isomer: RT = 7.53min; minor isomer RT = 7.41.

Example 123.

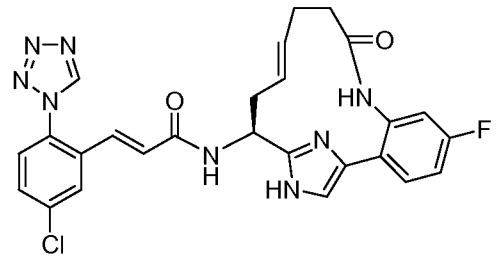
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,13,17,19-tetraaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00619] Example 123 was prepared following the procedures described in step 117B, by replacing 117A with 4-oxobutanoic acid and by replacing 2-(methylamino) acetic acid with 20B; followed by steps 20D; 10C (alternate); 20F; 2G; 1G; and 10H. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 9.54 (s, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.60 (d, *J*=8.8 Hz, 1 H), 7.48 - 7.56 (m, 2 H), 7.44 (s, 1 H), 7.37 - 7.43 (m, 1 H), 7.24 (d, *J*=15.9 Hz, 1 H), 6.69 (d, *J*=15.4 Hz, 1 H), 5.52 (dd, *J*=8.2, 3.8 Hz, 1 H), 3.74 (s, 3 H), 3.42 - 3.61 (m, 2 H), 3.24 - 3.29 (m, 2 H), 2.50 - 2.78 (m, 2 H), 2.02 - 2.33 (m, 2 H). MS (ESI) *m/z*: 591.3 $(M+H)^+$. Analytical HPLC: RT = 3.88min. (Method B).

Example 124.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-5-fluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, 1 TFA salt

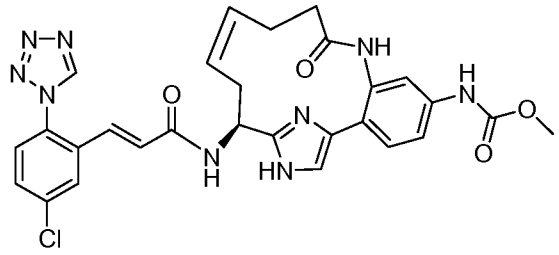


[00620] Example 124 was prepared following the procedures described in step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 17; followed by steps 2B; 2C; 10C; 10D, by replacing with but-3-enoic acid with pent-4-enoic acid; 2E; 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.33 - 2.62 (m, 5 H), 2.75 - 2.84 (m, 1 H), 5.05 - 5.12 (m, 1 H), 5.37 - 5.47 (m, 1 H), 5.52 - 5.62 (m, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H),

7.11 - 7.21 (m, 3 H), 7.43 (br. s., 1 H), 7.50 - 7.56 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.66 - 7.71 (m, 1 H), 7.97 (br. s., 1 H), 9.51 (br. s., 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -111.20. MS (ESI) *m/z*: 533.1 $(M+H)^+$. Analytical HPLC: RT = 5.03 min.

Example 125.

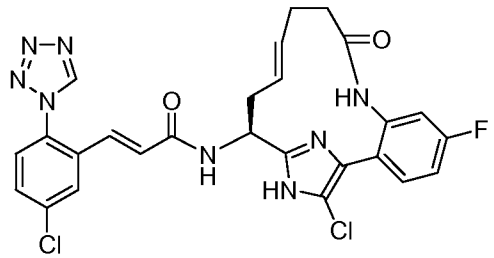
{(Z)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00621] Example 125 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with pent-4-enoic acid; followed by steps 2F; 10H, by running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.64 - 7.68 (m, 2 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.41 (d, *J*=8.8 Hz, 1 H), 7.35 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.31 (s, 1 H), 7.18 (d, *J*=15.4 Hz, 1 H), 6.70 (d, *J*=15.4 Hz, 1 H), 5.57 - 5.64 (m, 1 H), 5.42 - 5.50 (m, 1 H), 5.16 - 5.22 (m, 1 H), 3.76 (s, 3 H), 2.87 - 2.97 (m, 1 H), 2.68 - 2.77 (m, 1 H), 2.47 - 2.64 (m, 2 H), 2.31 - 2.43 (m, 2 H). MS (ESI) *m/z*: 588.2 $(M+H)^+$. Analytical HPLC: RT = 4.86 min.

Example 126.

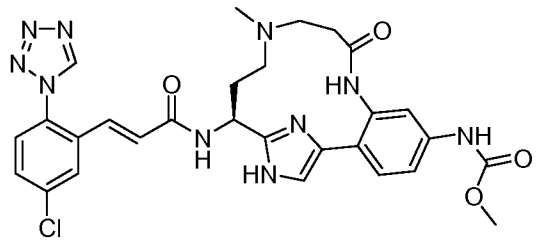
(E)-*N*-((E)-(S)-18-Chloro-5-fluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt



[00622] Example 126 was prepared following the procedure described in 17A, by replacing 16A with Example 124. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.31 - 2.50 (m, 5 H), 2.66 - 2.74 (m, 1 H), 4.96 (dd, *J*=10.5, 4.4 Hz, 1 H), 5.30 - 5.40 (m, 1 H), 5.50 - 5.59 (m, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 7.11 - 7.18 (m, 3 H), 7.48 - 7.53 (m, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -112.21. MS (ESI) *m/z*: 567.2 $(M+H)^+$. Analytical HPLC: RT = 7.41 min.

Example 127.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-methyl-9-oxo-8,12,17,19-tetraaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00623] 127A. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid methyl ester: To a suspension of 10C (200 mg, 0.376 mmol) in DCM (3 ml) at 0 °C was added triethylamine (0.157 ml, 1.128 mmol), followed by trifluoroacetic anhydride (0.064 ml, 0.451 mmol). The reaction mixture was allowed to stir at rt for 1 h, then diluted with EtOAc, washed with 1 N HCl and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 127A (271 mg, 0.432 mmol, 115 % yield) as a yellow foam. MS (ESI) *m/z*: 628.5$(M+H)^+$.

[00624] 127B. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-3-oxo-propyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid methyl ester: This compound was prepared following the procedures described in 117A, by replacing 10B with 127A. MS (ESI) *m/z*: 630.4$(M+H)^+$.

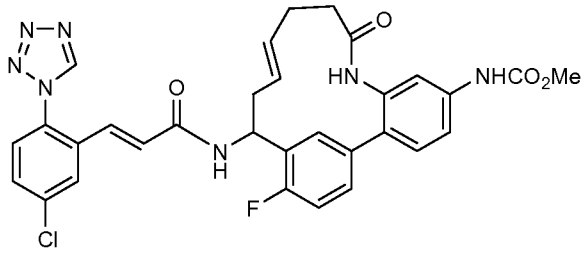
[00625] 127C. 3-({(S)-3-*tert*-Butoxycarbonylamino-3-[4-[4-methoxycarbonylamino-2-(2,2,2-trifluoro-acetylamino)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-propyl}-methyl-amino)-propionic acid: To a solution of 127B (97 mg, 0.154 mmol) in MeOH (2 ml) was added 3-(methylamino)propanoic acid (23.83 mg, 0.231 mmol) and 1 drop acetic acid, then sodium cyanoborohydride (4.84 mg, 0.077 mmol) was added and the reaction was stirred at rt overnight. The reaction was quenched with sat. sodium bicarbonate, extracted with EtOAc and washed the organic layer with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 127C (86 mg, 0.120 mmol, 78 % yield) as a light orange solid. MS (ESI) *m/z*: 717.5$(M+H)^+$.

[00626] 127D. [(S)-5-Methoxycarbonylamino-11-methyl-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,11,16,18-tetraaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To a mixture of 127C (86 mg, 0.120 mmol) in methanol (3 mL) was added potassium carbonate (116 mg, 0.840 mmol). The resulting mixture was stirred at rt for 1 h, then stored at -10 °C over the weekend. Water (0.150 mL) and 1 N aq. sodium hydroxide (0.4 mL, 0.400 mmol) were added and the reaction was heated to 50 °C for four hours. Purification by reverse phase chromatography afforded 127D (41 mg, 0.066 mmol, 55.0 % yield) as a dark orange solid. MS (ESI) *m/z*: 621.2$(M+H)^+$.

[00627] 127E. Example 127 was prepared following the procedures described in step 23E, by replacing 23D with 127D; followed by steps 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.96 (1 H, d, *J*=2.5 Hz), 7.66 (1 H, dd, *J*=8.5, 2.2 Hz), 7.58 (2 H, d, *J*=8.5 Hz), 7.53 (1 H, d, *J*=8.5 Hz), 7.48 (1 H, s), 7.33 (1 H, dd, *J*=8.5, 2.2 Hz), 7.19 (1 H, d, *J*=15.7 Hz), 6.69 (1 H, d, *J*=15.7 Hz), 5.40 (1 H, dd, *J*=7.4, 3.9 Hz), 3.71 - 3.78 (3 H, m), 3.60 (1 H, br. s.), 3.39 - 3.49 (1 H, m), 3.01 (3 H, s), 2.84 - 2.92 (2 H, m), 2.38 - 2.46 (2 H, m). MS (ESI) *m/z*: 605.4$(M+H)^+$. Analytical HPLC: RT = 4.55 min.

Example 128.

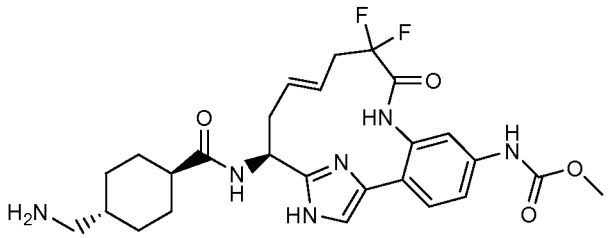
{(E)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-fluoro-9-oxo-8-aza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2,4,6,12,16,18-heptaen-5-yl}-carbamic acid methyl ester



[00628] Example 128 was prepared following the procedures described in step 93A, by replacing 3-bromobenzaldehyde with 3-bromo-6-fluorobenzaldehyde; followed by steps 88C; 88E; 88F, by replacing methanol with acetone and by replacing solid ammonium chloride with a saturated aqueous solution of ammonium chloride; 88G, by running the reaction without pTsOH; 3C; and 1G. ^{1}H NMR (400 MHz, MeOD/DMSO-d_6) δ ppm 9.38 (s, 1H), 8.60(s, 1H), 7.01(d, *J* = 2.0Hz, 1H), 6.72-6.63(dd, *J* = 2.0 & 8.3Hz, 3H), 6.63(dd, *J* = 2.0 & 8.2Hz, 1H), 6.32-6.20m, 5H), 6.09-6.05(d, *J* = 15.4Hz, 1H), 5.94-5.91(d, *J* = 15.6Hz, 1H), 4.58(m, 1H), 4.47(m, 2H), 2.80(s, 3H), 1.67(m, 1H), 1.51-1.46(m, 4H)ppm. MS (ESI) *m/z*: 616.0 $(M+H)^+$. Analytical HPLC: RT = 8.55 min.

Example 129.

{(E)-(S)-15-[(4-Aminomethyl-cyclohexanecarbonyl)-amino]-10,10-difluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt

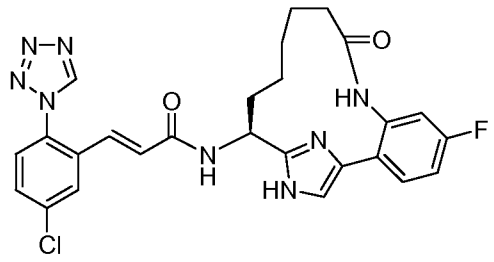


[00629] Example 129 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 2,2-difluoropent-4-enoic acid; followed by steps 2E; 10H; 3B; and 3C. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.67 (s, 1 H), 7.58 (d, *J*=2.2 Hz, 1 H), 7.53 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.38 - 7.46 (m, 2 H), 5.66 - 5.80 (m, 1 H), 5.20 - 5.31 (m, 1 H), 4.99 (dd, *J*=11.0, 4.4 Hz, 1 H), 3.76 (s, 3 H), 2.73 - 3.00 (m, 5 H), 2.48 - 2.61 (m, 1 H), 2.26 - 2.39 (m, 1 H), 1.83 - 2.00 (m, 3 H), 1.54 - 1.69 (m, 1 H), 1.38 - 1.54 (m,

2 H), 1.01 - 1.19 (m, 2 H). MS (ESI) *m/z*: 531.3 $(M+H)^+$. Analytical HPLC: RT = 1.73 min. (Method B).

Example 130.

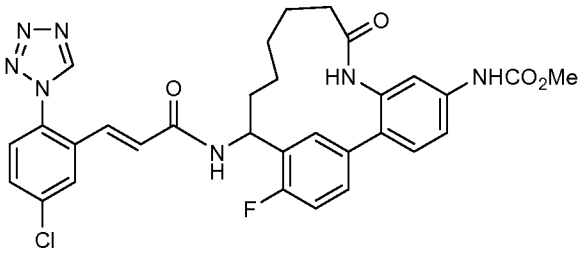
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-5-fluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-acrylamide, 1 TFA salt



[00630] Example 130 was prepared following the procedures step 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with Intermediate 17; followed by steps 2B; 2C; 10C; 10D, by replacing with but-3-enoic acid with pent-4-enoic acid; 2F; 10G, by replacing the hydrogen balloon with hydrogen (55 psi); 10H; and 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.81 - 0.91 (m, 1 H), 0.94 - 1.05 (m, 1 H), 1.41 - 1.60 (m, 2 H), 1.61 - 1.78 (m, 2 H), 1.99 - 2.09 (m, 1 H), 2.16 - 2.24 (m, 1 H), 2.30 - 2.42 (m, 2 H), 5.03 (dd, *J*=10.2, 4.7 Hz, 1 H), 6.74 (d, *J*=15.7 Hz, 1 H), 7.10 - 7.19 (m, 2 H), 7.22 (dd, *J*=9.5, 2.3 Hz, 1 H), 7.48 (s, 1 H), 7.55 - 7.62 (m, 2 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -111.56. MS (ESI) *m/z*: 535.2 $(M+H)^+$. Analytical HPLC: RT = 5.18 min.

Example 131.

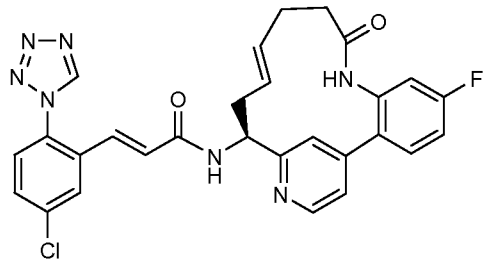
{15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-fluoro-9-oxo-8-aza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2,4,6,16,18-hexaen-5-yl}-carbamic acid methyl ester



[00631] Example 131 was prepared following the procedures described in step 93A, by replacing 3-bromobenzaldehyde with 3-bromo-6-fluorobenzaldehyde; followed by steps 88C; 88E; 88F, by replacing methanol with acetone and by replacing solid ammonium chloride with a saturated aqueous solution of ammonium chloride; 88G, by running the reaction without pTsOH; 2G, by replacing the hydrogen balloon with hydrogen (55 psi); 3C, replacing TFA and DCM with 4M HCl in dioxane; and 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.83(s, 1H), 9.76(s, 1H), 9.20(s, 1H), 8.77(bs, 1H), 8.54(d, 1H), 7.90(s, 1H), 7.73-7.69(m, 2H), 7.50-7.42(m, 2H), 7.29-7.23(m, 3H), 6.83(s, 2H), 4.98(m, 1H), 3.69(s, 3H), 2.50-2.25(m, 4H), 1.90(m, 1H), 1.7(m, 1H), 1.50-1.01(m, 4H). MS (ESI) *m/z*: 618.1 $(M+Na)^+$. Analytical HPLC: RT = 7.95 min.

Example 132.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((E)-(S)-5-fluoro-9-oxo-8,17-diaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2(7),3,5,12,16,18-heptaen-15-yl)-acrylamide, 1 TFA salt



[00632] 132A. 2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-5-fluoro-phenylamine: This compound was prepared following the procedure described in Intermediate 12, by replacing 2-bromo-5-nitroaniline with 2-bromo-5-fluoroaniline. MS (ESI) *m/z*: 224.3$(M+H)^+$.

[00633] 132B. 2-Methyl-propane-2-sulfinic acid {(S)-1-[4-(2-amino-4-fluoro-phenyl)-pyridin-2-yl]-but-3-enyl}-amide: A round bottom flask was charged with 88B (0.377 g, 1.314 mmol), 132A (0.586 g, 2.63 mmol), $PdCl_2$(dppf)-CH_2Cl_2Adduct (0.107 g, 0.131 mmol), and Potassium phosphate, tribasic (0.558 g, 2.63 mmol), then evacuated and flushed with Ar three times. DMSO (6.57 mL) and water (0.118 mL, 6.57 mmol) were added, and the reaction was once again evacuated and flushed with Ar three times. The reaction was heated at 90 °C for 2 hours, then left at room temperature overnight. The reaction was diluted with water and extracted three times with EtOAc. The

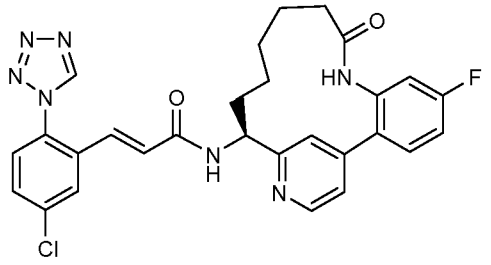
combined organic layer was washed with water and brine, then dried over $MgSO_4$, filtered, and condensed to yield a brown residue. The crude residue was redissolved in MeOH, filtered through a small pad of CELITE® and purified by reverse phase chromatography. Fractions from main peak were neutralized with saturated $NaHCO_3$, partially condensed to remove the MeOH, then extracted three times with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield an orange residue, 132B (0.280 g, 0.775 mmol, 58.9 % yield). MS (ESI) *m/z*: 362.3$(M+H)^+$.

[00634] 132C. ((E)-(S)-5-Fluoro-9-oxo-8,17-diaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2(7),3,5,12,16,18-heptaen-15-yl)-carbamic acid *tert*-butyl ester: This compound was prepared from 132B in four steps by cleavage of the *t*-butylsulfinamide and introduction of a Boc-protection group, reduction of the nitro to the corresponding aniline, coupling with 4-pentenoic acid and subsequent RCM of the resulting diene, following the procedures described for compounds 88D, 52D, 88E and 88G. MS (ESI) *m/z*: 412.3$(M+H)^+$.

[00635] 132D. Example 132 was prepared from 132C by removal of the Boc protecting group and coupling to Intermediate 1, following the procedures described in steps 3C and 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.85 (1 H, s) 9.46 (1 H, s) 8.64 (1 H, d, *J*=7.70 Hz) 8.61 (1 H, d, *J*=4.95 Hz) 7.97 (1 H, d, *J*=1.65 Hz) 7.69 - 7.76 (2 H, m) 7.40 (1 H, dd, *J*=7.97, 6.32 Hz) 7.28 (1 H, d, *J*=4.95 Hz) 7.17 - 7.25 (2 H, m) 7.06 (1 H, d, *J*=15.39 Hz) 7.01 (1 H, s) 6.81 (1 H, d, *J*=15.39 Hz) 5.44 (1 H, ddd, *J*=15.12, 7.42, 7.15 Hz) 5.22 (1 H, ddd, *J*=15.53, 5.22, 5.08 Hz) 4.87 - 4.96 (1 H, m) 2.19 - 2.40 (6 H, m). MS (ESI) *m/z*: 544.3$(M+H)^+$. Analytical HPLC: RT = 6.18min.

Example 133.

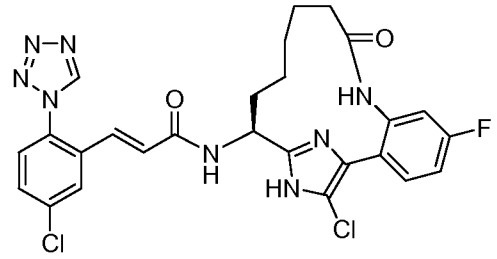
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-5-fluoro-9-oxo-8,17-diaza-tricyclo[14.3.1.$0^{2,7}$]icosa-1(20),2(7),3,5,16,18-hexaen-15-yl)-acrylamide, 1 TFA salt



[00636] Example 133 was prepared from 132C by hydrogenation of the double bond, deprotection of the Boc-protecting group and coupling with Intermediate 1, following the procedures described in steps 2G, 3C and 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.84 (1 H, s) 9.50 (1 H, s) 8.67 (1 H, d, *J*=4.95 Hz) 8.62 (1 H, d, *J*=7.70 Hz) 7.94 (1 H, d, *J*=1.65 Hz) 7.69 - 7.77 (2 H, m) 7.48 (1 H, dd, *J*=9.07, 6.32 Hz) 7.33 (1 H, dd, *J*=4.95, 1.65 Hz) 7.21 - 7.28 (2 H, m) 7.15 (1 H, s) 6.99 (1 H, d, *J*=15.39 Hz) 6.79 (1 H, d, *J*=15.94 Hz) 4.88 (1 H, ddd, *J*=11.54, 7.42, 4.12 Hz) 2.21 (2 H, t, *J*=5.77 Hz) 1.88 (1 H, dd, *J*=13.19, 9.34 Hz) 1.71 (2 H, t, *J*=12.09 Hz) 1.42 (1 H, dd, *J*=13.74, 4.40 Hz) 1.32 (1 H, br. s.) 1.11 - 1.26 (2 H, m) 0.91 (1 H, d, *J*=4.40 Hz). MS (ESI) *m/z*: 546.4(M+H)$^+$. Analytical HPLC: RT = 6.34 min.

Example134.

(E)-*N*-((S)-18-Chloro-5-fluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,16(19)-pentaen-15-yl)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acrylamide, 1 TFA salt

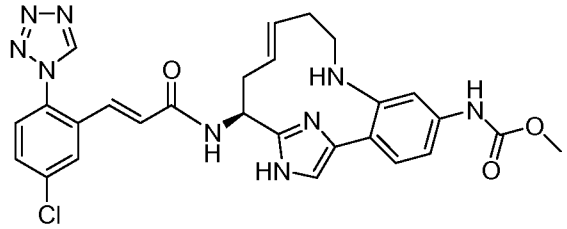


[00637] Example 134 was prepared following the procedure described in 17A, by replacing 16A with Example 130. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.81 - 0.94 (m, 1 H), 1.04 - 1.21 (m, 1 H), 1.34 - 1.54 (m, 2 H), 1.63 - 1.72 (m, 2 H), 1.90 - 2.01 (m, 1 H), 2.04 - 2.15 (m, 1 H), 2.28 - 2.38 (m, 2 H), 4.91 - 4.95 (m, 1 H), 6.74 (d, *J*=15.4 Hz, 1 H), 7.10 (d, *J*=15.7 Hz, 1 H), 7.13 - 7.20 (m, 2 H), 7.52 - 7.58 (m, 2 H), 7.64 (dd, *J*=8.5, 2.2

Hz, 1 H), 7.93 (d, *J*=2.5 Hz, 1 H), 9.49 (s, 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -112.04. MS (ESI) *m/z*: 569.2 $(M+H)^+$. Analytical HPLC: RT = 7.54 min.

Example 135.

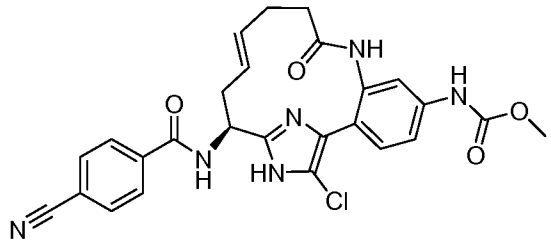
{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00638] Example 135 was prepared following the procedures described in step 10C, by replacing ammonium hydroxide with but-3-enylamine and running the reaction at 90 °C; followed by steps 10E; 1F, by replacing ethanol with methanol and running the reaction at 75 °C; and 1G. ^{1}H NMR (500 MHz, 50 °C, CD_3OD) δ ppm 9.47 (s, 1 H), 7.96 (d, *J*=1.6 Hz, 1 H), 7.79 (s, 1 H), 7.66 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 - 7.62 (m, 2 H), 7.41 (s, 1 H), 7.30 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.19 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 5.87 - 5.96 (m, 1 H), 5.20 - 5.28 (m, 1 H), 5.13 (ddd, *J*=15.3, 7.6, 7.4 Hz, 1 H), 3.77 (s, 3 H), 3.29 - 3.35 (m, 2 H), 2.54 - 2.68 (m, 2 H), 2.43 - 2.50 (m, 2 H). MS (ESI) *m/z*: 560.2 $(M+H)^+$. Analytical HPLC: RT = 5.53 min.

Example 136.

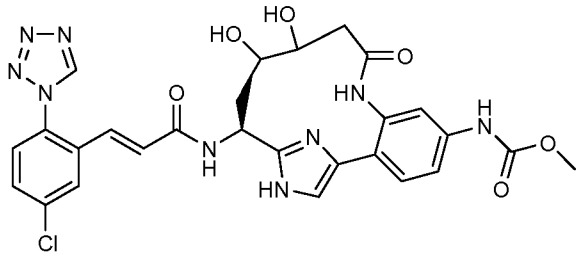
[(E)-(S)-18-Chloro-15-(4-cyano-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.0^{2,7}]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid methyl ester, 1 TFA salt



[00639] Example 136 was prepared following the procedure described in step 15D, by replacing 15C with 76B, by replacing Intermediate 2 with 4-cyano-benzoic acid, by replacing Hunig's base with triethylamine and running the reaction at 55 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 1 drop of D_2O) δ ppm 8.01 (d, *J*=8.2 Hz, 2 H), 7.93 (d, *J*=8.8 Hz, 2 H), 7.45 (s, 1 H), 7.29 - 7.37 (m, 2 H), 5.51 (ddd, *J*=15.3, 7.6, 7.4 Hz, 1 H), 5.22 - 5.32 (m, 1 H), 5.07 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.65 (s, 3 H), 2.19 - 2.61 (m, 6 H). MS (ESI) *m/z*: 519.0 $(M+H)^+$. Analytical HPLC: RT = 6.12 min.

Example 137.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11,12-dihydroxy-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt, Diastereomers A:B (1: 1.3)



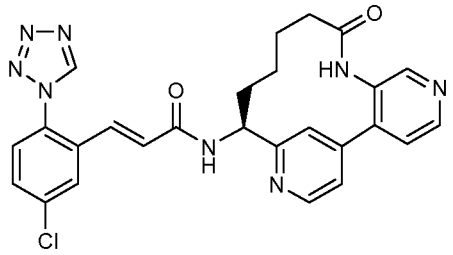
[00640] 137A. [(S)-11,12-Dihydroxy-5-methoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt, Diastereomers A:B (1:1.3) and 137B. [(S)-11,12-Dihydroxy-5-methoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester, 1 TFA salt, Diastereomer C: The content of 1 g sealed vial of OsO_4 was dissolved in 200 ml *t*-Butanol. The pale green solution was treated with 3 drops of 30% H_2O_2, and allowed to remain at rt overnight. If the solution turned dark, the dropwise addition of 30% H_2O_2 was repeated, until the pale green persisted. Compound 10E (67 mg, 0.117 mmol) in acetone (1.17 mL) was cooled down to 0 °C. Subsequently H_2O (0.021 mL, 1.172 mmol), NMO (21.23 mg, 0.176 mmol) and osmium tetroxide (0.293 mL, 5.86 µmol) were added. The reaction was stirred at 0 °C and gradually warmed up to rt overnight. $MgSO_4$ was added to the reaction mixture. The solid was filtered off, rinsed with MeOH

and the filtrate was concentrated to yield a black crude product. Purification by reverse phase chromatography provided 9 mg of 137A, as a mixture Diastereomers A:B (1:1.3), as a white solid and 7 mg of 137B (Diastereomer C), as a white solid. For 137A: MS (ESI) *m/z*: 606.4 $(M+H)^+$. For 137B: MS (ESI) *m/z*: 606.4 $(M+H)^+$.

[00641] 137C. Example 137 was prepared following the procedures described in step 1F, by replacing 1D with 137A; followed by step1G. MS (ESI) *m/z*: 608.3 $(M+H)^+$. Analytical HPLC: RT = 3.90, 4.06 min, ratio 1.3 :1. (Method B).

Example 138.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-9-oxo-5,8,16-triaza-tricyclo[13.3.1.02,7]nonadeca-1(19),2,4,6,15,17-hexaen-14-yl)-acrylamide, 2 TFA salt



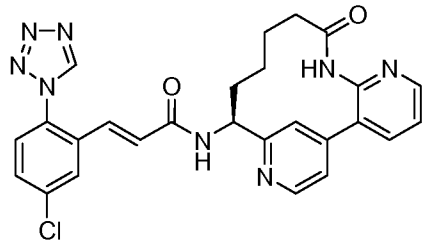
[00642] 138A. 2-Methyl-propane-2-sulfinic acid [(S)-1-(3′-amino-[4,4′]bipyridinyl-2-yl)-but-3-enyl]-amide**:** 088B (591 mg, 2.483 mmol) in a microwave tube was added Dioxane (9 ml) and potassium phosphate tribasic (2.483 ml, 4.97 mmol). The mixture was degassed by bubbling through Ar for several minutes. *Tetrakis*(triphenylphosphine)palladium (0) (191 mg, 0.166 mmol) was added and continued to bubble for a few minutes. Capped and heated at 100 °C overnight. More *Tetrakis*(triphenylphosphine)palladium (0) (80 mg) was added and the reaction was heated at 100 °C for additional 5 hrs. The reaction was cooled down to rt and concentrated to remove dioxane, diluted with EtOAc/H_2O, extracted 2 more times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave 350 mg (50%) of 138A as slightly brownish foam. MS (ESI) *m/z*: 345.2 $(M+H)^+$.

[00643] 138B. Example 138 was prepared following the procedures described in step 88D, by replacing 88C with 138A; followed by steps 88E, by replacing pentenoic acid with but-3-enoic acid; 88G, by replacing 1.1 eq. of pTsOH with 2.2 eq. of pTsOH; 2G;

3C; and 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.49 (1 H, s), 8.82 (1 H, d, *J*=5.5 Hz), 8.75 (1 H, d, *J*=5.5 Hz), 8.62 (1 H, s), 7.98 (1 H, d, *J*=2.2 Hz), 7.87 - 7.95 (2 H, m), 7.74 (1 H, dd, *J*=5.5, 2.2 Hz), 7.66 (1 H, dd, *J*=8.8, 2.2 Hz), 7.56 (1 H, d, *J*=8.8 Hz), 7.08 (1 H, d, *J*=15.4 Hz), 6.81 (1 H, d, *J*=15.4 Hz), 5.12 (1 H, dd, *J*=11.0, 5.5 Hz), 2.47 - 2.59 (1 H, m), 2.04 - 2.18 (1 H, m), 1.53 - 2.01 (5 H, m), 1.29 - 1.49 (1 H, m), 0.63 (1 H, none). MS (ESI) *m/z*: 515.5 $(M+H)^+$. Analytical HPLC: RT = 4.17 min (Method B).

Example 144.

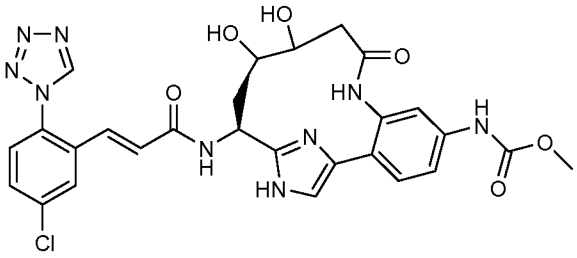
(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-9-oxo-6,8,16-triaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2,4,6,15,17-hexaen-14-yl)-acrylamide, 2 TFA salt



[00644] Example 144 was prepared following the procedures described in step 138A, by replacing *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ylcarbamate with *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ylcarbamate; followed by steps 88D; 88E, by replacing pentenoic acid with but-3-enoic acid; 88G, by replacing 1.1 eq. of pTsOH with 2.2 eq. of pTsOH; 2G; 3C; and 1G. MS (ESI) *m/z*: 515.2$(M+H)^+$.

Example 145

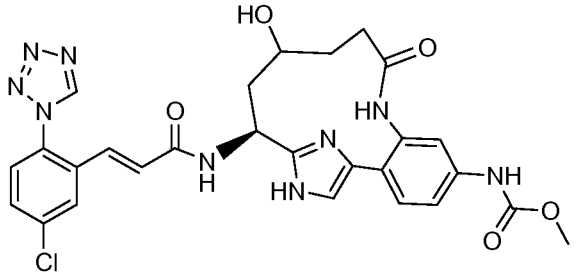
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11,12-dihydroxy-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt, Diastereomer C



[00645] Example 145 was prepared following the procedures described in step 1F, by replacing 1D with 137B; followed by step 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.43 - 7.50 (m, 2 H), 7.38 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.10 (dd, *J*=10.4, 6.6 Hz, 1 H), 3.91 - 3.97 (m, 1 H), 3.75 (s, 3 H), 3.01 (m, 1 H), 2.63 (dd, *J*=11.6, 3.3 Hz, 1 H), 2.42 - 2.58 (m, 2 H), 2.02 - 2.12 (m, 1 H). MS (ESI) *m/z*: 608.3 $(M+H)^+$. Analytical HPLC: RT = 4.21 min. (Method B).

Example 152.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-12-hydroxy-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00646] 152A. [(S)-11-Hydroxy-5-methoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To a solution of 10E/10F (56 mg, 0.098 mmol) in THF (1 mL) was added borane tetrahydrofuran complex (0.294 mL, 0.294 mmol) at 0 °C dropwise. After addition, the ice water bath was removed and the reaction was warmed up to room temperature. After 2 hrs, reaction mixture was recooled to 0 °C and aqueous solution of sodium acetate (0.653 mL, 1.959 mmol) was added. Hydrogen peroxide (0.300 mL, 2.94 mmol) was added dropwise. After addition, the reaction was warmed up to room temperature and stirred at room temperature for 2 hrs. The reaction was extracted with EtOAc twice. Combined EtOAc layer washed with brine, dried over Na_2SO_4, filtered off solid, concentrated. Purification by reverse phase chromatography gave 152A (3.8 mg, pale yellow solid), 152B (3 mg, pale yellow solid) and 152C (7.8 mg, pale yellow solid).

[00647] 152A: MS (ESI) *m/z*: 590.4 $(M+H)^+$. Analytical HPLC(Method B): RT = 6.09 min.

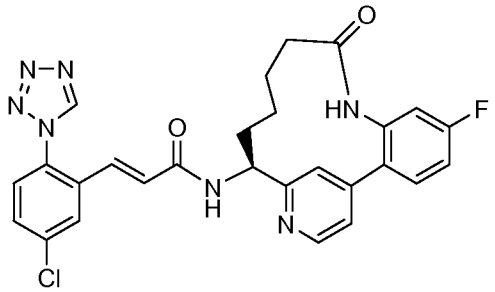
[00648] 152B: MS (ESI) *m/z*: 590.4 $(M+H)^+$. Analytical HPLC(Method B): RT = 6.17 min.

[00649] 152C: MS (ESI) *m/z*: 590.4 $(M+H)^+$. Analytical HPLC(Method B): RT = 6.44 min.

[00650] 152D. Example 152 was prepared following the procedures described in step 1F, by replacing 1D with152A; followed by step 1G. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.93 - 8.00 (m, 1 H), 7.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.46 - 7.52 (m, 1 H), 7.42 - 7.46 (m, 1 H), 7.41 (s, 1 H), 7.18 (d, *J*=15.7 Hz, 1 H), 6.72 (d, *J*=15.4 Hz, 1 H), 5.11 - 5.18 (m, 1 H), 3.75 (s, 3 H), 3.19 - 3.27 (m, 1 H), 2.42 - 2.49 (m, 2 H), 2.16 - 2.24 (m, 2 H), 1.86 - 1.95 (m, 1 H), 1.21 - 1.34 (m, 1 H). MS (ESI) *m/z*: 592.2 $(M+H)^+$. Analytical HPLC: RT = 3.76 min (Method B).

Example 153.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-*N*-((S)-5-fluoro-9-oxo-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-yl)-acrylamide, 1 TFA salt



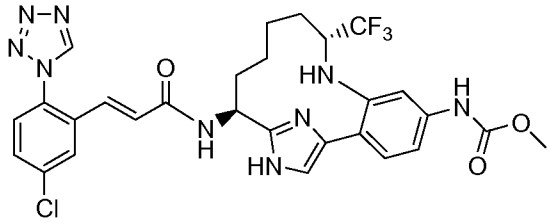
[00651] 153A. ((E)-(S)-5-Fluoro-9-oxo-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-yl)-carbamic acid *tert*-butyl ester: This compound was prepared from 132B by cleavage of the *t*-butylsulfinamide and introduction of a Boc-protection group, coupling with 3-butenoic acid and subsequent RCM of the resulting diene, following the procedures described for compounds 88D, 88E (replacing pentenoic acid with but-3-enoic acid), and 88G. MS (ESI) *m/z*: 398.3$(M+H)^+$.

[00652] 153B. Example 153 was prepared from 153A by hydrogenation, Boc-deprotection and coupling to Intermediate 1 following the procedures described for

compounds 2G, 3C and 1G. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.85 (1 H, s) 9.84 (1 H, s) 8.74 (1 H, d, *J*=6.60 Hz) 8.71 (1 H, d, *J*=5.23 Hz) 7.93 (1 H, d, *J*=2.20 Hz) 7.70 - 7.77 (2 H, m) 7.62 - 7.68 (2 H, m) 7.53 (1 H, d, *J*=4.40 Hz) 7.31 (1 H, td, *J*=8.46, 2.61 Hz) 7.11 (1 H, dd, *J*=9.77, 2.61 Hz) 6.93 - 6.99 (1 H, m) 6.81 - 6.86 (1 H, m) 4.99 - 5.06 (1 H, m) 2.35 (1 H, dd, *J*=10.32, 6.74 Hz) 1.85 - 1.93 (1 H, m) 1.73 - 1.81 (1 H, m) 1.61 - 1.73 (2 H, m) 1.48 (1 H, ddd, *J*=11.14, 6.74, 4.40 Hz) 1.21 (1 H, dd, *J*=6.33, 4.40 Hz) 0.51 - 0.62 (1 H, m). MS (ESI) *m/z*: 532.2 $(M+H)^+$. Analytical HPLC: RT = 5.90min.

Example 154.

{(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00653] 154A. {4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-3-[2,2,2-trifluoro-eth-(E)-ylideneamino]-phenyl}-carbamic acid methyl ester: To a solution of 10C (0.805 g, 1.514 mmol) in DCM (30.3 mL) was added 1-ethoxy-2,2,2-trifluoroethanol (0.436 g, 3.03 mmol), 5 Å molecular sieves (5 g, 1.514 mmol) and p-toluenesulfonic acid monohydrate (0.014 g, 0.076 mmol). The reaction was warmed to 40 °C. After 2 days additional 1-ethoxy-2,2,2-trifluoroethanol (0.436 g, 3.03 mmol) was added. After 12 days, the reaction was filtered through a 0.45 micron GMF filter and the filter cake was rinsed with DCM. The filtrate was concentrated and then toluene (3 mL) was added and then concentrated. This process repeated one more time to afford 154A (0.926 g, 100 % yield) as a brown oil and as a mixture of diastereomers. MS (ESI) *m/z*: 612.6 $(M+H)^+$. This was used in the next step without further purification.

[00654] 154B. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-3-(1-trifluoromethyl-but-3-enylamino)-phenyl]-carbamic acid methyl ester: To a cooled (0 °C) solution of 154A

(0.926 g, 1.514 mmol) in THF (30 mL) was added allylmagnesium bromide (1M in Et_2O, 5.00 mL, 5.00 mmol). After 30 min, the reaction was allowed to warm to rt. After 1.5 h, the reaction was quenched with sat. NH_4Cl. Then the reaction mixture was diluted with EtOAc, washed with water, brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography afforded 154B (0.49 g, 49.5 % yield) as a yellow solid and as a mixture of diastereomers. MS (ESI) *m/z*: 654.5 $(M+H)^+$.

[00655] 154C. [(9R,14S)-14-*tert*-Butoxycarbonylamino-9-trifluoromethyl-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl]-carbamic acid methyl ester, 2 TFA salt (Diastereomer A) and 154D. [(9S,14S)-14-*tert*-Butoxycarbonylamino-9-trifluoromethyl-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl]-carbamic acid methyl ester, 2 TFA salt (Diastereomer B). The ring-closing methathesis products (a mixture of E- and Z-alkene isomers as well as diastereomers at the alpha amine) were prepared following the procedures described in step 2E/2F, by replacing 2D with 154B. To a solution of the ring-closing metathesis product (1.01 g, 1.614 mmol) in EtOAc (32.3 mL) was added TFA (0.249 mL, 3.23 mmol) and 10% palladium on carbon (0.172 g, 0.161 mmol). The reaction vessel was pressurized with hydrogen to 55 psi. After 3 days the reaction was stopped and the reaction was filtered through a 0.45 μm GMF and the catalyst was rinsed with MeOH. The filtrate was concentrated. Purification by reverse phase chromatography afforded 0.074 g (5.4%) of 154 C (diastereomer A) and 0.410 g (30%) of 154 D (diastereomer B). MS (ESI) *m/z*: 628.4 $(M+H)^+$. Alternatively, the palladium on carbon catalyst can be replaced with platinum oxide.

[00656] 154E. ((9R,14S)-14-Amino-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester. A high-pressure vial, with a teflon-coated screw cap, containing a slightly cloudy mixture of 154D (diastereomer B) (0.0590 g, 0.069 mmol) and 2-amino-3-mercaptopropanoic acid (0.042 g, 0.345 mmol) in 4M HCl in dioxane (1.551 mL, 6.20 mmol) was warmed to 75 °C. A white precipitate forms overtime. After 1.5 h, the reaction was stopped and concentrated to give a solid. The solid was dissolved in sat. $NaHCO_3$ and then extracted with EtOAc (3x). The combined organic layers were

washed with brine, dried over Na_2SO_4, filtered and concentrated to give 154E as a pale-yellow foam. MS (ESI) *m/z*: 398.1 $(M+H)^+$.

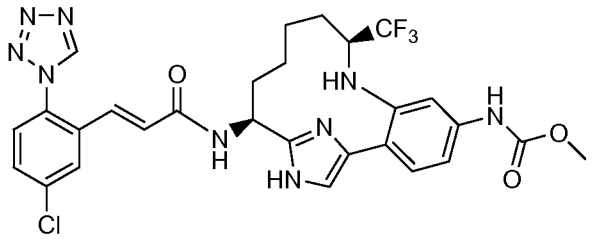
[00657] 154F. Example 154 was prepared following the procedure described in 15D, by replacing 15C with 154 E. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.94 (d, J=2.2 Hz, 1 H), 7.66 (dd, J=8.8, 2.2 Hz, 1 H), 7.57 (d, J=8.2 Hz, 1 H), 7.50 (s, 1 H), 7.34 (s, 1 H), 7.27 (d, J=8.2 Hz, 1 H), 7.06 - 7.14 (m, 2 H), 6.76 (d, J=15.4 Hz, 1 H), 5.13 (t, J=7.1 Hz, 1 H), 3.73 (s, 3 H), 2.93 - 3.01 (m, 1 H), 2.34 - 2.43 (m, 1 H), 1.95 - 2.04 (m, 1 H), 1.62 - 1.75 (m, 2 H), 1.48 - 1.59 (m, 2 H), 1.35 - 1.46 (m, 1 H), 0.48 - 0.59 (m, 1 H). ^{19}F NMR (470 MHz, CD_3OD) δ ppm -75.22. MS (ESI) *m/z*: 630.4 $(M+H)^+$. Analytical HPLC: RT = 6.13 min.

[00658] Alternatively, 10C can be condensed with 1-ethoxy-2,2,2-trifluoroethanol to give the 154G rather than the imine (154A) according to the following procedure. Compound 154G can replace 154A in step 154B.

[00659] 154G. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-3-(1-ethoxy-2,2,2-trifluoro-ethylamino)-phenyl]-carbamic acid methyl ester: To a clear, dull yellow solution of 10C (2.0 g, 3.76 mmol) in EtOH (7.52 mL) was added 1-ethoxy-2,2,2-trifluoroethanol (1.734 ml, 15.05 mmol). The reaction was heated at 120 °C in a microwave for 3 h. The reaction was cooled to RT and then the reaction was concentrated. Purification by normal phase chromatography gave 1.75 g (66%) of 154A, as an orange foam and as a mixture of diastereomers. MS (ESI) *m/z*: 658.4 $(M+H)^+$.

Example 155.

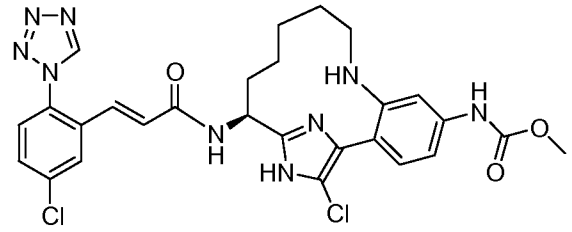
{(9S,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00660] 155A. (9S,14S)-14-Amino-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester. Compound 155A was prepared following the procedure described in 154E, by replacing 154D with 154C (diastereomer A). MS (ESI) *m/z*: 398.1 $(M+H)^+$.

[00661] 155B. Example 155 was prepared following the procedure described in 15D, by replacing 15C with 155A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.54 (s, 1 H), 7.39 (s, 1 H), 7.31 (d, *J*=8.2 Hz, 1 H), 7.09 - 7.18 (m, 2 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.24 (dd, *J*=11.0, 7.1 Hz, 1 H), 3.75 (s, 3 H), 2.90 - 2.99 (m, 1 H), 2.24 - 2.37 (m, 1 H), 1.97 - 2.08 (m, 1 H), 1.67 - 1.84 (m, 2 H), 1.43 - 1.63 (m, 3 H), 0.30 - 0.42 (m, 1 H). ^{19}F NMR (470 MHz, CD_3OD) δ ppm -74.66. MS (ESI) *m/z*: 630.4 $(M+H)^+$. Analytical HPLC: RT = 6.29 min.

Example 156.
{(S)-17-Chloro-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt

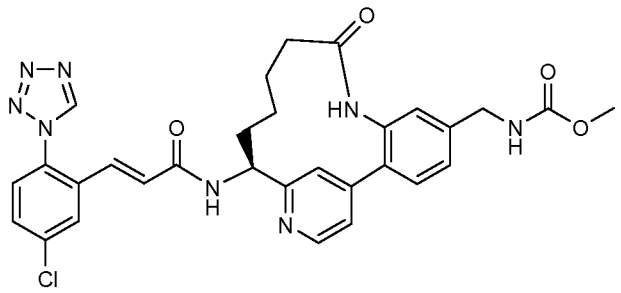


[00662] Example 156 was synthesized according to the procedure described in Example 7, by replacing Example 6 with Example 11. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 8.02 (d, *J*=2.5 Hz, 1 H), 7.91 (br. s., 1 H), 7.84 (d, *J*=8.8 Hz, 1 H), 7.69 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.61 (d, *J*=8.5 Hz, 1 H), 7.32 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.26 (d,

J=15.7 Hz, 1 H), 6.81 (d, *J*=15.7 Hz, 1 H), 5.20 (dd, *J*=11.0, 6.3 Hz, 1 H), 3.72 (s, 3 H), 3.18 - 3.25 (m, 1 H), 2.92 - 3.00 (m, 1 H), 1.97 - 2.19 (m, 3 H), 1.82 - 1.90 (m, 1 H), 1.62 - 1.72 (m, 2 H), 1.33 - 1.43 (m, 1 H), 0.76 - 0.87 (m, 1 H). MS (ESI) *m/z*: 596.5 $(M+H)^+$. Analytical HPLC: RT = 6.01 min.

Example 159.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-ylmethyl}-carbamic acid methyl ester, TFA salt



[00663] 159A. 3-Amino-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-benzonitrile: This compound was prepared following the procedures described for Intermediate 12, by replacing 2-bromo-5-nitroaniline with 3-amino-4-bromobenzonitrile. MS (ESI) *m/z*: 163.1$(M+H)^+$.

[00664] 159B. ((E)-(S)-5-Cyano-9-oxo-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-yl)-carbamic acid *tert*-butyl ester: This compound was prepared from 159A in four steps by Suzuki coupling to 88B, cleavage of the *t*-butylsulfinamide and introduction of a Boc-protection group, coupling with 3-butenoic acid and subsequent RCM of the resulting diene, following the procedures described for compounds 88C, 88D, 88E (substituting 3-butenoic acid for 4-pentenoic acid), and 88G. MS (ESI) *m/z*: 405.2$(M+H)^+$.

[00665] 159C. ((S)-5-Aminomethyl-9-oxo-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-yl)-carbamic acid *tert*-butyl ester: 155B (0.023 g, 0.057 mmol) was dissolved in MeOH (2.0 mL) and transferred to a flask containing a suspension of 10% Pd/C in 1-2 mL MeOH under argon. The mixture was evacuated and back-filled with Ar 3x, then stirred under 1 atm of hydrogen for 3 days. The catalyst was

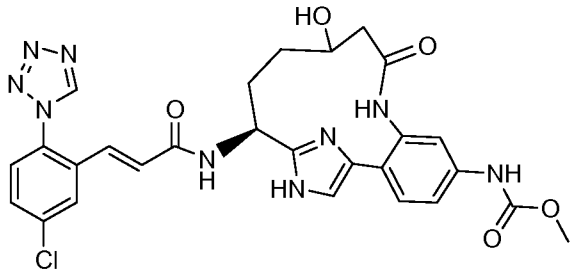
removed by filtration through CELITE® and washed with MeOH; the filtrate was condensed to yield 155C (0.023 g, 99 %), MS (ESI) *m/z* 411.3(M+H)$^+$.

[00666] 159D. [(S)-5-(Methoxycarbonylamino-methyl)-9-oxo-8,16-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-yl]-carbamic acid *tert*-butyl ester: 155C (0.023 g, 0.056 mmol) was dissolved in CH_2Cl_2 (0.5 mL), and TEA (0.016 mL, 0.112 mmol) was added. This mixture was stirred under Ar in an ice/salt water bath. Methyl chloroformate (4.56 µL, 0.059 mmol) was added dropwise to the cold mixture. The reaction was allowed to gradually assume room temperature over 2 hours as the ice bath melted. The reaction was quenched with water and diluted with EtOAc. The organic layer was then washed with saturated $NaHCO_3$ and brine, dried briefly over anhydrous $MgSO_4$, filtered and evaporated to yield 159D as a light yellow glass (0.017 g, 64.8 %). MS (ESI) *m/z*: 469.3(M+H)$^+$.

[00667] 159E. Example 159 was prepared from 159D by Boc-deprotection and coupling with Intermediate 1, following the procedures described for steps 3C and 1G. ^{1}H NMR (500 MHz, MeOD) δ ppm 9.48 (1 H, s) 8.71 (1 H, d, *J*=5.78 Hz) 7.97 (2 H, d, *J*=1.93 Hz) 7.77 (1 H, dd, *J*=5.64, 1.51 Hz) 7.62 - 7.69 (2 H, m) 7.57 (1 H, d, *J*=8.53 Hz) 7.42 (1 H, d, *J*=7.98 Hz) 7.23 (1 H, s) 7.10 (1 H, d, *J*=15.68 Hz) 6.79 (1 H, d, *J*=15.68 Hz) 5.11 (1 H, dd, *J*=10.87, 5.64 Hz) 4.36 (2 H, s) 3.67 (3 H, s) 2.46 - 2.53 (1 H, m) 2.07 - 2.18 (1 H, m) 1.83 - 2.00 (2 H, m) 1.70 - 1.81 (1 H, m) 1.60 - 1.70 (1 H, m) 1.35 - 1.44 (1 H, m) 0.70 - 0.81 (1 H, m). MS (ESI) *m/z*: 601.3 (M+H)$^+$. Analytical HPLC: RT = 5.54min.

Example 160.

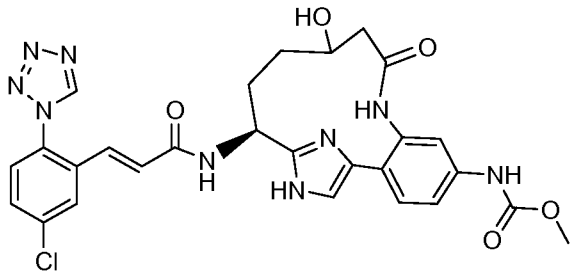
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-hydroxy-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00668] Example 160 was prepared following the procedures described in step 1F, by replacing 1D with 152B; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.49 (s, 1 H), 7.91 - 8.01 (m, 1 H), 7.65 - 7.72 (m, 1 H), 7.55 - 7.63 (m, 2 H), 7.43 - 7.52 (m, 2 H), 7.34 - 7.43 (m, 1 H), 7.15 (d, *J*=15.7 Hz, 1 H), 6.73 (d, *J*=15.7 Hz, 1 H), 5.08 - 5.19 (m, 1 H), 3.85 - 3.95 (m, 1 H), 3.76 (s, 3 H), 2.68 - 2.76 (m, 1 H), 2.40 - 2.54 (m, 1 H), 2.12 - 2.23 (m, 1 H), 1.93 - 2.06 (m, 1 H), 1.39 - 1.51 (m, 1 H), 1.21 - 1.34 (m, 1 H). MS (ESI) *m/z*: 592.2 $(M+H)^+$. Analytical HPLC: RT = 3.86 min (Method B).

Example 161.

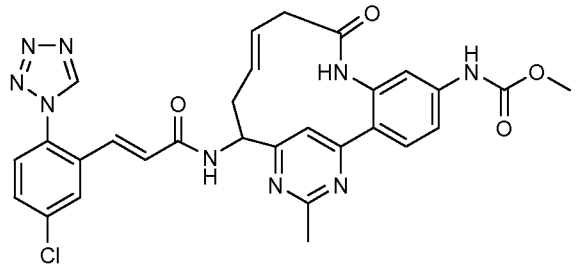
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-hydroxy-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 1 TFA salt



[00669] Example 161 was prepared following the procedures described in step 1F, by replacing 1D with 152C; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.92 - 8.04 (m, 1 H), 7.64 - 7.72 (m, 1 H), 7.56 - 7.63 (m, 2 H), 7.50 - 7.56 (m, 1 H), 7.41 - 7.49 (m, 2 H), 7.17 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.26 - 5.38 (m, 1 H), 3.76 (s, 3 H), 3.63 - 3.72 (m, 1 H), 2.51 - 2.64 (m, 1 H), 2.30 - 2.44 (m, 2 H), 1.95 - 2.05 (m, 1 H), 1.65 - 1.78 (m, 1 H), 1.30 - 1.47 (m, 1 H). MS (ESI) *m/z*: 592.2 $(M+H)^+$. Analytical HPLC: RT = 3.69 min (Method B).

Example 167.

{(E)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-methyl-9-oxo-8,16,18-triaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,11,15,17-heptaen-5-yl}-carbamic acid methyl ester



[00670] 167A. (S)-4-*tert*-Butoxycarbonylamino-3-oxo-hept-6-enoic acid ethyl ester. To a solution of (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid (5.0g, 23.23 mmol) in THF (40 mL) was added carbonyldiimide (4.52 g, 27.9 mmol) at rt. The reaction was stirred under argon at rt for 5 h. To another flask containing a solution of 3-ethoxy-3-oxopropanoic acid (4.60 g, 34.8 mmol) in THF (40 mL) was added dropwise isopropylmagnesium chloride (34.8 mL, 69.7 mmol) at 0 °C. Following the addition, the reaction was stirred at 0 °C for 30 min, at rt for 30 min and then at 48 °C for 30 min. The reaction was cooled to rt and transferred to the cooled solution (0 °C) prepared in the first flask to give a milky suspension. The reaction was allowed to stir at rt over night. The reaction mixture was slowly poured into 1.0N HCl (200 ml) at 0 °C and gas was evolved. The reaction mixture was extracted with EtOAc, washed with sat $NaHCO_3$ and brine. The organic phase was dried over sodium sulfate, filtered and concentrated to give a clear colorless oil. The crude product was purified by normal phase chromatography to give 167A (5.36 g, 81% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.61 - 5.78 (1 H, m), 5.17 (1 H, d, *J*=3.26 Hz), 5.13 (2 H, d, *J*=2.26 Hz), 4.32 - 4.50 (1 H, m), 4.20 (2 H, q, *J*=7.28 Hz), 3.47 - 3.64 (2 H, m), 2.52 - 2.70 (1 H, m), 2.35 - 2.52 (1 H, m), 1.44 (9 H, s), 1.28 (3 H, t, *J*=7.15 Hz). MS (ESI) *m/z*: 308.1 $(M+Na)^+$.

[00671] 167B. [1-(6-Hydroxy-2-methyl-pyrimidin-4-yl)-but-3-enyl]-carbamic acid *tert*-butyl ester. To a solution of acetimidamide HCl salt (0.928 g, 9.81 mmol) in MeOH (30 mL) were added sodium methoxide solution (25% wt/wt, 4.49 mL, 19.63 mmol) and a solution of 167A(2.0g, 7.01 mmol) dissolved in MeOH (15mL) at rt. The reaction was stirred under argon at rt for 3 h. The reaction was neutralized with 1.0 N HCl. Most solvent was removed. The reaction mixture was extracted with chloroform. The organic phase was washed with brine and dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give 167B (1.82 g, 93% yield) as a white solid. MS (ESI) *m/z*: 280.1 $(M+H)^+$.

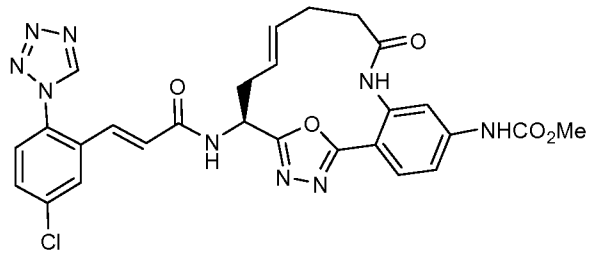
[00672] 167C. [1-(6-Chloro-2-methyl-pyrimidin-4-yl)-but-3-enyl]-carbamic acid *tert*-butyl ester. To a flask containing 167B (1.82 g, 6.52 mmol) was added $POCl_3$ (12.15 mL, 130 mmol) at rt. The suspension was stirred under argon at 50 °C and the suspension turned a clear light brown solution. After 2 h, excess $POCl_3$ was removed under reduced pressure and the residue was co-evaporated twice with toluene to give a dark tar. This intermediate was dissolved in acetonitrile (30 mL), to which were added Na_2CO_3 (3.46 g, 32.6 mmol) and BOC_2O (1.817 mL, 7.82 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 1.5 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give 167C (0.65 g, 34% yield) as a light yellow solid. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.30 (1 H, s), 5.70 - 5.88 (1 H, m, *J*=17.13, 10.16, 6.93, 6.93 Hz), 5.02 - 5.15 (2 H, m), 4.63 (1 H, dd, *J*=8.28, 5.27 Hz), 2.64 (3 H, s), 2.54 - 2.62 (1 H, m), 2.36 - 2.49 (1 H, m), 1.43 (9 H, s). MS (ESI) *m/z*: 298.1 $(M+H)^+$.

[00673] 167D. {3-But-3-enoylamino-4-[6-(1-*tert*-butoxycarbonylamino-but-3-enyl)-2-methyl-pyrimidin-4-yl]-phenyl}-carbamic acid methyl ester: This compound was prepared following the procedures described in step 88C, by replacing 88B with 167C; followed by steps 88E; and 88F. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.23 (1 H, s), 7.63 - 7.72 (2 H, m), 7.40 (1 H, s), 5.92 - 6.07 (1 H, m, *J*=17.07, 10.10, 7.00, 7.00 Hz), 5.61 - 5.72 (1 H, m), 5.19 - 5.30 (2 H, m), 5.08 (2 H, d, *J*=12.05 Hz), 4.62 - 4.78 (1 H, m), 3.75 (3 H, s), 3.18 (2 H, d, *J*=7.03 Hz), 2.73 (3 H, s), 2.45 - 2.64 (2 H, m), 1.40 (9 H, br. s.). MS (ESI) *m/z*: 496.1 $(M+H)^+$.

[00674] 167E. ((E)-5-Methoxycarbonylamino-17-methyl-9-oxo-8,16,18-triaza-tricyclo[13.3.1.02,7]nonadeca-1(19),2,4,6,11,15,17-heptaen-14-yl)-carbamic acid *tert*-butyl ester. A solution of 167D (25mg, 0.050 mmol) in DCM (100mL) was purged with argon and then was added 4 M HCl in dioxane (0.1 mL, 0.400 mmol) at rt. The solution was heated up to reflux and then Grubbs (II) catalyst (17.13 mg, 0.020 mmol) was added. The reaction was stirred under argon at reflux for 4 h. The reaction was cooled to rt and solvent was removed. Purification by reverse phase chromatography gave 167E (5.1 mg, 22% yield) as a dark brown solid. MS (ESI) *m/z*: 468.0 $(M+H)^+$.

[00675] 167F. Example 167 was prepared following the procedures described in step 3C, by replacing 3B with 167E; followed by step 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.55 (1 H, s), 9.50 (1 H, s), 8.01 (1 H, d, *J*=2.26 Hz), 7.66 (1 H, dd, *J*=8.53, 2.26 Hz), 7.59 - 7.63 (2 H, m), 7.56 (1 H, d, *J*=8.53 Hz), 7.48 (1 H, dd, *J*=8.66, 2.13 Hz), 7.11 (1 H, d, *J*=15.56 Hz), 6.96 (1 H, s), 6.89 (1 H, d, *J*=15.56 Hz), 5.74 - 5.85 (1 H, m), 4.96 - 5.03 (2 H, m), 3.76 (3 H, s), 3.00 (1 H, dd, *J*=11.80, 9.29 Hz), 2.75 - 2.85 (2 H, m), 2.74 (3 H, s), 2.21 - 2.33 (1 H, m). MS (ESI) *m/z*: 600.1 $(M+H)^+$. Analytical HPLC: RT = 6.383 min.

Example 168.



[00676] 168A. Methyl 4-amino-2-nitrobenzoate: A suspension of 4-amino-2-nitrobenzoic acid (1.0 g, 5.49 mmol) in MeOH (25 mL) was cooled in an ice/salt water bath with stirring under nitrogen while $SOCl_2$ (0.601 mL, 8.24 mmol) was slowly added dropwise. The resulting amber solution was heated at reflux overnight. Reaction was cooled to room temperature and evaporated to remove MeOH. Residue was partitioned between EtOAc and sat'd aq. $NaHCO_3$ solution, and aq. layer reextracted 2X with EtOAc. Combined organic extracts were washed with brine, dried over anh. Na_2SO_4, filtered and evaporated to give the ester as a yellow-orange solid (0.95 g, 88 %). ^{1}H NMR (500 MHz, DMSO-d_6) d ppm 7.61 (1 H, d, *J*=8.53 Hz) 6.83 (1 H, d, *J*=2.20 Hz) 6.74 (1 H, dd, *J*=8.67, 2.34 Hz) 6.54 (2 H, s) 3.72 (3 H, s).

[00677] 168B. Methyl 4-(hydrazinecarbonyl)-3-nitrophenylcarbamate: 168A (0.94 g, 4.79 mmol) was suspended in DCM (25 mL), pyridine (0.775 mL, 9.58 mmol) was added, and the mixture was cooled in an ice bath with stirring under nitrogen. Methylchloroformate (0.390 mL, 5.03 mmol) was then added dropwise to the cold mixture. Stirring was continued for ~ 30 min in the ice bath then at room temperature for 4 h. Reaction was diluted with additional DCM, washed 2X with 1M HCl, water and

brine, then dried over anh. Na_2SO_4, filtered and evaporated to a light orange solid. The solid obtained (1.2 g, 4.72 mmol) was suspended in ethanol (24 ml), and hydrazine (2.4 ml, 76 mmol) was added. The mixture was heated at reflux under nitrogen with stirring overnight in an 80 °C oil bath, then cooled to room temperature and filtered. Pale yellow solid was washed with EtOH and Et_2O then air-dried. The filtrate was evaporated and residue suspended in EtOAc/H_2O. Solid which separated was collected by filtration, washed with EtOAc and Et_2O, dried and combined with initial solid. The crude hydrazide was suspended in MeOH and sonicated for 10-15, insoluble solid removed by filtration and washed with MeOH. Evaporation of the filtrate gave the product, 168B, as a bright yellow solid. (0.363 g, 30.2 %). ^{1}H NMR (500 MHz, DMSO-d_6) d ppm 10.28 (1 H, s) 9.60 - 9.71 (1 H, m) 8.13 (1 H, d, *J*=1.93 Hz) 7.71 (1 H, dd, *J*=8.39, 2.06 Hz) 7.51 (1 H, d, *J*=8.53 Hz) 4.45 (2 H, d, *J*=4.13 Hz) 3.72 (3 H, s).

[00678] 168C. {4-[5-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1,3,4-oxadiazol-2-yl]-3-nitro-phenyl}-carbamic acid methyl ester: 168B (0.3 g, 0.393 mmol) and (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid (0.085 g, 0.393 mmol) were dissolved in DMF (2 mL) in a 15 mL rbf and TEA (0.274 mL, 1.967 mmol) was added. Mixture was stirred under nitrogen at room temperature while propane phosphonic acid anhydride (T3P), 50% in EtOAc (0.293 mL, 0.983 mmol) was added dropwise. The flask was fitted with a reflux condenser, and the resulting mixture was stirred in an 80 °C oil bath for 5 h. Reaction mixture was poured into ice water and extracted 3X with EtOAc. Combined extracts were washed with sat'd aq. $NaHCO_3$, water and brine, dried over anh. Na_2SO_4, filtered and evaporated to provide {4-[N'-((S)-2-*tert*-butoxycarbonylamino-pent-4-enoyl)-hydrazinocarbonyl]-3-nitro-phenyl}-carbamic acid methyl ester, (0.46 g, 86%) as a light yellow solid which was used without further purification. The solid (0.46 g, 1.019 mmol) was dissolved in anhydrous THF (20 mL) under argon and the solution transferred to a 75 mL pressure flask. Burgess reagent (1.33 g, 5.58 mmol) was added, the flask was sealed with a pressure relief cap and then heated in a 75 °C oil bath for 2h behind a blast shield then left standing overnight at room temperature. Reaction mixture was evaporated on rotary evaporator. Residue was purified by normal phase chromatography to give 168C as a light yellow foam (0.315 g, 71.3 %). MS (ESI) *m/z*: 434.3 $(M+H)^+$ 378.3 $(M+H\text{-}tBu)^+$.

[00679] 168D. {3-Amino-4-[5-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1,3,4-oxadiazol-2-yl]-phenyl}-carbamic acid methyl ester: 168C (0.315 g, 0.727 mmol) was dissolved in ethanol (4.5 mL) and iron powder (0.812 g, 14.54 mmol) was added. The mixture was stirred at room temperature for 1-2 min, then 0.1 M HCl (3.63 mL, 0.363 mmol) was added, and the reaction was heated with stirring under nitrogen in a 50 °C oil bath for 1.5 h. Reaction was cooled to room temperature and filtered through a pad of CELITE,® and solids washed with water, EtOH and EtOAc, then discarded. Filtrate was evaporated and remaining aqueous was diluted with $NaHCO_3$ to pH 8, then extracted 3x with EtOAc. Combined extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and filtered. Evaporation of solvents provided 168D as a crystalline solid. (0.257 g, 88 %). MS (ESI) *m/z*: 404.3 $(M+H)^+$ 348.3 $(M+H\text{-}tBu)^+$.

[00680] 168E. -[5-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1,3,4-oxadiazol-2-yl]-3-pent-4-enoylamino-phenyl}-carbamic acid methyl ester: 168D (0.275 g, 0.682 mmol) was dissolved in DCM (3.5 mL) and pyridine (0.110 mL, 1.363 mmol) was added. The solution was cooled in an ice/salt water bath to ~ 0 °C, then 4-pentenoyl chloride (0.075 mL, 0.682 mmol) was added dropwise. The resulting mixture was stirred at 0-5 °C for 1 h then allowed to warm to room temperature. After an additional 2h at room temperature, the reaction was diluted with EtOAc and washed with water, 1M HCl, sat'd $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by normal phase chromatography to provide 168E as a white solid (0.276 g, 83 %). MS (ESI) *m/z*: 486.3 $(M+H)^+$ 430.3 $(M+H\text{-}tBu)^+$

[00681] 168F. ((E)-(S)-15-*tert*-Butoxycarbonylamino-9-oxo-19-oxa-8,17,18-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16-hexaen-5-yl)-carbamic acid methyl ester: 168E (0.15 g, 0.309 mmol) was dissolved in DCE (500 mL) in a 1L flame-dried 3-neck flask fitted with a septum, reflux condenser and argon inlet. The solution was degassed by bubbling Ar through the solution for 30 min. Grubbs (II) (0.094 g, 0.111 mmol) catalyst was weighed out under argon and dissolved in 5 mL of degassed DCE and the dark red solution was added dropwise over 5-10 min to the above solution. The resulting mixture was heated in a 75 °C oil bath for ~ 2h. Reaction was cooled to room temperature and solvent removed on rotary evaporator. Residue was taken back up in DCM and 0.375 g tris(hydroxymethyl)phosphine and 0.78 mL TEA were added. Mixture

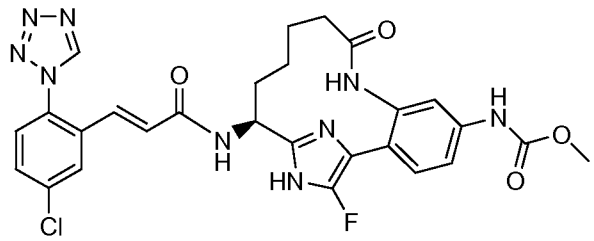
was stirred for 10 min then water was added and vigorous stirring was continued for 15 min. Phases were separated and organic layer washed with brine and dried over anhydrous Na_2SO_4. The crude product mixture was purified by silica gel chromatography to provide 168F, the trans isomer, as the major product (27 mg, 19.1 %). MS (ESI) *m/z*: 458.3 $(M+H)^+$ 402.1 $(M+H\text{-}tBu)^+$.

[00682] 168G: Example 168 was prepared from 168F by removal of the Boc protecting group and coupling with Intermediate 1, following the procedures described for compounds 3C and 1G. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.04 (1 H, s) 9.91 (1 H, s) 9.84 (1 H, s) 9.04 (1 H, d, *J*=7.33 Hz) 7.96 (1 H, d, *J*=1.77 Hz) 7.64 - 7.81 (3 H, m) 7.52 (1 H, s) 7.41 (1 H, dd, *J*=8.46, 1.64 Hz) 6.91 (1 H, d, *J*=16.00 Hz) 6.81 (1 H, d, *J*=16.00 Hz) 5.43 - 5.63 (2 H, m) 5.11 - 5.22 (1 H, m) 3.70 (3 H, s) 2.57 - 2.70 (1 H, m) 2.35 - 2.47 (3 H, m) 2.15 - 2.27 (2 H, m). MS (ESI) *m/z*: 590.2 $(M+H)^+$. Analytical HPLC RT = 5.80 min.

[00683] Unless otherwise stated, the compounds listed in the following tables can be prepared by one skilled in the art of organic synthesis using the procedures described in Examples 1-168.

[00684] Examples I-1 to I-17 (Table I-1) were prepared by coupling 10H with appropriately substituted carboxylic acid derivatives (R-CO_2H) using coupling conditions described in step 15D. In the case of Examples I-4, I-12, and I-15, an additional Boc-deprotection step as described in step 3C was required. Example I-18 was prepared by coupling 10H with an appropriately substituted carboxylic acid derivative (R-CO_2H) using coupling conditions described in step 15D followed by chlorination as described in Example 7.

Example I-20.
{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-fluoro-9-oxo-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, trifluoroacetic acid salt



[00685] I-20A. ((S)-14-*tert*-Butoxycarbonylamino-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester: To a brown solution of 10H (74.1 mg, 0.178 mmol) in THF (4 mL) and water (2 mL) was added potassium carbonate (98 mg, 0.712 mmol), followed by di-*tert*-butyl dicarbonate (0.062 mL, 0.267 mmol). The reaction was stirred at rt for 12h. To the solution was added aq. NH_4Cl (10 mL) and 100 ul sat NH_4OH to quench the reaction. The reaction mixture was then extracted with EtOAc (30 mL x 2). Organic solution was dried over $MgSO_4$ and concentrated *in vacuo*, yielding oily mixture, which was purified on normal phase column chromatography (EtOAc/Hex) to provide 40 mg (0.090 mmol, 50.7 % yield) of I-20A as light brown oil. MS (ESI) *m/z*: 444.2 $(M+1)^+$.

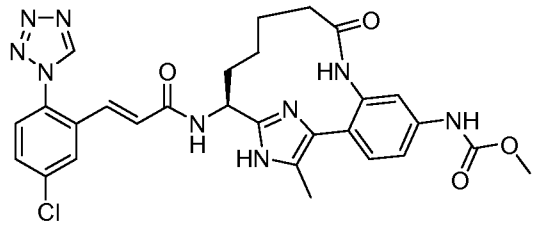
[00686] I-20B. ((S)-14-Amino-17-fluoro-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester: To a solution of I-20A (40 mg, 0.090 mmol) in DMF (3mL) was added sodium carbonate (12.43 mg, 0.117 mmol) and 1-Fluoro-4-hydroxy-1,4 diazoniabicyclo[2,2,2]octanebis(tetrafluoroborate) (50% in alumina) (62.9 mg, 0.090 mmol) in a portion, respectively and the resulting solution was stirred for 2h at rt. The reaction mixture was diluted with MeOH and purified by reverse phase chromatography which gave both ((S)-14-*tert*-Butoxycarbonylamino-17-fluoro-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester and ((S)-14-Amino-17-fluoro-9-oxo-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester. The mixture was dissolved in 4N HCl dioxane (10 mL) and stirred overnight at 50 °C. Concentration of the solution provided 11 mg of I-20B (34%).

[00687] I-20C. Example I-20 was prepared following the procedures described in step 1G, by replacing 1F with I-20B. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.40 - 9.59 (m, 1 H), 7.88 - 8.10 (m, 1 H), 7.62 - 7.85 (m, 1 H), 7.53 - 7.62 (m, 1 H), 7.31 - 7.52 (m, 2 H),

7.07 - 7.22 (m, 1 H), 6.71 - 6.94 (m, 1 H), 4.92 - 5.03 (m, 1 H), 2.36 - 2.50 (m, 1 H), 1.94 - 2.30 (m, 2 H), 1.75 (br. s., 2 H), 1.45 (br. s., 2 H), 0.99 (br. s., 1 H). MS(ESI) *m/z*: 594.2 $(M+H)^+$. Analytical HPLC: RT = 6.79 min.

Example I-22.

Methyl N-[(14S)-14-[(2E)-3-[5-chloro-2-(1H-1,2,3,4- tetrazol-1-yl)phenyl]prop-2-enamido]-17-methyl-9-oxo-8,16,18-triazatricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2(7),3,5,15(18)-pentaen-5-yl]carbamate, trifluoroacetic acid.



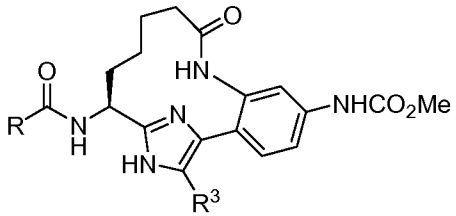
[00688] I-22A. *tert*-Butyl N-[(14S)-17-bromo-5- [(methoxycarbonyl)amino]-9-oxo-16-{[2- (trimethylsilyl)ethoxy]methyl}-8,16,18- triazatricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2(7),3,5,15(18)-pentaen-14-yl]carbamate: To a cooled (< 0 °C) solution of 10G (0.53 g, 0.924 mmol) in $CHCl_3$ (10 mL) was added NBS (0.164 g, 0.924 mmol). The reaction was stirred under argon at 0 °C for 30 min. The solvent was removed. The crude product was purified by normal phase chromatography to give I-22A (0.58 g, 96%) as a solid. MS (ESI) *m/z*: 652.2 $(M+H)^+$ and 654.2 $(M+2+H)^+$.

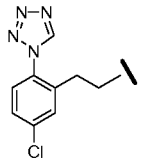
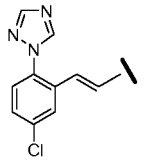
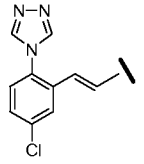
[00689] I-22B. *tert*-Butyl N-[(14S)-5-[(methoxycarbonyl)amino]-17-methyl-9-oxo-16-{[2-(trimethylsilyl)ethoxy]methyl}- 8,16,18-triazatricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2(7),3,5,15(18)-pentaen-14-yl]carbamate: To a solution of I-22A (0.53g, 0.812 mmol) in dioxane (15 mL) were added Na_2CO_3 (0.430 g, 4.06 mmol), methylboronic acid (0.097 g, 1.624 mmol) and bis(tri-*t*-butylphosphine) palladium(0) (0.042 g, 0.081 mmol) at RT. The reaction mixture was purged with argon and then the reaction was stirred under argon at 80 °C for 5 h. The reaction was cooled to RT. The reaction mixture was diluted with EtOAc, washed with sat $NaHCO_3$ and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. In order to remove the des-Br by-product for better purification, it was converted back to bromoimidazole starting material

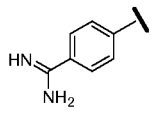
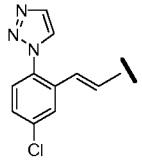
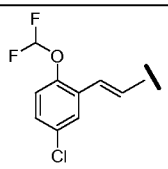
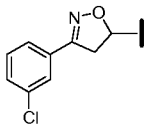
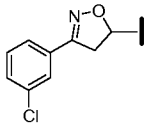
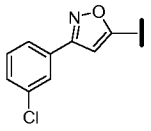
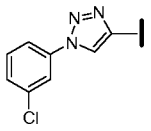
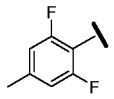
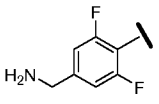
following the procedure described in I-22A. The crude product was purified by reverse phase chromatography to give I-22B (44 mg, 10% yield). MS (ESI) *m/z*: 588.4 $(M+H)^+$.

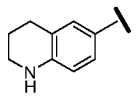
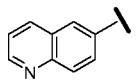
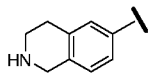
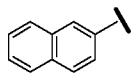
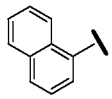
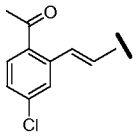
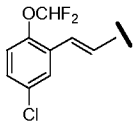
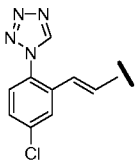
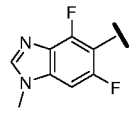
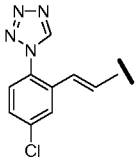
[00690] I-22C. Example I-22 was prepared following the procedures described in 10H, by replacing 10G with I-22B; followed by step1G. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.57 (1 H, s, br), 9.50 (1 H, s), 7.96 (1 H, d, J=2.01 Hz), 7.68 (1 H, dd, J=8.53, 2.26 Hz), 7.55 - 7.61 (2 H, m), 7.39 - 7.47 (2 H, m), 7.14 (1 H, d, J=15.56 Hz), 6.73 (1 H, d, J=15.81 Hz), 5.03 (1 H, dd, J=10.16, 6.40 Hz), 3.76 (3 H, s), 2.37 - 2.48 (1 H, m), 2.31 (3 H, s), 2.15 - 2.28 (1 H, m), 2.00 - 2.12 (1 H, m), 1.84 - 1.97 (1 H, m), 1.41 - 1.66 (3 H, m), 0.96 - 1.18 (1 H, m). MS (ESI) *m/z*: 590.2 $(M+H)^+$. Analytical HPLC: RT = 4.38 min.

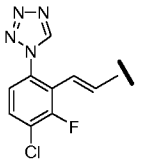
Table I-1: Examples I-1 to I-23



Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-1		H	578.2	4.7
I-2		H	575.2	4.5
I-3		H	575.2	4.2

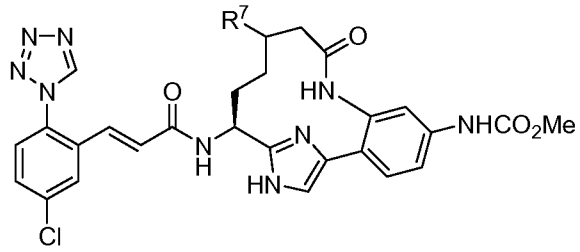
Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-4		H	490.1	2.0 (B)
I-5		H	575.2	5.0
I-6		H	574.2	6.1
I-7		H	551.1	5.0 4.8 (B)
I-8		H	551.1	5.0 4.9 (B)
I-9		H	549.2	6.2
I-10		H	549.2	5.6
I-11		H	498.2	4.0
I-12		H	513.2	6.2 (C)

Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-13		H	503.4	5.2
I-14		H	499.2	3.7
I-15		H	503.3	4.0
I-16		H	498.3	5.9
I-17		H	498.3	5.6
I-18		Cl	584.3	5.9 (B)
I-19		Cl	608.2	8.0
I-20		F	594.2	6.8
I-21		F	556.2	4.9
I-22		Me	590.2	4.4

Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-23		Me	608.2	5.2

[00691] Examples I-24 and I-25 (Table I-2) were prepared following the procedures described in Example 116 and 118 by replacing 2-methylbut-3-enoic acid with 3-methylbut-3-enoic acid.

Table I-2: Examples I-24 and I-25

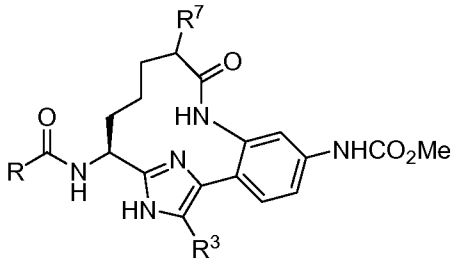


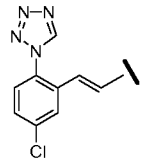
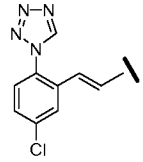
Ex. #	R^7	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-24	Me (homochiral)	590.3	5.0
I-25	Me (homochiral)	590.3	5.0

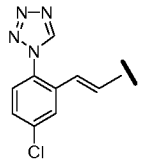
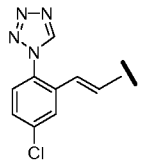
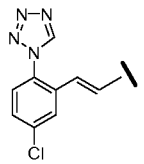
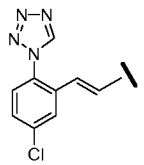
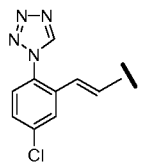
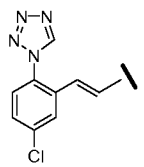
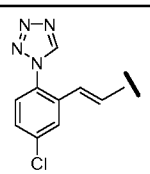
[00692] Examples I-26 to I-34 (Table I-3) were prepared following the general procedures described in Examples 116 and 118. Example I-26 and I-27 were prepared by replacing benzyl 2-methylbut-3-enoate with methyl 2-hydroxybut-3-enoate as described in Example 116C, followed by 116D, additional step of replacement of hydroxyl group with fluoride by DAST; followed by steps 116E; 116F; and 116I. Examples I-30 and I-31

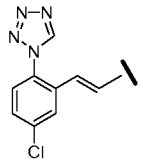
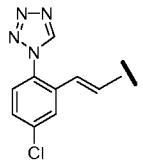
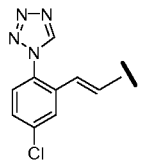
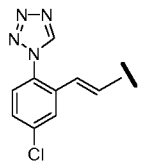
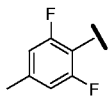
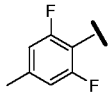
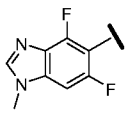
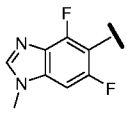
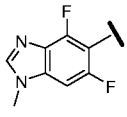
were prepared by replacing benzyl 2-methylbut-3-enoate with methyl 2-methoxybut-3-enoate as described in Example 116C. Examples I-28, I-29 and I-33 were prepared by replacing benzyl 2-methylbut-3-enoate with benzyl 2-ethylbut-3-enoate or benzyl 2-isopropylbut-3-enoate as described in Example 116C. Example I-32 was prepared by replacing benzyl 2-methylbut-3-enoate with methyl 2-hydroxybut-3-enoate as described in Example 116C; followed by 116D; additional step of oxidation of the hydroxyl group to the ketone by Dess-Martin's reagent followed by fluorination with DAST; followed by steps116E; 116F; and 116I. Examples I35-I38 were prepared by clorination of Examples 116G, 116H, I-33, and I-34 as described in Example 7. Examples I-39 to I-59 were prepared by coupling macrocyclic cores with appropriately substituted carboxylic acid derivatives (R-CO_2H) using coupling conditions described in step 15D. Example I-40, I-44, I-49 to I-51, I-54, I-55, I-57, I-59 were prepared by coupling macrocyclic core with an appropriately substituted carboxylic acid derivative (R-CO_2H) using coupling conditions described in step 15D followed by chlorination as described in Example 7.

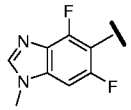
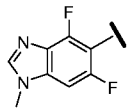
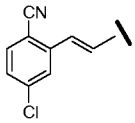
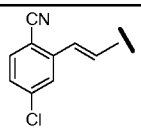
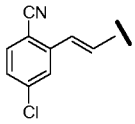
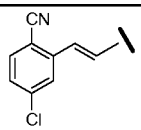
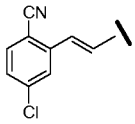
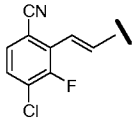
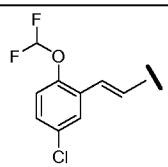
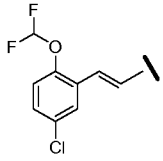
Table I-3: Examples I-26 to I-59

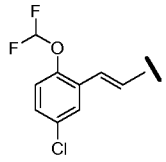
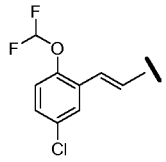
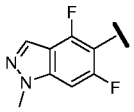
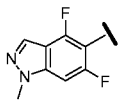
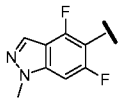
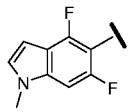


Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-26		F (homochiral)	H	593.9	3.7 (B)
I-27		F (homochiral)	H	593.9	3.6 (B)

Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-28		Et	H	604.1	4.2 (B)
I-29		Et	H	604.1	4.2 (B)
I-30		OMe (homochiral)	H	606.2	5.3
I-31		OMe (homochiral)	H	606.3	6.0
I-32		Bis-F	H	612.1	3.8 (B)
I-33		(diastereomer A)	H	618.3	4.5 (B)
I-34		(diastereomer B)	H	618.3	4.5 (B)

Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-35		Me	Cl	624.3	7.0
I-36		Me	Cl	624.3	6.7
I-37		(diastereomer B)	Cl	652.3	5.8 (B)
I-38		(diastereomer A)	Cl	652.3	5.8 (B)
I-39		Me	H	512.2	4.8
I-40		Me	Cl	546.2	6.9
I-41		Me	H	552.2	3.5
I-42		Me (diastereomer mixture)	H	552.4	3.3
I-43		(diastereomer A)	H	580.3	4.3

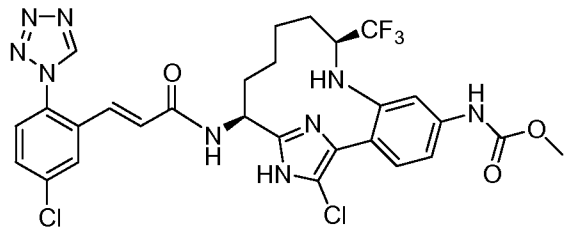
Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-44		Me (diastereomer mixture)	Cl	586.3	4.7 4.9
I-45		Me	H	552.3	2.9
I-46		Me	H	547.3	5.2
I-47		Et	H	561.3	5.7
I-48		(diastereomer A)	H	575.3	5.3 (B)
I-49		Me	Cl	581.3	7.5
I-50		Et	Cl	595.3	7.7
I-51		Me	Cl	599.2	7.8
I-52		Et	H	602.3	6.4
I-53		Me	H	588.2	5.9

Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-54		Me	Cl	622.3	7.9
I-55		Et	Cl	636.3	8.4
I-56		Me	H	552.3	3.8 (B)
I-57		Me	Cl	586.2	4.9 (B)
I-58		Et	H	566.4	4.6
I-59		Me	Cl	585.4	7.7

[00693] Example I-60 was prepared following the procedures described in Example 7, by replacing Example 6 with Example 154.

Example I-61.

{(9S,14S)-17-Chloro-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00694] I-61A and I-61AA. [(9S,14S)-17-Chloro-5-methoxycarbonylamino-9-trifluoromethyl-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester, 2TFA salt (I-61A) and [(9S,14S)-4,17-Dichloro-5-methoxycarbonylamino-9-trifluoromethyl-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester, 2TFA salt (I-61AA): To the solution of 154C (diastereomer A) (0.124 g, 0.145 mmol) in acetonitrile (1 mL)/chloroform (1.000 mL) was added NCS (0.029 g, 0.217 mmol) and DIPEA (0.076 mL, 0.435 mmol). The reaction mixture was stirred at rt for 44 h. Another NCS (0.029 g, 0.217 mmol) added. After another 2.5 h, the reaction mixture was concentrated. Purification by reverse phase chromatography gave 0.024 g (18.6 %) of I-61A as a yellow solid and 0.010 g (7.5%) of I-61AA as a white solid. For I-61A: MS (ESI) *m/z*: 662.4 $(M+H)^+$. For I-61AA: MS (ESI) *m/z*: 696.3 $(M+H)^+$.

[00695] I-61B. ((9S,14S)-14-Amino-17-chloro-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester, 3TFA salt: To the solution of I-61A (0.032 g, 0.036 mmol) in MeOH (0.5 mL) was added 5 N HCl (0.5 mL, 2.5 mmol) and methoxylamine hydrochloride (25-30 wt. % in water, 0.055 mL, 0.180 mmol). The reaction mixture was warmed to 75 °C for 1 h and then it was cooled to rt. Purification by reverse phase chromatography gave I-61B (0.02 g, 71.9 %) as a white solid. MS (ESI) *m/z*: 432.2 $(M+H)^+$.

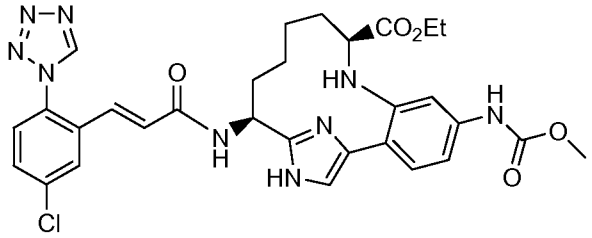
[00696] I-61C. Example I-61 was prepared following the procedure described in 15D, by replacing 15C with I-61B. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.98 (d, *J*=2.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.30 - 7.34 (m, 2 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.07 (dd, *J*=8.3, 2.2 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 5.14 (dd, *J*=10.6, 7.0 Hz, 1 H), 3.74 (s, 3 H), 2.84 - 2.92 (m, 1 H), 2.13 - 2.22 (m, *J*=13.0, 13.0, 7.1, 2.9 Hz, 1 H), 1.87 - 1.95 (m, 1 H), 1.63 - 1.81 (m, 2 H), 1.39 - 1.55 (m, 3 H), 0.44 -

0.55 (m, 1 H). ^{19}F NMR (471MHz, CD_3OD) δ -74.96, -77.49. MS (ESI) *m/z*: 664.3 $(M+H)^+$. Analytical HPLC, RT = 8.89 min.

[00697] Examples I-62 to I-64 were synthesized by coupling the amine 155A, with appropriately substituted carboxylic acid derivatives (R-CO_2H) using coupling conditions described in step 15D. In the case of Examples I-62 and I-63 an additional Boc-deprotection step as described in step 3C was required.

Example I-67.

(9S,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester, 2 TFA salt



[00698] I-67A. 2-{2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-5-methoxycarbonylamino-phenylamino}-pent-4-enoic acid ethyl ester. To a clear yellowish-brown solution of 10C (4.50 g, 8.46 mmol) and maleic acid (0.982 g, 8.46 mmol) in acetonitrile (33.9 mL) was added a 50% solution ethyl 2-oxoacetate in toluene (2.52 mL, 12.69 mmol) followed by allyltributyltin (4.72 mL, 15.23 mmol). The resulting orange solution was stirred vigorously. After 18 h, the reaction was diluted with EtOAc and then the reaction was washed with 1.0 N NaOH (75 mL x 2), brine, dried over Na_2SO_4, filtered and concentrated to give a viscous, orange oil. Purification by normal phase chromatography gave 3.96 g (76%) of I-67A as an orange foam. ^1H NMR indicated approximately a 1:1 mixture of diastereomers. MS (ESI) *m/z*: 658.4 $(M+H)^+$.

[00699] I-67B. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester (Diastereomer A), 2 TFA salt

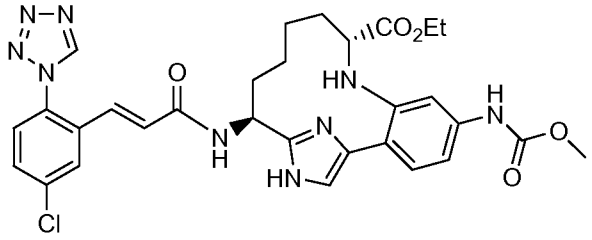
and I-67C. (9S,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester (Diastereomer B), 2 TFA salt.

[00700] Compounds I-67B (diastereomer A) and I-67C (diastereomer B) were prepared following the procedures described in I-74C, by replacing I-74B with I-67A; followed by step I-74D. The diastereomers were separated by reverse phase chromatography. MS (ESI) *m/z*: 632.5 $(M+H)^+$.

[00701] I-67D. Example I-67 was prepared following the procedures described in 154E, by replacing 154D with I-67C (diastereomer B); followed by step 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 9.39 (s, 1 H), 7.94 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 1 H), 7.51 (s, 1 H), 7.41 (s, 1 H), 7.28 - 7.35 (m, *J*=8.2 Hz, 1 H), 7.09 - 7.15 (m, 2 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.15 (t, *J*=6.6 Hz, 1 H), 3.96 - 4.12 (m, 2 H), 3.73 (s, 3 H), 3.09 (d, *J*=10.4 Hz, 1 H), 2.31 - 2.42 (m, 1 H), 1.94 - 2.07 (m, 1 H), 1.56 - 1.79 (m, 2 H), 1.44 - 1.55 (m, 3 H), 1.14 (t, *J*=7.2 Hz, 3 H), 0.54 - 0.66 (m, 1 H). MS (ESI) *m/z*: 634.3 $(M+H)^+$ and 636.2 $(M+2+H)^+$. Analytical HPLC (Method D): RT = 4.9 min.

Example I-68.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester, 2 TFA salt

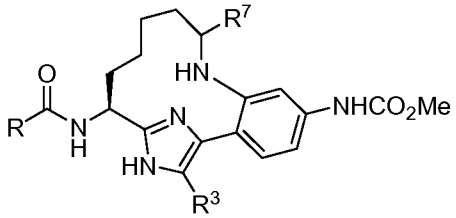


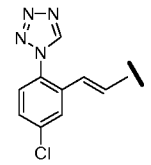
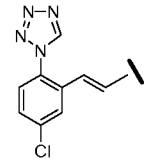
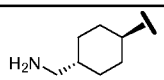
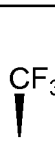
[00702] I-68A. (9R,14S)-14-Amino-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester: Compound I-68A was prepared following the procedure described in 154E, by replacing 154D with I-67B (diastereomer A). MS (ESI) *m/z*: 632.5 $(M+H)^+$.

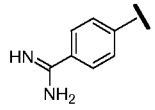
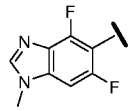
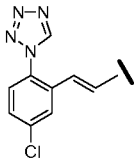
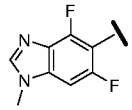
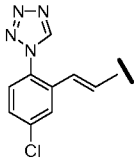
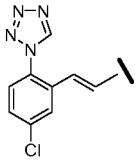
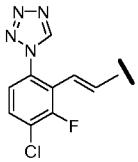
[00703] I-68B. Example I-68 was prepared following the procedures described in 15D, by replacing 15C with I-68A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 9.41 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.56 (s, 1 H), 7.44 (s, 1 H), 7.35 (d, *J*=8.2 Hz, 1 H), 7.12 - 7.19 (m, 2 H), 6.77 (dd, *J*=15.4, 2.2 Hz, 1 H), 5.20 - 5.30 (m, 1 H), 3.94 - 4.11 (m, 2 H), 3.74 (s, 3 H), 3.05 (d, *J*=10.4 Hz, 1 H), 2.22 - 2.37 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.72 - 1.93 (m, 2 H), 1.37 - 1.62 (m, 3 H), 1.12 (t, *J*=7.2 Hz, 3 H), 0.30 - 0.43 (m, 1 H). MS (ESI) *m/z*: 634.3 $(M+H)^+$ and 636.2 $(M+2+H)^+$. Analytical HPLC (Method D): RT = 5.2 min.

[00704] Example I-69 was prepared by following the procedure described in 15D, by replacing 15C with I-68A and by replacing Intermediate 2 with Intermediate 3A.

Table I-4: Examples I-60 to I-69



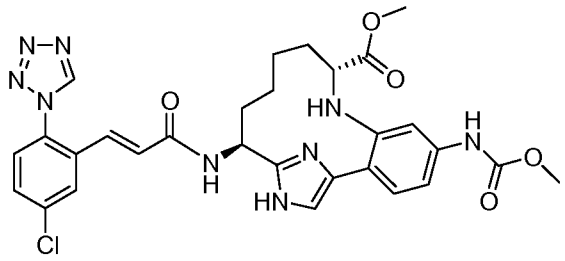
Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-60			Cl	664.1	8.6
I-61			Cl	664.3	8.9
I-62			H	537.2	3.8

Ex. #	R	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-63		CF_3	H	544.4	4.1
I-64		CF_3	H	592.3	4.4 (D)
I-65		CF_3	F	648.2	8.8
I-66		CF_3	F	610.2	7.1
I-67		CO_2Et	H	634.3	4.9 (D)
I-68		CO_2Et	H	634.3	5.2 (D)
I-69		CO_2Et	H	652.3	5.7 (D)

[00705] Examples I-72 and I-73 were prepared according to the procedures described for Example I-67, by replacing ethyl 2-oxoacetate with the appropriately substituted aldehydes.

Example I-74.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, 2 TFA salt



[00706] I-74A. (R)-2-(2-(2-((S)-1-(*tert*-Butoxycarbonylamino)but-3-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)-5-(methoxycarbonylamino)phenylamino)pent-4-enoic acid: A thick-walled flask was charged with 10B (5 g, 8.39 mmol), copper(I) iodide (0.160 g, 0.839 mmol), potassium carbonate (2.90 g, 20.99 mmol), (R)-2-aminopent-4-enoic acid (1.160 g, 10.07 mmol) and DMSO (16.8 mL). The flask was vacuumed and back-filled with argon three times and then the flask was sealed with a teflon screw cap. The reaction was capped, heated to 90 °C for 18 h, and then the reaction was cooled to RT. The reaction mixture was diluted with ethyl acetate and water and the layers were separated. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give I-74A (5.5 g, 83%) as a yellow solid. MS (ESI) *m/z*: 630.4 $(M+H)^+$. The material was carried onto the next step without further purification.

[00707] I-74B. (R)-2-{2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-5-methoxycarbonylamino-phenylamino}-pent-4-enoic acid methyl ester: To a solution of I-74A (5.5 g, 6.99 mmol) in DMF (100 mL) was added K_2CO_3 (0.966 g, 6.99 mmol) and MeI (0.437 mL, 6.99 mmol). The reaction was stirred at RT for 24 h. The reaction was partitioned between EtOAc and water and the layers were separated. The aqueous layer was extracted with EtOAc (1x). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave I-74B (2.36 g, 52.5%) as brown solid. MS (ESI) *m/z*: 644.5 $(M+H)^+$.

[00708] I-74C. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaene-9-carboxylic acid methyl ester: A solution of I-74B (0.4 g, 0.621 mmol), Grubbs (II) (0.211 g, 0.249 mmol) in DCE (15.53 ml) was heated in a microwave at 120 °C for 20 min. The reaction was cooled to RT. The same reaction was repeated eight more times. All nine reactions were combined, washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave I-74C (1.03 g, 30%) as a brown solid. MS (ESI) *m/z*: 616.5 $(M+H)^+$.

[00709] I-74D. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester (diastereomer A), 2 TFA salt and I-74E. (9S,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester (diastereomer B), 2 TFA salt. To the solution of I-74C (1.03 g, 1.673 mmol) in EtOAc (15 mL)/EtOH (5.00 mL) was added TFA (0.258 ml, 3.35 mmol) and 10% palladium on carbon (0.178 g, 0.167 mmol). Hydrogen was bubbled through the reaction mixture for 5 min. The reaction was stirred under a hydrogen balloon for 4 days. The reaction was filtered through a 0.45μm GMF containing CELITE®. The solid was rinsed with MeOH, and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave I-74D (0.3 g, 29.0% yield) as a yellow solid. MS (ESI) *m/z*: 618.4 $(M+H)^+$. A mixture of I-74D and I-74E (0.55 g) was also obtained as a yellow solid. This mixture was purified by reverse phase chromatography to give 0.325 g (23.0%) of I-74D (diastereomer A) as a white solid and 0.23 g (16.3%) I-74E (diastereomer B) as a white solid. For I-74D: MS (ESI) *m/z*: 618.5 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.73 (s, 1 H), 7.37 (d, J=1.9 Hz, 1 H), 7.30 (d, J=8.3 Hz, 1 H), 7.17 (dd, J=8.4, 2.1 Hz, 1 H), 5.66 (d, J=10.5 Hz, 1 H), 5.53 (d, J=10.5 Hz, 1 H), 5.12 (t, J=9.1 Hz, 1 H), 3.65 - 3.77 (m, 5 H), 3.51 (s, 3 H), 3.03 (d, J=10.7 Hz, 1 H), 2.07 - 2.16 (m, 2 H), 1.68 - 1.81 (m, 2

H), 1.31 - 1.55 (m, 12 H), 0.90 - 1.04 (m, 2 H), 0.26 - 0.38 (m, 1 H), 0.01 (s, 9 H). [α] = -6.9 (c = 1.23, MeOH).

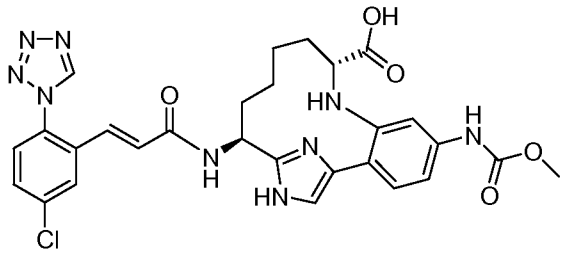
[00710] For I-74E: MS (ESI) *m/z*: 618.4 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.71 (s, 1 H), 7.39 (s, 1 H), 7.32 (d, J=8.3 Hz, 1 H), 7.13 - 7.17 (m, 1 H), 5.85 (d, J=10.7 Hz, 1 H), 5.51 (d, J=11.0 Hz, 1 H), 5.13 (t, J=6.3 Hz, 1 H), 3.70 - 3.76 (m, 5 H), 3.52 - 3.57 (m, 3 H), 3.09 (dd, J=9.4, 3.3 Hz, 1 H), 2.27 - 2.36 (m, 1 H), 1.91 - 2.00 (m, 1 H), 1.70 - 1.79 (m, 1 H), 1.31 - 1.69 (m, 13 H), 0.89 - 1.07 (m, 2 H), 0.43 - 0.54 (m, 1 H), 0.00 (s, 9 H).

[00711] I-74F. (9R,14S)-14-Amino-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: Compound I-74F was prepared following the procedure described in 154E, by replacing 154D with I-74D (diastereomer A). MS (ESI) *m/z*: 388.1 $(M+H)^+$.

[00712] I-74G. Example I-74 was prepared following the procedure described in 1G, by replacing 1F with I-74F. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.8, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.41 (d, J=2.2 Hz, 1 H), 7.35 (d, J=8.2 Hz, 1 H), 7.12 - 7.21 (m, 2 H), 6.76 (d, J=15.4 Hz, 1 H), 5.25 (dd, J=11.0, 7.1 Hz, 1 H), 3.75 (s, 3 H), 3.57 (s, 3 H), 3.07 (d, J=10.4 Hz, 1 H), 2.25 - 2.36 (m, 1 H), 1.97 - 2.06 (m, 1 H), 1.72 - 1.90 (m, 2 H), 1.38 - 1.62 (m, 3 H), 0.30 - 0.43 (m, 1 H). MS (ESI) *m/z*: 620.3 $(M+H)^+$. Analytical HPLC: RT = 5.66 min.

[00713] Example I-75 was prepared by following the procedure described in Example 7, by replacing Example 6 with Example I-74 and by running the reaction at rt in acetonitrile.

Example I-76.
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid, 2 TFA salt

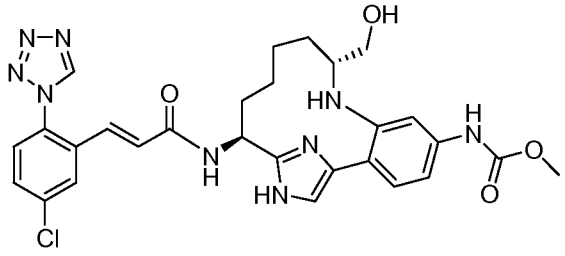


[00714] I-76A. (9R,14S)-14-Amino-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid, 3 HCl salt: To a clear, pale yellow solution of I-74F (0.079 g, 0.204 mmol) in MeOH (2.0 mL) was added 1N sodium hydroxide (0.408 ml, 0.408 mmol). The solution was stirred vigorously at 55 °C for 1.5 h, cooled to RT, acidified with 1.0 N HCl (1 mL), and concentrated to give I-76A (0.098 g, 0.187 mmol, 92 % yield) as an off-white solid. MS (ESI) *m/z*: 374.1 $(M+H)^+$. The material was carried onto the next step without further purification.

[00715] I-76B. Example I-76 was prepared following the procedure described in 1G, by replacing 1F with I-76A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.5, 2.2 Hz, 1 H), 7.58 (d, J=8.5 Hz, 1 H), 7.55 (s, 1 H), 7.40 (d, J=1.9 Hz, 1 H), 7.36 (d, J=8.5 Hz, 1 H), 7.21 (dd, J=8.4, 2.1 Hz, 1 H), 7.16 (d, J=15.7 Hz, 1 H), 6.76 (d, J=15.7 Hz, 1 H), 5.26 (dd, J=11.0, 7.2 Hz, 1 H), 3.74 (s, 3 H), 3.04 (d, J=10.2 Hz, 1 H), 2.26 - 2.35 (m, J=13.3, 13.3, 7.2, 3.0 Hz, 1 H), 1.98 - 2.06 (m, 1 H), 1.73 - 1.94 (m, 2 H), 1.44 - 1.63 (m, 3 H), 0.35 - 0.46 (m, 1 H). MS (ESI) *m/z*: 606.3 $(M+H)^+$. Analytical HPLC: RT = 5.47 min.

Example I-77.

{(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-hydroxymethyl-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt

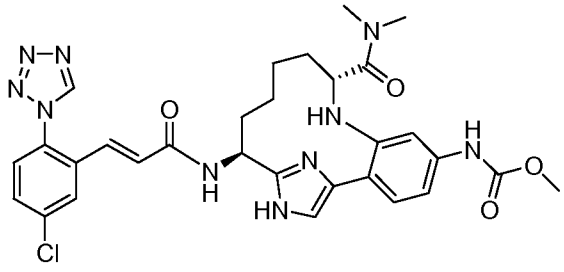


[00716] I-77A. [(9R,14S)-14-*tert*-Butoxycarbonylamino-9-hydroxymethyl-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl]-carbamic acid methyl ester: To a cooled (0 °C) solution of I-74D (0.22 g, 0.356 mmol) in THF (5 mL) was added LAH (0.178 ml, 0.356 mmol) (2M in THF). The reaction was allowed to stir at 0 °C. After 1 h, additional LAH (0.05 ml, 0.1 mmol) (2M in THF) was added. After an additional 1 h, the reaction was quenched with 1N HCl (aq, 1 mL). The reaction was diluted with EtOAc, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give 0.217 g (103%) of I-77A as a yellow solid. MS (ESI) *m/z*: 590.5 $(M+H)^+$. The material was carried onto the next step without further purification.

[00717] I-77B. Example I-77 was prepared following the procedures described in 154E, by replacing 154D with I-77A; followed by step 15D. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.99 (d, J=2.2 Hz, 1 H), 7.65 - 7.71 (m, 2 H), 7.53 - 7.61 (m, 2 H), 7.49 (s, 1 H), 7.30 (dd, J=8.5, 2.2 Hz, 1 H), 7.16 (d, J=15.7 Hz, 1 H), 6.77 (d, J=15.7 Hz, 1 H), 5.29 (dd, J=11.1, 6.7 Hz, 1 H), 3.76 (s, 3 H), 3.52 (dd, J=11.6, 4.7 Hz, 1 H), 3.39 - 3.43 (m, 1 H), 2.82 - 2.88 (m, 1 H), 2.16 - 2.26 (m, J=13.0, 13.0, 6.9, 3.4 Hz, 1 H), 1.98 - 2.09 (m, 2 H), 1.86 - 1.94 (m, 1 H), 1.44 - 1.64 (m, 3 H), 0.58 - 0.69 (m, 1 H). MS (ESI) *m/z*: 592.4 $(M+H)^+$. Analytical HPLC: RT = 5.62 min.

Example I-78.

{(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-dimethylcarbamoyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00718] I-78A. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid, 2 HCl salt: Compound I-78A was

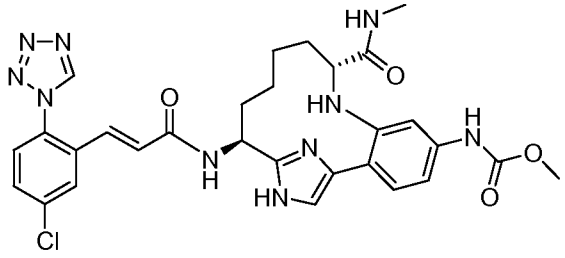
prepared by following the procedure described in I-76A, by replacing I-74F with I-74D. MS (ESI) *m/z*: 604.5 $(M+H)^+$. The material was carried onto the next step without further purification.

[00719] I-78B. [(9R,14S)-9-Dimethylcarbamoyl-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To the solution of I-78A (0.088 g, 0.074 mmol) in DMF (2 mL) was added EDC (0.028 g, 0.148 mmol), HOBT (0.023 g, 0.148 mmol), dimethylamine, HCl (7.26 mg, 0.089 mmol) and TEA (0.041 mL, 0.297 mmol). The reaction was stirred at RT. After18h, the reaction was diluted with EtOAc and then washed with water, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give 0.047 g (100%) of I-78B as a brown solid. MS (ESI) *m/z*: 631.5 $(M+H)^+$. The material was carried onto the next step without further purification.

[00720] I-78C. Example I-78 was prepared following the procedures described in 154E, by replacing 154D with I-78B; followed by step 1G. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.5, 2.2 Hz, 1 H), 7.56 - 7.63 (m, 2 H), 7.38 (d, J=8.5 Hz, 1 H), 7.29 (dd, J=8.3, 1.9 Hz, 1 H), 7.24 (d, J=1.4 Hz, 1 H), 7.16 (d, J=15.7 Hz, 1 H), 6.76 (d, J=15.7 Hz, 1 H), 5.27 (dd, J=11.3, 7.2 Hz, 1 H), 3.75 (s, 3 H), 3.52 (d, J=10.7 Hz, 1 H), 2.80 (s, 3 H), 2.66 (s, 3 H), 2.26 - 2.36 (m, 1 H), 1.87 - 2.06 (m, 2 H), 1.68 - 1.77 (m, 1 H), 1.56 - 1.66 (m, 1 H), 1.43 - 1.54 (m, 1 H), 1.25 - 1.33 (m, 1 H), 0.32 - 0.43 (m, 1 H). MS (ESI) *m/z*: 633.5 $(M+H)^+$. Analytical HPLC: RT = 6.64 min.

Example I-79.

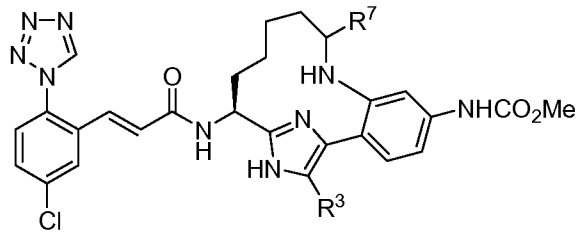
{(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-methylcarbamoyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



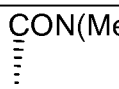
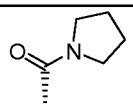
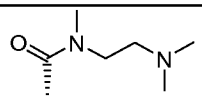
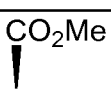
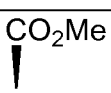
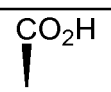
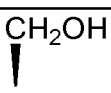
[00721] Example I-79 was prepared following the procedure described in 15D, by replacing Intermediate 2 with Example I-76 and by replacing15C with methanamine hydrochloride. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.5 Hz, 1 H), 7.68 (dd, J=8.5, 2.2 Hz, 1 H), 7.58 (d, J=8.5 Hz, 1 H), 7.53 (s, 1 H), 7.37 - 7.41 (m, 1 H), 7.25 - 7.29 (m, 2 H), 7.16 (d, J=15.7 Hz, 1 H), 6.76 (d, J=15.7 Hz, 1 H), 5.26 (dd, J=11.1, 7.0 Hz, 1 H), 3.74 (s, 3 H), 3.03 (dd, J=11.7, 1.5 Hz, 1 H), 2.57 (s, 3 H), 2.24 - 2.33 (m, 1 H), 1.76 - 2.03 (m, 3 H), 1.41 - 1.58 (m, 2 H), 1.26 - 1.34 (m, 1 H), 0.43 - 0.54 (m, 1 H). MS (ESI) *m/z*: 619.4 $(M+H)^+$. Analytical HPLC: RT = 4.78 min.

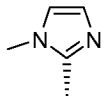
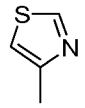
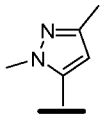
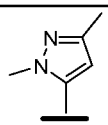
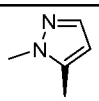
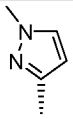
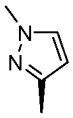
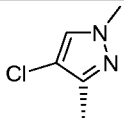
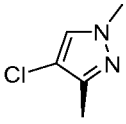
[00722] Examples I-80 and I-81 were prepared according to Example I-79 by replacing methanamine hydrochloride with the appropriately substituted amines. Examples I-82 to I-85 were prepared according to the procedures described for Examples I-74 to I-77. Examples I-86 to I-100 were prepared according to the procedures described for Example I-67, by replacing ethyl 2-oxoacetate with the appropriately substituted aldehydes. For the preparation of compounds I-99 and I-100, the Boc and SEM deprotection was accomplished by replacing the 4M HCl in dioxane, cysteine at 75 °C with 5M aqueous H_2SO_4, cysteine in methanol at 75 °C.

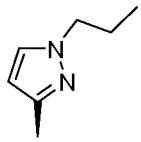
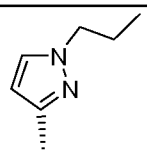
Table I-5: Examples I-70 to I-100



Ex. #	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-70		Me	644.4	6.3
I-71		Me	644.4	6.5

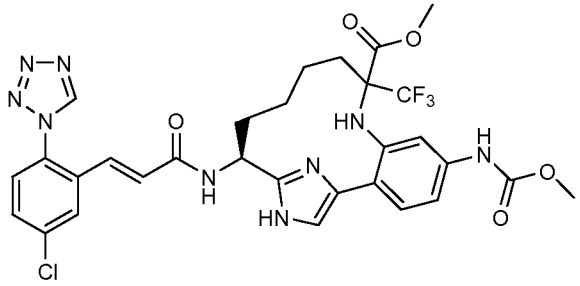
Ex. #	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-72		H	612.2	6.0
I-73		H	612.2	6.1
I-74		H	620.3	5.6
I-75		Cl	654.3	6.9 (D)
I-76		H	606.3	4.6
I-77		H	592.4	5.6
I-78		H	633.3	5.5
I-79		H	619.4	4.8
I-80		H	659.4	6.5 (D)
I-81		H	690.4	5.6 (D)
I-82		H	620.2	5.6
I-83		Cl	654.2	7.5
I-84		H	606.3	5.1
I-85		H	592.3	4.3

Ex. #	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-86		H	642.3	4.6
I-87	 (diastereomer mixture)	H	645.2	5.4 6.0
I-88	 (homochiral)	H	656.3	5.4
I-89	 (homochiral)	H	656.4	5.4
I-90		H	642.3	5.3
I-91		H	642.3	5.8
I-92		H	642.3	5.7
I-93		H	676.3	7.2
I-94		H	676.3	7.1

Ex. #	R^7	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-95		H	670.4	7.3
I-96		H	670.3	7.3
I-97	Me (diastereomer A)	H	576.3	5.6
I-98	Me (diastereomer B)	H	576.3	5.5
I-99	 (diastereomer B)	H	632.4	6.8
I-100	 (diastereomer A)	H	632.3	9.3

Example I-103.

(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-9-trifluoromethyl-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester



[00723] I-103A. 2-{(E)-2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-5-methoxycarbonylamino-phenylimino}-3,3,3-trifluoro-propionic acid methyl ester: To a solution of Example 10C (164 mg, 0.308 mmol), methyl 3,3,3-trifluoro-2-oxopropanoate (39 mg, 0.250 mmol) and triethylamine (95 µl, 0.679 mmol) in 1 ml Toluene (Volume: 1028 µl) at 0 °C under Ar was added titanium(IV) chloride (1M in DCM) (308 µl, 0.308 mmol) dropwise. After addition, the ice bath was removed and the reaction was stirred at rt overnight. The reaction mixture was quenched with 1N NaOH (aq), partitioned between water and DCM, DCM layer dried over $Na2SO_4$, filtered off solid, concentrated to yield an orange oil. Purification by normal phase chromatography gave I-103A (95 mg, 46%) as an orange solid. MS (ESI) *m/z*: 670.4 $(M+H)^+$.

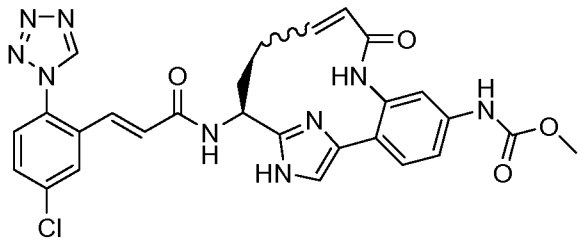
[00724] I-103B. 2-{2-[2-((S)-1-Amino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-5-methoxycarbonylamino-phenylamino}-2-trifluoromethyl-pent-4-enoic acid methyl ester: To a solution of I-103A (87 mg, 0.130 mmol) in CH_2Cl_2 (Volume: 2 mL) was added allyltrimethylsilane (0.15 mL, 0.940 mmol). The reaction was cooled down to -78 °C under Ar. Perchlorostannane (1M in DCM) (0.162 mL, 0.162 mmol) was added dropwise. After addition, the dry ice acetone bath was removed and the reaction was warmed up to rt and stirred for 2 days. The reaction mixture was concentrated under vacuo to yield a crude solid product. Purification by reverse phase chromatography gave I-103B (35 mg, 44%) as a pale yellow solid. MS (ESI) *m/z*: 612.3 $(M+H)^+$.

[00725] I-103C. 2-{2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-5-methoxycarbonylamino-phenylamino}-2-trifluoromethyl-pent-4-enoic acid methyl ester: To a solution of I-103B (35 mg, 0.057 mmol) in Dioxane (Volume: 0.3 mL) was added di-*tert*-butyl dicarbonate (0.020 mL, 0.086 mmol) and sodium hydroxide (1N in aq) (0.229 mL, 0.229 mmol). The reaction was stirred at RT for 3 hrs, diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by normal phase chromatography gave I-103C (20 mg, 49%) as a pale yellow solid. MS (ESI) *m/z*: 712.5 $(M+H)^+$.

[00726] I-103D. Example I-103 was prepared following the procedures described in I-74C by replacing I-74B with I-103C; followed by steps I-74D/I-74E; I-74F; I-74G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, *J*=1.9 Hz, 1 H), 7.67 (d, *J*=2.2 Hz, 1 H), 7.54 - 7.61 (m, 1 H), 7.36 (s, 3 H), 7.11 - 7.22 (m, 2 H), 6.71 - 6.81 (m, 1 H), 5.03 - 5.12 (m, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H), 2.77 - 2.90 (m, 1 H), 1.99 - 2.17 (m, 2 H), 1.55 - 1.73 (m, 2 H), 1.42 - 1.54 (m, 1 H), 0.93 - 1.07 (m, 1 H), 0.80 - 0.93 (m, 1 H). MS (ESI) *m/z*: 688.3 $(M+H)^+$.

Example I-106.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,10,15(18)-hexaen-5-yl}-carbamic acid methyl ester (90755-098)



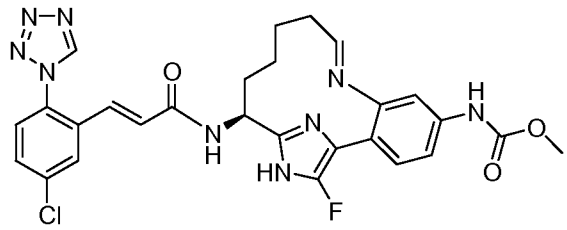
[00727] I-106A. [(S)-5-Methoxycarbonylamino-9-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,10,15(18)-hexaen-14-yl]-carbamic acid *tert*-butyl ester: To a solution of mixture of 152A,152B and 152C (20 mg, 0.034 mmol) in 0.5 ml DCM at -78 °C under Ar was added methanesulfonyl chloride (5.83 mg, 0.051 mmol) in 0.5 ml DCM dropwise. After 5 mins, triethylamine (10.29 mg, 0.102 mmol) was added dropwise. The reaction bath was replaced with ice-salt bath, gradually warmed up to 0 °C. The reaction mixture was partitioned between water and DCM. DCM layer washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by reverse phase chromatography gave I-106A (5.3 mg, 27%) as a pale yellow solid. MS (ESI) *m/z*: 572.3 $(M+H)^+$.

[00728] I-106B. Example I-106 was prepared following the procedures described in 1F, by replacing 1D with I-106A; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.65 - 9.77 (m, 1 H), 9.51 - 9.56 (m, 1 H), 7.92 - 8.06 (m, 1 H), 7.65 - 7.74 (m, 1 H), 7.56 - 7.64 (m, 2 H), 7.36 - 7.55 (m, 3 H), 7.18 - 7.28 (m, 1 H), 6.61 - 6.76 (m, 1 H), 5.21

- 5.48 (m, 1 H), 4.40 - 4.64 (m, 1 H), 3.74 - 3.80 (m, 3 H), 2.09 - 2.61 (m, 4 H). MS (ESI) *m/z*: 574.1 $(M+H)^+$. Analytical HPLC: RT = 3.91 min. (Method B).

Example I-107.

{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-fluoro-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,8,15(18)-hexaen-5-yl}-carbamic acid methyl ester, trifluoroacetic acid salt

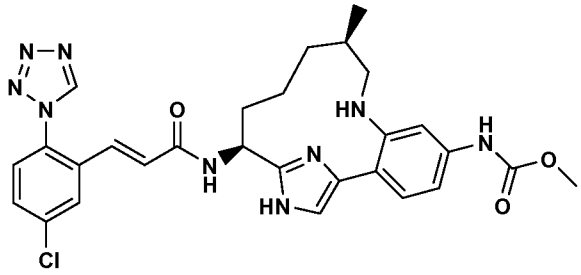


[00729] I-107A. ((E)-(S)-14-Amino-17-fluoro-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,8,15(18)-hexaen-5-yl)-carbamic acid methyl ester: To a yellow suspension of I-20B (18.67 mg, 0.043 mmol) in THF (4 mL) was added borane-THF complex (1M) (0.430 mL, 0.430 mmol) dropwise. It was sealed and heated at 60 °C for 1 hr and then cooled down to rt. To the solution was added MeOH, followed by 0.5 ml HCl (4M in dioxane). The reaction mixture was sealed and stored at rt overnight. The reaction mixture was then concentrated and purified by reverse phase chromatography to yield I-107A (4 mg, 25%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.31 (d, *J*=8.34 Hz, 1 H) 7.16 (d, *J*=1.52 Hz, 1 H) 6.79 (dd, *J*=8.46, 2.15 Hz, 1 H) 5.69 (dd, *J*=9.98, 3.41 Hz, 1 H) 4.69 (dd, *J*=11.37, 4.04 Hz, 1 H) 3.68 - 3.77 (m, 3 H) 2.11 - 2.32 (m, 1 H) 1.43 - 2.03 (m, 6 H) 0.68 - 0.97 (m, 1 H). MS (ESI) *m/z*: 329.3 $(M+H-NH_3)^+$.

[00730] I-107B. Example 1-107 was prepared following the procedures described in step 1G, by replacing 1F with I-107A. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H) 8.02 (d, *J*=2.26 Hz, 1 H) 7.66 (dd, *J*=8.53, 2.26 Hz, 1 H) 7.50 - 7.59 (m, 1 H) 7.27 (d, *J*=8.03 Hz, 1 H) 7.13 (d, *J*=15.56 Hz, 2 H) 6.73 - 6.90 (m, 2 H) 5.74 (br. s., 1 H) 5.18 (br. s., 1 H) 3.72 (s, 3 H) 2.03 - 2.19 (m, 1 H) 1.55 - 1.97 (m, 5 H) 1.07 - 1.23 (m, 2 H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -139.71 (br. s., 1 F). MS(ESI) *m/z*: 578.3 $(M+H)^+$.

Example I-109.

{(10R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-10-methyl-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2TFA salt



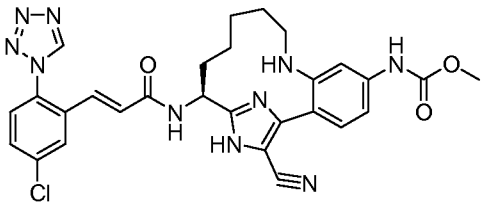
[00731] I-109A. ((10R,14S)-14-Amino-10-methyl-9-oxo-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester, 3 HCl salt: I-109A was prepared following the procedure described in 1F, by replacing 1D with 116G.

[00732] I-109B. ((10R,14S)-14-Amino-10-methyl-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl)-carbamic acid methyl ester, 3 TFA salt: To a yellow suspension of I-109A HCl salt (0.05 g, 0.116 mmol) in tetrahydrofuran (5 mL) was added Borane-THF complex (1M) (1.162 mL, 1.162 mmol), The reaction became clear colorless. It was sealed and heated at 60 °C for 1 hr before cooling down to rt. MeOH was added followed by addition of 1 ml HCl (4M in dioxane). The reaction was sealed and heated at 60 °C overnight. The reaction mixture was concentrated, dissolved in MeOH, filtered off solid. Purification by reverse phase chromatography gave I-109B (5.3 mg, 27%) as a pale yellow solid. MS (ESI) *m/z*: 344.3 $(M+H)^+$.

[00733] I-109C. Example I-109 was prepared following the procedures described in 1G, by replacing 1F with I-109B. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 8.03 (d, *J*=2.5 Hz, 1 H), 7.71 - 7.76 (m, 1 H), 7.69 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.61 (d, *J*=8.5 Hz, 1 H), 7.43 - 7.49 (m, 1 H), 7.23 - 7.32 (m, 3 H), 6.83 (d, *J*=15.7 Hz, 1 H), 5.31 (dd, *J*=11.3, 6.3 Hz, 1 H), 3.69 (s, 3 H), 3.02 - 3.04 (m, 1 H), 2.99 - 3.02 (m, 1 H), 2.67 - 2.74 (m, 1 H), 2.24 - 2.39 (m, 2 H), 2.05 - 2.15 (m, 1 H), 1.83 - 1.92 (m, 1 H), 1.54 - 1.65 (m, 1 H), 1.40 - 1.51 (m, 1 H), 0.96 (d, *J*=7.2 Hz, 3 H). MS (ESI) *m/z*: 576.2 $(M+H)^+$. Analytical HPLC: RT = 6.26 min.

Example I-115.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyano-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00734] I-115A. [(S)-5-Methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: I-115A was prepared from 10B following the procedures described in step 10C, by replacing ammonium hydroxide with but-3-enylamine and running the reaction at 90 °C; followed by steps 2E/F; and 10G, by adding 2 equiv. of TFA and replacing the methanol/EtOAc mixture with EtOAc. MS (ESI) *m/z*: 560.5 $(M+H)^+$.

[00735] I-115B. [(S)-5-Methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: A mixture of 115A (1.21 g, 2.162 mmol) and TEA (0.362 ml, 2.59 mmol) in EtOAc (10.81 ml) was cooled to 0 °C under Argon, and then TFAA (0.336 ml, 2.378 mmol) was added dropwise. After ~2 h at 0 °C, the reaction mixture was diluted with EtOAc, washed with water (2x) and brine, dried over $MgSO_4$, filtered, and concentrated. Residue was purified by flash column chromatography to yield I-115B as an off-white foam (1.14 g, 80%). MS (ESI) *m/z*: 656.5 $(M+H)^+$.

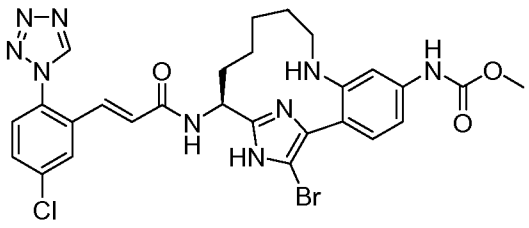
[00736] I-115C. [(S)-17-Bromo-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: To a cooled (< 0 °C) solution of I-115B (1.14 g, 1.738 mmol) in $CHCl_3$ (5.79 ml) was added NBS (0.325 g, 1.825 mmol). The reaction was stirred under argon at 0 °C for 20 min. Reaction mixture was evaporated and residue purified by flash column chromatography to yield I-115C as a light peach foam (1.3 g, 102%). MS (ESI) *m/z*: 734.5 $(M+H)^+$.

[00737] I-115D. [(S)-17-Cyano-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: In a microwave vial, I-115C (0.1 g, 0.136 mmol) was added to a solution of zinc cyanide (0.016 g, 0.136 mmol) in DMF (2.72 ml). The mixture was evacuated/flushed with Ar three times, and then tetrakis(triphenylphosphine)palladium(0) (7.86 mg, 6.81 μmol) was added. The vial was again evacuated/flushed with Ar three times, then capped and heated at 120 °C in the microwave for 20 min. Another 0.05 eq. of catalyst (7.86 mg) was added, the reaction vial was capped and evacuated/flushed with Ar three times, then heated at 120 °C in the microwave for another 20min. Reaction was evaporated to dryness and the residue was purified by normal phase chromatography to yield I-115D as a white foam, (0.088 g, 95%). MS (ESI) *m/z*: 681.5 $(M+H)^+$.

[00738] I-115E. Example I-115 was prepared from I-115D following the procedures described in step I-61B and 1G to provide Example 115 as a white solid (0.0077 g, 19.8%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.91 (1 H, s) 9.55 (1 H, d, *J*=1.10 Hz) 8.07 (1 H, br. s.) 8.02 (1 H, d, *J*=2.20 Hz) 7.97 (1 H, dd, *J*=8.25, 4.40 Hz) 7.69 (1 H, dd, *J*=8.80, 2.20 Hz) 7.59 - 7.63 (1 H, m) 7.41 (1 H, dd, *J*=8.80, 2.20 Hz) 7.19 - 7.25 (1 H, m) 6.83 (1 H, dd, *J*=15.95, 2.20 Hz) 5.29 (1 H, dd, *J*=11.00, 6.05 Hz) 3.76 (3 H, s) 3.28 (1 H, br. s.) 2.99 - 3.07 (1 H, m) 2.14 - 2.23 (1 H, m) 2.04 - 2.14 (2 H, m) 1.85 - 1.93 (1 H, m) 1.69 (2 H, t, *J*=12.92 Hz) 1.42 (1 H, t, *J*=9.62 Hz) 0.88 (1 H, q, *J*=11.18 Hz). MS (ESI) *m/z*: 587.3 $(M+H)^+$. Analytical HPLC: RT = 5.83 min.

Example I-116.

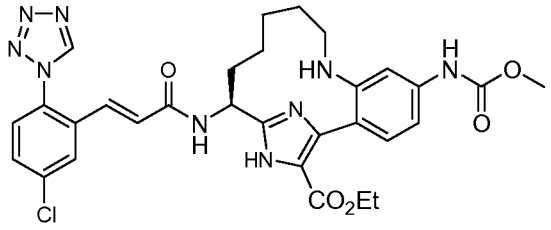
{(S)-17-Bromo-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA



[00739] Example I-116 was prepared from I-115C following the procedures described in step I-61B and 1G, as a white solid (0.046 g, 78%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.75 (1 H, s) 9.55 (1 H, s) 8.88 (1 H, d, *J*=4.40 Hz) 8.02 (1 H, d, *J*=2.20 Hz) 7.98 (1 H, d, *J*=8.80 Hz) 7.96 (1 H, br. s.) 7.70 (1 H, dd, *J*=8.80, 2.20 Hz) 7.60 - 7.64 (1 H, m) 7.33 (1 H, dd, *J*=8.80, 2.20 Hz) 7.24 (1 H, d, *J*=15.40 Hz) 6.81 (1 H, d, *J*=15.40 Hz) 5.22 (1 H, dd, *J*=11.00, 6.60 Hz) 3.73 (3 H, s) 3.19 - 3.25 (1 H, m) 2.95 (1 H, t, *J*=12.10 Hz) 2.10 - 2.19 (1 H, m) 1.97 - 2.09 (2 H, m) 1.82 - 1.91 (1 H, m) 1.68 (2 H, t, *J*=12.37 Hz) 1.37 (1 H, br. s.) 0.72 - 0.84 (1 H, m). MS (ESI) *m/z*: 640.3 $(M+H)^+$. Analytical HPLC: RT = 6.34 min.

Example I-118.

(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaene-17-carboxylic acid ethyl ester, 2 TFA

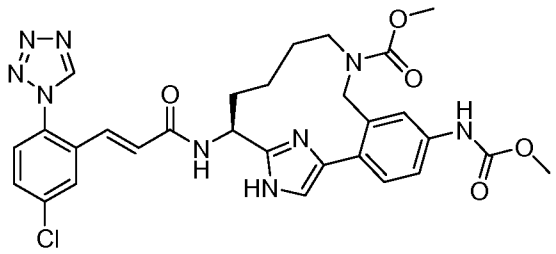


[00740] I-118A. (S)-14-Amino-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaene-17-carboxylic acid ethyl ester, 3TFA**:** I-115D (0.086 g, 0.126 mmol) was dissolved in EtOH (0.5 ml), and then concentrated H_2SO_4 (10.10 µl, 0.189 mmol) was added at room temperature. The reaction was refluxed at 90 °C under Ar overnight. Additional EtOH (2 mL) and conc. H_2SO_4 (0.2 mL) were added, and the reaction was heated at 90 °C for an additional 18 h then cooled to room temperature and poured into cold water. The aqueous layer was adjusted to pH ~10 with 1N NaOH and extracted 3x with EtOAc; the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by reverse phase HPLC to provide I-118A (0.019 g, 20.2 %). MS (ESI) *m/z*: 402.3 $(M+H)^+$.

[00741] I-118B. Example I-118 was obtained as a light yellow solid from I-118A following the procedure described in Step 1G (0.014 g, 58.5%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.78 (1 H, s) 9.52 (1 H, s) 8.32 (1 H, dd, *J*=8.67, 1.51 Hz) 8.03 (1 H, d, *J*=2.20 Hz) 8.01 (1 H, d, *J*=2.20 Hz) 7.68 (1 H, dd, *J*=8.39, 2.34 Hz) 7.60 (1 H, d, *J*=8.53 Hz) 7.32 (1 H, d, *J*=8.80 Hz) 7.19 (1 H, d, *J*=15.41 Hz) 6.80 (1 H, d, *J*=15.41 Hz) 5.32 (1 H, dd, *J*=10.04, 6.46 Hz) 4.32 - 4.41 (2 H, m) 3.77 (3 H, s) 3.21 (1 H, ddd, *J*=12.52, 4.13, 3.99 Hz) 2.93 - 3.03 (1 H, m) 2.09 - 2.19 (1 H, m) 1.81 - 2.05 (3 H, m) 1.68 (2 H, t, *J*=12.24 Hz) 1.37 (3 H, t, *J*=7.15 Hz) 1.30 (1 H, d, *J*=6.88 Hz) 0.69 - 0.81 (1 H, m). MS (ESI) *m/z*: 634.4 $(M+H)^+$. Analytical HPLC: RT = 6.46 min.

Example I-119.

(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-9,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, 1TFA salt



[00742] I-119A. {4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-formyl-phenyl}-carbamic acid methyl ester: To a solution of 10B (351 mg, 0.589 mmol) in THF (3 ml) at -78 °C was added methyllithium (0.786 ml, 1.179 mmol). The reaction was stirred at -78 °C for 30 min, then butyllithium (0.552 ml, 0.884 mmol) in hexanes was added dropwise. After 30 mins, DMF (0.055 ml, 0.707 mmol) was added to the reaction mixture. The reaction was stirred at -78 °C before it was quenched with conc. NH_4Cl (aq), extracted with ether (2x), combined ether layers was washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Purification by normal phase chromatography gave I-119A as a pale yellow foam (187 mg, 58%). MS (ESI) *m/z*: 545.2 $(M+H)^+$.

[00743] I-119B. {3-Allylaminomethyl-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid

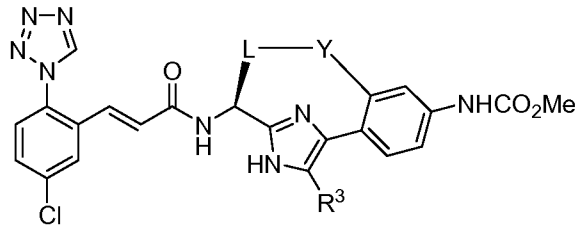
methyl ester: To a solution of I-119A (187 mg, 0.343 mmol) in DCM (3.433 ml) was added prop-2-en-1-amine (19.60 mg, 0.343 mmol) and a drop of AcOH. The reaction was stirred at rt for 30 min, sodium triacetoxyborohydride (109 mg, 0.515 mmol) was added. After 3 hrs, the reaction was diluted with DCM, washed with sat. Na_2CO_3, brine, dried over $MgSO_4$. Filtered and concentrated. Purification by normal phase chromatography gave I-119B as a white foam (145 mg, 72%). MS (ESI) *m/z*: 586.5 $(M+H)^+$.

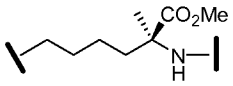
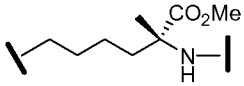
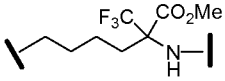
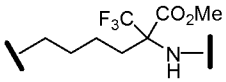
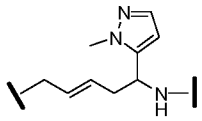
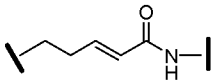
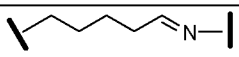
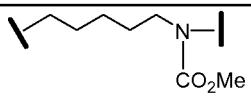
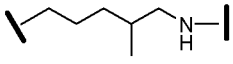
[00744] I-119C. [(S)-5-Methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-9,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: I-119C was prepared following the procedures described in 2E/2F, by replacing 2D with I-119B; followed by 2G. MS (ESI) *m/z*: 560.4 $(M+H)^+$.

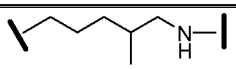
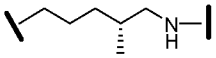
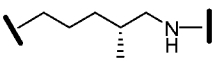
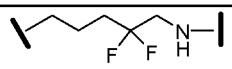
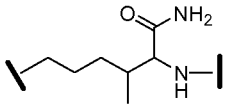
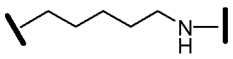
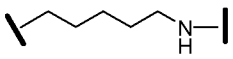
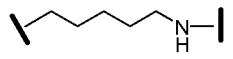
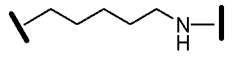
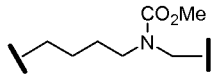
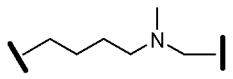
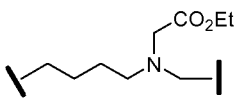
[00745] I-119D. (S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-9,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: To a solution of I-119C (14 mg, 0.021 mmol) in CH_2Cl_2 (Volume: 1 mL) was added methyl chloroformate (1.967 µl, 0.025 mmol) in 0.4 ml DCM, followed by TEA (0.014 mL, 0.099 mmol). The reaction was stirred at rt. for 30min. The reaction mixture was concentrated, redissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, filtered off solid, concentrated. Purification by normal phase chromatography gave I-119D as a white solid (7 mg, 55%). MS (ESI) *m/z*: 618.5 $(M+H)^+$.

[00746] I-119E. Example I-119 was prepared following the procedures described in 1F, by replacing 1D with I-119D; followed by 1G. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.51 - 9.53 (m, 1 H), 7.98 (d, *J*=2.5 Hz, 1 H), 7.67 - 7.72 (m, 2 H), 7.55 - 7.61 (m, 2 H), 7.49 (s, 1 H), 7.40 (d, *J*=8.2 Hz, 1 H), 7.18 (d, *J*=15.7 Hz, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 4.92 - 4.98 (m, 1 H), 4.31 - 4.52 (m, 1 H), 3.77 (s, 3 H), 3.62 - 3.65 (m, 2 H), 3.61 (s, 3 H), 3.04 - 3.18 (m, 1 H), 2.98 - 3.01 (m, 1 H), 2.13 - 2.28 (m, 1 H), 1.77 - 1.92 (m, 1 H), 1.51 - 1.69 (m, 1 H), 1.20 - 1.43 (m, 2 H). MS (ESI) *m/z*: 620.3 $(M+H)^+$. Analytical HPLC: RT = 4.56 min. (Method B).

Table I-6: Examples I-101 to I-121

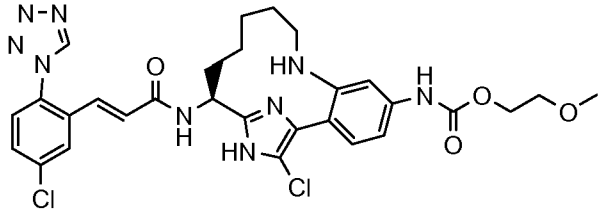


Ex. #	L-Y	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-101		H	634.3	4.5 (B)
I-102		H	634.3	5.0 (B)
I-103	 (homochiral)	H	688.3	5.1 (B)
I-104	 (homochiral)	H	688.3	5.8 (B)
I-105	 (diastereomer mixture)	H	640.2	5.4
I-106		H	573.9	3.9 (B)
I-107		F	578.3	8.6
I-108		H	620.2	5.5
I-109	 (diastereomer mixture)	H	576.3	4.8 (B)

Ex. #	L-Y	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-110	 (2:1 diastereomer mixture)	H	576.2	6.2
I-111		H	576.3	6.3
I-112		Cl	610.3	5.7 (B)
I-113		H	598.2	4.9 (B)
I-114	 (diastereomer mixture)	H	619.3	5.0
I-115		CN	587.3	5.8
I-116		Br	640.3	6.3
I-117		Me	576.4	5.8
I-118		CO_2Et	634.4	6.5
I-119		H	620.3	4.6 (B)
I-120		H	576.4	7.2
I-121		H	648.5	7.6

Example I-123.

{(S)-17-Chloro-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid 2-methoxy-ethyl ester, 2 TFA



[00747] I-123A. {(S)-1-[4-(4-Amino-2-bromo-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a stirred solution of 10B (1.5 g, 2.52 mmol) dissolved in MeOH (36 mL) was added 1N NaOH (50.4 mL, 50.4 mmol) dropwise at room temperature. The reaction was stirred at 85 °C under a reflux condenser overnight. Solvent was removed under reduced pressure and the residue was partitioned between EtOAc/water. Aqueous layer was extracted with EtOAc 3x, combined organic phases were washed with brine, dried with sodium sulfate, filtered and evaporated to yield the crude product, I-123A (1.42 g, 105%), as a yellow solid. MS (ESI) *m/z*: = 537.2 $(M+H)^+$.

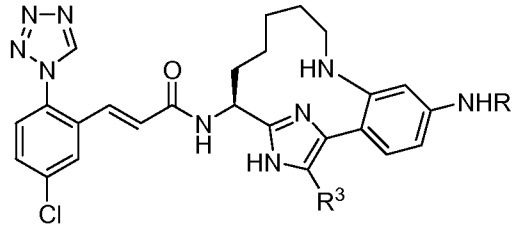
[00748] I-123B. {3-Bromo-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester: I-123A (1.42 g, 2.64 mmol) was dissolved in DCM (26.4 ml). Pyridine (0.855 ml, 10.57 mmol) was added followed by dropwise addition of 2-methoxyethyl carbonochloridate at 0 °C. The reaction was allowed to warm to RT and stirred ON. Another 2 equiv. of 2-methoxyethyl carbonochloridate (0.439 g, 3.17 mmol) was added and stirring was continued at RT for 2 hours. The reaction was quenched with sat.'d sodium bicarbonate and extracted with EtOAc 3x. Combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated. Crude product was purified by silica gel chromatography to provide I-123B (1.23 g, 72.8 %) as a yellow, oily solid. MS (ESI) *m/z*: = 639.3/641.3 $(M+H)^+$.

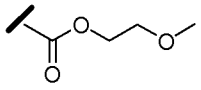
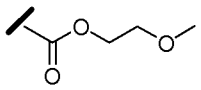
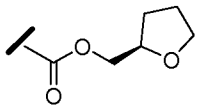
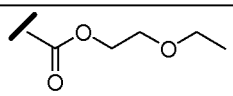
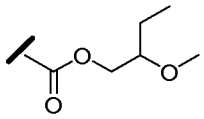
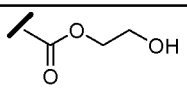
[00749] I-123C. {(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid 2-methoxy-ethyl ester: I-123C was prepared from I-123B using the procedures

described for 115A, 61B and 1G. Crude product was used without purification in the next step. MS (ESI) *m/z*: = 606.4 $(M+H)^+$.

[00750] I-123D. Example I-123: I-123C (.085 g, 0.140 mmol) was dissolved in acetonitrile (1 ml)/chloroform (1 ml) and TFA (0.086 ml, 1.122 mmol) was added followed by NCS (0.022 g, 0.168 mmol),and the mixture was stirred at 65 °C under Ar for 1.75 h. Reaction was diluted with water and extracted with EtOAc 2x. Combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by reverse phase chromatography to provide Example I-123 (0.056 g, 44.6%) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.79 (1 H, br. s.), 9.54 (1 H, s), 8.90 (1 H, d, *J*=5.50 Hz), 8.02 (1 H, d, *J*=2.20 Hz), 7.93 (1 H, br. s.), 7.86 (1 H, d, *J*=8.80 Hz), 7.67 - 7.72 (1 H, m), 7.58 - 7.64 (1 H, m), 7.32 (1 H, dd, *J*=8.80, 2.20 Hz), 7.18 - 7.28 (1 H, m), 6.81 (1 H, d, *J*=15.95 Hz), 5.20 (1 H, dd, *J*=11.27, 6.32 Hz), 4.17 - 4.29 (2 H, m), 3.61 (2 H, t, *J*=4.67 Hz), 3.37 (3 H, s), 3.18 - 3.26 (1 H, m), 2.90 - 3.02 (1 H, m), 1.94 - 2.21 (3 H, m), 1.78 - 1.91 (1 H, m), 1.62 - 1.74 (2 H, m), 1.30 - 1.45 (1 H, m), 0.72 - 0.91 (1 H, m). MS (ESI) *m/z*: = 640.3 $(M+H)^+$. Analytical HPLC: RT = 5.9 min.

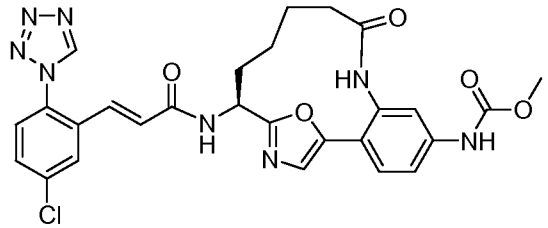
Table I-7: Examples I-122 to I-127



Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min)
I-122		H	606.3	6.2
I-123		Cl	640.3	5.9
I-124		H	632.4	5.9
I-125		H	620.4	5.9
I-126		H	634.4	6.3
I-127		H	592.4	5.2

Example I-134.

Methyl N-[(14S)-14-[(2E)-3-[5-chloro-2-(1H-1,2,3,4- tetrazol-1-yl)phenyl]prop-2-enamido]-9-oxo-18-oxa- 8,16-diazatricyclo[13.2.1.$0^{2,7}$]octadeca- 1(17),2(7),3,5,15-pentaen-5-yl]carbamate, trifluoroacetic acid salt



[00751] I-134A. Methyl 4-(2-aminoacetyl)-3-bromophenylcarbamate: To a solution of Intermediate 8 (3.0 g, 8.55 mmol) in acetonitrile (40 mL) was added sodium diformylamide (0.975 g, 10.26 mmol). The suspension was stirred under argon at RT for 5 hrs. The mixture was filtered and the solid was washed with warm MeCN. The filtrate was concentrated to give a tan solid. Next, aq. 4 N HCl (25 mL) was added and the resulting suspension was warmed to reflux. After 2 h, the clear reaction was cooled to RT and the solution was concentrated to give 2.45 g (100%) of I-134A as a light tan solid. MS (ESI) *m/z*: 287.0 $(M+H)^+$ and 288.9 $(M+2+H)^+$.

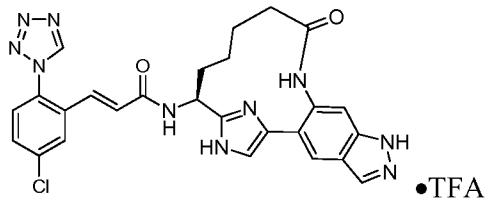
[00752] I-134B. *tert*-Butyl N-[(1S)-1-[(2-{2-bromo-4-[(methoxycarbonyl)amino]phenyl}-2-oxoethyl)carbamoyl]but-3-en-1-yl]carbamate: To a solution of (S)-2-(*tert*-butoxycarbonylamino)pent-4-enoic acid (515 mg, 2.393 mmol) in DMF (15 mL) was added HOBt (476 mg, 3.11 mmol) and EDC (596 mg, 3.11 mmol). After 5 min, a solution of I-134A (774 mg, 2.393 mmol) and DIEA (0.418 ml, 2.393 mmol) in DMF (5 mL) was added. The reaction was stirred under argon at RT for 2 h. The reaction mixture was diluted with EtOAc, washed with 1M HCl, sat $NaHCO_3$ and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography gave 1.05 g (91%) of I-134B as a tan solid. MS (ESI) *m/z*: 484.0 $(M+H)^+$ and 485.9 $(M+2+H)^+$.

[00753] I-134C. *tert*-Butyl N-[(1S)-1-(5-{2-bromo-4-[(methoxycarbonyl)amino]phenyl}-1,3-oxazol-2-yl)but-3-en-1-yl]carbamate: A solution of I-134B (900 mg, 1.858 mmol) and Burgess reagent (1771 mg, 7.43 mmol) in THF(10 mL) was microwaved at 120 °C for 12 min. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography which gave 398 mg (46%) of I-134C as a solid. MS (ESI) *m/z*: 466.0 $(M+H)^+$ and 468.0 $(M+2+H)^+$.

[00754] I-134D. Example I-134 was prepared following the procedures described in 10C (alternative), by replacing 10B with I-134C; followed by steps 10D; 2E/2F, by replacing DCM with DCE and running the reaction at 70 °C; 2G; 3C; and 1G. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.72 (1 H, s), 9.70 (1 H, s), 9.59 (1 H, s), 8.64 (1 H, d, J=7.53 Hz), 7.78 (1 H, d, J=2.01 Hz), 7.60 (1 H, dd, J=8.53, 2.26 Hz), 7.57 (1 H, d,

J=8.53 Hz), 7.38 (1 H, d, J=8.53 Hz), 7.27 (1 H, dd, J=8.66, 1.88 Hz), 7.16 (1 H, d, J=1.76 Hz), 7.13 (1 H, s), 6.75 (1 H, d, J=15.56 Hz), 6.68 (1 H, d, J=15.56 Hz), 4.91 - 5.02 (1 H, m), 3.53 (3 H, s), 1.84 - 1.94 (1 H, m), 1.73 - 1.84 (1 H, m), 1.60 - 1.73 (2 H, m), 1.40 - 1.54 (1 H, m), 1.12 - 1.25 (1 H, m), 0.73 - 0.91 (1 H, m). MS (ESI) *m/z*: 577.2 $(M+H)^+$. Analytical HPLC: RT = 6.39 min.

Example I-136.



•TFA

[00755] I-136A. 5-Bromo-6-nitro-1H-indazole: A solution of sodium nitrite (2.189 g, 31.7 mmol) in water (6.29 mL) was added dropwise to a solution of 4-bromo-2-methyl-5-nitroaniline prepared according to *J. Org. Chem.*, 44:4609 (1979) (7.33 g, 31.7 mmol) in glacial acetic acid (793 ml), and the reaction mixture was stirred under argon at room temperature overnight. The mixture was concentrated to give an oily residue. Water was added to precipitate the crude product which was collected via filtration and washed with water, then dried *in vacuo* to yield an orange solid. The solid was dried by lyophilization to yield I-136A (6.77 g, 88%). $(M+H)^+$ MS (ESI) *m/z*: 242.1 $(M+H)^+$.

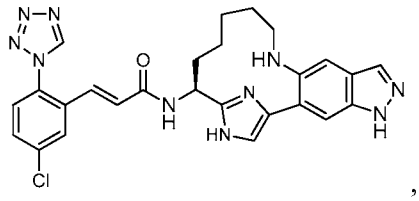
[00756] I-136B. 5-(1-Ethoxyvinyl)-6-nitro-1H-indazole: A solution of I-136A (7.65 g, 31.6 mmol), tributyl(1-ethoxyvinyl)stannane (12.81 ml, 37.9 mmol), and $(Ph_3P)_2PdCl_2$ (1.109 g, 1.580 mmol) in toluene (63.2 ml) was heated at 115 °C under Ar. The reaction was cooled to room temperature and filtered. The filtrate was concentrated and dried under vacuum to yield a dark brown oil, which was dissolved in DCM and absorbed on a dry pad of silica gel. The pad was washed sequentially with Hex and EtOAc. The EtOAc fraction was condensed to a dark brown oil, which was further purified by normal phase chromatography to provide an ~3:1 mixture of SM to product. This mixture was dissolved in dioxane, and tributyl(1-ethoxyvinyl)stannane (3.46 ml, 10.23 mmol), CuI (0.162 g, 0.852 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.492 g, 0.426 mmol) were added. The mixture was degassed and then heated at 110 °C under Ar for 3 hrs, then allowed to sit at rt overnight. The reaction mixture was filtered and solids washed with EtOAc. Filtrate was stripped to a brown oil which was purified by flash

chromatography to yield I-136B as an orange oil, (1.93 g, 61.1%). MS (ESI) *m/z*: 234.1 $(M+H)^+$.

[00757] I-136C. 2-Bromo-1-(6-nitro-1H-indazol-5-yl)ethanone: To a soln of I-136B (1.39 g, 5.96 mmol) in THF (8.83 ml) and water (3.09 ml) was added NBS (1.061 g, 5.96 mmol). The reaction was stirred at rt for ~45 min, then partitioned between EtOAc/brine. The brine layer was re-extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$, filtered, concentrated, and dried under vacuum to yield an 2.01 g of an orange solid which was combined with 0.698 g from a second prep and dissolved in a small amount of methylene chloride. The insoluble tan solid was filtered off to provide 0.381 g (16.6%) of product. The filtrate was purified by normal phase chromatography to provide and additional 0.783 of I-136C (34%). MS (ESI) *m/z*: 284.1 $(M+H)^+$.

[00758] Example I-136D. The title compound was prepared from I-136C following the procedures described for 2A; 1B; 10B; 122C; 10D; 2E; 2G; 10H; and 1G. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 14.27 (1 H, br. s.) 13.26 (1 H, s) 9.86 (1 H, s) 9.63 (1 H, br. s.) 8.89 (1 H, br. s.) 8.17 (1 H, s) 7.99 (1 H, s) 7.92 (1 H, d, *J*=2.20 Hz) 7.72 - 7.80 (2 H, m) 7.64 (1 H, br. s.) 7.43 (1 H, br. s.) 6.91 - 6.97 (1 H, m) 6.80 - 6.85 (1 H, m) 5.04 (1 H, dt, *J*=9.83, 4.85 Hz) 2.34 - 2.40 (1 H, m) 2.10 (1 H, br. s.) 2.00 (1 H, br. s.) 1.82 (1 H, br. s.) 1.63 (1 H, br. s.) 1.39 (1 H, br. s.) 1.28 (1 H, br. s.) 0.89 (1 H, br. s.). MS (ESI) *m/z*: 543.3 $(M+H)^+$. Analytical HPLC: RT = 4.8 min.

Example I-140.



, 2TFA

[00759] I-140A. 3-Amino-N-methoxy-N,4-dimethylbenzamide: 3-amino-4-methylbenzoic acid (5.0 g, 33.1 mmol) was dissolved in DMF (165 ml) and TEA (23.05 ml, 165 mmol), EDC (7.93 g, 41.3 mmol), HOBT (6.33 g, 41.3 mmol), and N,O-dimethylhydroxylamine hydrochloride (8.07 g, 83 mmol) were added. The reaction was stirred under Ar at room temperature overnight. The mixture was diluted with EtOAc and washed 3x with water. The combined aq. washes were re-extracted with EtOAc.

The organic layers were combined and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The resulting orange residue was purified by normal phase chromatography to yield the product as a colorless oil (2.87 g, 44.7%). MS (ESI) *m/z*: 195.1 *m/z* $(M+H)^+$.

[00760] I-140B. 5-Amino-2-bromo-N-methoxy-N,4-dimethylbenzamide: NBS (2.52 g, 14.16 mmol) was added to a solution of I-140A (2.75 g, 14.16 mmol) in DMF (28.3 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted 3x with EtOAc. The organic extracts were combined and washed with brine, then dried over $MgSO_4$, filtered, and evaporated. Residue was dissolved in a small amount of methylene chloride and the precipitate was filtered off to provide product as a white solid (1.53 g, 39.6%). The filtrate was purified by normal phase chromatography to provide additional product (1.13g, 29.2%). MS (ESI) *m/z*: 273.1 *m/z* $(M+H)^+$.

[00761] I-140C. 5-Bromo-N-methoxy-N-methyl-1H-indazole-6-carboxamide: This compound was prepared from I-140B (2.66 g, 9.74 mmol) following the procedure described for step I-136A The product was isolated as a yellow solid (2.55g, 92%). MS (ESI) *m/z*: 284.1 *m/z* $(M+H)^+$.

[00762] I-140D. *tert*-Butyl 5-bromo-6-(methoxy(methyl)carbamoyl)-1H-indazole-1-carboxylate: A solution of I-140C (2.55 g, 8.98 mmol), $(Boc)O_2$ (4.79 ml, 20.64 mmol), TEA (5.00 ml, 35.9 mmol), and DMAP (0.658 g, 5.39 mmol) in THF (44.9 ml) was stirred under Ar at rt overnight. The reaction mixture was concentrated to remove THF and partitioned between EtOAc and saturated aq. NH_4Cl solution. Layers were separated, and aqueous phase re-extracted with EtOAc. The org layers were combined and washed with brine, then dried over $MgSO_4$, filtered, and evaporated. Crude product was purified by normal phase chromatography to provide I-140D as a light yellow foam (3.23 g, 94%). MS (ESI) *m/z*: 384.1 *m/z* $(M+H)^+$

[00763] I-140E. 1-(5-Bromo-1H-indazol-6-yl)ethanone: To a solution of I-140D (3.1 g, 8.07 mmol) in THF (81 ml) in a 3-neck rbf at 0 °C was added 4 eq. of methylmagnesium bromide (1.4 M in THF:Toluene, 23.05 ml, 32.3 mmol) dropwise over 20min. The resulting yellow soln was stirred under argon at 0 °C. After ~1.5 hrs from the start of the addition an additional 3 eq of methylmagnesium bromide (1.4 M in

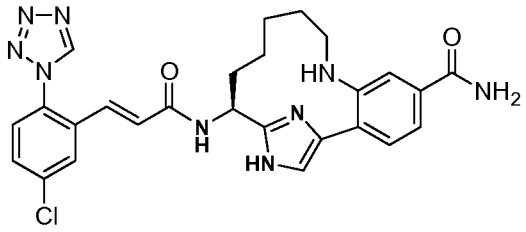
THF:Toluene, 17.29 ml, 24.20 mmol) was added dropwise to the cold soln. The mixture was then stirred under Ar overnight allowing the reaction to gradually assume room temperature. Another 1.5 eq. of methylmagnesium bromide (1.4 M in THF:Toluene. 8.64 ml, 12.10 mmol) was then added dropwise over ~10min at rt, and the reaction was stirred at rt under Ar for an additional 3 h prior to workup. The reaction was quenched at 0 °C with MeOH followed by a little water, then diluted with EtOAc. The suspension was adjusted to pH5 to dissolve the solids and then evaporated to remove THF. Additional EtOAc was added, and organics were washed with dilute aq. acid (pH ~5), sat. $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by normal phase chromatography to provide I-140E as a white solid (1.45 g, 75%). MS (ESI) *m/z*: 239.1 *m/z* $(M+H)^+$

[00764] I-140F. 2-Bromo-1-(5-bromo-1H-indazol-6-yl)ethanone: I-140E (1.45 g, 6.07 mmol) was taken up in THF (30.3 ml), and pyridinium tribromide (1.959 g, 6.13 mmol) was added. The mixture was stirred under Ar at rt for 15min then at 40 °C for 20min. The reaction was evaporated and the resulting pale yellow solid was partitioned between EtOAc/water. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography to provide the desired monobromoproduct, I-140F (1.14 g, 59%). MS (ESI) *m/z*: 319.0 *m/z* $(M+H)^+$

[00765] Example I-140. The title compound was prepared from I-140F following the procedures described for steps 2A; 1B; 10B; 10C by substituting 3-butenamine for ammonium hydroxide; 2E/F; 154C/D; I-61B; and 1G. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.56 (1 H, s) 8.18 (1 H, d, *J*=1.10 Hz) 8.02 (1 H, d, *J*=2.75 Hz) 7.79 (1 H, s) 7.69 (1 H, dd, *J*=8.80, 2.20 Hz) 7.62 (1 H, d, *J*=8.25 Hz) 7.60 (1 H, br. s.) 7.51 (1 H, s) 7.25 (1 H, d, *J*=15.40 Hz) 6.85 (1 H, d, *J*=15.95 Hz) 5.28 (1 H, dd, *J*=11.00, 6.60 Hz) 3.20 (1 H, d, *J*=12.65 Hz) 2.94 (1 H, t, *J*=12.37 Hz) 2.13 - 2.22 (1 H, m) 2.09 (2 H, t, *J*=12.65 Hz) 1.86 - 1.94 (1 H, m) 1.61 - 1.79 (2 H, m) 1.30 - 1.40 (1 H, m) 0.73 (1 H, d, *J*=12.65 Hz). MS (ESI) *m/z*: 529.4 *m/z* $(M+H)^+$. Analytical HPLC: RT = 5.43 min.

Example I-141.

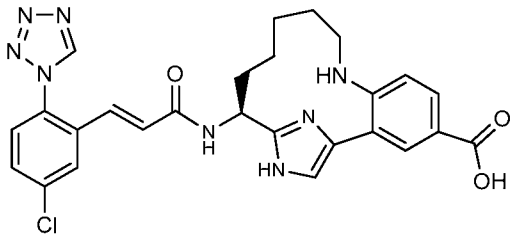
(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-5-carboxylic acid amide, 2 TFA



[00766] I-141-A. (S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-5-carboxylic acid, 2 TFA: I-141A was prepared following the procedures described for Example 142 substituting 3-bromo-4-methylbenzoic for 4-bromo-3-methylbenzoic acid. MS (ESI) *m/z*: 533.3 *m/z* $(M+H)^+$.

[00767] Example I-141. I-141A (.012 g, 0.016 mmol) was dissolved in DMF (1 mL). Hunig's base (0.028 mL, 0.158 mmol) was added, followed by ammonium chloride (8.43 mg, 0.158 mmol), HOBT (2.90 mg, 0.019 mmol) and EDC (3.63 mg, 0.019 mmol). The reaction was stirred at room temperature for 48 h, stripped to dryness, and residue purified by reverse phase chromatography to provide the title compound as a white solid. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.53 (1 H, s), 8.87 (1 H, d, *J*=5.50 Hz), 8.00 (1 H, d, *J*=2.20 Hz), 7.91 - 7.98 (2 H, m), 7.86 (1 H, d, *J*=7.70 Hz), 7.65 - 7.70 (2 H, m), 7.59 (1 H, d, *J*=8.25 Hz), 7.18 (1 H, d, *J*=15.40 Hz), 6.80 (1 H, d, *J*=15.95 Hz), 5.30 (1 H, dd, *J*=10.72, 6.32 Hz), 3.24 - 3.29 (1 H, m), 2.95 - 3.06 (1 H, m), 1.98 - 2.22 (3 H, m), 1.80 - 1.96 (1 H, m), 1.58 - 1.78 (2 H, m), 1.24 - 1.44 (1 H, m), 0.76 - 1.00 (1 H, m). MS (ESI) *m/z*: 532.4 $(M+H)^+$. Analytical HPLC: RT = 4.94 min.

Example I-142.
(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-4-carboxylic acid, 2TFA



[00768] I-142A. *tert*-Butyl 4-bromo-3-methylbenzoate: To a suspension of 4-bromo-3-methylbenzoic acid (2.8 g, 13.02 mmol) in THF (20 mL) and hexane (20 mL) in an ice bath under N_2, was added *tert*-butyl 2,2,2-trichloroacetimidate (3.50 mL, 19.53 mmol). After 10 min, BF_3•OEt_2 (0.165 mL, 1.302 mmol) was added. The resulting mixture was allowed slowly to warm to rt and stirred overnight. The mixture was diluted with Et_2O, washed with 1.5 M K_2HPO_4 solution, dried over anh. Na_2SO_4, filtered and evaporated. The residue was triturated with 20% Et_2O/hexane, and the solid was filtered off. Filtrate was evaporated. Residue was purified by flash chromatography to provide I-142A as a light peach color oil (2.141 g, 60.6%). MS (ESI) *m/z*: 293.1/295.1 $(M+Na)^+$ 271.2/273.1 $(M+H)^+$ 215,1/217.1 $(M+H\text{-}tBu)^+$.

[00769] I-142B. *tert*-Butyl 4-bromo-3-formylbenzoate: I-142A (2.14 g, 7.89 mmol) was dissolved in CCl_4 (39.5 ml) and NBS (3.09 g, 17.36 mmol) and benzoyl peroxide (0.191 g, 0.789 mmol) were added. The mixture was stirred under nitrogen at reflux in a 90 °C oil bath overnight. Reaction was diluted with EtOAc and washed with water and brine, dried over anh. Na_2SO_4, filtered and evaporated. Crude product (3.39 g, 7.90 mmol) was dissolved in morpholine (10 ml, 115 mmol), and the mixture was heated with stirring in a 60 °C oil bath under nitrogen overnight. After cooling to room temperature, the mixture was diluted with EtOAc, then stirred for ~30 min. Solids were removed by filtration and washed with EtOAc. The filtrate was transferred to a separatory funnel and washed 3X with 5% aq. citric acid and once with brine, then dried over anh. Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography to provide I-142B as a white solid (1.885 g, 84%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 10.39 (1 H, s) 8.47 (1 H, d, J=2.20 Hz) 8.05 (1 H, dd, J=8.25, 2.20 Hz) 7.73 (1 H, d, J=8.53 Hz) 1.61 (9 H, s).

[00770] I-142C. *tert*-Butyl 4-bromo-3-(1-hydroxyethyl)benzoate: I-142B was dissolved in THF (50 mL) and cooled in a dry ice/acetone bath. To the cold solution was

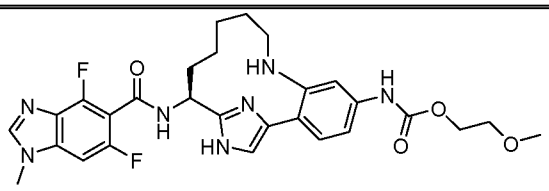
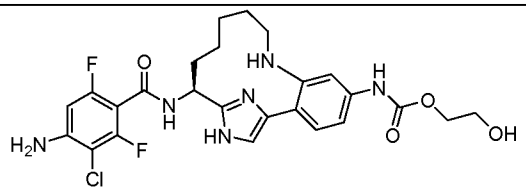
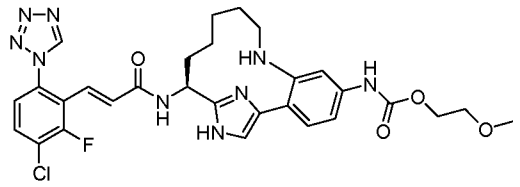
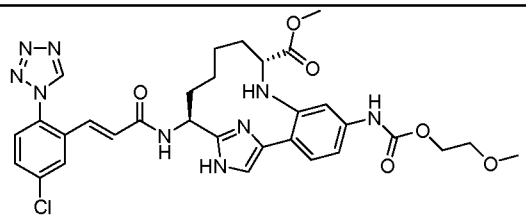
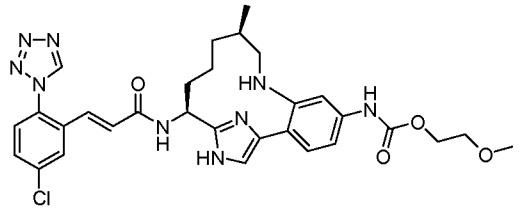
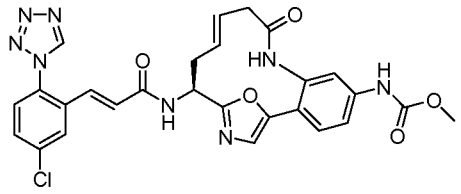
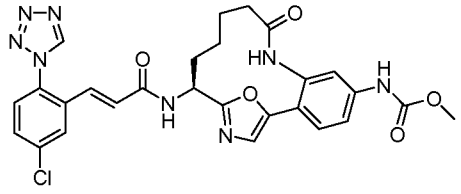
added methylmagnesium chloride (3.0 M in THF, 2.86 ml, 8.59 mmol) dropwise over 10-15 min. Stirring was continued at -78 °C for 1 h at which point the reaction was quenched with 10% aqueous $KHSO_4$ solution and warmed to room temperature. The mixture was diluted with water and extracted 3x with EtOAc. Extracts were combined and washed with water and brine, dried over anh. Na_2SO_4, filtered and evaporated. Residue was purified by flash chromatography to provide the desired product (1.18 g, 59.6%) along with recovered starting material (0.425g, 22%). MS (ESI) *m/z*: 301.1/303.1 $(M+H)^+$ 245.1/247.1 $(M+H\text{-}tBu)^+$.

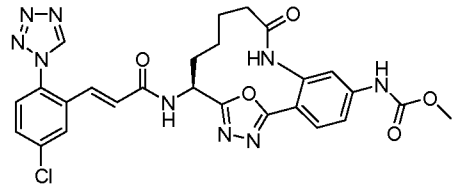
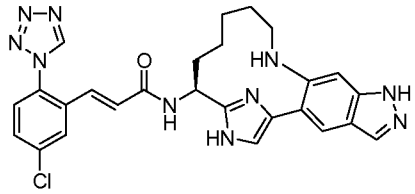
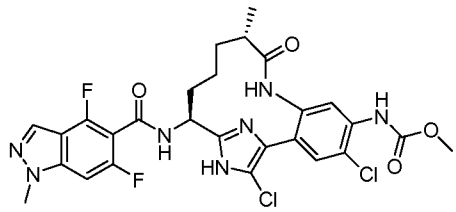
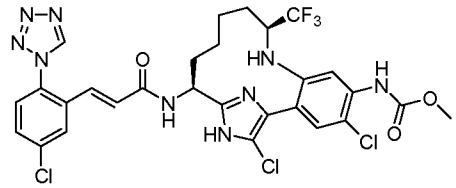
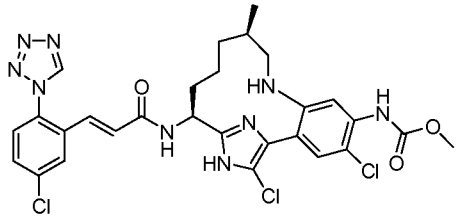
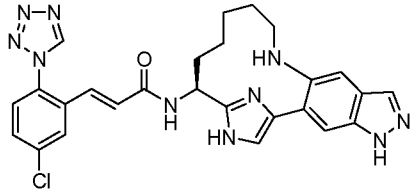
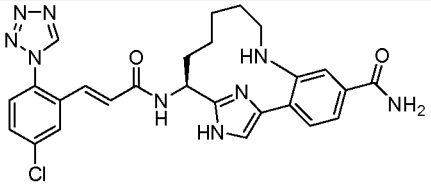
[00771] I-142D. *tert*-Butyl 3-acetyl-4-bromobenzoate: I-142C (1.186 g, 3.94 mmol) was dissolved in DCM (50 ml) and treated with PCC (1.02 g, 4.73 mmol) with stirring under nitrogen. The resulting mixture was stirred at room temperature for 4 h then filtered through a pad of CELITE®. Filtrate was evaporated to dryness, and residue was purified by flash chromatography to provide the product as a colorless liquid (0.938g, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.04 (1 H, d, *J*=2.20 Hz) 7.88 (1 H, dd, *J*=8.25, 2.20 Hz) 7.67 (1 H, d, *J*=8.25 Hz) 2.65 (3 H, s) 1.59 (9 H, s).

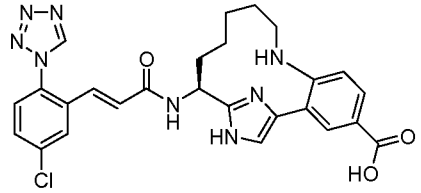
[00772] I-142E. *tert*-Butyl 4-bromo-3-(2-bromoacetyl)benzoate: I-142D (0.209 g, 0.699 mmol) was dissolved in THF (3.5 ml) and pyridinium tribromide (0.226 g, 0.706 mmol) was added with stirring under nitrogen. Mixture was stirred at room temperature for ~ 30 min. Reaction was diluted with EtOAc and washed with brine, dried over anh. Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography to yield I-142E (0.214g, 81%) contaminated with a small amount of starting material. MS (ESI) *m/z*: 323.0 $(M+H\text{-}tBu)^+$.

[00773] Example 142. I-142E was converted into the title compound using the same series of steps described for conversion of I-140F into Example 140. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s) 8.29 (1 H, d, *J*=1.65 Hz) 7.95 - 8.03 (2 H, m) 7.64 - 7.74 (2 H, m) 7.59 (1 H, d, *J*=8.53 Hz) 7.43 (1 H, d, *J*=8.53 Hz) 7.18 (1 H, d, *J*=15.68 Hz) 6.78 (1 H, d, *J*=15.68 Hz) 5.28 (1 H, dd, *J*=10.45, 6.33 Hz) 3.07 - 3.17 (1 H, m) 2.83 - 2.94 (1 H, m) 2.10 - 2.26 (1 H, m) 1.86 - 2.05 (3 H, m) 1.55 - 1.72 (2 H, m) 1.32 - 1.45 (1 H, m) 0.78 - 0.95 (1 H, m). MS (ESI) *m/z*: 533.2 $(M+H)^+$ Analytical HPLC: RT = 5.71 min.

Table I-8: Examples I-128 to I-142

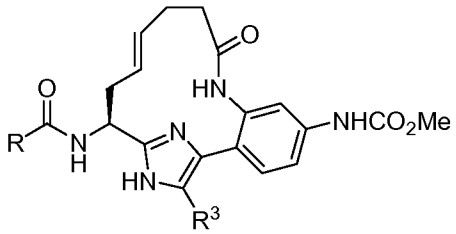
Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min)
I-128		568.4	4.2
I-129		549.3	4.7
I-130		624.3	5.7
I-131		664.4	6.2
I-132		620.3	6.0
I-133		575.2	7.2
I-134		577.2	6.4

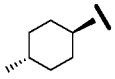
Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min)
I-135		578.0	7.2
I-136		543.3	4.8
I-137		586.2	5.7 (B)
I-138		698.1	10.0
I-139		644.3	5.9
I-140		529.4	5.4
I-141		532.4	4.9

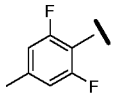
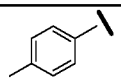
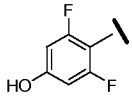
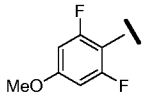
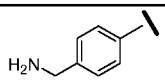
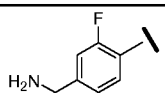
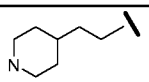
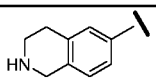
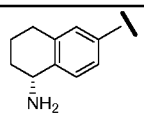
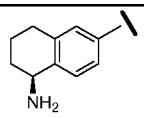
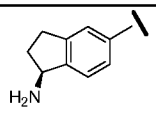
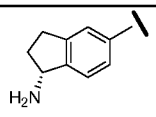
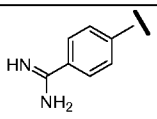
Ex. #	Structure	LCMS [M+H]+	HPLC RT (min)
I-142		533.0	5.7

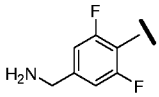
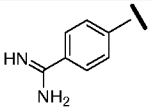
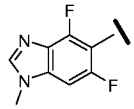
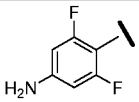
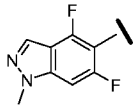
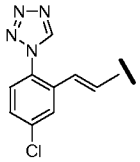
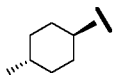
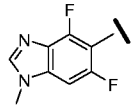
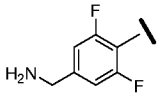
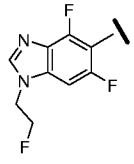
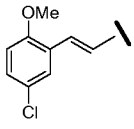
[00774] Examples I-143 to I-147 were prepared following the sequence of procedures described in step10H, by replacing 10G with 39A; followed by step 15D, by replacing Intermediate 2 with appropriately substituted carboxylic acid derivatives (R-CO_2H). Examples I-148 to I-157 were prepared following the sequence of procedures described in step10H, by replacing 10G with 39A; followed by step 15D, by replacing Intermediate 2 with appropriately substituted carboxylic acid derivatives (R-CO_2H); and finally Boc-deprotection according to the procedure described in 3C. Examples I-158 to I-161 were prepared by coupling 76B with appropriately substituted carboxylic acid derivatives (R-CO_2H) using coupling conditions described in step 15D. In the case of Example I-158, an additional Boc-deprotection step as described in step 3C was required. Examples I-162 to I-176 were prepared in a similar manner as described above.

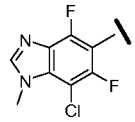
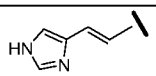
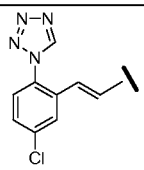
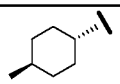
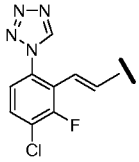
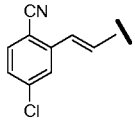
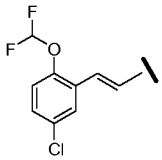
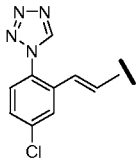
Table I-9: Examples I-143 to I-176



Ex. #	R	R^3	LCMS [M+H]+	HPLC RT (min) (method)
I-143		H	480.2	4.2 (D)

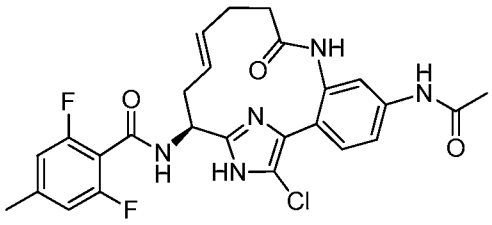
Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-144		H	510.1	3.6 (D)
I-145		H	474.1	3.8 (D)
I-146		H	512.1	3.8
I-147		H	526.2	4.4
I-148		H	489.2	3.0 (D)
I-149		H	507.1	3.0 (D)
I-150		H	495.2	6.3 (C)
I-151		H	515.2	7.4 (C)
I-152		H	529.2	8.3 (C)
I-153		H	529.2	8.3 (C)
I-154		H	515.2	7.7 (C)
I-155		H	515.2	7.7 (C)
I-156		H	502.2	6.4 (C)

Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-157		H	525.2	6.7 (C)
I-158		Cl	536.1	3.5
I-159		Cl	584.0	5.0
I-160		Cl	545.2	5.2
I-161		Cl	584.0	6.1
I-162		F	606.0	7.1
I-163		F	498.2	7.7
I-164		F	568.2	5.3
I-165		F	543.1	3.5
I-166		F	600.2	10.1
I-167		F	568.2	8.1

Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min) (method)
I-168		F	602.1	6.4
I-169		F	494.3	4.0
I-170		F	584.4 $[M-H]^+$	6.1
I-171		Me	602.2	4.8
I-172		Me	494.3	5.3
I-173		Me	620.3	5.2
I-174		Me	559.3	6.4
I-175		Me	600.3	6.0
I-176		CN	613.2	6.9

Example I-177.

N-((E)-(S)-5-Acetylamino-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-2,6-difluoro-4-methyl-benzamide, TFA



[00775] I-177A and 177-B. (E)-(S)-5,15-Diamino-18-chloro-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-9-one and ((E)-(S)-15-amino-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl)-carbamic acid ethyl ester**:** 76B (0.377g, 0.815 mmol) was dissolved in a mixture of ethanol (3.3 ml), water (9.8 ml), and THF (3.3 ml), and LiOH (0.156 g, 6.52 mmol) was added. The reaction was stirred at 60 °C for 48 h, cooled to room temperature, neutralized with 1M HCl and concentrated. The crude products were isolated by reverse phase chromatography to provide I-177A (0.559 g) and I-177B (30 mg) which were used without further purification.

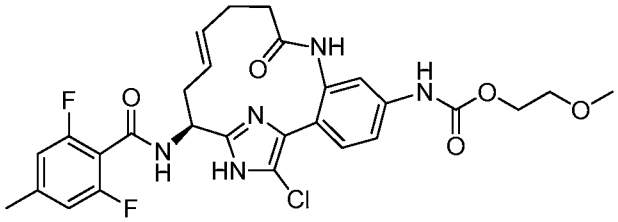
[00776] I-177C. 2,5-Dioxopyrrolidin-1-yl 2,6-difluoro-4-methylbenzoate: To a solution of 2,6-difluoro-4-methylbenzoic acid (2.0 g, 11.62 mmol) in THF (61.8 mL) was added 1-hydroxypyrrolidine-2,5-dione (1.471 g, 12.78 mmol) and 1,3-diisopropylcarbodiimide (2.00 mL, 12.78 mmol) at rt. The reaction mixture was stirred under N_2 at rt overnight. Reaction mixture was filtered, and the filtrate was evaporated. The residue was resuspended in MeOH, filtered, and washed several times with MeOH. The remaining white solid was dried under vacuum to yield I-177C (2.80 g, 90%). MS (ESI) *m/z*: 155.1 $(M+H)^+$.

[00777] I-177D (Example I-184. *N*-((E)-(S)-5-Amino-18-chloro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-2,6-difluoro-4-methyl-benzamide): I-177D was prepared from I-177A following the procedure described in step 1G, by replacing Intermediate 1 with I-177C. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.17 (1 H, d, *J*=8.25 Hz), 6.89 (2 H, d, *J*=8.80 Hz), 6.68 (1 H, dd, *J*=8.25, 2.20 Hz), 6.60 (1 H, d, *J*=2.20 Hz), 5.49 - 5.61 (1 H, m), 5.23 - 5.34 (1 H, m), 5.14 (1 H, dd, *J*=9.35, 3.85 Hz), 2.55 - 2.66 (1 H, m), 2.41 - 2.52 (1 H, m), 2.33 - 2.41 (7 H, m). MS (ESI) *m/z*: 486.1 $(M+H)^+$. Analytical HPLC: RT = 4.92 min.

[00778] Example I-177. I-177D (0.03 g, 0.062 mmol) was dissolved in DCM (0.5 ml) and a solution of acetic anhydride (6.30 mg, 0.062 mmol) in DCM (0.1 mL) was added dropwise. The reaction was stirred overnight at room temperature. Reaction mixture was concentrated, and residue was purified by reverse phase chromatography to provide the title compound (12.6 mg, 31.6%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.45 (1 H, br. s.), 10.08 - 10.13 (1 H, m), 9.32 (1 H, br. s.), 9.21 (1 H, d, *J*=7.70 Hz), 7.63 (1 H, br. s.), 7.44 (1 H, d, *J*=10.45 Hz), 7.33 (1 H, d, *J*=8.25 Hz), 6.98 (2 H, d, *J*=8.80 Hz), 5.41 - 5.61 (1 H, m), 5.20 - 5.35 (1 H, m), 5.04 - 5.19 (1 H, m), 2.39 - 2.45 (1 H, m), 2.32 (3 H, s), 2.29 - 2.40 (2 H, m), 2.16 - 2.31 (2 H, m), 2.04 (3 H, s). MS (ESI) *m/z*: 528.2 $(M+H)^+$. Analytical HPLC: RT = 6.05 min.

Example I-178.

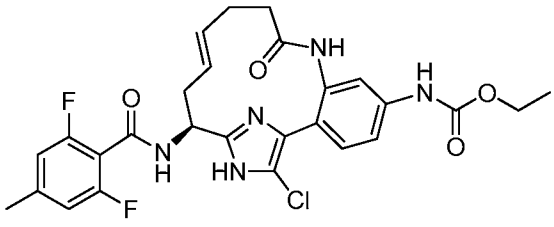
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid 2-methoxy-ethyl ester, TFA



[00779] I-177C was dissolved in DCM (5mL) and pyridine (0.02mL, 0.247 mmol) was added, followed by dropwise addition of a solution of 2-methoxyethyl carbonochloridate (8.55 mg, 0.062 mmol) in DCM (0.5 mL). The resulting mixture was stirred overnight at room temperature. The reaction was concentrated to dryness, and residue purified by reverse phase HPLC to provide Example I-178 as a white solid (10.6 mg, 24.21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.38 (1 H, br. s.), 9.96 (1 H, br. s.), 9.33 (1 H, br. s.), 9.22 (1 H, d, *J*=8.25 Hz), 7.45 (1 H, br. s.), 7.35 - 7.41 (1 H, m), 7.27 - 7.35 (1 H, m), 6.99 (2 H, d, *J*=8.25 Hz), 5.45 - 5.58 (1 H, m), 5.20 - 5.34 (1 H, m), 5.05 - 5.18 (1 H, m), 4.17 - 4.27 (2 H, m), 3.47 - 3.61 (2 H, m), 3.27 (3 H, s), 2.43 - 2.50 (2 H, m), 2.31 - 2.38 (2 H, m), 2.33 (3 H, s), 2.18 - 2.28 (2 H, m). MS (ESI) *m/z*: 588.3 $(M+H)^+$. Analytical HPLC: RT = 6.8 min.

Example I-179.

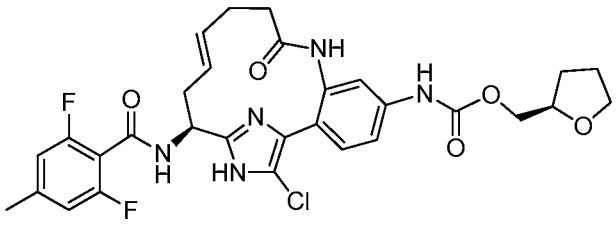
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid ethyl ester, TFA



[00780] Example I-179 was prepared following the procedure described for I-177D by replacing I-177A with I-177B. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.26 (1 H, br. s.), 9.65 (1 H, s), 9.19 (1 H, br. s.), 9.00 (1 H, d, J=7.70 Hz), 7.50 (1 H, br. s.), 7.38 - 7.45 (1 H, m), 7.31 - 7.36 (1 H, m), 6.92 - 7.03 (2 H, m), 5.49 - 5.62 (1 H, m), 5.23 - 5.36 (1 H, m), 5.07 - 5.22 (1 H, m), 4.16 (2 H, q, J=6.97 Hz), 2.40 - 2.50 (2 H, m), 2.33 - 2.43 (5 H, m), 2.25 - 2.33 (2 H, m), 1.27 (3 H, t, J=7.02 Hz). MS (ESI) *m/z*: 558.2 $(M+H)^+$. Analytical HPLC: RT = 7.35 min.

Example I-180.

[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester, TFA



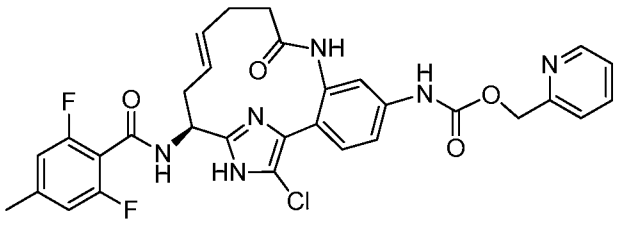
[00781] I-180A. (R)-4-Nitrophenyl (tetrahydrofuran-2-yl)methyl carbonate: A solution of 4-nitrophenyl carbonochloridate (0.2 g, 1.998 mmol) in DCM (8 mL) was added dropwise to a solution of (R)-hydroxy(tetrahydrofuran-2-yl)methylium (0.2 g, 1.998 mmol) in DCM (6.66 ml)/pyridine (0.162 ml, 1.998 mmol) at 0 °C. The reaction was maintained at 0 °C for 2 hours then allowed to warm to RT overnight. Reaction was quenched with water and diluted with DCM. Organic phase was washed 3x with sat'd. sodium bicarbonate, and once with brine, dried over sodium sulfate, filtered and

concentrated. I-180A (0.442 g, 83%), was obtained as a white solid. MS (ESI) *m/z*: 290.2 $(M+Na)^+$

[00782] Example I-180. I-177D (0.026 g, 0.054 mmol) was dissolved in pyridine. I-180A (0.029 g, 0.107 mmol) was added followed by DMAP (6.54 mg, 0.054 mmol). Reaction was stirred at RT overnight. Another 2 equiv. of I-180A was added, and the mixture was stirred for 2 more hours, then evaporated. Residue was purified by reverse phase chromatography to provide the title compound (5.6 mg, 13.80%) as a white solid. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.63 (1 H, br. s.), 7.55 (1 H, s), 7.36 - 7.46 (2 H, m), 6.91 (2 H, d, *J*=8.80 Hz), 5.45 - 5.64 (1 H, m), 5.29 - 5.46 (1 H, m), 5.06 - 5.23 (1 H, m), 4.04 - 4.32 (3 H, m), 3.85 - 3.96 (1 H, m), 3.70 - 3.84 (1 H, m), 2.70 - 2.84 (1 H, m), 2.21 - 2.62 (8 H, m), 2.00 - 2.14 (1 H, m), 1.81 - 2.01 (2 H, m), 1.52 - 1.80 (1 H, m). MS (ESI) *m/z*: 614.2 $(M+H)^+$. Analytical HPLC: RT = 7.65 min.

Examples I-181.

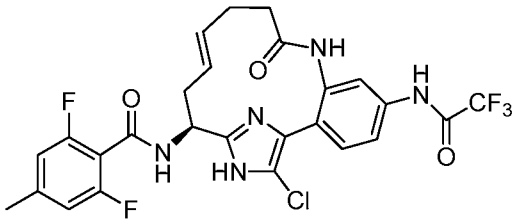
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid pyridin-2-ylmethyl ester, TFA



and

Example I-182.

N-[(E)-(S)-18-Chloro-9-oxo-5-(2,2,2-trifluoro-acetylamino)-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl]-2,6-difluoro-4-methyl-benzamide, TFA

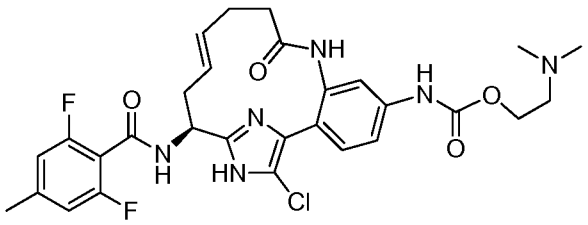


[00783] I-177D (0.013 g, 0.018 mmol) was dissolved in DCM (0.5 ml). TEA (0.018 ml, 0.127 mmol) was added, followed by triphosgene (10.81 mg, 0.036 mmol). The

mixture was stirred for 30 min at RT, and then a solution of pyridin-2-ylmethanol (9.93 mg, 0.091 mmol) in DCM (0.1 mL) was added. Stirring was continued at RT overnight. Reaction mixture was evaporated, and residue was purified by reverse phase chromatography to provide Example I-181 (1.6 mg, 9.83%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.68 (1 H, d, J=4.95 Hz), 8.22 (1 H, td, J=7.84, 1.37 Hz), 7.82 (1 H, d, J=7.70 Hz), 7.64 - 7.70 (1 H, m), 7.56 - 7.60 (1 H, m), 7.43 - 7.46 (2 H, m), 6.91 (2 H, d, J=8.80 Hz), 5.47 - 5.61 (1 H, m), 5.41 (2 H, s), 5.26 - 5.40 (1 H, m), 5.08 - 5.17 (1 H, m), 2.67 - 2.80 (1 H, m), 2.26 - 2.55 (8 H, m). MS (ESI) *m/z*: 623.1 $(M+H)^+$. Analytical HPLC: RT = 5.31 min., and Example I-182 (5.6 mg, 43.8%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.79 (1 H, d, J=2.20 Hz), 7.65 (1 H, dd, J=8.53, 2.20 Hz), 7.56 (1 H, d, J=8.53 Hz), 6.91 (2 H, d, J=8.80 Hz), 5.48 - 5.60 (1 H, m), 5.32 - 5.44 (1 H, m), 5.09 - 5.19 (1 H, m), 2.69 - 2.79 (1 H, m), 2.29 - 2.57 (8 H, m). MS (ESI) *m/z*: 582.3 $(M+H)^+$. Analytical HPLC: RT = 8.06 min.

Example 183.

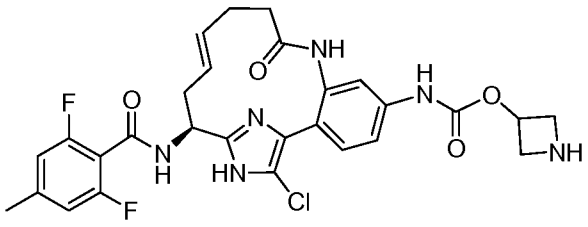
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid 2-dimethylamino-ethyl ester, 2 TFA



[00784] Example I-183 was prepared using the procedure described for Example I-181 by replacing pyridin-2-ylmethanol with 2-(dimethylamino)ethanol. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.10 (1 H, s), 7.58 (1 H, s), 7.44 - 7.47 (2 H, m), 6.90 (2 H, d, *J*=8.80 Hz), 5.49 - 5.59 (1 H, m), 5.28 - 5.41 (1 H, m), 5.07 - 5.15 (1 H, m), 4.49 - 4.55 (2 H, m), 3.46 - 3.56 (2 H, m), 3.00 (6 H, s), 2.60 - 2.75 (2 H, m), 2.25 - 2.56 (7 H, m). MS (ESI) *m/z*: 601.3 $(M+H)^+$. Analytical HPLC: RT = 4.66 min.

Example 185.

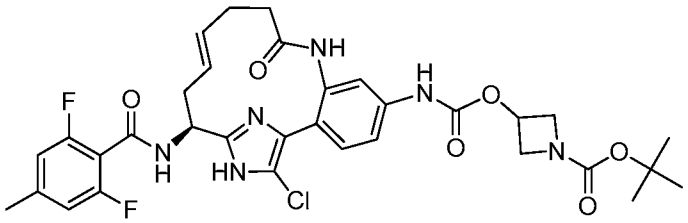
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid azetidin-3-yl ester, 2 TFA



[00785] Example 186 was dissolved in DCM (1 mL) and TFA (0.25 mL) was added. After stirring for 1h at RT, the reaction mixture was evaporated to dryness to provide the title compound. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.44 - 7.50 (1 H, m), 7.33 - 7.41 (2 H, m), 6.80 - 6.86 (2 H, m), 5.38 - 5.52 (1 H, m), 5.23 - 5.34 (2 H, m), 5.00 - 5.07 (1 H, m), 4.33 - 4.43 (2 H, m), 4.09 - 4.19 (2 H, m), 2.61 - 2.73 (1 H, m), 2.17 - 2.49 (8 H, m). MS (ESI) *m/z*: 585.2 $(M+H)^+$. Analytical HPLC: RT = 4.53 min.

Example 186.

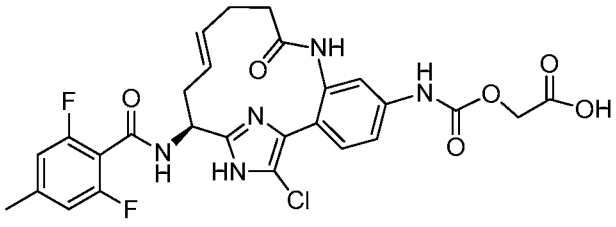
3-[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-ylcarbamoyloxy]-azetidine-1-carboxylic acid *tert*-butyl ester, TFA



[00786] Example 186 was prepared using the procedures described for Ex. I-180, by replacing (R)-hydroxy(tetrahydrofuran-2-yl)methylium with *tert*-butyl 3-hydroxyazetidine-1-carboxylate in step I-180A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.81 (1 H, br. s.), 7.52 - 7.58 (1 H, m), 7.37 - 7.48 (2 H, m), 6.90 (2 H, d, *J*=8.80 Hz), 5.45 - 5.59 (1 H, m), 5.29 - 5.41 (1 H, m), 5.16 - 5.24 (1 H, m), 5.07 - 5.16 (1 H, m), 4.23 - 4.35 (2 H, m), 3.85 - 3.99 (2 H, m), 2.68 - 2.78 (1 H, m), 2.25 - 2.56 (8 H, m), 1.44 (9 H, s). MS (ESI) *m/z*: 685.3 $(M+H)^+$. Analytical HPLC: RT = 8.63 min.

Example I-187.

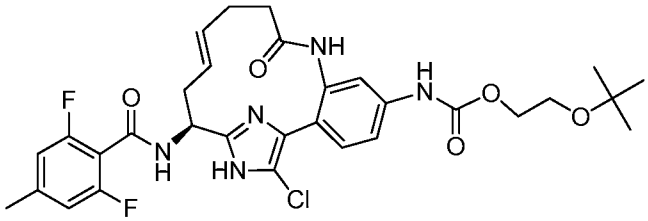
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-ylcarbamoyloxy]-acetic acid, TFA



[00787] Example I-187 was prepared following the procedure described for Example 181, by replacing pyridin-2-ylmethanol with ethyl 2-hydroxyacetate, followed by hydrolysis of the crude ethyl ester with LiOH in THF. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.80 (1 H, br. s.), 7.57 (1 H, s), 7.43 (2 H, s), 6.90 (2 H, d, *J*=8.80 Hz), 5.47 - 5.62 (1 H, m), 5.29 - 5.41 (1 H, m), 5.01 - 5.20 (1 H, m), 4.66 (2 H, s), 2.68 - 2.79 (1 H, m), 2.25 - 2.56 (8 H, m). MS (ESI) *m/z*: 588.2 $(M+H)^+$. Analytical HPLC: RT = 6.08 min.

Example I-188.

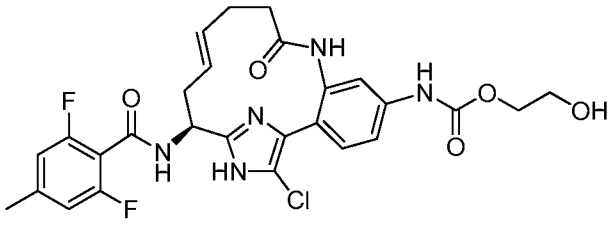
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid 2-*tert*-butoxy-ethyl ester, TFA



[00788] Example 188 was prepared similarly to Ex. I-180, by replacing (R)-hydroxy(tetrahydrofuran-2-yl)methylium with 2-*tert*-butoxyethanol in step I-180A ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (1 H, br. s.), 7.50 (1 H, s), 7.37 (2 H, s), 6.86 (2 H, d, *J*=8.80 Hz), 5.40 - 5.58 (1 H, m), 5.22 - 5.33 (1 H, m), 5.08 (1 H, dd, *J*=10.17, 4.12 Hz), 4.13 - 4.21 (2 H, m), 3.56 - 3.64 (2 H, m), 2.59 - 2.70 (1 H, m), 2.34 (8 H, s), 1.17 (9 H, s). MS (ESI) *m/z*: 630.3 $(M+H)^+$. Analytical HPLC: RT = 8.0 min.

Example I-189.

[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid 2-hydroxy-ethyl ester, TFA

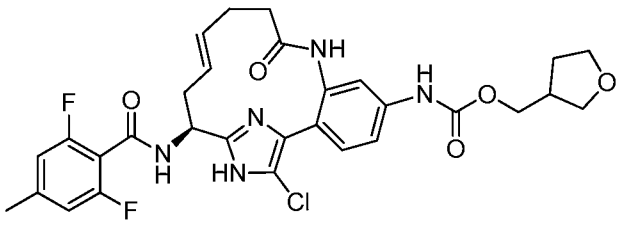


[00789] I-189A. 2-*tert*-Butoxyethyl carbonochloridate: To a solution of 2-*tert*-butoxyethanol (0.444 mL, 3.38 mmol) and pyridine (0.274 mL, 3.38 mmol) in ether (10 mL) was added triphosgene (0.331 g, 1.117 mmol) dissolved in 2 mL of ether. The reaction mixture was maintained at 0 °C for one hour. Reaction mixture was filtered and concentrated to provide the crude 2-*tert*-butoxyethyl carbonochloridate (0.424 g, 69.3%), as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.38 - 4.43 (2 H, m), 3.60 - 3.65 (2 H, m), 1.20 (9 H, s).

[00790] Example I-189. This compound was prepared from I-177D according to the procedure described for step I-123B, by replacing 2-methoxyethyl carbonochloridate with I-189A, followed by deprotection of the crude *t*-butyl ether with TFA/DCM. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.57 (1 H, br. s.), 7.55 - 7.66 (1 H, m), 7.39 - 7.51 (2 H, m), 6.94 (2 H, d, *J*=8.80 Hz), 5.48 - 5.61 (1 H, m), 5.32 - 5.46 (1 H, m), 5.16 (1 H, dd, *J*=10.59, 4.54 Hz), 4.21 - 4.34 (2 H, m), 3.77 - 3.86 (2 H, m), 2.74 - 2.84 (1 H, m), 2.31 - 2.59 (8 H, m). MS (ESI) *m/z*: 574.2 $(M+H)^+$. Analytical HPLC: RT = 5.77 min.

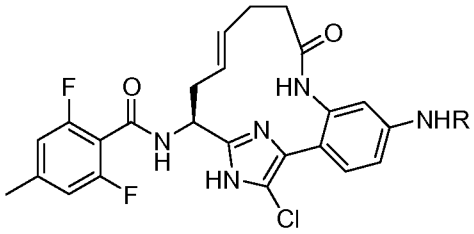
Example 190.

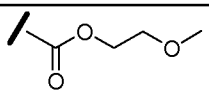
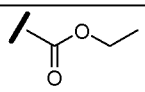
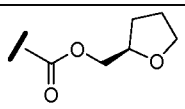
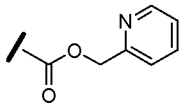
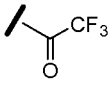
[(E)-(S)-18-Chloro-15-(2,6-difluoro-4-methyl-benzoylamino)-9-oxo-8,17,19-triaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl]-carbamic acid tetrahydro-furan-3-ylmethyl ester, TFA

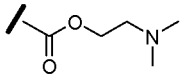
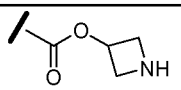
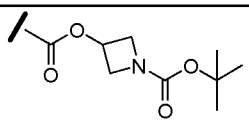
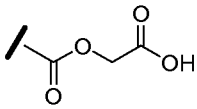
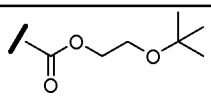
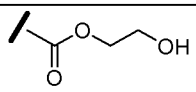
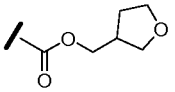


[00791] Example I-190 was prepared following the procedures described for Ex. I-189, by replacing 2-*tert*-butoxyethanol with (tetrahydrofuran-3-yl)methanol in step I-189A and omitting the TFA treatment. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.54 (1 H, br. s.), 8.25 (1 H, d, *J*=9.35 Hz), 7.47 - 7.53 (1 H, m), 7.24 - 7.45 (2 H, m), 6.85 (2 H, d, *J*=8.80 Hz), 5.41 - 5.57 (1 H, m), 5.24 - 5.35 (1 H, m), 5.06 (1 H, dd, *J*=10.72, 4.12 Hz), 4.06 - 4.28 (1 H, m), 3.94 - 4.04 (1 H, m), 3.74 - 3.87 (2 H, m), 3.63 - 3.73 (1 H, m), 3.53 - 3.62 (1 H, m), 2.62 - 2.74 (1 H, m), 2.53 - 2.63 (1 H, m), 2.20 - 2.50 (8 H, m), 1.90 - 2.10 (1 H, m), 1.58 - 1.75 (1 H, m). MS (ESI) *m/z*: 614.3 $(M+H)^+$. Analytical HPLC: RT = 6.86 min.

Table I-10: Examples I-177 to I-190



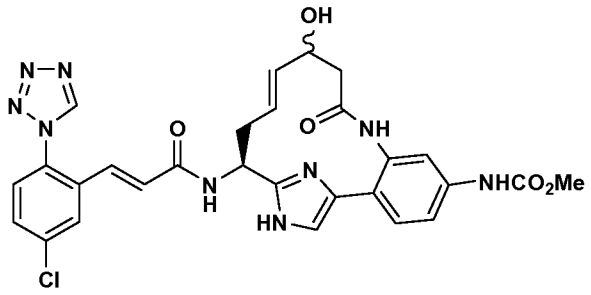
Ex. #	R	LCMS $[M+H]^+$	HPLC RT (min)
I-177		528.2	6.1
I-178		588.3	6.8
I-179		558.2	7.3
I-180		614.2	7.7
I-181		621.3	5.3
I-182		582.3	8.1

Ex. #	R	LCMS $[M+H]^+$	HPLC RT (min)
I-183		601.3	4.7
I-184	H	486.1	4.9
I-185		585.2	4.5
I-186		685.3	8.6
I-187		588.2	6.1
I-188		630.3	8.0
I-189		574.2	5.8
I-190		614.3	6.9

[00792] Example I-192 was prepared following the procedure described in Example 47. Examples I-193 to I-195 were prepared following the procedures described in Example 53, by replacing 15B with 10C.

Example I-196.

{(E)-(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-hydroxy-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-yl}-carbamic acid methyl ester, trifluoroacetic acid salt



[00793] I-196A. {3-Amino-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-phenyl}-carbamic acid methyl ester (0.15g, 0.28 mmol) was dissolved in DMF (3 mL). To this solution was added 3-Hydroxy-pent-4-enoic acid (0.064g, 0.55 mmol), followed by T3P (0.326g, 0.423 mmol) and Hunig's base (0.073g, 0.56 mmol) and the reaction mixture was stirred at room temperature overnight. Quenched the reaction with water (100ml), and extracted organics with EtOAc (2x100 mL), dried ($MgSO_4$) and evaporated to a greenish semi-solid mass. Purified the crude via normal phase chromatography. Pure fractions were collected and concentrated to a pale yellow solid (0.11g, 62%). ^1H NMR (500 MHz, CD_3OD) δ ppm 8.39 (m, 1H), 7.58-7.43 (m, 2H), 7.21 (s, 1H), 5.80 (m, 1H), 5.55-5.05 (m, 8H), 3.76 (s, 3H), 3.54 (m. 2H), 2.80 (m, 2H), 1.46 (s, 9H), 0.94 (m, 2H), 0.00 (s, 9H). MS (ESI) *m/z*: 630.3 $(M+H)^+$.

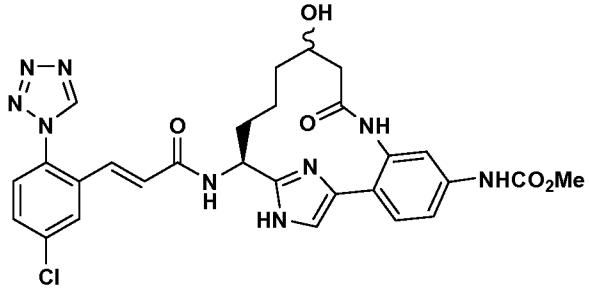
[00794] I-196 B. The product from I-196A was dissolved in DCM (35 mL) and degassed. After 0.5 h pTsOH (0.03g, 0.18 mmol) was added and the reaction mixture was stirred for an additional 0.5h while being degassed. To this solution was added Grubbs II catalyst (0.06g, 0.07 mmol) and the reaction mixture was heated to 40 °C overnight. Reaction mixture was cooled and quenched with sodium phase phase solution (10%, 50 mL) and the organics layer separated. The aqueous layer was further extracted with EtOAc (2x100ml), and the combined extracts was dried ($MgSO_4$) and evaporated to a brown oil. The crude material was purified via normal phase chromatography to afford the desired macrocycle as a colorless oil. MS (ESI) *m/z*: 602.2 $(M+H)^+$.

[00795] I-196C. The removal of the Boc and Sem protecting groups as in Example 1 (step 1F) of the product from I-196B, followed by the coupling of the crude amino macrocycle with Intermediate 1 as described for Example 1 (step 1G) afforded the title compound as a white solid (10mg, 23%). ^1H NMR (500 MHz, CD_3OD) δ ppm 9.55 (s,

1H), 9.50 (d, *J* = 2.5Hz, 1H), 7.98 (m, 1H), 7.69 (dd, *J* = 2.3 & 8.5Hz, 1H), 7.60-7.57 (m, 2H), 7.41-7.37 (m, 2H), 7.18-7.13 (dd, *J* = 4.3 & 8.7Hz, 1H), 6.77 (d, *J* = 15.8Hz, 1H), 5.84-5.73 (m, 1H), 5.55-5.43 (m, 1H), 5.17-5.09 (m, 1H), 4.44 (m, 1H), 3.75 (s, 3H), 2.9-2.45 (m, 5H). MS (ESI) *m/z*: 604.3 $(M+H)^+$. Analytical HPLC: RT = 5.12 min.

Example I-197.

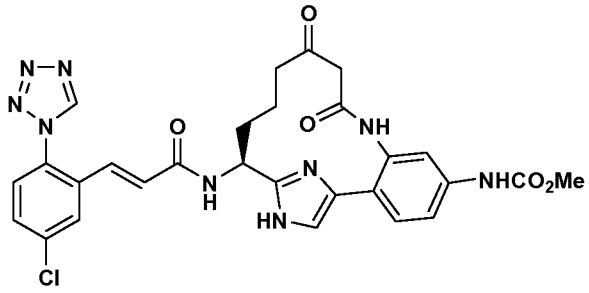
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-hydroxy-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, trifluoroacetic acid salt



[00796] The reduction of I-196B as in Example 2 (step 2G), deprotection of the Boc and Sem protecting groups as in Example 1 (step 1F), and coupling with Intermediate 1 as described for Example 1 (step 1G) afforded the title compound as a brown solid (7 mg, 13%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1H), 9.51 (s, 1H), 7.98 (dd, *J* = 2.3 & 8.3Hz, 1H), 7.69-7.66(m, 1H), 7.61-7.56(m, 1H), 7.44-7.41(m, 2H), 7.16-7.10(t, 1H), 6.79-6.69 (dd, *J* = 15.6Hz, 2H), 5.05-4.97 (m, 1H), 4.00 (m, 1H), 3.76 (s, 3H), 2.66-2.63 (m, 1H), 2.34-2.22 (m, 2H), 2.05 (m, 1H), 1.80 (m, 1H), 1.62 (m, 1H), 1.58 (m, 1H), 1.38-1.22 (m, 2H), 1.00-0.74 (m, 2H). MS (ESI) *m/z*: 606.4 $(M+H)^+$. Analytical HPLC: RT = 4.36 min.

Example I-198.

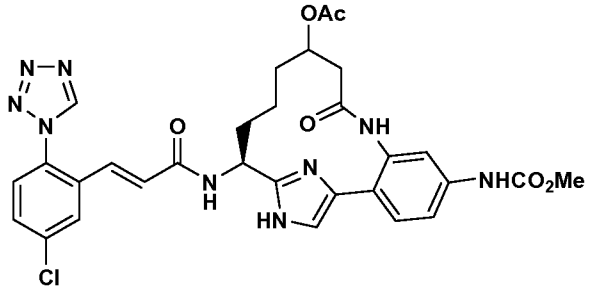
{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9,11-dioxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, trifluoroacetic acid salt



[00797] The reduction of I-196B as in Example 2 (step 2G), followed by the oxidation of the reduced product (0.04g, 0.06 mmol) with Dess-Martin periodinane (0.03g, 0.076 mmol) in DCM (5 mL), deprotection of the Boc and SEM protecting groups as in Example 1 (step 1F), and coupling with Intermediate 1 as described for Example 1 (step 1G) afforded the title compound as a brown solid (6 mg, 15%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.41(s, 1H), 7.87 (d, J = 2.7Hz, 1H), 7.52-7.45 (m, 4H), 7.40-7.30 (m, 4H), 7.04 (d, J = 16.4Hz, 1H), 6.65 (d, J = 15.4Hz, 1H), 4.97 (m, 1H), 3.66 (s, 3H), 3.63 (t, 1H). 3.18-3.10 (m, 1H), 2.25-2.05 (m, 2H), 1.75 (bm, 2H). MS (ESI) *m/z*: 604.2 $(M+H)^+$. Analytical HPLC: RT = 5.79 min.

Example I-199.

Acetic acid (S)-15-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,16(19)-pentaen-11-yl ester, trifluoroacetic acid salt



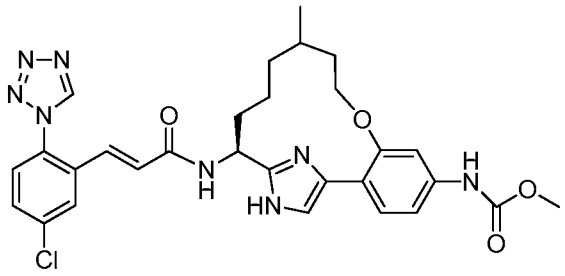
[00798] The reduction of I-196B as in Example 2 (step 2G), followed by the acetylation with acetic anhydride of the reduced product, deprotection of the Boc and SEM protecting groups as in Example 1 (step 1F), and coupling with Intermediate 1 as described for Example 1 (step 1G) afforded the title compound as a brown solid (4 mg, 5%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.39 (s, 1H), 7.88-7.85 (dd, J = 2.3 & 8.8Hz, 1H), 7.63-7.56 (m, 1H), 7.54-7.47 (m, 2H), 7.48-7.39 (m, 2H), 7.08-7.03 (m, 1H), 6.69-

6.57 (q, 2H), 5.12-4.98 (m, 1H), 4.48 (m, 1H), 3.66 (s, 3H), 2.78 (dd, 2H), 2.40-2.30 (m, 1H), 2.12 (bm, 1H), 1.95 (s, 3H), 1.51-1.00 (m, 4H). MS (ESI) *m/z*: 648.2 $(M+H)^+$. Analytical HPLC: RT = 4.93 min.

[00799] Examples I-200 and I-201 were prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 2-methylpent-4-enoic acid; followed by steps 2E/2F; 10H; and 1G. Examples I-202 and I-203 were prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 2-methylpent-4-enoic acid; followed by steps 2E/2F; 2G; 10H; and 1G.

Examples I-205 and I-206.

{(S)-15-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-11-methyl-8-oxa-17,19-diaza-tricyclo[14.2.1.02,7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-yl}-carbamic acid methyl ester, TFA, Diastereomer A and Diastereomer B



[00800] I-205A. Methyl 2-hydroxy-4-(methoxycarbonylamino)benzoate: Methyl 4-amino-2-hydroxybenzoate (10 g, 59.8 mmol) was dissolved in DCM (120 mL), and pyridine (5.32 mL, 65.8 mmol) was added. The mixture was cooled to 0 °C, and methyl chloroformate (4.87 mL, 62.8 mmol) was added dropwise. The reaction was stirred for 1.5h, then quenched with 1.5M dibasic potassium phosphate solution, and extracted 2x with DCM. The combined org. phases were washed 2x with 1M HCl and 1x with brine, dried with sodium sulfate, filtered and concentrated to yield I-205A (14.2 g) which was used without further purification in the next step. MS (ESI) *m/z*: 226.2 $(M+H)^+$.

[00801] I-205B. Methyl 2-(allyloxy)-4-(methoxycarbonylamino)benzoate: I-205A (14.22 g, 63.1 mmol) was dissolved in acetone (210 mL). Allyl bromide (16.39 mL, 189 mmol) was added followed by potassium carbonate (43.6 g, 316 mmol). The reaction was heated at 60 °C under Ar and a reflux condensor for 8 hours. The reaction was

concentrated under reduced pressure and diluted with EtOAc/water. The aq. phase was washed with EtOAc 2x, then the combined organic phases were washed with brine and dried with sodium sulfate and concentrated. Residue was purified by normal phase chromatography to provide I-205B (8.03 g, 47.9%), as a yellow solid. MS (ESI) *m/z*: 266.1 $(M+H)^+$

[00802] I-205C. Methyl 3-(allyloxy)-4-(2-chloroacetyl)phenylcarbamate: To trimethylsulfoxonium chloride (12.12 g, 94 mmol) and 1 M potassium *t*-butoxide (99 mL, 99 mmol) was added an additional 80 mL of THF. The mixture was refluxed for 2 hours, then allowed to cool to room temperature. A solution of I-205B (5 g, 18.85 mmol) dissolved in 100 mL of THF was added dropwise. The reaction was allowed to stir at RT overnight under Ar. The reaction mixture and was concentrated, and the residue was partitioned between EtOAc and water. Aqueous phase was extracted 2x with EtOAc. Combined organic phases were washed with brine, dried with sodium sulfate, filtered and concentrated. Residue was taken up in methylene chloride and filtered. Filtrate was purified by normal phase chromatography, and fractions containing product combined with the insoluble solid above to provide the intermediate sulfonium species (5.76 g, 94%, MS (ESI) *m/z*: 326.1 $(M+H)^+$), which was dissolved in THF (89 mL). a solution of 4M HCl in Dioxane (8.85 mL, 35.4 mmol) was added, and the mixture was stirred at 70 °C overnight in a sealed tube. The reaction mixture was concentrated, and residue was purified by normal phase chromatography to provide I-205C (2.01 g, 40.0%) as a yellow solid. MS (ESI) *m/z*: 284.1 $(M+H)^+$

[00803] I-205D. {3-Allyloxy-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: I-205D was prepared in three steps following the procedures described for steps 2A, by replacing 2-bromo-1-(2-bromophenyl)ethanone with I-205C; 2B; and 10B. MS (ESI) *m/z*: 573.4 $(M+H)^+$.

[00804] I-205E. {4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-hydroxy-phenyl}-carbamic acid methyl ester: I-205D (.663 g, 1.158 mmol) was dissolved in methanol (5.79 ml) and added to a 3 neck flask along with potassium carbonate (0.480 g, 3.47 mmol) . The flask was degassed and backfilled with Ar 3x. $(Ph_3P)_4Pd$ (0.134 g, 0.116 mmol) was added under a stream of Ar. The mixture was degassed and backfilled 3 more times with Ar.

The reaction was stirred for 10 min at RT, then an additional portion of potassium carbonate (0.480 g, 3.47 mmol) was added under a stream of Ar, and the mixture was stirred for 1 hr under Ar. Reaction was diluted with EtOAc/water; aq. phase was extracted 2x with EtOAc; combined organic phases were washed with brine, dried with sodium sulfate concentrated. Residue was purified by flash chromatography to provide I-205E (0.45 g, 0.845 mmol, 73.0%) as a white solid. MS (ESI) *m/z*: 533.4 $(M+H)^+$.

[00805] I-205F. 5-Iodo-3-methylpent-1-ene: To a cooled solution (0 °C) of 1M lithium aluminum hydride in Et_2O (21.90 mL, 21.90 mmol) and 10 mL of additional ether, was added dropwise 3-methylpent-4-enoic acid (1.064 mL, 8.76 mmol) dissolved in 15 mL of ether. Reaction was allowed to warm to RT and stirred overnight. The reaction was carefully poured onto ice in small portions, and 15 mL of 5M H_2SO_4 was added to dissolve most of the salts. The aq. phase was extracted 2x with ether and combined organic phases were washed with brine, dried with sodium sulfate, filtered and concentrated to provide the crude 3-methylpent-4-en-1-ol, which was taken on without further purification. The alcohol (0.877 g, 8.76 mmol) was dissolved in 20 mL of anhydrous DCM, and triphenylphosphine (2.99 g, 11.38 mmol) and imidazole (0.894 g, 13.13 mmol) were added. The reaction mixture was cooled to 0 °C, and a solution of iodine (2.89 g, 11.38 mmol) in 20 mL of DCM was added dropwise. After 30 min at 0 °C, the reaction was warmed to RT and stirred overnight. The reaction was washed 3x with 10% aq. sodium sulfite and 1x with brine, dried with sodium sulfate, filtered and concentrated. Residue was purified on a pad of silica gel eluted with pentane to provide the iodide (0.937 g, 4.46 mmol, 50.9%) as a clear oil.

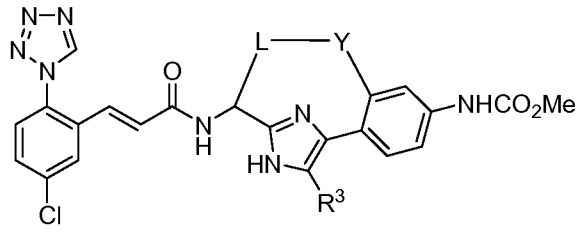
[00806] I-205G. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(3-methyl-pent-4-enyloxy)-phenyl]-carbamic acid methyl ester: I-205E (.206 g, 0.335 mmol, 79%) was dissolved in acetone (3 mL) and potassium carbonate (0.292 g, 2.112 mmol) and I-205F (0.444 g, 2.112 mmol) were added. Reaction mixture was stirred at 55 °C in a sealed vial for 1h, then at 70 °C overnight. The reaction was concentrated and partitioned between water and EtOAc. Aq. phase was re-extracted 2x with EtOAc, and combined organic extracts were washed with brine dried with sodium sulfate, filtered and concentrated. Residue was purified by normal phase chromatography to provide I-205G (0.206 g, 79%) as a white solid. MS (ESI) *m/z*: 615.5 $(M+H)^+$.

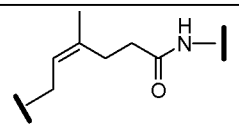
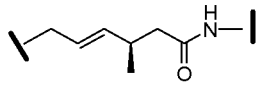
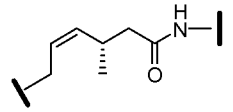
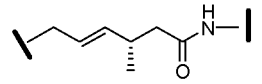
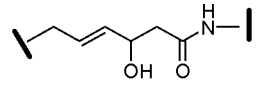
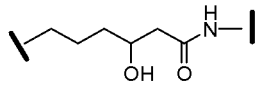
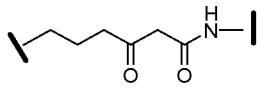
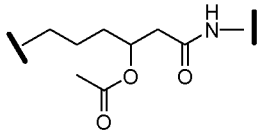
[00807] Examples I-205 and I-206. The title compounds were prepared in four steps from I-205G using the procedures described in steps 2E/F and 2G, at which point the diastereomers were separated by reverse phase chromatography and carried on individually through the deprotection and amide coupling steps using the procedures described in steps 10H and 1G. Example I-205 (Diastereomer A): ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.99 (1 H, d, J=2.20 Hz), 7.69 (1 H, dd, J=8.53, 2.48 Hz), 7.60 (1 H, d, J=8.53 Hz), 7.40 (1 H, s), 7.33 - 7.40 (2 H, m), 7.19 (1 H, d, J=15.41 Hz), 7.02 - 7.09 (1 H, m), 6.80 (1 H, d, J=15.41 Hz), 5.14 (1 H, dd, J=8.80, 4.40 Hz), 3.99 - 4.13 (2 H, m), 3.76 (3 H, s), 2.22 - 2.41 (1 H, m), 1.71 - 1.91 (3 H, m), 1.55 - 1.71 (2 H, m), 1.41 - 1.55 (1 H, m), 0.94 - 1.05 (2 H, m), 0.95 (3 H, d, J=6.60 Hz). MS (ESI) *m/z*: 591.2 $(M+H)^+$. Analytical HPLC: RT = 6.98 min. Example I-206 (Diastereomer B): ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (1 H, s), 7.95 (1 H, d, J=2.20 Hz), 7.67 (1 H, dd, J=8.79, 2.20 Hz), 7.52 - 7.62 (1 H, m), 7.40 - 7.43 (1 H, m), 7.37 - 7.40 (1 H, m), 7.36 (1 H, d, J=8.25 Hz), 7.14 (1 H, d, J=15.39 Hz), 7.05 (1 H, dd, J=8.25, 1.65 Hz), 6.70 (1 H, d, J=15.94 Hz), 5.01 (1 H, dd, J=9.89, 4.95 Hz), 3.94 - 4.12 (2 H, m), 3.75 (3 H, s), 1.99 - 2.25 (2 H, m), 1.47 - 1.81 (4 H, m), 0.96 - 1.34 (3 H, m), 0.94 - 1.03 (3 H, m). MS (ESI) *m/z*: 591.2 $(M+H)^+$. Analytical HPLC: RT = 6.976 min

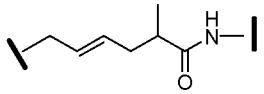
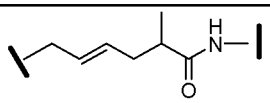
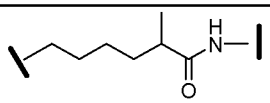
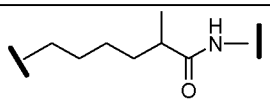
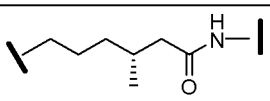
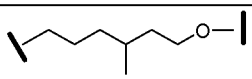
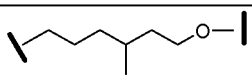
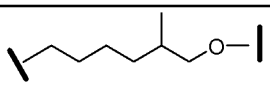
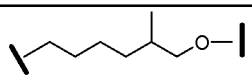
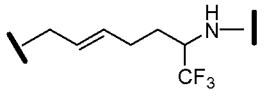
[00808] Examples I-207 and I-208 were prepared in a similar manner as Examples I-205 and I-206 starting from Intermediate I-205E and substituting 2-methylpent-4-enoic acid for 3-methylpent-4-enoic acid in step I-205F.

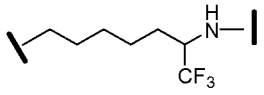
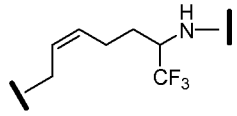
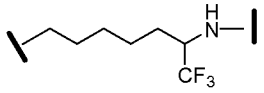
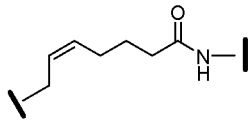
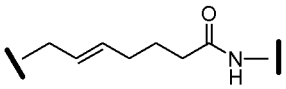
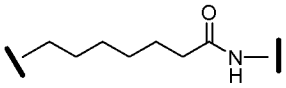
[00809] Examples I-209 to I-212 were prepared following the procedures described for the preparation of Examples 154 and 155, replacing allylmagnesium bromide with but-3-enylmagnesium bromide. Examples I-213 to I-215 were prepared following the procedures described for the preparation of Examples 125, 39, and 34, replacing pent-4-enoic acid with hex-5-enoic acid.

Table I-11: Examples I-191 to I-215



Ex. #	L-Y	R^3	LCMS $[M+H]^+$	HPLC RT (min)
I-191	-$(CH_2)_5$-C(O)NH-	F	608.3	7.0
I-192		H	602.0	5.4
I-193		H	602.2	5.5
I-194		H	602.2	5.4
I-195		H	602.2	5.4
I-196	 (diastereomer mixture)	H	604.2	5.1
I-197	 (diastereomer mixture)	H	604.4 $[M-H]^+$	4.4
I-198		H	604.2	5.8
I-199	 (diastereomer mixture)	H	648.2	4.9

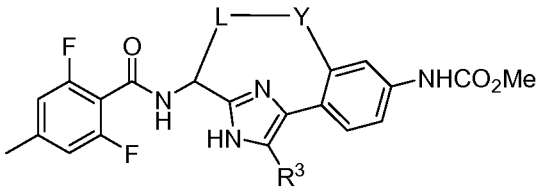
Ex. #	L-Y	R^3	LCMS $[M+H]^+$	HPLC RT (min)
I-200	 (diastereomer B)	H	602.2	5.4
I-201	 (diastereomer A)	H	602.3	5.3
I-202	 (diastereomer B)	H	604.3	4.9
I-203	 (diastereomer A)	H	604.3	4.9
I-204		Cl	638.2	6.9
I-205	 (homochiral)	H	591.2	7.0
I-206	 (homochiral)	H	591.2	7.0
I-207	 (homochiral)	H	591.3	6.8
I-208	 (homochiral)	H	591.2	6.8
I-209	 (homochiral)	H	642.3	7.3

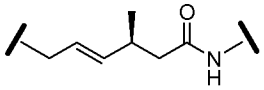
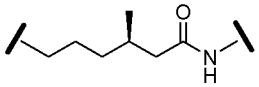
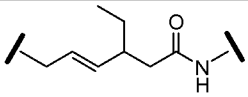
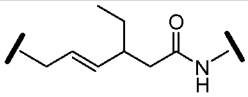
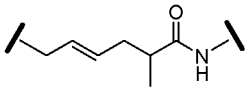
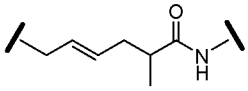
Ex. #	L-Y	R^3	LCMS $[M+H]^+$	HPLC RT (min)
I-210	 (homochiral)	H	644.3	7.2
I-211	 (homochiral)	H	642.3	5.7
I-212	 (homochiral)	H	644.3	6.3
I-213		H	602.1	5.3
I-214		H	602.2	5.6
I-215		H	604.2	5.5

[00810] Example I-216 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 3-methyl-4-pentenoic; followed by steps 2E; 10H; and 15D, by replacing Intermediate 2 with 2,6-difluoro-4-methylbenzoic acid. Example I-217 was prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 3-methyl-4-pentenoic; followed by steps 2E/2F; 10G; 10H; and 15D, by replacing Intermediate 2 with 2,6-difluoro-4-methylbenzoic acid. Examples I-218 to I-219 were prepared following the procedures described in step 10D, by replacing but-3-enoic acid with 3-ethyl pent-4-enoic acid; followed by steps 2E/2F; 10H; and 15D, by replacing Intermediate 2 with 2,6-difluoro-4-methylbenzoic acid. Examples I-220 and I-221 were prepared following the procedures described in step 10D, by replacing but-3-

enoic acid with 2-methyl-4-pentenoic acid; followed by steps 2E/2F; 10H; and 15D, by replacing Intermediate 2 with 2,6-difluoro-4-methylbenzoic acid.

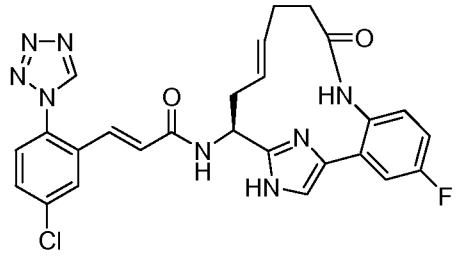
Table I-12: Examples I-216 to I-221



Ex. #	L-Y	R^3	LCMS $[M+H]^+$	HPLC RT (min)
I-216		Cl	558.1	7.5
I-217		Cl	560.0	7.1
I-218	 (diastereomer A)	H	538.2	4.9
I-219	 (diastereomer B)	H	538.2	4.9
I-220	 (diastereomer B)	H	524.3	5.1
I-221	 (diastereomer A)	H	524.2	5.0

Example I-226.

(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-N-((E)-(S)-4-fluoro-9-oxo-8,17,19-triaza-tricyclo[14.2.1.$0^{2,7}$]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-yl)-acrylamide, trifluoroacetic acid salt.



[00811] I-226A. 2-Methyl-propane-2-sulfinic acid {(S)-1-[4-(5-fluoro-2-nitro-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-but-3-enyl}-amide: A microwave vial containing a mixture of Intermediate 37 (409.6mg, 0.909 mmol), 5-fluoro-2-nitrophenylboronic acid (336 mg, 1.818 mmol) and potassium carbonate (251 mg, 1.818 mmol) in dioxane (5.82 mL) and water (1.46 mL) was degassed with argon for 5 min. Next, bis(tri-*t*-butylphosphine)palladium (0) (23.23 mg, 0.045 mmol) was added and the vial was sealed and heated in a microwave to 130 °C for 10 min. Additional 5-fluoro-2-nitrophenylboronic acid (1 eq) and potassium carbonate (1 eq) was added to the vial and the vial was degassed with argon for 5 min. Additional bis(tri-*t*-butylphosphine)palladium (0) (23.23 mg, 0.045 mmol) was added and the vial was sealed and heated in a microwave at 130 °C for 10 min. Additional 5-fluoro-2-nitrophenylboronic acid (1 eq) and potassium carbonate (1 eq) was added to the vial and the vial was degassed with argon for 5 min. Additional bis(tri-*t*-butylphosphine)palladium (0) (23.23 mg, 0.045 mmol) was added and the vial was sealed and heated in a microwave at 130 °C for 10 min. The reaction was partitioned between water and ethyl acetate and the layers were separated. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with sat. $NaHCO_3$(aq), brine, dried over Na_2SO_4, filtered and concentrated to a thick brown oil. Purification by normal phase chromatography gave 168.4 mg (36.3 %) of I-226A as a yellow oil. MS (ESI) *m/z*: 511.2 $(M+H)^+$.

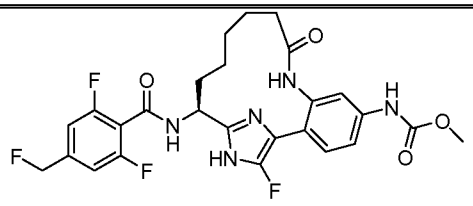
[00812] I-226B. {(S)-1-[4-(5-Fluoro-2-nitro-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-but-3-enyl}-carbamic acid *tert*-butyl ester: To a dark yellow solution of I-226A (314.6 mg, 0.616 mmol) in MeOH (6.16 mL) was added

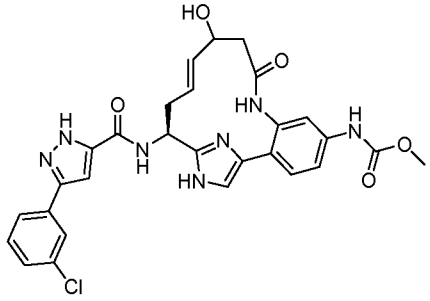
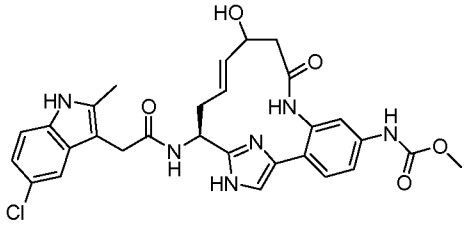
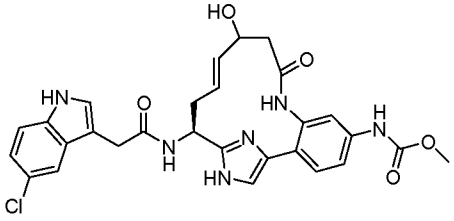
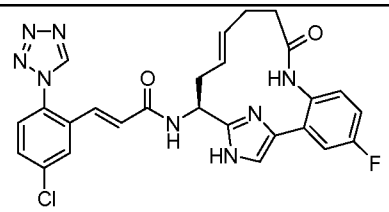
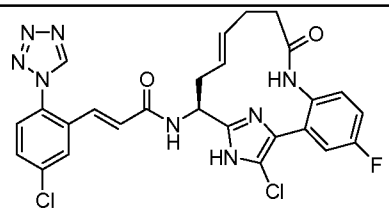
dropwise 4M HCl in dioxane (0.77 mL, 3.08 mmol). The reaction was allowed to stir at RT. After 30 min, the reaction was quenched with the dropwise addition of sat. $NaHCO_3$(aq) and then it was concentrated to give a light brown oil. The oil was then partitioned between sat. $NaHCO_3$(aq) and DCM and the layers were separated. The aqueous layer was extracted with DCM (1x). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to give 204.7 mg (82 %) of the amine as an orange oil. MS (ESI) *m/z*: 407.1 $(M+H)^+$.

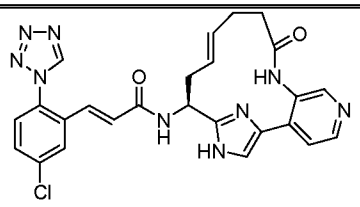
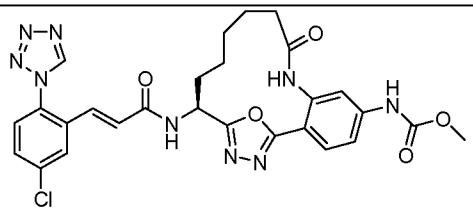
[00813] To a solution of amine (196.9 mg, 0.444 mmol) in DCM (1.4 mL) was added triethylamine (0.248 mL, 1.778 mmol). Next, BOC_2O (0.114 mL, 0.489 mmol) was added. After 30min, the reaction was partitioned between DCM and sat. $NaHCO_3$(aq) and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to an orange oil. Purification by normal phase chromatography gave 195.7 mg (87 %) of I-226B as a yellow-green residue. MS (ESI) *m/z*: 507.3 $(M+H)^+$.

[00814] I-226C. Example I-226 was prepared following the procedures described in 15B, by replacing 15A with I-226B; followed by steps 10D, by replacing but-3-enoic acid with pent-4-enoic acid; 2E/2F; 10H; and 15D. MS (ESI) *m/z*: 533.1 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ: 2.33 - 2.51 (m, 4 H), 2.53 - 2.61 (m, 1 H), 2.77 - 2.86 (m, 1 H), 5.09 (dd, *J*=9.9, 4.7 Hz, 1 H), 5.37 - 5.46 (m, 1 H), 5.52 - 5.60 (m, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 7.15 (d, *J*=15.7 Hz, 1 H), 7.27 - 7.38 (m, 3 H), 7.49 (s, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.5 Hz, 1 H), 9.51 (s, 1 H).

Table I-13: Examples I-222 to I-230

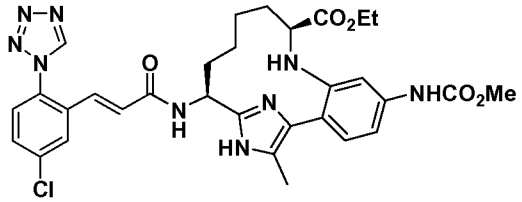
Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min)
I-222		548.1	6.9

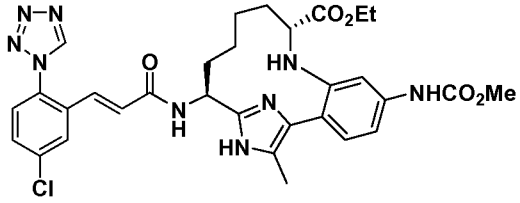
Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min)
I-223	 (diastereomer mixture)	576.2	5.4
I-224	 (diastereomer mixture)	577.2	4.3
I-225	 (diastereomer mixture)	563.2	4.1
I-226		533.1	5.2
I-227		567.0	7.5

Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min)
I-228		516.1	5.4
I-229		592.0	7.6

Examples I-241 and I-242.

(9S,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-17-methyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester, bis-trifluoroacetic acid salt, and (9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-17-methyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester, bis-trifluoroacetic acid salt





[00815] These compounds were prepared using a variation of the procedures employed to make compounds I-67 and I-68.

[00816] I-241A. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid methyl ester: To a suspension of Example 10C (3 g, 5.64 mmol) in CH_2Cl_2 (40 ml) at 0 °C was added Et_3N (0.944 ml, 6.77 mmol), followed by $(CF_3CO)_2O$ (0.797 ml, 5.64 mmol). The solvent was removed *in vacuo* and the residue was purified by normal phase chromatography to give to give a yellow foam (3.0 g, 4.54 mmol, 80 % yield): MS (ESI) *m/z*: 628.5.

[00817] I-241B. [4-[5-Bromo-2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid methyl ester: To a solution of Example I-241A (1.0 g, 1.593 mmol) in $CHCl_3$ (10 mL) at 0 °C was added 1-bromopyrrolidine-2,5-dione (0.284 g, 1.593 mmol) and stirred at the same temperature for 10 min. The reaction mixture was concentrated *in vacuo* and purified by normal phase chromatography: MS (ESI) *m/z*:708.

[00818] I-241C. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-5-methyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid methyl ester: To a mixture of Example I-241C (200 mg, 0.283 mmol), methylboronic acid (85 mg, 1.415 mmol) and K_3PO_4 (148 mg, 0.849 mmol) in a microwave vial was added dioxane (5 mL), which had been degassed by bubbling argon through it for 30 min. The reaction mixture was again degassed for 15 mins. To this mixture was then added $PdCl_2$(dppf)-CH_2Cl_2 adduct (46.2 mg, 0.057 mmol) and sealed immediately and subjected to microwave heating for 25 mins at 150 °C. The reaction mixture was diluted with EtOAc and washed with brine. Drying over Na_2SO_4, filtration, removal of solvent *in vacuo* and purification of the residue by normal phase chromatography gave an oil: MS (ESI) *m/z* = 642.3.

[00819] I-241D. {3-Amino-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-5-methyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-phenyl}-carbamic acid methyl ester: To a solution of I-241C (420 mg, 0.654 mmol) in MeOH (5 mL) was added a solution of LiOH (7 mL, 7 mmol) and stirred at 60 °C for 1.5 h. The reaction mixture was acidified to pH 6 with 1N HCl and extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by normal phase chromatography to give an oil. MS (ESI) *m/z*: 546.3.

[00820] Examples I-241 and I-242. The synthesis followed the procedures for I-67 and I-68 using Example I-241D instead of Example 10C. This gave rise to ethyl ester diastereomers instead of methyl ester diastereomers. Each diastereomer was separately carried on through the rest of the sequence as described for Examples I-67 and I-68.

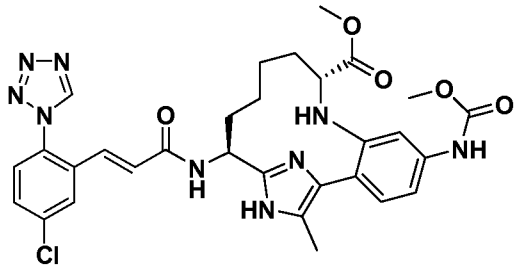
[00821] For Example I-241: ^{1}H NMR (500MHz, CD_3CN) δ 9.11 (s, 1H), 8.81 (d, *J* = 6.1 Hz, 1H), 7.85 - 7.79 (m, 2H), 7.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 2.2 Hz, 1H), 7.20 - 7.16 (m, 1H), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.98 (d, *J* =

15.4 Hz, 1H), 6.66 (d, *J* = 15.7 Hz, 1H), 5.33 (m, 1H), 4.09 - 3.94 (m, 2H), 3.70 (s, 3H), 3.07 (dd, *J* = 9.8, 2.9 Hz, 1H), 2.30 - 2.21 (m, 5H), 1.94 (m, 1H), 1.85 (br. s., 1H), 1.63 - 1.50 (m, 2H), 1.45 - 1.31 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 4H), 0.75 - 0.65 (m, 1H).

[00822] For Example I-242, ^{1}H NMR (500MHz, CD_3CN) δ: 10.02 (d, *J* = 8.5 Hz, 1H), 9.08 (s, 1H), 7.82 (d, *J* = 2.2 Hz, 1H), 7.66 (s, 1H), 7.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.21 - 7.15 (m, 2H), 7.15 - 7.10 (m, 1H), 6.79 - 6.72 (m, 1H), 6.63 - 6.58 (m, 1H), 5.84 (dt, *J* = 10.9, 8.2 Hz, 1H), 4.02 - 3.88 (m, 2H), 3.74 - 3.67 (m, 3H), 2.96 (d, *J* = 11.3 Hz, 1H), 2.39 - 2.31 (m, 4H), 2.17 - 2.02 (m, 2H), 1.94 (m, 1H), 1.76 - 1.63 (m, 2H), 1.56 - 1.44 (m, 2H), 1.44 - 1.32 (m, 1H), 1.11 - 1.02 (m, 3H), 0.44 - 0.32 (m, 1H).

Example I-243.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-17-methyl-8,16,18-triaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, bis-trifluoroacetic acid salt



[00823] I-243A. (R)-Methyl 2-(N-(2-(2-((S)-1-(*tert*-butoxycarbonylamino)but-3-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)-5-(methoxycarbonylamino)phenyl)-2,2,2-trifluoroacetamido)pent-4-enoate: Example I-74B (3.66 g, 5.68 mmol) was dissolved in EtOAc (50 mL) and the reaction mixture was cooled to 0 °C. Et_3N (1.585 ml, 11.37 mmol) was added followed by $(CF_3CO)_2O$ (0.964 ml, 6.82 mmol). The reaction mixture was allowed to warm to RT over 72h. The reaction mixture was diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by normal phase chromatography: Wt = 500 mg; MS (ESI) *m/z*: 740.

[00824] I-243B. (E)-(9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaene-9-carboxylic acid methyl ester: Example I-243A (500 mg, 0.676 mmol) was dissolved in DCE (15 ml) and reacted with Grubbs II catalyst according to the procedure described for I-74C. Workup and purification by normal phase chromatography provided a solid (Wt = 730 mg): MS (ESI) *m/z*: 712.5.

[00825] I-243C. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: Example I-243C was prepared according to the procedure described for I-74D using precursor I-243B (730 mg). Workup and normal phase chromatography provided the desired intermediate (Wt = 520 mg): MS (ESI) *m/z*: 714.

[00826] I-243D. (9R,14S)-17-Bromo-14-*tert*-butoxycarbonylamino-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: Example I-243C (520 mg, 0.628 mmol) was dissolved in $CHCl_3$ (10 mL). Reaction mixture cooled to 0 °C and NBS (123 mg, 0.691 mmol) was added. The reaction was allowed to stir at 0 °C. The reaction mixture was concentrated *in vacuo* and the residue was purified by normal phase chromatography. (Wt = 225 mg): MS (ESI) *m/z*: 795, 793. ^{1}H NMR (500 MHz, MeOH-d3) δ ppm 9.57 (1 H, br. s.), 7.83 - 7.95 (1 H, m), 7.60 (1 H, dd, J=8.25, 1.65 Hz), 7.39 (1 H, d, J=8.25 Hz), 5.75 (1 H, d, J=11.55 Hz), 5.42 (1 H, d, J=11.00 Hz), 4.97 - 5.02 (1 H, m), 4.48 - 4.62 (1 H, m), 3.80 (3 H, s), 3.78 (3 H, s), 3.58 - 3.71 (1 H, m), 2.22 - 2.36 (1 H, m), 1.84 - 1.97 (1 H, m), 1.64 - 1.81 (2 H, m), 1.44 (9 H, s), 0.84 - 1.05 (3 H, m), 0.00 (9 H, s).

[00827] I-243E. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-17-methyl-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: To a mixture of Example I-243D (78 mg, 0.098 mmol), methylboronic acid (10.57 mg, 0.177 mmol) and K_3PO_4 (18.46 mg, 0.106 mmol) in a microwave vial was added dioxane (1 mL) which was degassed by bubbling argon through it for 30 min. The reaction

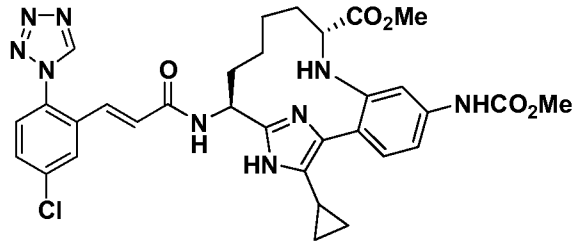
mixture was again degassed for 15 mins. To this mixture was then added $PdCl_2(dppf)$-CH_2Cl_2 adduct (5.77 mg, 7.06 μmol) and the reaction vial was sealed immediately and subjected to microwave heating for 15 min at 150 °C. The reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Normal phase chromatography provided a solid (Wt = 33 mg): MS (ESI) *m/z*: 696.4.

[00828] I-243F. (9R,14S)-14-Amino-5-methoxycarbonylamino-17-methyl-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, di-hydrochloride salt: Example I-243F was prepared from Example I-243E (42.7 mg, 0.227 mmol) using the procedure described for Example I-61B. Workup and reverse phase chromatography provided a solid which was a trifluoroacetic acid salt (Wt = 11 mg): MS (ESI) *m/z*: 402.3.

[00829] Example I-243. Example I-243F (11 mg, 0.015) and (E)-2,5-dioxopyrrolidin-1-yl 3-(5-chloro-2-(1H-tetrazol-1-yl)phenyl)acrylate (5.2 mg, 0.015 mmol) were reacted according to the procedure for Example 1G. Workup and reverse phase chromatography gave the desired product as a bis-trifluoroacetic acid salt (Wt = 6 mg): MS (ESI) *m/z*: 634.4. ^1H NMR (500MHz, CD_3CN) δ 9.91 (d, J = 8.3 Hz, 1H), 9.08 (s, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.74 - 7.42 (m, 3H), 7.26 - 7.06 (m, 3H), 6.77 (d, J = 15.7 Hz, 1H), 6.65 - 6.57 (m, 1H), 5.80 (dt, J = 11.3, 7.8 Hz, 1H), 3.76 - 3.65 (m, 3H), 3.55 - 3.46 (m, 3H), 3.01 (d, J=11.6 Hz, 1H), 2.39 - 2.31 (m, 3H), 2.19 - 2.02 (m, 2H), 1.94 (m, 2 H) 1.77 - 1.62 (m, 2H), 1.56 - 1.32 (m, 3H), 0.46 - 0.29 (m, 1H).

Example I-244.

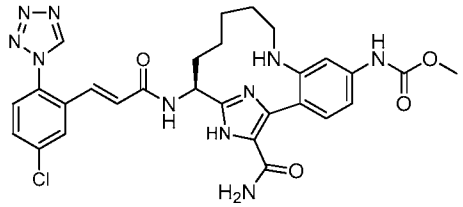
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyclopropyl-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, bis-trifluoroacetic acid salt



[00830] The synthesis for this compound followed the procedure for Example I-243 using cyclopropylboronic acid instead of methyl boronic acid in the step to make Example I-243E. Example I-244 was isolated as a bis-trifluoroacetic acid salt. MS (ESI) *m/z*: 660.3; ^{1}H NMR (500MHz, CD_3CN) δ 10.36 (d, *J* = 8.8 Hz, 1H), 9.08 (s, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.65 - 7.54 (m, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.18 - 6.98 (m, 2H), 6.63 - 6.56 (m, 2H), 5.97 - 5.86 (m, 1H), 3.71 (s, 3H), 3.48 (s, 3H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.14 - 2.02 (m, 2H), 1.75 - 1.42 (m, 6H), 1.34 (t, *J* = 13.2 Hz, 2H), 1.08 - 0.98 (m, 1H), 0.94 - 0.77 (m, 3H), 0.32 - 0.16 (m, 1H).

Example I-245.

{(S)-17-Carbamoyl-14-[(E)-3-(5-chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, 2 TFA

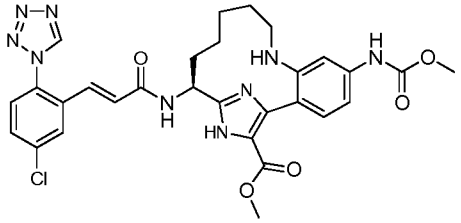


[00831] I-115D (0.050 g, 0.073 mmol) was dissolved in DMSO (0.367 ml) and K_2CO_3 (0.030 g, 0.220 mmol) was added followed by dropwise addition of 30% hydrogen peroxide (0.083 ml, 0.808 mmol). A thick white precipitate formed. The reaction was stirred at room temperature for 5.5 h under Ar. Reaction mixture was diluted with EtOAc and washed with water (3x) and brine, then dried over $MgSO_4$, filtered, and evaporated to yield a mixture of product, partially deprotected product (loss of trifluoroacetamide) and SM. This mixture was purified by reverse phase HPLC to remove the unreacted SM, and the product mixture was fully deprotected using the procedure described for step I-61B, followed by coupling of the resulting amine with Intermediate 1 using the procedure described in step 1G to yield Example I-245 as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.71 (1 H, s) 9.55 (1 H, s) 7.94 (1 H, d, *J*=1.65 Hz) 7.89 (1 H, d, *J*=8.25 Hz) 7.86 (1 H, br. s.) 7.61 - 7.67 (1 H, m) 7.55 - 7.60 (1 H, m) 7.26 (1 H, dd, *J*=8.52, 1.92 Hz) 7.23 (1 H, d, *J*=15.40 Hz) 6.79 (1 H, d, *J*=15.40 Hz) 5.15 (1 H, dd, *J*=10.45, 6.60 Hz) 3.73 (3 H, s) 3.20 (1 H, d, *J*=12.65 Hz) 2.97 (1 H, t, *J*=12.65 Hz) 2.09 - 2.18 (1 H, m)

2.00 (1 H, t, *J*=11.27 Hz) 1.79 - 1.92 (2 H, m) 1.61 (2 H, t, *J*=13.75 Hz) 1.32 (1 H, br. s.) 0.62 (1 H, d, *J*=12.65 Hz). MS (ESI) *m/z*: 605.4 $(M+H)^+$. Analytical HPLC: RT = 4.98 min.

Example I-246.

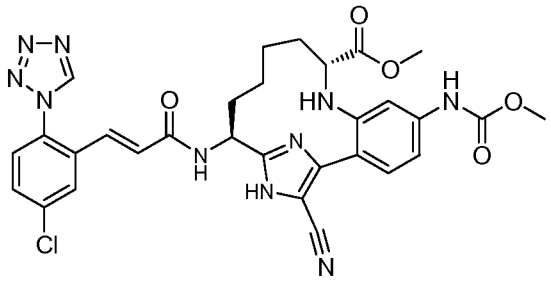
(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-17-carboxylic acid methyl ester, 2TFA



[00832] I-115D (0.025 g, 0.037 mmol) was dissolved in MeOH (0.5 ml), and then concentrated H_2SO_4 (0.050 ml) was added at rt. The reaction was heated at 75 °C under Ar overnight at which point the desired product, (S)-14-amino-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-17-carboxylic acid methyl ester (I-246A) was obtained along with (S)-5,14-diamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-17-carboxylic acid methyl ester (I-246B) from cleavage of the methylcarbamate. The reaction mixture was cooled to rt and diluted with MeOH, then filtered and purified by reverse phase HPLC. I-246A was deprotected using the procedure described in step I-61B, and the resulting amine coupled with Intermediate 1 using the procedure described for step 1G to provide Example I-246. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 13.28 (1 H, br. s.) 10.76 (1 H, br. s.) 10.18 (1 H, br. s.) 9.86 (1 H, s) 8.43 (1 H, d, *J*=5.50 Hz) 8.03 (1 H, d, *J*=7.15 Hz) 7.99 (1 H, d, *J*=2.20 Hz) 7.95 (1 H, br. s.) 7.69 - 7.79 (2 H, m) 7.44 (1 H, d, *J*=7.70 Hz) 6.84 - 6.93 (2 H, m) 5.19 - 5.28 (1 H, m) 3.80 (3 H, s) 3.72 (3 H, s) 3.05 (1 H, d, *J*=11.00 Hz) 2.83 (1 H, t, *J*=11.28 Hz) 1.91 - 2.00 (1 H, m) 1.79 (2 H, br. s.) 1.66 (1 H, q, *J*=10.73 Hz) 1.36 - 1.49 (2 H, m) 1.17 (1 H, br. s.) 0.61 (1 H, d, *J*=13.75 Hz). MS (ESI) *m/z*: 620.4 $(M+H)^+$. Analytical HPLC: RT = 5.55 min.

Example I-247.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyano-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, 2TFA



[00833] I-247A. (R)-Methyl 2-(N-(2-(2-((S)-1-(*tert*-butoxycarbonylamino)but-3-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)-5-(methoxycarbonylamino)phenyl)-2,2,2-trifluoroacetamido)pent-4-enoate: I-74B (12 g, 13.98 mmol) was dissolved in ethyl acetate (100 ml). Pyridine (1.357 ml, 16.77 mmol) was added, and the reaction was cooled to 0 °C. TFAA (2.172 ml, 15.38 mmol) was added dropwise with stirring, and reaction allowed to reach RT, then stirred at room temperature under Ar overnight. Reaction was diluted with EtOAc and water. Aq. phase was extracted 3x with EtOAc, and the combined organic phases were dried with sodium sulfate, filtered and concentrated. Residue was purified by flash chromatography to provide the desired trifluoroacetamide containing minor impurities which do not separate on silica gel. This crude product was taken on without further purification.

[00834] I-247B. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8-(2,2,2-trifluoroacetyl)-16-(2-trimethylsilanylethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: I-247A (6.15 g, 8.31 mmol) was dissolved in DCE (208 ml) in a rbf equipped with an argon inlet and reflux condenser. The solution was degassed by bubbling with Ar for 15 minutes. The reaction mixture was heated to 84 °C, and a solution of Grubbs II (1.059 g, 1.247 mmol) dissolved in 15 mL of DCE was added. Reaction mixture was stirred at 84 °C under Ar for 15 hours. Reaction was quenched by addition of a saturated $NaHCO_3$ solution and diluted with DCM. The organic layer was extracted one more time with saturated $NaHCO_3$ solution and once with brine. Organic phase was dried with Na_2SO_4, filtered and concentrated. Residue was purified by flash chromatography to provide the RCM product in ~37% yield as a mixture of cis/trans isomers. A portion of this

intermediate (1.9 g, 2.67 mmol) was taken up in MeOH (26.7 ml) and Pd/C (0.284 g, 0.267 mmol) added. The mixture was then stirred at room temperature under 50 psi H_2 for 48 h to provide I-127-B (1.66g, 87%) after removal of catalyst and evaporation of solvent. MS (ESI) *m/z*: 714.3 $(M+H)^+$.

[00835] I-247C. (9R,14S)-14-*tert*-Butoxycarbonylamino-17-cyano-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: (9R,14S)-17-Bromo-14-*tert*-butoxycarbonylamino-5-methoxycarbonylamino-8-(2,2,2-trifluoro-acetyl)-16-(2-trimethylsilanyl-ethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, prepared from I-247B using the procedure described for I-115C, (2.0 g, 2.52 mmol) was dissolved in DMF (12.61 ml). Zinc cyanide (0.178 g, 1.514 mmol) was added and the reaction was degassed by bubbling with Ar for 15 minutes. $(Ph_3)_4Pd$ (0.292 g, 0.252 mmol) was added and the mixture stirred at 120 °C for 10 hours under Ar. Reaction mixture was diluted with EtOAc, washed 4x with 10% LiCl, brine, dried with sodium sulfate, filtered and concentrated. Residue was purified by flash chromatography to provide 1.44 g of a 3:1 mixture cyano product to starting bromide. This mixture was re-subjected to the above reaction conditions and isolation to yield I-247C in ~60% yield after chromatography. MS (ESI) *m/z*: 739.3 $(M+H)^+$.

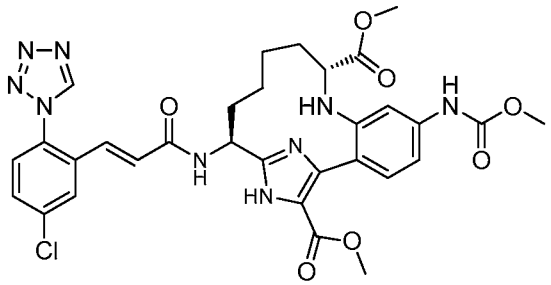
[00836] I-247D. (9R,14S)-14-Amino-17-cyano-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester, 3TFA: I-247C (0.106 g, 0.143 mmol) was dissolved in MeOH (2 mL) and a solution of O-methylhydroxylamine in H_2O (25% w/w, 0.135 mL, 0.717 mmol) was added followed by 6M HCl (2 mL). The mixture was heated with stirring in a sealed tube at 75 °C ON. Reaction mixture was concentrated, and HCl/Dioxane (0.5 mL) and MeOH (2 mL) were added followed by stirring overnight at room temperature. The mixture was concentrated and residue purified by reverse phase HPLC to provide I-247D (0.031 g, 28.6%) as a white solid. MS (ESI) *m/z*: 413.3 $(M+H)^+$.

[00837] I-247E. Example I-247 was prepared from I-247D by coupling with Intermediate 1 using the procedure described for step 1G. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (1 H, br. s.), 8.00 (1 H, d, *J*=2.20 Hz), 7.65 (1 H, dd, *J*=8.80, 2.20 Hz), 7.56

(1 H, d, *J*=8.80 Hz), 7.46 (1 H, d, *J*=8.25 Hz), 7.42 - 7.45 (1 H, m), 7.16 (1 H, dd, *J*=8.52, 1.92 Hz), 7.10 (1 H, d, *J*=15.40 Hz), 6.80 (1 H, d, *J*=15.95 Hz), 5.19 (1 H, dd, *J*=10.72, 6.87 Hz), 3.74 (3 H, s), 3.58 (3 H, s), 3.01 - 3.07 (1 H, m), 2.05 - 2.17 (1 H, m), 1.80 - 1.92 (2 H, m), 1.69 - 1.80 (1 H, m), 1.32 - 1.53 (4 H, m), 0.33 - 0.51 (1 H, m). MS (ESI) *m/z*: 645.4 $(M+H)^+$. Analytical HPLC: RT = 8.23 min.

Example I-248.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9,17-dicarboxylic acid dimethyl ester, 2TFA

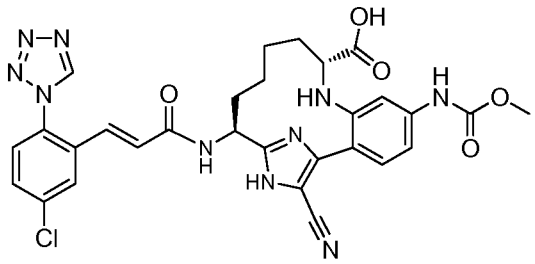


[00838] I-248A. (9R,14S)-14-*tert*-Butoxycarbonylamino-17-carbamoyl-5-methoxycarbonylamino-8-(2,2,2-trifluoroacetyl)-16-(2-trimethylsilanylethoxymethyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid methyl ester: I-247C (60 mg, 0.081 mmol), acetaldehyde oxime (9.90 µl, 0.162 mmol), triphenylphosphine (4.26 mg, 0.016 mmol) and palladium(II) acetate (1.823 mg, 8.12 µmol) were weighed into a 1 dram pressure-rated vial, and ethanol (0.2 mL) and water (0.050 mL) were added. The vial was flushed with argon and capped, and the reaction mixture was heated at 80 °C with stirring for ~1 h. Reaction was cooled to room temperature, filtered through a syringe filter, which was further washed with mix of $MeOH/CH_2Cl_2$, and the filtrate was stripped to dryness. Residue was purified by flash chromatography to provide I-248A (42.1 mg, 68.5 %). MS (ESI) *m/z*: 757.4 $(M+H)^+$

[00839] I-248B. (9R,14S)-14-Amino-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9,17-dicarboxylic acid dimethyl ester, 3TFA: I-248B was obtained from I-248A using the procedure described for step I-61B and isolated as the tris-TFA salt after reverse phase HPLC.

[00840] I-248C. Example I-248 was prepared from I-248B by coupling with Intermediate 1 using the procedure described for step 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (1 H, s), 7.98 (1 H, d, *J*=2.2 Hz), 7.67 (1 H, dd, *J*=8.8, 2.2 Hz), 7.59 (1 H, s), 7.57 (1 H, s), 7.45 (1 H, s), 7.09 - 7.16 (2 H, m), 6.76 (1 H, d, *J*=15.4 Hz), 5.18 (1 H, dd, *J*=11.0, 7.1 Hz), 3.88 (3 H, s), 3.75 (3 H, s), 3.59 (3 H, s), 3.05 (1 H, d, *J*=11.5 Hz), 2.21 - 2.33 (1 H, m), 1.99 - 2.08 (1 H, m), 1.67 - 1.78 (2 H, m), 1.51 - 1.62 (1 H, m), 1.37 - 1.50 (2 H, m), 0.40 - 0.55 (1 H, m). MS (ESI) *m/z*: 678.1 $(M+H)^+$. Analytical HPLC: RT = 6.52 min.

Example I-250.
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyano-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid, 2 TFA

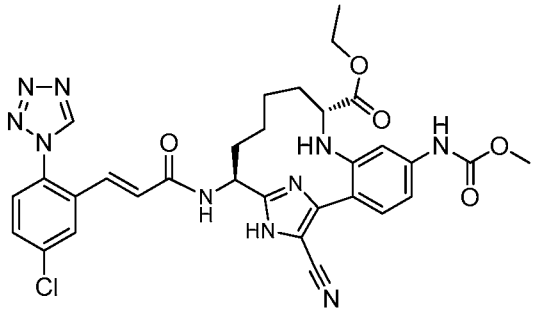


[00841] I-250A. (9R,14S)-14-Amino-17-cyano-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid, 3 TFA: A mixture of I-247C (165 mg, 0.193 mmol), O-methoxyamine hydrochloride (30% in water, 0.245 mL, 0.967 mmol), 6M HCl (1.29 ml, 7.74 mmol) and MeOH (1.6 ml) was heated with stirring in a 75 °C oil bath overnight in a sealed 5 mL pressure-rated vial. Reaction was cooled to room temperature and determined by LCMS to be an ~ 1:1 mixture of methyl ester and acid products. The mixture was stripped to dryness, and residue was redissolved in a mixture of 4 mL THF, 2.5 mL 1M LiOH and ~0.5 mL MeOH, then stirred overnight at room temperature under nitrogen. Reaction mixture was neutralized with 1M HCl and stripped to dryness. Residue was purified by reverse phase HPLC to provide I-250A (29.3 mg, 29.6 %) and the corresponding methyl ester, I-247D (23.2 mg, 22.78 %). I-250A MS (ESI) *m/z*: 399.2 $(M+H)^+$.

[00842] I-250B. Example I-250 was prepared from I-250A by coupling with Intermediate 1 using the procedure described for step 1G. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.98 (1 H, br. s.), 9.86 (1 H, s), 9.79 (1 H, s), 8.76 (1 H, d, *J*=7.7 Hz), 7.93 (1 H, d, *J*=2.2 Hz), 7.67 - 7.80 (2 H, m), 7.34 (1 H, br. s.), 7.28 (1 H, d, *J*=8.2 Hz), 7.10 (1 H, d, *J*=8.2 Hz), 6.82 - 6.96 (2 H, m), 5.14 - 5.27 (1 H, m), 5.00 (1 H, br. s.), 3.67 (3 H, s), 2.68 - 2.85 (1 H, m), 1.99 (1 H, br. s.), 1.59 - 1.79 (3 H, m), 1.17 - 1.36 (3 H, m), 0.33 (1 H, br. s.). MS (ESI) *m/z*: 631.4 $(M+H)^+$ Analytical HPLC: RT = 7.66 min.

Example I-251.

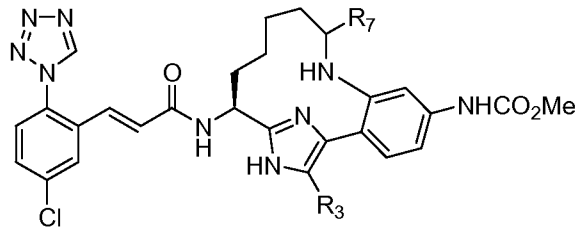
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyano-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid ethyl ester, 2 TFA

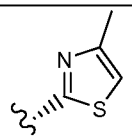
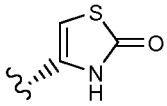
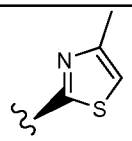
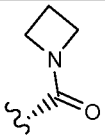
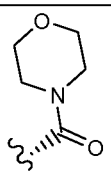


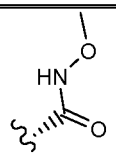
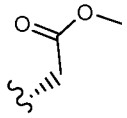
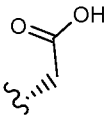
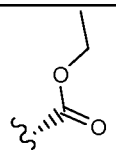
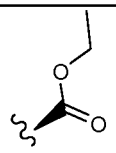
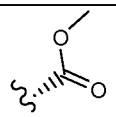
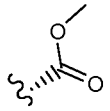
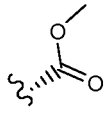
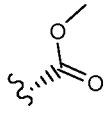
[00843] Example I-251. Example I-250 (15.8 mg, 0.018 mmol) was dissolved in EtOH (0.5 ml) and TMS-Cl (5.64 µl, 0.044 mmol) was added under nitrogen. Reaction mixture was stirred at room temperature overnight. Only a small amount of desired product was observed, therefore, the solution was transferred to a pressure-rated vial using ~ 0.2 mL additional EtOH to rinse. An additional 20 µL TMS-Cl were added, and the vial was capped and heated with stirring at 75 °C for 4 h. LCMS shows complete conversion to ethyl ester. Reaction mixture was stripped to dryness and crude product was redissolved in MeOH, filtered and purified by reverse phase HPLC to provide Example I-251 (6.8 mg, 40.4 %) as a white solid. ^{1}H NMR (500 MHz, CD_3CN) δ ppm 9.10 (1 H, s), 7.88 (1 H, d, *J*=2.2 Hz), 7.86 (1 H, s), 7.61 (1 H, dd, *J*=8.5, 2.2 Hz), 7.52 (2 H, dd, *J*=11.8, 8.5 Hz), 7.41 (1 H, d, *J*=1.9 Hz), 7.36 (1 H, d, *J*=7.4 Hz), 7.17 (1 H, dd, *J*=8.3, 2.2 Hz), 7.01 (1 H, d, *J*=15.4 Hz), 6.65 (1 H, d, *J*=15.7 Hz), 5.30 (1 H, ddd, *J*=10.9, 7.0, 6.9 Hz), 3.92 - 4.07 (2 H, m), 3.71 (3 H, s), 2.94 - 3.05 (1 H, m), 2.05 - 2.16

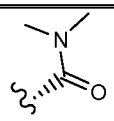
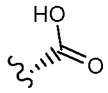
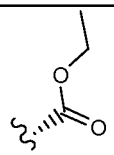
(1 H, m), 1.66 - 1.83 (3 H, m), 1.32 - 1.57 (3 H, m), 1.10 (3 H, t, *J*=7.2 Hz), 0.42 (1 H, d, *J*=12.7 Hz). MS (ESI) *m/z*: 659.2 $(M+H)^+$. Analytical HPLC: RT = 9.00 min.

Table I-14: Examples I-231 to I-251



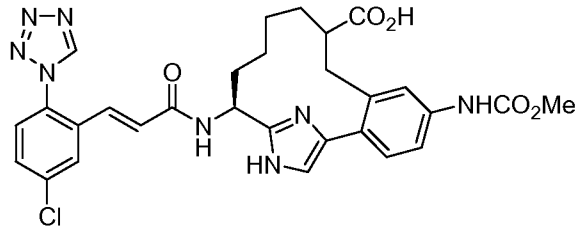
Ex. #	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-231	CH_2OMe (homochiral)	H	606.3	9.1
I-232	CH_2OMe (homochiral)	H	606.3	9.0
I-233		H	659.3	5.9
I-234		H	661.2	5.8
I-235		H	659.2	5.8
I-236		H	645.3	5.1
I-237		H	675.3	5.1

Ex. #	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-238		H	635.2	5.4
I-239		H	634.2	6.8
I-240		H	620.1	5.3
I-241		Me	648.4	6.1
I-242		Me	648.4	5.9
I-243		Me	634.4	5.8
I-244			660.3	6.2
I-245	H	$CONH_2$	605.4	5.0
I-246	H	CO_2Me	620.4	5.5
I-247		CN	645.4	8.2
I-248		CO_2Me	678.3	6.1

Ex. #	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-249		CN	658.4	7.8
I-250		CN	631.4	7.7
I-251		CN	659.2	9.0

Example I-252.

(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid *tert*-butyl ester, trifluoroacetic acid salt



[00844] I-252A. 3-{2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-5-methoxycarbonylamino-phenyl}-propionic acid *tert*-butyl ester: (Molander, G.A., *Organic Letters*, 10(9):1795 (2008).) A thick-walled 150-mL screw top flask containing potassium 3-trifluoroboratopropionate *tert*-butyl ester (2.180 g, 9.23 mmol), 10B (5.0 g, 8.39 mmol), palladium acetate (0.141 g, 0.630 mmol), 2-dicyclohexylphosphino-2′,6′-di-i-propoxy-1,1′-biphenyl (Ru-Phos) (0.588 g, 1.259 mmol), and potassium carbonate (3.48 g, 25.2 mmol) was purged with argon for several minutes. Next, degassed toluene (33.6 ml) and degassed water (8.4 ml) were added and under a blanket of argon the septum was replaced with a teflon screw cap possessing a Viton O-ring. The biphasic orange mixture was warmed to 85 °C. After 24 h, the reaction was stopped and cooled to RT. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with

brine, dried over Na_2SO_4, filtered and concentrated to give a yellow foam weighing 6.63 g. Purification by normal phase chromatography (gradient elution 0-20% EtOAc/DCM) gave 1.45 g (27%) of I-252A, as a white foam. MS (ESI) *m/z*: 645.4 $(M+H)^+$.

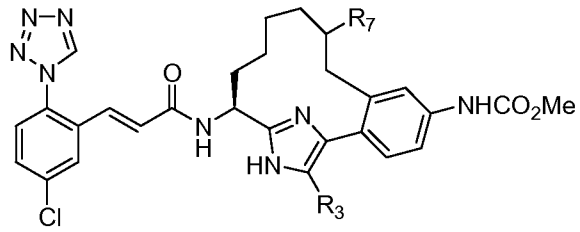
[00845] I-252B. 2-{2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-5-methoxycarbonylamino-benzyl}-pent-4-enoic acid *tert*-butyl ester: To a cooled solution (-78 °C) of diisopropylamine (1.167 ml, 8.19 mmol) in degassed THF (14 mL) was added dropwise n-BuLi (4.65 ml, 7.44 mmol). The resulting clear, pale yellow solution was stirred at -78 °C for 45 min. Next, a clear, pale yellow solution of I-252A (1.20 g, 1.86 mmol) in THF (degassed, 9 ml) was added dropwise over 30 min. The resulting yellow suspension was stirred vigorously at -78 °C. After 1.5 h, allyl bromide (0.161 ml, 1.861 mmol) was added dropwise. The reaction mixture was stirred at -78 °C. After 1 h, the clear, pale yellow solution was allowed to slowly warm to -15 °C. The reaction was quenched with the dropwise addition of sat. ammonium chloride and the reaction was allowed to warm to RT. The reaction was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated to give a yellow foam. Purification by normal phase chromatography (gradient elution 0-20% EtOAc/DCM) gave 1.04 g (70%) as a 1:2.6 mixture of I-252A:I-252B. Compound I-252B is a mixture of diastereomers. MS (ESI) *m/z*: 686.7 $(M+H)^+$.

[00846] I-252C. (S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid *tert*-butyl ester, trifluoroacetic acid salt (Diastereomer A) and I-252D. (S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-(2-trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid *tert*-butyl ester, trifluoroacetic acid salt (Diastereomer B). The title compounds I-252C (Diastereomer A) and I-252D (Diastereomer B) were prepared by following the procedures described in 2E/2F, by replacing 2D with the 1:2.6 mixture of I-253A:I-253B; followed by step 2G, by replacing methanol with ethanol. The diastereomers were separated by reverse phase chromatography.

[00847] I-252E. Example I-252 was prepared by following the procedures described in step10H, by replacing 10G with I-252C (diastereomer A) and by running the reaction at 75 °C; followed by step 1G. ^{1}H NMR (500 MHz, CD_3OD) 50 °C, δ ppm 9.46 (s, 1 H), 7.94 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.8, 2.2 Hz, 1 H), 7.57 (d, J=8.8 Hz, 1 H), 7.45 - 7.52 (m, 3 H), 7.38 (d, J=8.2 Hz, 1 H), 7.17 (d, J=15.9 Hz, 1 H), 6.74 (d, J=15.9 Hz, 1 H), 5.18 (t, J=6.0 Hz, 1 H), 3.74 (s, 3 H), 2.79 - 2.91 (m, 2 H), 2.18 - 2.27 (m, 2 H), 1.97 - 2.06 (m, 1 H), 1.30 - 1.67 (m, 4 H), 1.05 - 1.16 (m, 1 H), 0.40 - 0.55 (m, 1 H). MS (ESI) *m/z*: 605.3 $(M+H)^+$. Analytical HPLC: RT = 8.82 min.

[00848] Examples I-253 to I-255 were prepared from I-252C (diastereomer A) according to the procedures described in the previous examples. Examples I-256 to I-259 were prepared from I-252D (diastereomer B) according to the procedures described in the previous examples.

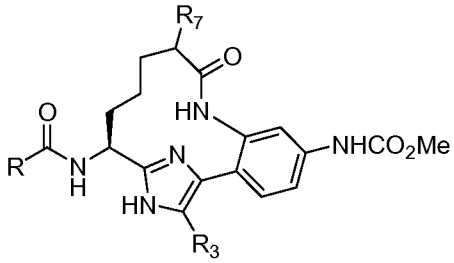
Table I-15: Examples I-252 to I-259

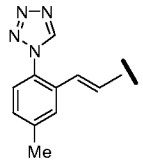
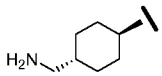
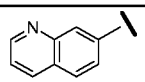
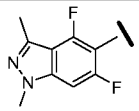


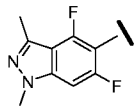
Ex. #	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-252	CO_2H (homochiral)	H	605.3	8.8
I-253	CO_2Me (homochiral)	H	619.4	9.2
I-254	$CONMe_2$ (homochiral)	H	632.5	8.7
I-255	$CONMe_2$ (homochiral)	Cl	666.2	7.4

Ex. #	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-256	CO_2H (homochiral)	H	605.3	8.8
I-257	CONHMe (homochiral)	H	618.5	8.6
I-258	$CONMe_2$ (homochiral)	H	632.5	8.7
I-259	$CONH_2$ (homochiral)	H	604.4	8.5

Table I-16: Examples I-260 to I-264

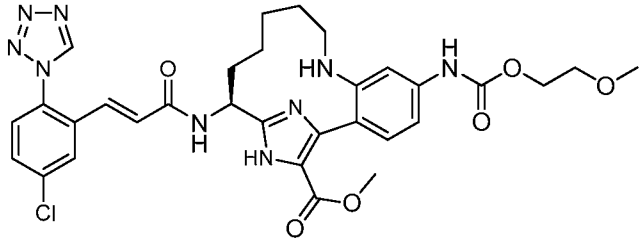


Ex. #	R	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-260		H	H	556.3	8.1
I-261		H	H	483.4	6.5 (C)
I-262		H	H	499.3	3.1
I-263			H	566.3	8.0

Ex. #	R	R7	R3	LCMS $[M+H]^+$	HPLC RT (min.)
I-264			Cl	600.3	7.5

Example 266.

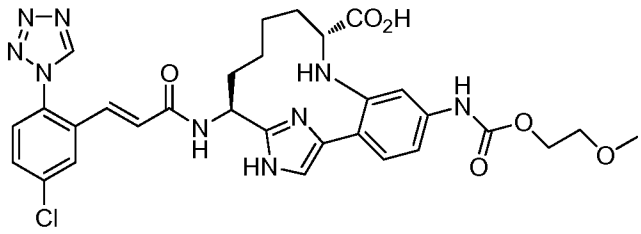
(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-(2-methoxy-ethoxycarbonylamino)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-17-carboxylic acid methyl ester, 2TFA



[00849] Example I-266 was prepared from aniline, I-246B following a similar procedure to that described for step I-123B. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.53 (1 H, s) 8.34 (1 H, d, *J*=8.80 Hz) 8.03 (1 H, br. s.) 8.02 (1 H, d, *J*=2.20 Hz) 7.67 - 7.71 (1 H, m) 7.59 - 7.62 (1 H, m) 7.31 (1 H, dt, *J*=8.80, 1.10 Hz) 7.19 (1 H, d, *J*=15.95 Hz) 6.80 (1 H, d, *J*=15.40 Hz) 5.31 (1 H, dd, *J*=10.17, 6.32 Hz) 4.26 - 4.32 (2 H, m) 3.89 (3 H, s) 3.65 (2 H, t, *J*=4.67 Hz) 3.39 (3 H, s) 3.18 - 3.24 (1 H, m) 2.98 (1 H, t, *J*=11.27 Hz) 2.09 - 2.19 (1 H, m) 1.99 (1 H, br. s.) 1.83 - 1.96 (2 H, m) 1.67 (2 H, t, *J*=12.10 Hz) 1.31 (1 H, br. s.) 0.69 - 0.82 (1 H, m). MS (ESI) *m/z*: 664.4 $(M+H)^+$. Analytical HPLC: RT = 5.65 min.

Example I-267.

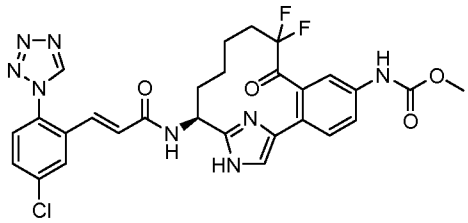
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-(2-methoxy-ethoxycarbonylamino)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid, 2 TFA



[00850] Example I-131 (13 mg, 0.015 mmol) was dissolved in 4M HCl/dioxane (2 mL)/water (0.5 mL) and heated to 55 °C in a sealed vial for 1.5 h. then at 45 °C for 9h. Reaction mixture was filtered and residue was purified by reverse phase HPLC to provide Example I-267 (4.41 mg, 32.7 %) as a yellow solid. ^{1}H NMR (500 MHz, CD_3CN) δ ppm 9.43 (1 H, br. s.), 9.09 (1 H, s), 7.73 - 7.89 (2 H, m), 7.60 (1 H, dd, *J*=8.25, 2.20 Hz), 7.47 (1 H, d, *J*=8.25 Hz), 7.39 (1 H, s), 7.21 - 7.29 (2 H, m), 7.09 - 7.18 (1 H, m), 6.82 - 6.93 (1 H, m), 6.62 (1 H, d, *J*=15.95 Hz), 5.59 - 5.76 (1 H, m), 4.13 - 4.31 (2 H, m), 3.58 (2 H, t, *J*=4.40 Hz), 3.33 (3 H, s), 3.26 (1 H, s), 3.01 (1 H, d, *J*=11.55 Hz), 2.08 - 2.18 (1 H, m), 1.97 - 2.08 (1 H, m), 1.64 - 1.77 (2 H, m), 1.35 - 1.55 (3 H, m), 0.21 - 0.37 (1 H, m). MS (ESI) *m/z*: 650.4 $(M+H)^+$. Analytical HPLC: RT = 5.18 min.

Example I-270.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9,9-difluoro-8-oxo-16,18-diaza-tricyclo[13.2.1.0^{2,7}]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl}-carbamic acid methyl ester, TFA salt



[00851] I-270A. 2,2-Difluoro-1-morpholinopent-4-en-1-one: To a solution of 2,2-difluoropent-4-enoic acid (701 mg, 5.15 mmol) in dichloromethane (10 mL) was added catalytic amount of DMF (0.05ml, 0.646 mmol). Then the reaction mixture was cooled in ice bath. To the solution was added oxalyl chloride (0.460 ml, 5.15 mmol) dropwise. The resulting solution was stirred for 2 hr at rt.

[00852] Reaction mixture was then cooled in ice bath, added TEA (1.436 ml, 10.30 mmol) and morpholine (0.497 ml, 5.7 mmol). The resulting solution was stirred for 1.5 h

at rt. The reaction mixture was then diluted with EtOAc (30 ml) and washed with aq. NH_4Cl. Organic solution was dried over $MgSO_4$ and concentrated *in vacuo*, yielding oily residue, which was purified on normal phase chromatography to provide 633 mg (3.1 mmol, 60 % yield) of I-270A as light brown oil. MS (ESI) *m/z*: 206.1 $(M+1)^+$.

[00853] I-270B. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-4-yl]-3-(2,2-difluoro-pent-4-enoyl)-phenyl]-carbamic acid methyl ester: To a solution of 10B (0.145 g, 0.243 mmol) in THF (2 mL) under N_2 was added BuLi 2.5M in hex (0.487 mL, 1.217 mmol) at -78 °C. The resulting solution was stirred for 0.5h and to the solution was added I-270A in 3 ml of THF dropwise for 10 min. The reaction mixture was allowed to warm up to RT. The reaction was then quenched by adding aq. NH_4Cl (2 mL). The reaction mixture was then diluted with EtOAc (30 ml) and washed with aq. NH_4Cl (10 mL). Organic solution was dried over $MgSO_4$ and concentrated *in vacuo*, yielding oily residue, which was purified on normal phase chromatography to yield I-270B. TFA to yield I-270B. TFA (43 mg, 0.057 mmol, 23.6%).

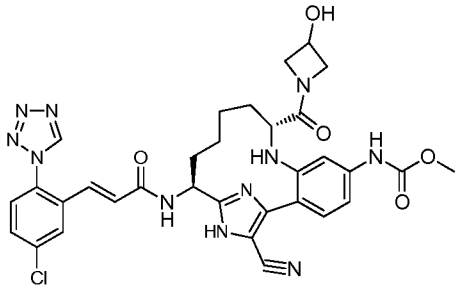
[00854] I-270C. [(E)-(S)-9,9-Difluoro-5-methoxycarbonylamino-8-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-yl]-carbamic acid *tert*-butyl ester: Compound I-270C was prepared following the procedure described step 2E/2F, by replacing 2D with I-270B. MS (ESI) *m/z* : 607.2 $(M+1)^+$.

[00855] I-270D. [(S)-9,9-Difluoro-5-methoxycarbonylamino-8-oxo-16-(2-trimethylsilanyl-ethoxymethyl)-16,18-diaza-tricyclo[13.2.1.$0^{2,7}$]octadeca-1(17),2,4,6,15(18)-pentaen-14-yl]-carbamic acid *tert*-butyl ester: A solution of I-270C (14 mg, 0.023 mmol) and PtO_2 (3 mg, 0.013 mmol) in EtOAc (5 mL) and MeOH (5ml) was stirred under H_2 (50 psi) for 14h. The reaction mixture was filtered and concentrated *in vacuo* to provide I-270D (14 mg, 100%), which was subjected to the following reaction without further purification. MS (ESI) *m/z*: 609.3 $(M+H)^+$.

[00856] I-270E. Example I-270 was prepared following the procedures described in step 10H, by replacing 10G with I-270D; followed by step 1G. ^{19}F NMR (376 MHz, acetonitrile-d_3) δ ppm -76.47 (2 F, br. s.). MS (ESI) *m/z*: 611.2 $(M+H)^+$. Analytical HPLC: RT = 5.59 min.

Example I-280.

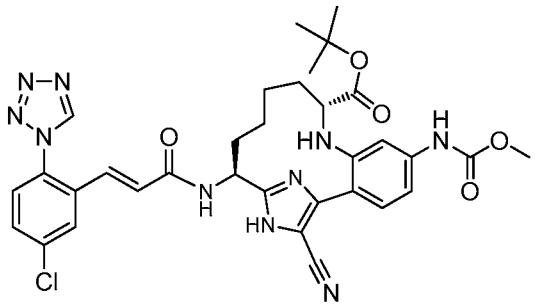
[(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyano-9-(3-hydroxy-azetidine-1-carbonyl)-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaen-5-yl]-carbamic acid methyl ester, 2TFA



[00857] A mixture of Example I-250 (0.020 g, 0.023 mmol), azetidin-3-ol hydrochloride (3.83 mg, 0.035 mmol), and BOP reagent (0.015 g, 0.035 mmol) in DMF (0.5 mL), was treated with DIPEA (0.020 mL, 0.116 mmol) and then stirred at room temperature under Ar overnight. Reaction was evaporated to remove DMF, and the residue was purified by reverse phase HPLC to provide Example I-280 (0.0196 g, 92 %) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 8.00 (1 H, d, *J*=2.2 Hz), 7.67 (1 H, dd, *J*=8.8, 2.2 Hz), 7.55 - 7.61 (2 H, m), 7.40 (1 H, dd, *J*=17.9, 1.9 Hz), 7.28 - 7.33 (1 H, m), 7.14 (1 H, dd, *J*=15.7, 1.4 Hz), 6.80 (1 H, d, *J*=15.9 Hz), 5.22 (1 H, dd, *J*=11.0, 6.6 Hz), 4.33 - 4.47 (1 H, m), 4.04 - 4.12 (1 H, m), 3.79 - 4.06 (1 H, m), 3.59 - 3.67 (1 H, m), 3.38 - 3.62 (1 H, m), 3.13 - 3.18 (1 H, m), 2.12 - 2.21 (1 H, m), 1.77 - 2.01 (3 H, m), 1.45 - 1.56 (2 H, m), 1.31 (1 H, t, *J*=14.0 Hz), 0.42 - 0.55 (1 H, m). MS (ESI) *m/z*: 686.1 $(M+H)^+$. Analytical HPLC: RT = 6.98 min.

Example I-283.

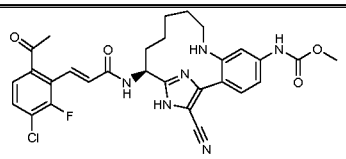
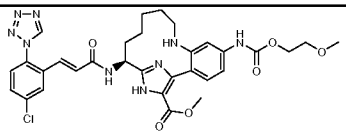
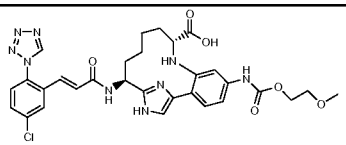
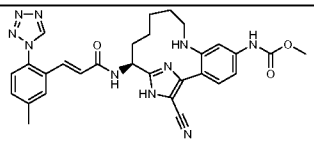
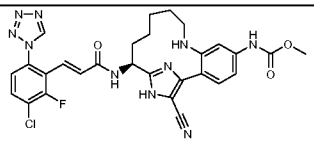
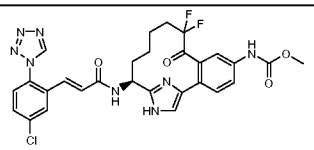
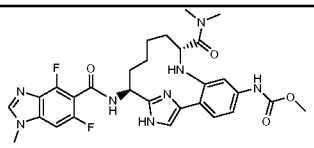
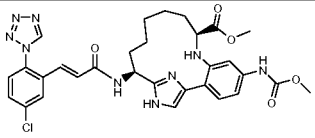
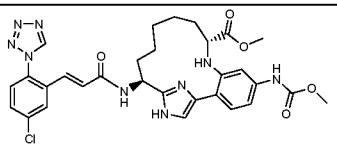
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-17-cyano-5-methoxycarbonylamino-8,16,18-triaza-tricyclo[13.2.1.02,7]octadeca-1(17),2,4,6,15(18)-pentaene-9-carboxylic acid *tert*-butyl ester

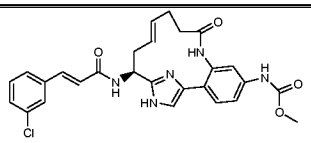
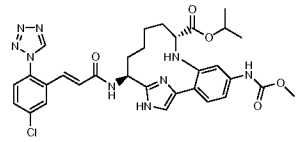
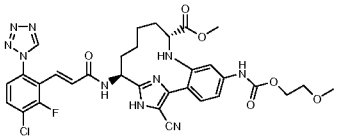
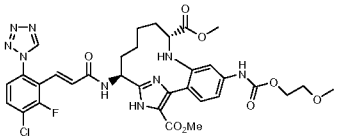
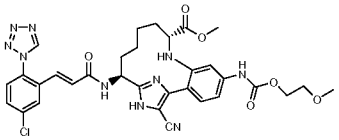
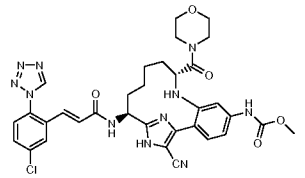
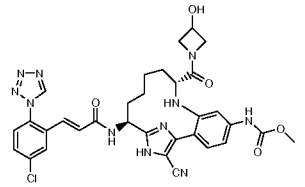
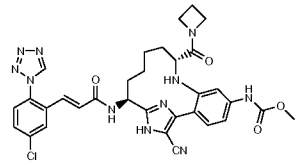


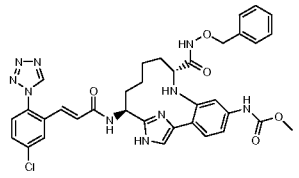
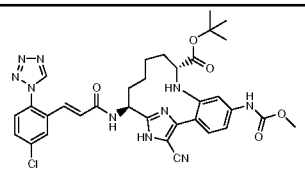
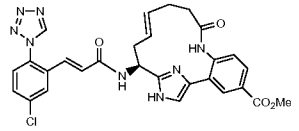
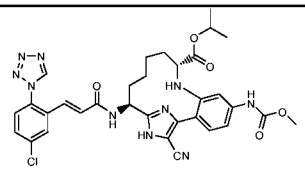
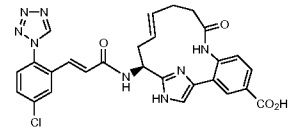
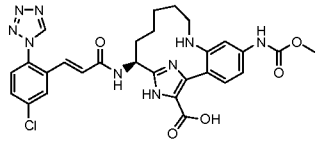
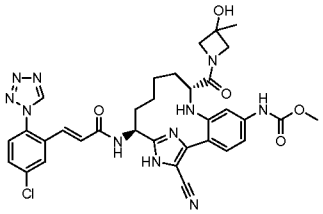
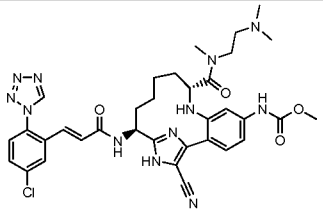
[00858] To a solution of Example I-250 (0.03 g, 0.048 mmol) in THF (0.5 ml)/Dichloromethane (0.5 ml) at RT was added *t*-BuOH (0.500 ml) and a solution of (E)-*tert*-butyl N,N′-diisopropylcarbamimidate (0.048 g, 0.238 mmol) dissolved in DCM (0.3 mL). Reaction was allowed to stir at RT ON. Reaction was concentrated and residue was purified by reverse phase HPLC. The fractions containing the product were neutralized by passing through a PL-HCO_3 MP SPE cartridge prior to evaporating to dryness to yield Example I-283 (12 mg, 36.4 %) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.53 (1 H, s), 8.02 (1 H, d, *J*=2.48 Hz), 7.68 (1 H, dd, *J*=8.53, 2.20 Hz), 7.59 (1 H, d, *J*=8.53 Hz), 7.46 (2 H, d, *J*=8.25 Hz), 7.05 - 7.18 (2 H, m), 6.83 (1 H, d, *J*=15.68 Hz), 5.22 (1 H, dd, *J*=10.73, 6.88 Hz), 3.77 (3 H, s), 2.77 - 2.87 (1 H, m), 2.09 - 2.19 (1 H, m), 1.78 - 1.96 (2 H, m), 1.64 - 1.78 (1 H, m), 1.40 - 1.53 (2 H, m), 1.28 - 1.40 (10 H, m), 0.39 - 0.55 (1 H, m). MS (ESI) *m/z*: 687.2 $(M+H)^+$. Analytical HPLC: RT = 9.28 min.

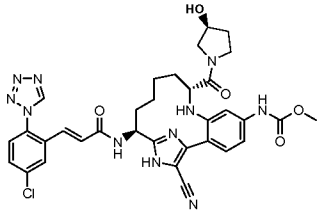
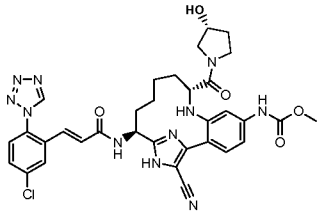
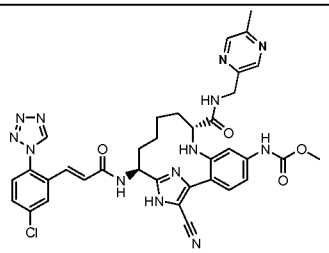
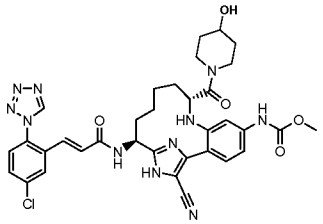
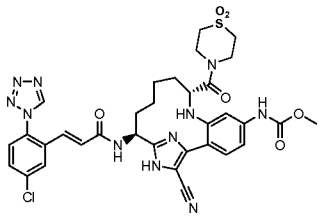
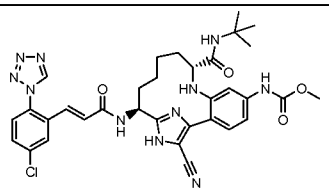
[00859] Example I-284 was prepared according to the procedure described in 88C, by replacing 88B with Intermediate 37 and by replacing Intermediate 12 with Intermediate 39; followed by steps I-226B; 10D, by replacing but-3-enoic acid with pent-4-enoic acid; 2E/2F; 10H; and 1G. Examples I-286 was prepared according to the procedure described in 88C, by replacing 88B with Intermediate 37 and by replacing Intermediate 12 with Intermediate 39; followed by steps I-226B; 10D, by replacing but-3-enoic acid with pent-4-enoic acid; 2E/2F; 10H; saponification of the methyl ester with 1.0 M aqueous sodium hydroxide in methanol at 45 °C; and 1G.

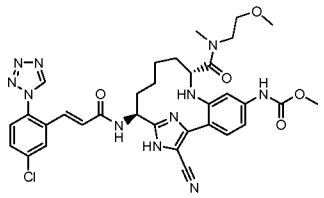
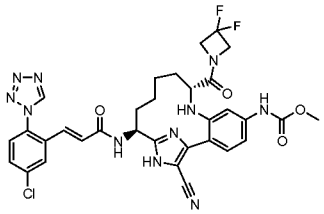
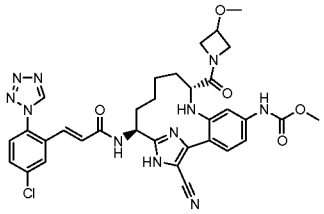
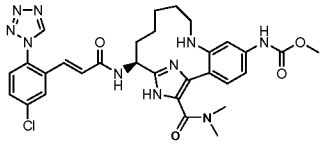
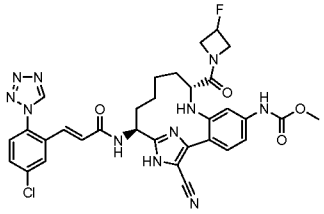
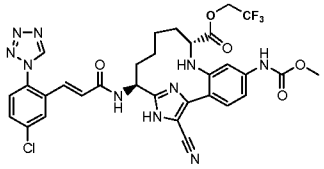
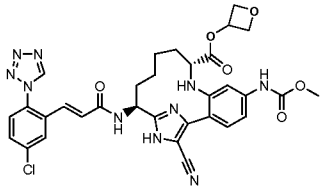
Table I-17: Examples I-265 to I-334

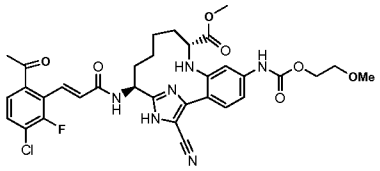
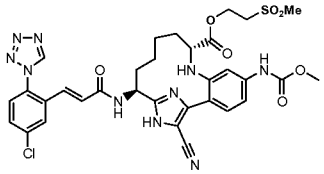
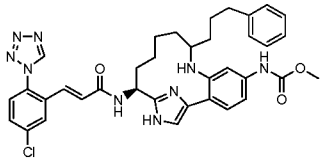
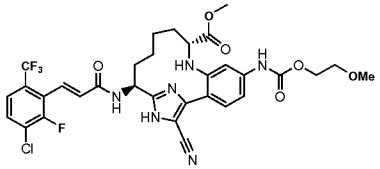
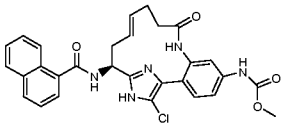
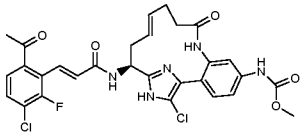
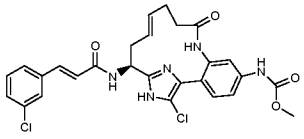
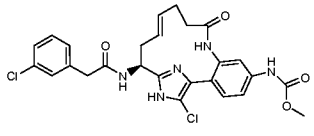
Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-265		579.2	6.4
I-266		664.4	5.7
I-267		650.4	5.2
I-268		567.4	5.8
I-269		605.4	5.9
I-270		611.2	6.9
I-271		595.2	5.1
I-272		634.2	6.2
I-273		634.2	7.0

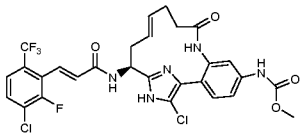
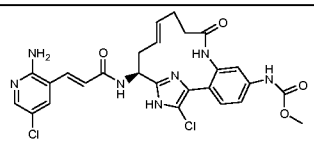
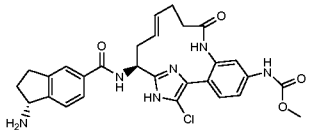
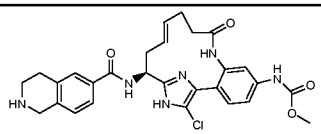
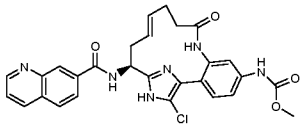
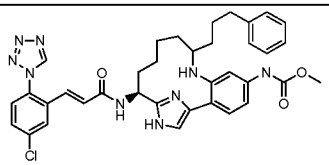
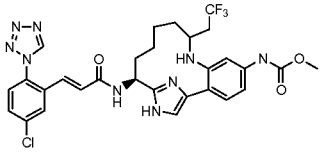
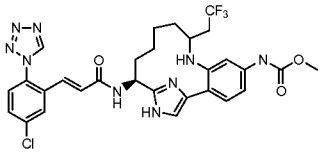
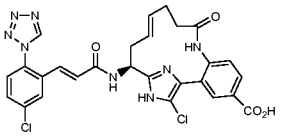
Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-274		520.3	5.4
I-275		648.1	7.4
I-276		707.3	8.8
I-277		740.3	6.7
I-278		689.4	8.6
I-279		700.3	7.7
I-280		686.1	6.9
I-281		670.1	7.7

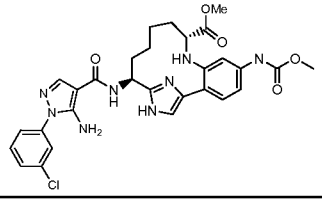
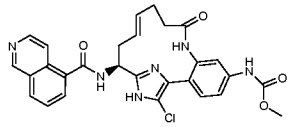
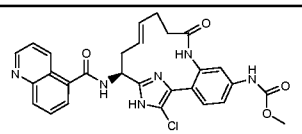
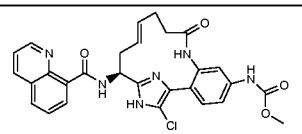
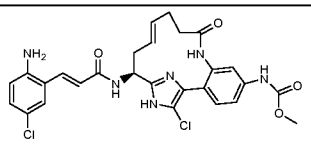
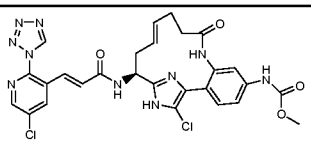
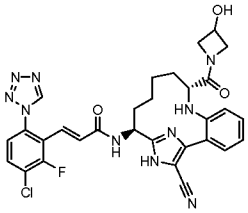
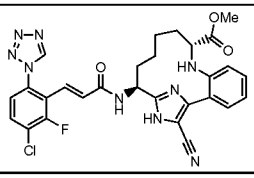
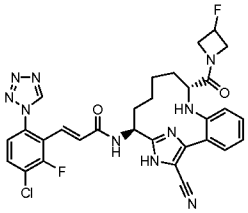
Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-282		711.2	6.2
I-283		687.2	9.3
I-284		573.0	5.25 (D)
I-285		673.1	8.9
I-286		559.0	7.50 (D)
I-287		606.1	5.55
I-288		700.1	7.16
I-289		715.2	5.35

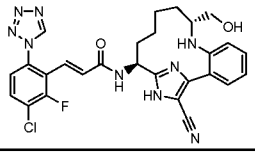
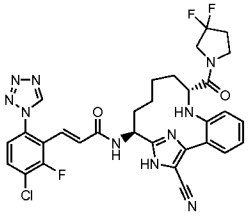
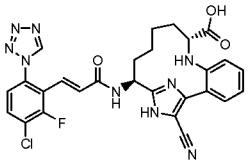
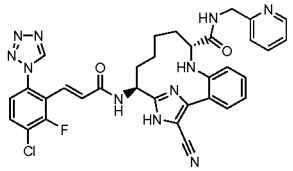
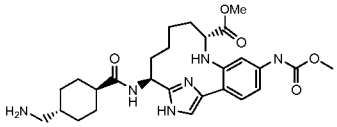
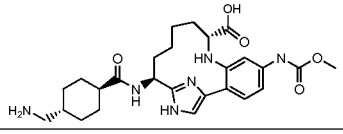
Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-290		700.1	7.01
I-291		700.1	7.00
I-292		736.1	6.87
I-293		714.2	7.01
I-294		748.1	7.77
I-295		686.1	8.01

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-296		702.2	7.42
I-297		706.2	8.45
I-298		700.2	7.75
I-299		633.1	5.50
I-300		688.1	7.93
I-301		713.1	9.13
I-302		687.1	7.87

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-303		681.1	8.89
I-304		737.0	7.68
I-305		680.3	7.07
I-306		707.0	9.92
I-307		544.0	6.8
I-308		615.9	7.1
I-309		554.0	7.4
I-310		542.0	6.9

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-311		639.9	8.3
I-312		570.0	4.5
I-313		549.0	3.5
I-314		549.0	6.5
I-315		545.0	4.2
I-316		680.2	7.44
I-317		644.0	6.61
I-318		644.0	6.37
I-319		592.9	6.41

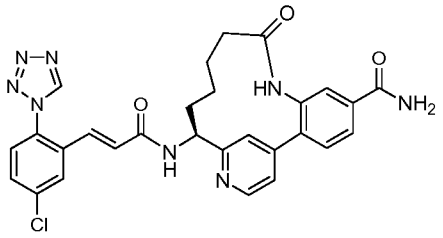
Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-320		607.0	6.67
I-321		545.0	3.61
I-322		545.0	3.75
I-323		544.9	5.37
I-324		568.9	7.38
I-325		622.9	6.05
I-326		631.0	7.09
I-327		590.0	9.21
I-328		633.0	8.21

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.) (Method)
I-329		562.0	6.05
I-330		665.0	8.97
I-331		575.9	8.01
I-332		666.1	6.02
I-333		527.1	4.51
I-334		513.1	3.88

[00860] Examples II-1 and II-2 were prepared in two steps by coupling 91A with an appropriately substituted carboxylic acid derivative (R-CO_2H) using coupling conditions described in step 15D, followed by a Boc-deprotection step as described in step 3C. Example II-3 was prepared by following the procedures described in step 3C, by replacing 3B with 88G; followed by step 15D, by replacing Intermediate 2 with an appropriately substituted carboxylic acid; followed by Boc-deprotection step 3C. Examples II-4 and II-5 were prepared by coupling 96A with an appropriately substituted carboxylic acid derivative using coupling conditions described in step 15D. In the case of II-5 an additional Boc-deprotection step as described in step 3C was required.

Example II-6.

(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-oxo-8,16-diaza-tricyclo[13.3.1.02,7]nonadeca-1(19),2(7),3,5,15,17-hexaene-5-carboxylic acid amide, TFA



[00861] II-6A. (S)-Benzyl 1-(4-chloropyridin-2-yl)but-3-enylcarbamate: 88B (1.135 g, 3.96 mmol) was taken up in MeOH (39.6 mL) and 4M HCl in dioxane (19.79 mL, 79 mmol) was added. Reaction was stirred at rt under Ar for ~2hrs then was evaporated to remove MeOH and triturated with Et_2O 2x to yield (S)-1-(4-chloropyridin-2-yl)but-3-en-1-amine, 2 HCl (1.005 g, 99%, MS (ESI) *m/z*: 183.1 $(M+H)^+$), which was taken up in MeOH (13.11 mL) and treated with benzyl 2,5-dioxopyrrolidin-1-yl carbonate (1.078 g, 4.33 mmol) and DIPEA (2.060 mL, 11.80 mmol). The resulting mixture was stirred at rt for 5 min then stripped to dryness, diluted with EtOAc and washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography to yield II-6A (1.19 g, 96%) as a colorless oil. MS (ESI) *m/z*: 317.2 $(M+H)^+$

[00862] II-6B. (S)-2-(1-(Benzyloxycarbonylamino)but-3-enyl)pyridin-4-ylboronic acid, TFA: A mixture of II-6A (0.75 g, 2.368 mmol), bis(neopentyl glycolato)diboron (0.802 g, 3.55 mmol), potassium acetate (0.697 g, 7.10 mmol), PdCl2(dppf)-CH_2Cl_2 adduct (1:1) (0.193 g, 0.237 mmol) and DMSO (7.89 mL) in a sealed tube was degassed by evacuating and backfilling with Ar 3x, and then the reaction was heated at 80 °C for 6-8 h, then left at room temperature overnight. A second reaction was carried out identically. The two reactions were combined and diluted with EtOAc, then filtered through a small pad of CELITE® which was rinsed several times with EtOAc. The filtrate was transferred to a separatory funnel and washed 3x with H_2O, refiltered again thru CELITE®, then washed with brine, dried and concentrated to yield a dark brown oil

which was purified by reverse phase HPLC to yield II-6B as a white foam (1.325 g, 63.6%). MS (ESI) *m/z*: 327.3 $(M+H)^+$.

[00863] II-6C. (S)-Benzyl 1-(4-(2-amino-4-cyanophenyl)pyridin-2-yl)but-3-enylcarbamate, 2 TFA: To II-6B (0.44 g, 1.000 mmol), 3-amino-4-bromobenzonitrile (0.164 g, 0.833 mmol) (81378-051-01), tetrabutylammonium bromide (0.013 g, 0.042 mmol), and 2M sodium carbonate (1.249 mL, 2.499 mmol) in a 20mL microwave tube was added toluene (6.92 mL) and EtOH (2.88 mL), and the solution was degassed by evacuating/flushing with Ar 3x. $(Ph_3P)_4Pd$ (0.048 g, 0.042 mmol) was added, and the vial was once again evacuated/flushed with Ar 3x. Two more vials were prepared identically. All 3 vials were capped and heated at 95 °C in an oil bath overnight. Then the reaction was allowed to stir at rt for 3 days. Contents of vials were combined and diluted with EtOAc and washed with water, sat. $NaHCO_3$, and brine, then dried over anhydrous magnesium sulfate, filtered, and evaporated. Residue was purified by flash chromatography to yield II-6C (0.758 g, 48.4%) as a light yellow foam. MS (ESI) *m/z*: 399.3 $(M+H)^+$.

[00864] II-6D. ((E)-(S)-5-Cyano-9-oxo-8,16-diaza-tricyclo[13.3.1.02,7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-yl)-carbamic acid benzyl ester: II-6D was prepared in two steps from II-6C using the procedures described for steps 10D and 2E/F. MS (ESI) *m/z*: 439.2$(M+H)^+$.

[00865] II-6E. ((E)-(S)-5-Carbamoyl-9-oxo-8,16-diaza-tricyclo[13.3.1.02,7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-yl)-carbamic acid benzyl ester: II-6D (0.015 g, 0.034 mmol) (81378-069-01) was dissolved in DMSO (0.171 mL) and K_2CO_3 (0.014 g, 0.103 mmol) was added. Then 30% H_2O_2 (0.038 mL, 0.376 mmol) was added dropwise. The light yellow suspension was stirred for ~1 h at room temperature under nitrogen. Reaction mixture was diluted with water and extracted 3x with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and condensed to yield the crude amide as a colorless residue (0.022 g) which was taken on to the next step without further purification. MS (ESI) *m/z*: 457.3 $(M+H)^+$.

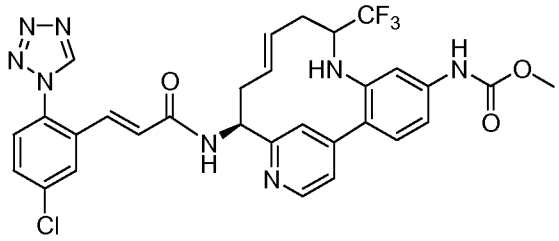
[00866] Example II-6. The title compound was prepared from II-6E using the procedures described for steps 10F and 1G. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.49 (1 H, s) 8.76 (1 H, d, *J*=5.78 Hz) 8.00 (1 H, d, *J*=1.10 Hz) 7.95 - 7.99 (2 H, m) 7.82 (1 H,

dd, *J*=5.78, 1.65 Hz) 7.80 (1 H, d, *J*=1.65 Hz) 7.77 (1 H, d, *J*=8.25 Hz) 7.66 (1 H, dd, *J*=8.39, 2.34 Hz) 7.57 (1 H, d, *J*=8.53 Hz) 7.10 (1 H, d, *J*=15.41 Hz) 6.79 (1 H, d, *J*=15.68 Hz) 5.12 (1 H, dd, *J*=10.73, 5.78 Hz) 2.50 (1 H, ddd, *J*=12.52, 6.74, 1.93 Hz) 2.07 - 2.19 (1 H, m) 1.93 - 2.01 (1 H, m) 1.82 - 1.92 (1 H, m) 1.70 - 1.80 (1 H, m) 1.60 - 1.69 (1 H, m) 1.33 - 1.42 (1 H, m) 0.71 - 0.86 (1 H, m). MS (ESI) *m/z*: 557.3 $(M+H)^+$. Analytical HPLC: RT = 4.95 min.

[00867] Example II-7 was prepared from 88B following the procedures described for steps II-6A, by replacing benzyl 2,5-dioxopyrrolidin-1-yl carbonate with di-*t*-butyldicarbonate; 88C, by replacing 88B with (S)-2-(1-(*tert*-butoxycarbonylamino)but-3-enyl)pyridin-4-ylboronic acid and Intermediate 12 with methyl 4-amino-3-bromobenzoate; 10D; 2E/F; and 2G; followed by hydrolysis of the methyl ester with 1M LiOH in THF; then steps 3A and 1G. Example II-8 was similarly prepared following the procedures described for steps II-6C, by substituting (S)-2-(1-(*tert*-butoxycarbonylamino)but-3-enyl)pyridin-4-ylboronic acid for II6-B and 4-amino-3-bromobenzonitrile for 3-amino-4-bromobenzonitrile; 10D, 2E/F, 3C and 1G.

Example II-11.

{(E)-(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-trifluoromethyl-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00868] II-11A. (S)-*tert*-Butyl 1-(4-(2-amino-4-nitrophenyl)pyridin-2-yl)but-3-enylcarbamate: Compound II-11A was prepared by following the procedure described in step 88C, by replacing 88B with (S)-*tert*-butyl 1-(4-chloropyridin-2-yl)but-3-enylcarbamate. MS (ESI) 385.1 $(M+H)^+$.

[00869] II-11B. (S)-*tert*-Butyl 1-(4-(2,4-diaminophenyl)pyridin-2-yl)but-3-enylcarbamate: To a clear, orange solution of II-11A (2.9 g, 7.54 mmol) in methanol (75

mL) was added sequentially zinc dust (4.93 g, 75 mmol) and ammonium chloride (4.04 g, 75 mmol). The resulting suspension was stirred vigorously for 4 h. The reaction was stopped and filtered through a 0.45 micron GMF eluting with methanol to give a clear, yellow filtrate. Concentration of the filtrate gave a yellow-black residue. The residue was partitioned between EtOAc and 0.25 M HCl (50 mL) and the layers were separated. The organic layer was extracted with 0.25 M HCl (1 x 50 mL). The combined aqueous layers were basified with 1.5M K_2HPO_4 and then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give II-11B (2.63 g, 98 %) as a brown foam. MS (ESI) *m/z*: 355.2 $(M+H)^+$.

[00870] II-11C. {3-Amino-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-phenyl}-carbamic acid methyl ester: To a cooled (-78 °C) clear, brown solution of II-11B (2.63 g, 7.42 mmol) and pyridine (0.600 ml, 7.42 mmol) in dichloromethane (74.2 ml) was added dropwise over 30 min methyl chloroformate (0.516 ml, 6.68 mmol). The reaction was stirred at -78 °C. After 1.5 h, the reaction was quenched with sat. NH_4Cl and the reaction was allowed to warm to RT. The reaction was diluted with DCM and water and the layers were separated. The aqueous layer was extracted with DCM (1x). The combined organic layers were washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. The residue dissolved in DCM (~10 mL) and then hexane (~300 mL) was added to give a brown suspension with brown gummy sticky substance at the bottom. The mixture was sonicated to give a mostly clear solution with the brown substance at the bottom. The solution decanted and the bottom substance rinsed with hexane, dried to give II-11C (2.7 g, 88 %) as a slightly brown foam. LCMS (ES) 413.2 $(M+H)^+$.

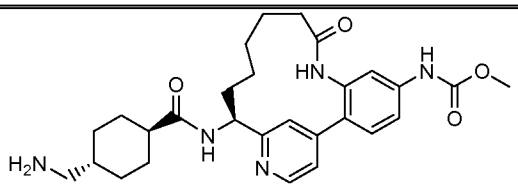
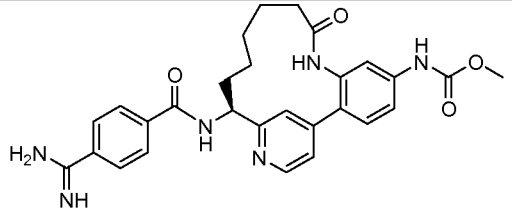
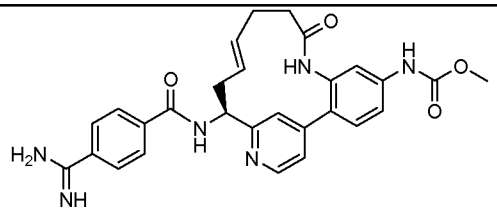
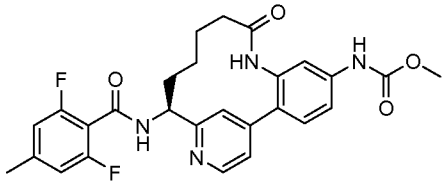
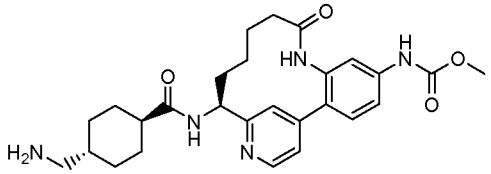
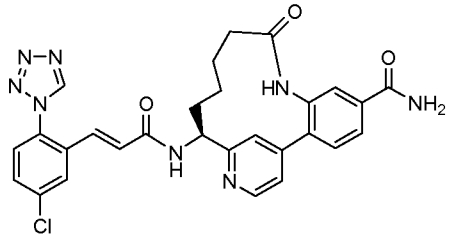
[00871] II-11D. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-3-(1-ethoxy-2,2,2-trifluoro-ethylamino)-phenyl]-carbamic acid methyl ester: A clear yellow solution of II-11C (2.296 g, 5.57 mmol), pTsOH (0.053 g, 0.278 mmol) and trifluoroacetaldehyde ethyl hemiacetal (2.63 ml, 22.27 mmol) in ethanol (11.13 ml) was microwaved at 120 °C for 3h. The reaction was concentrated, purified by normal phase chromatography which gave II-11D (1.61 g, 53.7 %) as a yellow solid and as a mixture of diastereomers. MS (ESI) *m/z*: 539.2 $(M+H)^+$.

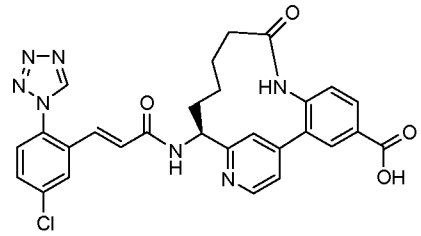
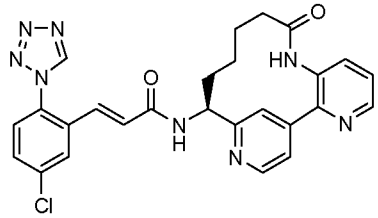
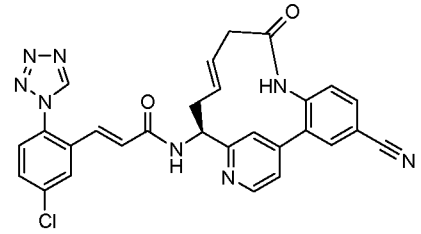
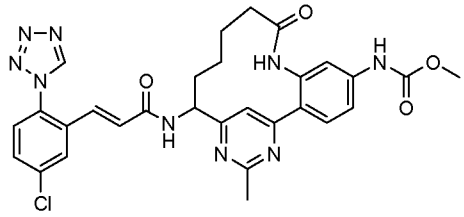
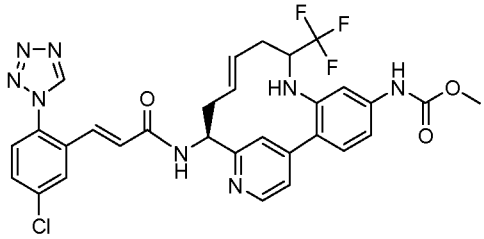
[00872] II-11E. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-3-(1-trifluoromethyl-but-3-enylamino)-phenyl]-carbamic acid methyl ester: To a cooled (-20 °C) solution of II-11D (1.816 g, 3.37 mmol) in THF (33.7 mL) was added dropwise allylmagnesium bromide (1M in Et_2O, 15.17 ml, 15.17 mmol). The resulting cloudy, red reaction mixture was stirred at -20 °C. After 3h, another allylmagnesium bromide (0.8 mL, 0.8 mmol) added. After another 20 min, the reaction mixture was quenched with sat. NH_4Cl and the reaction was warmed to RT. The reaction was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave II-11E (1.45 g, 80 %) as a yellow foam and as a mixture of diastereomers. MS (ESI) *m/z*: 535.3 $(M+H)^+$.

[00873] II-11F and II-11G. ((E)-(S)-14-*tert*-Butoxycarbonylamino-9-trifluoromethyl-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-yl)-carbamic acid methyl ester: Compounds II-11F (diastereomer A) and II-11G (diastereomer B) were prepared following the procedure described in 88G, by replacing 88F with II-11E. For II-11F: MS (ESI) *m/z*: 507.2 $(M+H)^+$. For II-11G: MS (ESI) *m/z*: 507.3 $(M+H)^+$.

[00874] II-11H. Example II-11 was prepared following the procedures described in step 3C, by replacing 3B with II-11F (diastereomer A); followed by step 1G. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 8.64 (d, *J*=5.5 Hz, 1 H), 8.06 (d, *J*=1.1 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.77 (dd, *J*=6.1, 1.6 Hz, 1 H), 7.67 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.33 (br. s., 1 H), 7.27 (d, *J*=8.2 Hz, 1 H), 7.09 - 7.18 (m, 2 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.59 - 5.72 (m, 1 H), 5.06 - 5.24 (m, 2 H), 3.75 (s, 3 H), 3.43 - 3.57 (m, 1 H), 2.83 - 2.94 (m, 1 H), 2.47 - 2.65 (m, 2 H), 2.26 - 2.39 (m, 1 H). ^{19}F NMR (471MHz, CD_3OD) δ -75.49, -77.15 . MS (ESI) *m/z*: 639.2 $(M+H)^+$. Analytical HPLC, RT = 6.74 min.

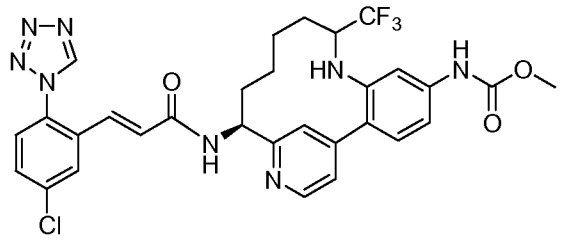
Table II-1: Examples II-1 to II-11

Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min) (method)
II-1		508.2	6.5 (C)
II-2		515.1	6.3 (C)
II-3		513.1	6.3 (C)
II-4		509.1	4.9
II-5		494.4	6.5 (C)
II-6		557.3	5.0

Ex. #	Structure	LCMS $[M+H]^+$	HPLC RT (min) (method)
II-7		558.2	5.2
II-8		515.2	4.1 (B)
II-9		537.2	6.2
II-10	 (racemate)	602.1	6.4
II-11	 (homochiral)	639.2	6.7

Example II-12.

{(S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-9-trifluoromethyl-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-yl}-carbamic acid methyl ester, 2 TFA salt



[00875] II-12A. ((S)-5-Methoxycarbonylamino-9-trifluoromethyl-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-yl)-carbamic acid *tert*-butyl ester: To the solution II-11F (diastereomer A) (0.46 g, 0.908 mmol) in EtOH (6 mL) was added TFA (0.070 mL, 0.908 mmol) and 10% palladium on carbon (0.097 g, 0.091 mmol). Hydrogen, from a balloon, was bubbled through the reaction for a few minutes, then the reaction was stirred under H_2-balloon for 24 h. Additional TFA (0.070 mL, 0.908 mmol) was added, and the reaction was stirred under a H_2-balloon for another 24 h. The reaction was filtered through 0.45 μm GMF rinsing with MeOH. The filtrate was concentrated. The residue was dissolved in EtOAc, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave II-12A (0.4 g, 87 % yield) as a yellow solid. MS (ESI) *m/z*: 509.3 $(M+H)^+$.

[00876] II-12B. ((S)-14-Amino-9-trifluoromethyl-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-yl)-carbamic acid methyl ester, 3 TFA salt: Compound II-12B was prepared following the procedure described in 3C, by replacing 3B with II-12A. MS (ESI) *m/z*: 409.1 $(M+H)^+$.

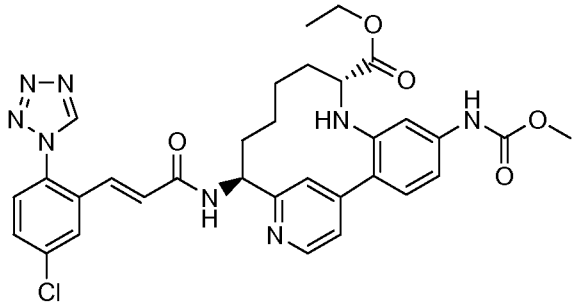
[00877] II-12C. Example II-12 was prepared following the procedure described in step 1G by replacing 1F with II-12B. ^1H NMR (500 MHz, CD_3OD) δ ppm 9.48 (s, 1 H), 8.73 (d, *J*=1.4 Hz, 1 H), 8.66 (d, *J*=6.1 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.89 (dd, *J*=6.2, 1.8 Hz, 1 H), 7.67 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.48 (d, *J*=8.5 Hz, 1 H), 7.40 (d, *J*=1.7 Hz, 1 H), 7.22 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (d, *J*=15.7 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.17 (dd, *J*=11.7, 6.5 Hz, 1 H), 3.76 (s, 3 H), 2.95 - 3.05 (m, 1 H), 2.20 - 2.31 (m, 1 H), 1.84 - 1.99 (m, 2 H), 1.71 - 1.80 (m, 1 H), 1.51 - 1.62 (m, 2 H), 1.41 - 1.50

(m, 1 H), 0.33 - 0.45 (m, 1 H). ^{19}F NMR (471MHz, CD_3OD) δ -75.06, -77.30 . MS (ESI) *m/z*: 641.3 $(M+H)^+$. Analytical HPLC: RT = 7.06 min.

[00878] Examples II-13 and II-14 were prepared in two steps by coupling II-12B with an appropriately substituted carboxylic acid derivative (R-CO_2H) using coupling conditions described in step 15D, followed by a Boc-deprotection step as described in step 3C.

[00879] Example II-15 were prepared according to the procedures described in II-12, by replacing II-11F with II-11G; followed by II-14.

Example II-17.
(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaene-9-carboxylic acid ethyl ester, diastereomer A, 2 TFA salt



[00880] II-17A. 2-{2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-5-methoxycarbonylamino-phenylamino}-pent-4-enoic acid ethyl ester: Compound II-17A was prepared following the procedure described in I-67A, by replacing 10C with II-11C. MS (ESI) *m/z*: 539 $(M+H)^+$.

[00881] II-17B. (E)-(9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaene-9-carboxylic acid ethyl ester (diastereomer A) and II-17C. (E)-(9S,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,11,15,17-heptaene-9-carboxylic acid ethyl ester (diastereomer B): Compounds II-17B (diastereomer A) and II-17C (diastereomer

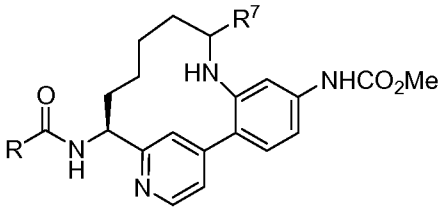
B) were prepared following the procedure described in 88G, by replacing 88F with II-17A. The diastereomers were separated by chiral HPLC (OJ column, 20:20:60 EtOH:MeOH:heptane). For II-17B (diastereomer A): MS (ESI) *m/z*: 512, 511 $(M+H)^+$. ^1H NMR (MeOH-d4, 400 MHz): δ ppm 8.56 (d, 1H, J = 5), 7.62 (s, 1H), 7.24 (d, 1H, J = 5), 7.20 (d, 1H, J = 8), 7.03 (s, 1H), 6.98 (d, 1H, J = 9), 5.44 (m, 1H), 5.07 (m, 1H), 4.71 (m, 1H), 4.12 (q, 2H, J = 7), 3.73 (s, 3H), 3.31 (m, 3H), 2.72 (m, 1H), 2.35 (m, 4H), 1.44 (s, 9H), 1.20 (m, 3H). For II-17C (diastereomer B): MS (ESI) *m/z*: 512, 511 $(M+H)^+$; ^1H NMR (MeOH-d4, 400 MHz): δ ppm 8.56 (d, 1H, J = 5), 7.49 (s, 1H), 7.21 (m, 2H), 6.99 (s, 1H), 6.94 (d, 1H, J = 9), 5.66 (m, 1H), 5.03 (m, 1H), 4.12 (m, 3H), 3.72 (s, 3H), 3.31 (m, 3H), 2.69 (m, 1H), 2.54 (m, 1H), 2.37 (m, 2H), 1.44 (s, 9H), 1.14 (t, 3H, J = 7).

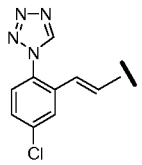
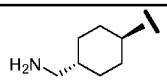
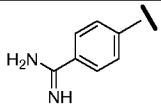
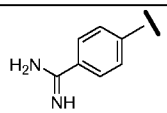
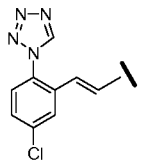
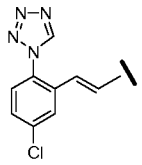
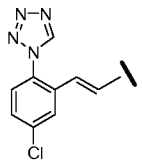
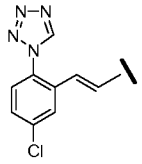
[00882] II-17D. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,15,17-hexaene-9-carboxylic acid ethyl ester: Compound II-17D was prepared following the procedure described in II-12A, by replacing II-11F with II-17B (diastereomer A). MS (ESI) *m/z*: 514, 513 $(M+H)^+$.

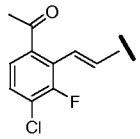
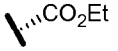
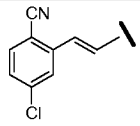
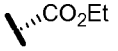
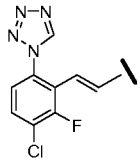
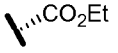
[00883] II-17E. (9R,14S)-14-Amino-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2(7),3,5,5,17-hexaene-9-carboxylic acid ethyl ester, 3HCl salt: A mixture of II-17D (175 mg, 0.341 mmol) and hydrogen chloride (1.71 ml, 6.83 mmol) (4 M in dioxane) and ethyl acetate (2 mL) was stirred at room temperature for 1 h. Solvent was removed *in vacuo* to give a light tan yellow solid (130 mg): MS (ESI) *m/z*: 414, 413 $(M+H)^+$. The product was taken on without further purification.

[00884] II-17F. Example II-17 was prepared following the procedure described in 1G, by replacing 1F with II-17E. MS (ESI) *m/z*: 647, 645 $(M+H)^+$. ^1H NMR (MeOH-d4, 400 MHz): 9.49 (s, 1H), 8.79 (s, 1H), 8.64 (d, 1H, J = 9), 7.97 (d, 1H, J = 2), 7.77 (d, 1H, J = 9), 7.67 (dd, 1H, J = 9, 2), 7.57 (d, 1H, J = 9), 7.47 (d, 1H, J = 8),7.38 (s, 1H), 7.23 (dd, 1H, J = 9, 2), 7.11 (d, 1H, J = 15), 6.80 (d, 1H, J = 15), 5.15 (m, 1H), 4.00 (m, 3H), 3.75 (s, 3H), 3.31 (m, 1H), 3.08 (d, 1H, J = 9), 2.20 (m, 2H), 1.94 (m, 2H), 1.77 (m, 2H), 1.50 (m, 2H), 1.39 (m, 1H), 1.12 (t, 3H, J = 7), 0.42 (m, 2H).

Table II-2: Examples II-12 to II-22

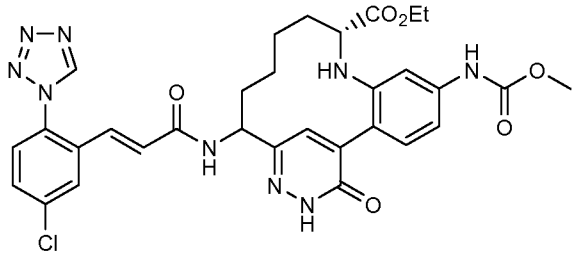


Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min)
II-12		CF_3 (from II-11F)	641.2	6.9
II-13		CF_3 (from II-11F)	548.4	4.8
II-14		CF_3 (from II-11F)	555.4	4.8
II-15		CF_3 (from II-11G)	555.3	3.9
II-16		H	573.3	6.2
II-17			645.4	6.5
II-18			645.4	6.1
II-19			617.4	5.7

Ex. #	R	R^3	LCMS $[M+H]^+$	HPLC RT (min)
II-20			637.5	7.0
II-21			602.5	7.1
II-22			663.4	6.9

Example II-24.

(R)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-18-oxo-8,16,17-triaza-tricyclo[13.3.1.02,7]nonadeca-1(19),2(7),3,5,15-pentaene-9-carboxylic acid ethyl ester



[00885] II-24A. ((S)-3-*tert*-Butoxycarbonylamino-2-oxo-hex-5-enyl)-phosphonic acid dimethyl ester: To a solution of dimethyl methylphosphonate (6.99 ml, 65.4 mmol) in THF (43.6 ml) at -78 °C was added BuLi (40.9 ml, 65.4 mmol) slowly. After addition, the reaction was stirred for 40 min and then a solution of (S)-methyl 2-(*tert*-butoxycarbonylamino)pent-4-enoate (3 g, 13.08 mmol) in THF (10 mL) was added drop-wise. Stirring was continued for another 40 min at -78 °C. The reaction was quenched by adding water, then EtOAc. It was washed with 1M HCl, sat $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give a clear oil. Purification by normal phase chromatography gave II-24A as a colorless oil (4.19g, 99%). MS (ESI) *m/z*: 344.0 $(M+Na)^+$.

[00886] II-24B. (4-Methoxycarbonylamino-2-nitro-phenyl)-oxo-acetic acid: To a solution of methyl 4-acetyl-3-nitrophenylcarbamate (10.5 g, 44.1 mmol) in pyridine (44.1 ml) was added selenium dioxide (7.34 g, 66.1 mmol) in portions. The reaction was stirred under argon at 60 °C overnight. Solvent was evaporated and pumped for several hours to remove most pyridine. 1.0N HCl (60 mL) was added and the mixture was filtered, rinsed with 1N HCl. The solid was put in a vacuum-oven at 45 °C overnight. MeOH (200 mL) was added, filtered, the filtrate was concentrated to give 13.8g of II-24B as a brownish foam. MS (ESI) *m/z*: 269.0, 223.0 $(M+NH)^+$.

[00887] II-24C. (4-Methoxycarbonylamino-2-nitro-phenyl)-oxo-acetic acid methyl ester: To a red oil of II-24B (5 g, 16.03 mmol) in DCM (57.3 ml) at 0 °C was added TEA (3.13 ml, 22.45 mmol). The mixture was sonicated to dissolve into a red-colored solution. Methyl carbonochloridate (1.739 ml, 22.45 mmol) was added dropwise at 0 °C. After 5 min, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with 1M HCl, sat. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give a red colored solid. Trituated with DCM and EtOAc, filtered. The solid was washed with DCM/Hex and dried in vacuum-oven at 45 °C to give 2.79g (62%)of II-24C as a light brownish solid. MS (ESI) *m/z*: 223.0 (fragmentation).

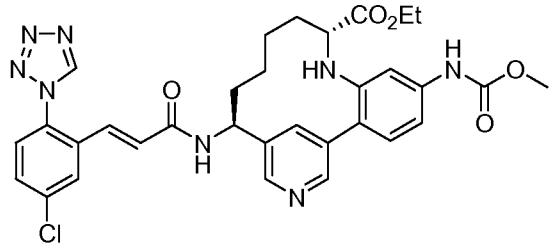
[00888] II-24D. {4-[6-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-3-nitro-phenyl}-carbamic acid methyl ester: To a clear solution of II-24A (911 mg, 2.84 mmol) in EtOH (30 ml) at rt were added potassium carbonate (588 mg, 4.25 mmol). The reaction mixture was stirred for 2 hr. The solvent was removed by rot-vap removed solvent and vacuum pump. THF (Volume: 30.0 ml) was added, followed by addition of II-24C. After 3 hrs, hydrazine (0.356 ml, 11.34 mmol) was added and the rxn was stirred at rt for 3 days. The reaction was diluted with EtOAc, washed with 1 N HCl, brine, dried over $MgSO_4$, filtered and concentrated. Purification by normal phase chromatography gave II-24D as a yellow foam (380 mg, 29%). MS (ESI) *m/z*: 460.2 $(M+NH)^+$.

[00889] II-24E. {4-[6-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-3-amino-phenyl}-carbamic acid methyl ester: Example II-24E was prepared following the procedures described in 15B by replacing 15A with II-24D.

[00890] II-24F. Example II-24 was prepared following the procedures described in I-67A, by replacing 10C with II-24E; followed by procedures described in steps II-17B/II-17C; II-17D; II-17E; and II-17F. ^{1}H NMR (500MHz, CD_3OD) d 9.52 (s, 1H), 8.30 (s, 1H), 7.99 (d, *J*=2.2 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 7.36 (d, *J*=1.9 Hz, 1H), 7.18 - 7.01 (m, 1H), 6.80 (d, *J*=15.4 Hz, 1H), 5.03 (dd, *J*=11.4, 5.9 Hz, 1H), 4.14 - 3.92 (m, 2H), 3.83 - 3.72 (m, 2H), 3.51 - 3.39 (m, 1H), 2.21 - 2.01 (m, 1H), 1.63 - 1.40 (m, 2H), 1.15 (t, *J*=7.2 Hz, 2H), 0.96 - 0.81 (m, 1H). MS (ESI) *m/z*: 662.2 $(M+H)^+$. Analytical HPLC: RT = 9.81 min. (Method D).

Example II-26.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-8,17-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2(7),3,5,15,17-hexaene-9-carboxylic acid ethyl ester, diastereomer A, 2 TFA salt



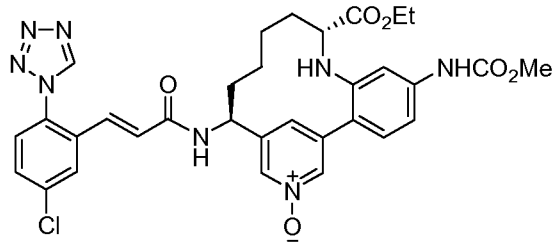
[00891] II-26A. (R,E)-N-((5-Bromopyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide: Example II-26A was prepared following the procedures described in 88A, by replacing 4-chloropicolinaldehyde with 5-bromonicotinaldehyde using (R)-2-methylpropane-2-sulfinamide. MS (ESI) *m/z*: 291.2 $(M+H)^+$.

[00892] II-26B. (R)-N-((S)-1-(5-Bromopyridin-3-yl)but-3-enyl)-2-methylpropane-2-sulfinamide: Reference: Lin (*Organic Letters*, 10:1259 (2008)). To a sat. aq. solution of sodium bromide (600 ml) was added powdered II-26A (8.3 g, 28.7 mmol) and indium (13.18 g, 115 mmol). Ally bromide (13.66 g, 115 mmol) was added via syringe pump, and the resulting light orange suspension was allowed to stir at rt overnight, generating a beige foam. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated to give a fluffy orange solid weighing 8 g. Purification by normal phase chromatography gave 4.25 g of II-26B as a beige solid. MS (ESI) *m/z*: 333.0 $(M+H)^+$.

[00893] II-26C. Example II-26 was prepared following the procedure described in 88D, by replacing 88C with II-26B; followed by steps as described in 88C; 88F; I-67A; 88G; 2G; II-17E; and 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.49 (1 H, s), 9.36 (1 H, d, *J*=13.5 Hz), 8.76 (1 H, d, *J*=5.2 Hz), 8.54 (1 H, br. s.), 7.97 (1 H, d, *J*=2.2 Hz), 7.66 (1 H, dd, *J*=8.5, 2.2 Hz), 7.57 (1 H, d, *J*=8.5 Hz), 7.41 (1 H, d, *J*=8.5 Hz), 7.35 (1 H, s), 7.23 (1 H, d, *J*=8.3 Hz), 7.11 (1 H, d, *J*=15.7 Hz), 6.75 (1 H, d, *J*=15.7 Hz), 5.11 - 5.19 (1 H, m), 3.94 - 4.06 (2 H, m), 3.75 (3 H, s), 3.12 (1 H, d, *J*=11.6 Hz), 2.14 - 2.22 (1 H, m), 1.69 - 1.95 (3 H, m), 1.36 - 1.51 (3 H, m), 1.11 (3 H, t, *J*=7.2 Hz), 0.57 (1 H, d, *J*=11.6 Hz) MS (ESI) *m/z*: 645.1 $(M+H)^+$. Analytical HPLC: RT = 6.82 min. (Method D).

Example II-28.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-17-oxy-8,17-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2,4,6,15,17-hexaene-9-carboxylic acid ethyl ester, diastereomer A, TFA salt

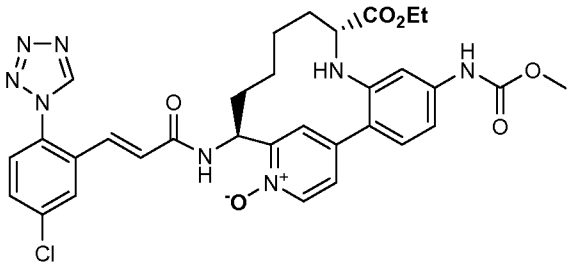


[00894] II-28A. Example II-26 (15 mg, 0.017 mmol) was diluted with MeOH and filtered through a cartridge of solid sodium bicarbonate to form the free base. The filtrate was concentrated and to the resulting solid was added DCM (1 mL) and mCPBA (5.78 mg, 0.026 mmol). The solution was stirred at rt for 1 h. The reaction mixture was washed with sat. Sodium sulfite, sat. aq. $NaHCO_3$, and brine, then dried over $MgSO_4$. Filtered and concentrated. Purification by reverse phase chromatography gave II-28 (8.7 mg, 65%) as a pale yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.49 (1 H, s), 8.53 (1 H, s), 8.37 (1 H, s), 8.18 (1 H, s), 7.98 (1 H, d, *J*=2.2 Hz), 7.66 (1 H, dd, *J*=8.4, 2.3 Hz), 7.56 (1 H, d, *J*=8.5 Hz), 7.27 - 7.39 (2 H, m), 7.05 - 7.22 (2 H, m), 6.73 (1 H, d, *J*=15.4 Hz), 5.01 - 5.12 (1 H, m), 3.88 - 4.07 (2 H, m), 3.74 (3 H, s), 3.18 (1 H, dd, *J*=11.8, 1.4 Hz), 2.05 - 2.19 (1 H, m), 1.79 - 1.94 (1 H, m), 1.67 - 1.79 (2 H, m), 1.35 - 1.53 (3 H, m),

1.10 (3 H, t, *J*=7.0 Hz), 0.56 - 0.72 (1 H, m) MS (ESI) *m/z*: 661.3 $(M+H)^+$. Analytical HPLC: RT = 7.91 min. (Method D).

Example II-29.

(9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-methoxycarbonylamino-16-oxy-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-9-carboxylic acid ethyl ester, trifluoroacetic acid salt



[00895] II-29A. 2-(*tert*-Butoxycarbonyl-{2-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-5-methoxycarbonylamino-phenyl}-amino)-pent-4-enoic acid ethyl ester, di-hydrochloride salt: To a solution of Example II-17A (125 mg, 0.232 mmol) in dichloromethane (2.5 mL) was added DMAP (28.4 mg, 0.232 mmol) and Boc_2O (0.119 mL, 0.511 mmol) followed by DIEA (0.101 mL, 0.580 mmol). The reaction mixture was stirred at rt for 1.5h. The reaction mixture is concentrated *in vacuo*, dissolved with ethyl acetate and washed with brine. The crude product is then purified using normal phase chromatography. MS (ESI) *m/z*: 639.

[00896] II-29B. (E)-(S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,11,15,17-heptaene-8,9-dicarboxylic acid 8-*tert*-butyl ester 9-ethyl ester: This compound was prepared by the following the procedure described for 88G, replacing 88F with II-29A. The compound as a mixture of diastereomers was purified by reverse phase chromatography. MS (ESI) *m/z*: 611.

[00897] II-29C. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-8,9-dicarboxylic acid 8-*tert*-butyl ester 9-ethyl ester: This Example was prepared by the procedure used in II-12A, by replacing II-11F with II-29B. The diastereomers of Example II-29C were separated by reverse phase chromatography. MS (ESI) *m/z*: 613 for both diastereomer 1

(shorter retention time) and diastereomer 2 (longer retention time); each is a mono-trifluoroacetate salt.

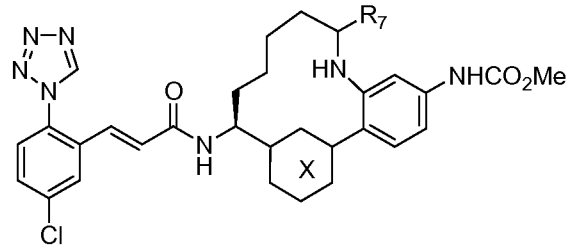
[00898] II-29D. (9R,14S)-14-*tert*-Butoxycarbonylamino-5-methoxycarbonylamino-16-oxy-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-8,9-dicarboxylic acid 8-*tert*-butyl ester 9-ethyl ester: To a solution of Example II-29C, diastereomer 2 (21 mg, 0.034 mmol) in ethyl acetate was added a saturated solution of sodium carbonate in water. After mixing, the layers were separated and the organic layer was dried over magnesium sulfate. Filtration and removal of solvent *in vacuo* gave the free base. This was then diluted with DCM (0.5 mL). m-Chloroperbenzoic acid (mCPBA) (11.52 mg, 0.051 mmol) was added. The reaction mixture was stirred at RT. The reaction mixture is diluted with ethyl acetate and washed with a saturated Na_2SO_3 solution, saturated $NaHCO_3$ solution, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was used without any further purification. MS (ESI) *m/z*: 629.

[00899] II-29E. (9R,14S)-14-Amino-5-methoxycarbonylamino-16-oxy-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-9-carboxylic acid ethyl ester: Example II-29D was mixed with a solution of HCl in dioxane and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* and used as the di-hydrochloride salt for the next step without any further purification. MS (ESI) *m/z*: 429.

[00900] Example II-29. Following the procedure used to make Example 1G, (E)-2,5-dioxopyrrolidin-1-yl 3-(5-chloro-2-(1H-tetrazol-1-yl)phenyl)acrylate (18 mg, 0.052 mmol) and II-29E (26 mg, 0.052 mmol) were dissolved in DMF (0.5 mL), and then DIPEA (0.090 mL, 0.518 mmol) was added. The reaction mixture was stirred at room temperature under argon for 4h. The reaction mixture is diluted with ethyl acetate (10 mL) and washed with 10% LiCl solution. Drying over Na_2SO_4, filtration and removal of solvent *in vacuo* gave the crude product, which was purified by reverse phase chromatography. Solvent was removed *in vacuo* by lyophilization to give a solid (wt = 9 mg, 21 % yield): MS (ESI) *m/z*: 660.4; ^{1}H NMR (500MHz, CD_3CN) δ 9.12 (s, 1H), 8.67 (d, *J* = 6.0 Hz, 1H), 8.41 - 8.23 (m, 2H), 7.96 - 7.80 (m, 2H), 7.64 - 7.44 (m, 3H), 7.32 - 7.21 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 15.4 Hz, 1H), 6.75 (d, *J* = 15.4

Hz, 1H), 5.50 - 5.37 (m, 1H), 4.01 - 3.83 (m, 3H), 3.76 - 3.69 (m, 4H), 2.95 (s, 1H), 2.32 (br. s., 1H), 1.95 (m, 1H) 1.92 - 1.72 (m, 1H), 1.61 (br. s., 1H), 1.42 (br. s., 3H), 1.15 - 0.93 (m, 3H).

Table II-3: Examples II-23 to II-29



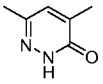
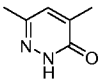
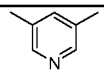
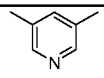
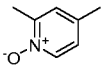
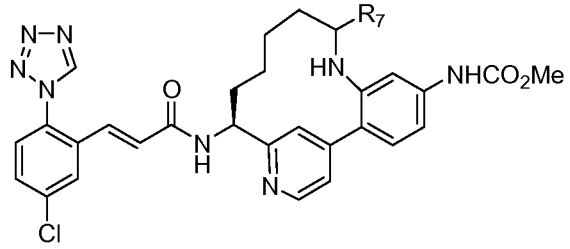
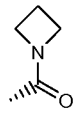
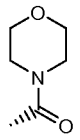
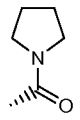
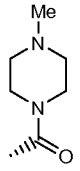
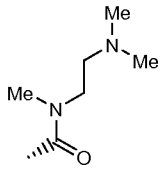
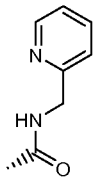
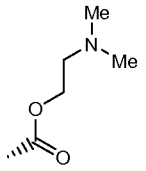
Ex. #	x	R7	LCMS $[M+H]^+$	HPLC RT (min.)
II-23		CO_2Et (diastereomer mixture)	662.2	9.5
II-24		CO_2Et (diastereomer mixture)	662.2	9.8
II-25			645.1	6.7
II-26			645.1	6.8
II-27			661.1	8.8
II-28			661.3	7.9
II-29			660.4	7.9

Table II-4: Examples II-30 to II-38

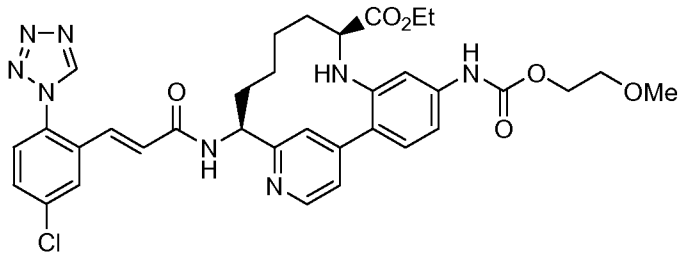


Ex. #	R7	LCMS $[M+H]^+$	HPLC RT (min.)
II-30		617.1	6.9
II-31		631.3	7.6
II-32		656.3	7.0
II-33		686.2	6.4
II-34		670.2	6.5
II-35		699.2	6.0
II-36		701.5	5.0
II-37		707.2	5.8

Ex. #	R7	LCMS [M+H]+	HPLC RT (min.)
II-38		688.1	9.9

Example II-39.

(9S,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-(2-methoxy-ethoxycarbonylamino)-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-9-carboxylic acid ethyl ester, bis-trifluoroacetic acid salt



[00901] The synthesis of Example II-39 followed the general procedures described for II-17. Example II-39AE (described below) was substituted for compound II-17A. The diastereomers corresponding to Example II-17B, diastereomers A and B, were not separated. They were hydrogenated and then separated by HPLC to give diastereomers corresponding to compound II-17C and its diastereomer. The diastereomers were then separately converted to Examples II-39 and II-40 (described below). The following data were collected for Example II-39: MS (ESI) *m/z* 689.3, 691.3; ^{1}H NMR (CD_3OD, 400 MHz): δ 9.37 (s, 1H), 8.55 (d, 1H, J = 6), 8.28 (s, 1H), 7.87 (d, 1H, J = 2), 7.55 (dd, 1H, J = 8, 2), 7.46 (d, 1H, J = 8), 7.27 (d, 1H, J = 8), 7.24 (d, 1H, J = 2), 6.99 (d, 1H, J = 16), 6.74 (d, 1H, J = 16), 5.07 (m, 1H), 4.17 (t, 2H, J = 6), 3.94 (m, 2H), 3.55 (t, 2H, J = 6), 3.29 (s, 3H), 3.20 (m, 5H), 3.12 (m, 2H), 2.17 (m, 1H), 1.89 (m, 1H), 1.60 (m, 2H), 1.40 (m, 4H), 1.03 (t, 3H, J = 7), 0.58 (m, 1H).

[00902] II-39AA. ((S)-1-{4-[4-Nitro-2-(2,2,2-trifluoro-acetylamino)-phenyl]-pyridin-2-yl}-but-3-enyl)-carbamic acid *tert*-butyl ester: To a solution of Example II-11A (0.40 g, 1.041 mmol) in THF (Volume: 9 mL) at -78 °C was added Et_3N (0.435 mL, 3.12 mmol),

followed by $(CF_3CO)_2O$ (0.154 mL, 1.093 mmol). The reaction mixture was warmed gradually to rt and stirred for 20.75 h. The reaction mixture was concentrated *in vacuo*. The residue was treated with water (10 mL) and extracted three times with EtOAc. The combined organics were washed once with 1N HCl (3 mL), then dried over $MgSO_4$. Filtration, removal of solvent *in vacuo* and purification of the residue by normal phase chromatography provided an oil (Wt = 239 mg): MS (ESI) *m/z*: 481.2.

[00903] II-39AB. ((S)-1-{4-[4-Amino-2-(2,2,2-trifluoro-acetylamino)-phenyl]-pyridin-2-yl}-but-3-enyl)-carbamic acid *tert*-butyl ester: To a clear yellow solution of II-39AA (0.269 g, 0.560 mmol) in MeOH (5.60 ml) was added sequentially zinc (0.366 g, 5.60 mmol) and NH_4Cl (0.300 g, 5.60 mmol). The resulting suspension was stirred vigorously for 6.5 h. The reaction mixture was filtered through a 0.45 micron GMF eluting with methanol to give a clear, yellow filtrate. Concentration gave a dark yellow residue. The residue was partitioned three times between EtOAc and 1 M HCl (10 mL) and the layers were separated. The combined aqueous layers were basified with a 1 N NaOH solution (pH ~ 8 by paper) and then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give an oil (Wt = 200 mg): MS (ESI) *m/z* = 451.3.

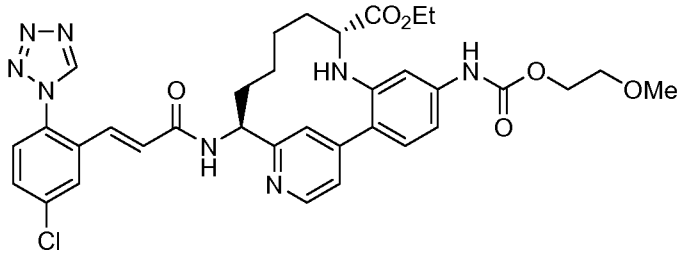
[00904] II-39AC. [4-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-3-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid 2-methoxy-ethyl ester: A solution of II-39AB (200 mg, 0.444 mmol) and pyridine (0.180 mL, 2.220 mmol) in dichloromethane (4 mL) was cooled to 0 °C under argon with stirring. Then 2-methoxyethyl carbonochloridate (0.103 mL, 0.888 mmol) was added dropwise. The reaction mixture was stirred for 50 min at 0oC for 2 h. Added 50 µL of the chloroformate reagent and stirred at room temperature for 17.75 h. The reaction mixture was diluted with EtOAc and washed once with 2.2 mL 1 N HCl, then twice with saturated Na_2CO_3 solution. The organic was dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give clear pale yellow oil (Wt = 160 mg). MS (ESI) *m/z* = 553.3. ^1H NMR (CD_3OD, 500 MHz): δ 11.94 (s, 1H), 10.90 (s, 1H), 9.32 (d, 1H, J = 5), 8.44 (s, 1H), 8.36 (dd, 1H, J = 10, 2), 8.20 (d, 1H, J = 10), 8.17 (s, 1H), 8.01 (m, 1H), 6.55 (m, 1H), 5.87 (d, 1H, J = 17), 5.81 (d, 1H, J = 9), 5.48 (M, 1H), 5.15 (m, 1H), 5.06 (m, 2H), 4.67 (m, 2H), 3.31 (s, 3H), 3.23 (m, 1H).

[00905] II-39AD. {3-Amino-4-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester: A mixture of Example II-39AC (160 mg, 0.290 mmol), a 1M solution of LiOH in water (0.290 mL, 0.290 mmol) and THF 0.5 mL) was stirred for ~20 h. Added 0.2 mL 1M LiOH solution and continued stirring for 24 h. A 1 N HCl solution (0.5 mL) was added and the mixture was extracted three times with EtOAc. The organic layers were washed with a saturated Na_2CO_3 solution, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo*. The residue was purified by normal phase chromatography to provide a yellow oil (Wt = 103 mg): MS (ESI) *m/z* = 457 (ES+) desired product.

[00906] II-39AE. 2-[2-[2-((S)-1-*tert*-Butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-5-(2-methoxy-ethoxycarbonylamino)-phenylamino]-pent-4-enoic acid ethyl ester: The synthesis of Example II-39AE followed the general procedure described for II-17A where Example II-39AD was substituted for Example II-11C. The crude product was purified by normal phase chromatography to provide a yellow oil: MS (ESI) *m/z* = 583.4 (ES+) desired product.

Example II-40.

9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-(2-methoxy-ethoxycarbonylamino)-8,16-diaza-tricyclo[13.3.1.$0^{2,7}$]nonadeca-1(19),2,4,6,15,17-hexaene-9-carboxylic acid ethyl ester, bis-trifluoroacetic acid salt

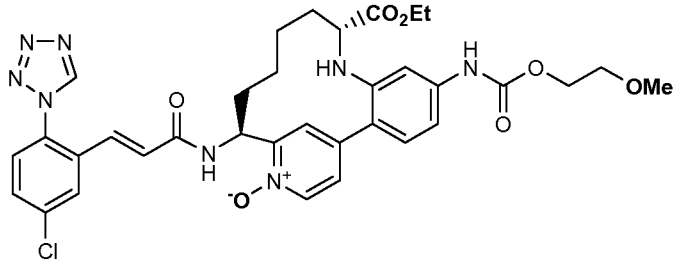


[00907] The synthesis of Example II-40 followed the general procedures described for II-17. Example II-39AE (described above) was substituted for Example II-17A. The diastereomers corresponding to Example II-17B, diastereomers A and B, were not separated. They were hydrogenated and then separated by normal phase chromatography to give diastereomers corresponding to Example II-17C and its diastereomer. The diastereomers were then separately converted to Examples II-39 and II-40 (described

below). The following data were collected for Example II-40: MS (ESI) *m/z* 689.3, 691.3; ^{1}H NMR (CD_3OD, 400 MHz): δ 9.49 (s, 1H), 8.71 (s, 1H), 8.64 (d, 1H, J = 6), 7.99 (d, 1H, J = 2), 7.72 (d, 1H, J = 3), 7.67 (dd, 1H, J = 8, 2), 7.57 (d, 1H, J = 9), 7.46 (d, 1H, J = 9), 7.38 (d, 1H, J = 2), 7.22 (dd, 1H, J = 9, 2), 7.11 (d, 1H, J = 16), 6.81 (d, 1H, J = 16), 5.15 (dd, 1H, J = 11, 5), 4.28 (t, 2H, J = 5), 4.00 (m, 2H), 3.66 (t, 2H, J = 4), 3.40 (s, 3H), 3.30 (m, 4H), 3.08 (d, 1H, J = 11), 2.19 (m, 1H), 1.90 (m, 2H), 1.76 (m, 1H), 1.49 (m, 2H), 1.38 (m, 1H), 1.09 (t, 3H, J = 7), 0.37 (m, 1H).

Example II-41.

9R,14S)-14-[(E)-3-(5-Chloro-2-tetrazol-1-yl-phenyl)-acryloylamino]-5-(2-methoxy-ethoxycarbonylamino)-16-oxy-8,16-diaza-tricyclo[13.3.1.0^{2,7}]nonadeca-1(19),2,4,6,15,17-hexaene-9-carboxylic acid ethyl ester, trifluoroacetic acid salt



[00908] This Example was prepared following the general procedures described for Example II-29.

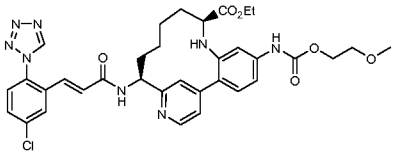
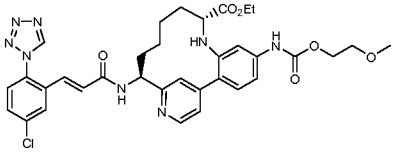
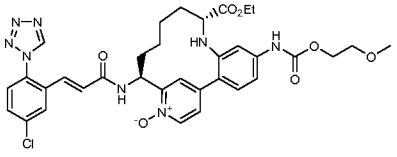
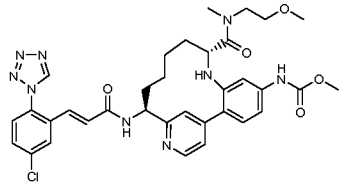
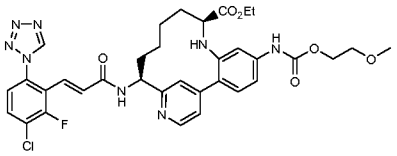
[00909] II-41A (described below) was substituted for Example II-29A. The following data were collected for Example II-41. MS (ESI) *m/z* = 705.3, 707.3. ^{1}H NMR (CD_3CN, 500 MHz): δ 9.02 (s, 1H), 8.38 (d, 1H, J = 8), 8.17 (d, 1H, J = 6), 7.85 (d, 1H, J = 3), 7.75 (s, 1H), 7.51 (dd, 1H, J = 11, 2), 7.41 (d, 1H, J = 8), 7.26 (d, 1H, J = 3), 7.19 (d, 1H, J = 8), 6.92 (d, 1H, J = 16), 6.66 (d, 1H, J = 16), 5.53 (m, 1H), 4.15 (t, 2H, J = 6), 3.86 (m, 2H), 3.49 (t, 2H, J = 6), 3.25 (s, 3H), 2.97 (d, 1H, J = 12), 2.38 (m, 5H), 1.74 (m, 2H), 1.54 (m, 1H), 1.27 (m, 4H), 0.97 (t, 3H, J = 7).

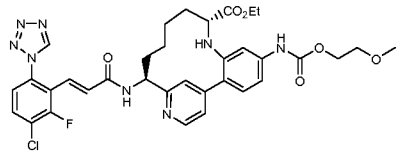
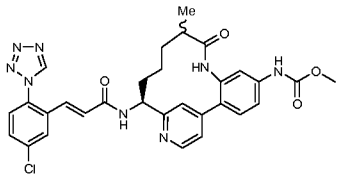
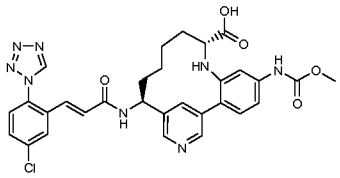
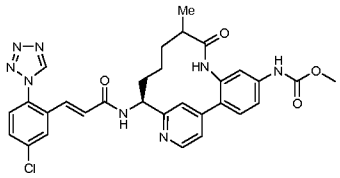
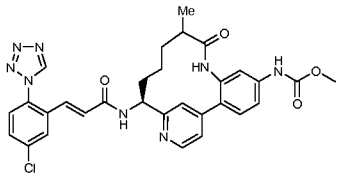
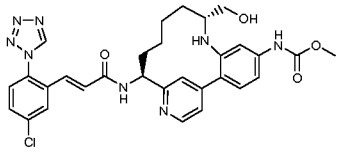
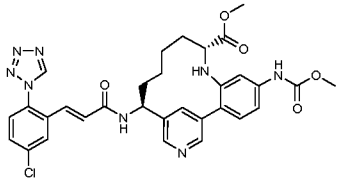
[00910] II-41A. 2-{*tert*-Butoxycarbonyl-[2-[2-((S)-1-*tert*-butoxycarbonylamino-but-3-enyl)-pyridin-4-yl]-5-(2-methoxy-ethoxycarbonylamino)-phenyl]-amino}-pent-4-enoic acid ethyl ester: To a solution of Example II-39AE (83 mg, 0.142 mmol) in DCM (1.5 mL) was added DMAP (17.40 mg, 0.142 mmol) and Boc_2O (68.4 mg, 0.313 mmol) followed by DIEA (0.062 mL, 0.356 mmol). The reaction mixture was stirred at rt for 3

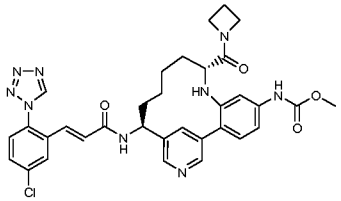
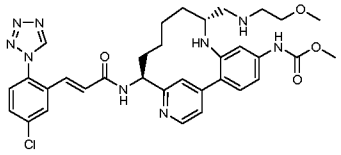
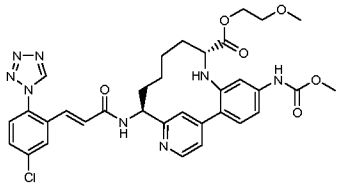
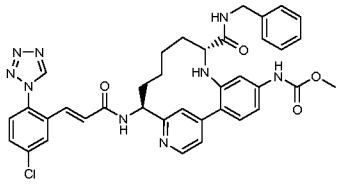
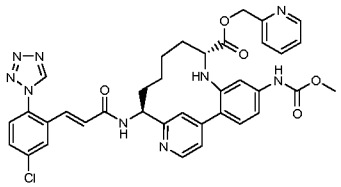
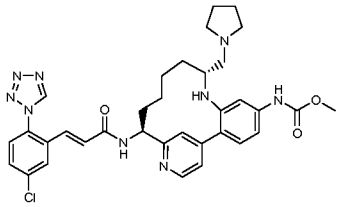
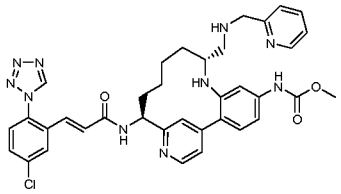
h. The reaction mixture was concentrated *in vacuo*, dissolved with EtOAc and washed with brine. The crude product was then purified by normal phase chromatography to give an oil (Wt = 98 mg): MS (ESI) *m/z* = 681.3.

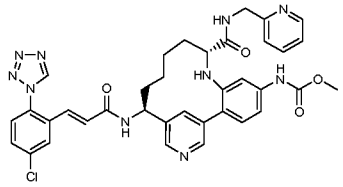
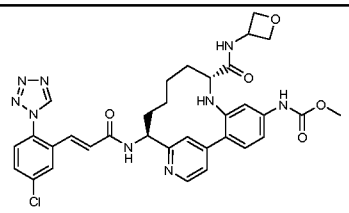
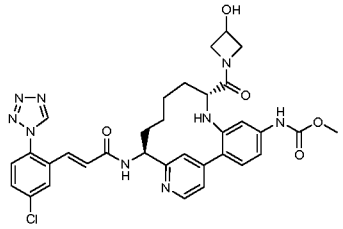
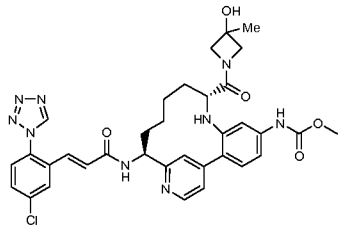
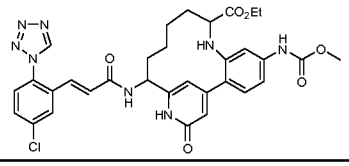
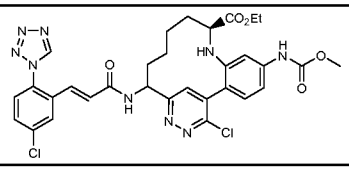
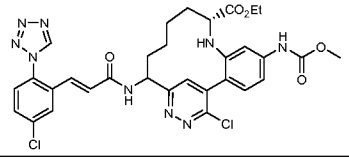
[00911] Compounds II-47 (diastereomer A) and II-48 (diastereomer B) were prepared following the procedures described in amide coupling step 88E, by replacing 88D with II-11C and by replacing pent-4-enoic acid with 2-methylbut-3-enoic acid; followed by ring-closing metathesis step 88G; hydrogenation step 2G where the diastereomers were separated by chiral prep hplc [Chiralcel OD, eluting with 80% isopropanol/heptane] to give diastereomer A and diastereomer B; Boc-deprotection step 3C; and 1G.

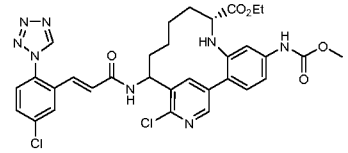
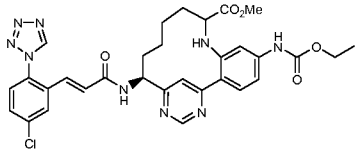
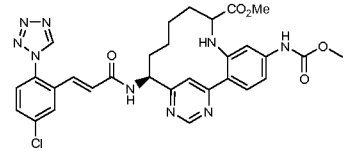
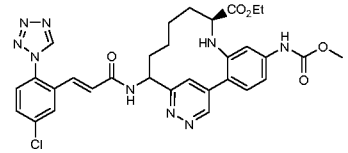
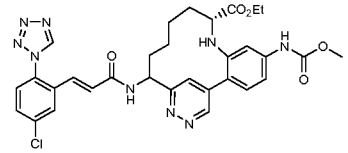
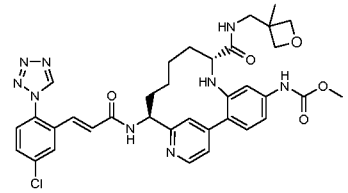
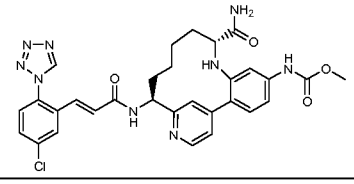
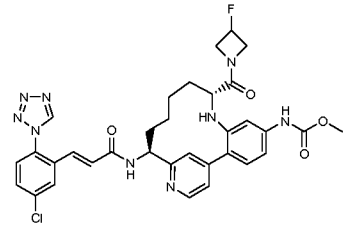
Table II-5: Examples II-39 to II-72

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.)
II-39		689.3	6.1
II-40		689.3	6.5
II-41		705.3	7.7
II-42		688.2	10.9
II-43		707.1	5.7

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.)
II-44		707.1	6.2
II-45		601.4	4.6/4.7
II-46		617.1	5.8
II-47 (Diastereomer A)		601.0	5.4
II-48 (Diastereomer B)		601.0	5.4
II-49		603.0	5.6
II-50		631.1	5.95

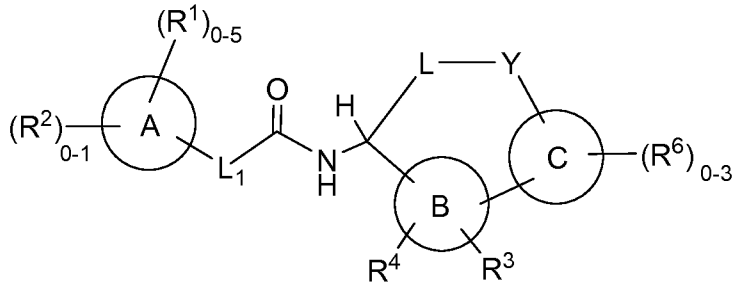
Ex. #		LCMS $[M+H]^+$	HPLC RT (min.)
II-51		656.1	5.40
II-52		660.2	5.02
II-53		675.1	7.1
II-54		706.1	7.3
II-55		708.1	6.0
II-56		656.1	5.16
II-57		693.1	5.22

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.)
II-58		707.0	4.44
II-59		672.1	5.4
II-60		672.1	5.2
II-61		686.1	5.3
II-62		661.2	7.41
II-63		680.2	10.21
II-64		680.3	10.56

Ex. #		LCMS $[M+H]^+$	HPLC RT (min.)
II-65		679.0	9.46 9.72
II-66		646.0	8.78
II-67		632.0	8.24
II-68		646.0	8.37
II-69		646.0	9.04
II-70		700.0	5.61
II-71		616.1	5.60
II-72		674.0	6.09

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

ring A is independently a C_{3-10} carbocycle or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$;

ring B is independently a benzene ring or a 5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

ring C is independently a benzene ring or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$;

L_1 is independently selected from the group consisting of: a bond, $-CHR^5-$, $-CHR^5CHR^5-$, $-CR^5=CR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR^5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CH_2NH-$, and $-CR^5R^5-$;

L is independently selected from the group consisting of: C_{3-8} alkylene, C_{3-8} alkenylene, and C_{4-8} alkynylene; wherein said alkylene, alkenylene and alkynylene are substituted with 0-2 R^7 and optionally one or more of the carbon atoms of said alkylene and alkenylene may be replaced by O, S, NH, $N(C_{1-4}$ alkyl), CO, CONH, NHCO, OCONH, $NHCO_2$, -NHCONH-, SO_2NH, $NHSO_2$, $CON(C_{1-4}$ alkyl), or $N(C_{1-4}$ alkyl)CO;

Y is independently selected from the group consisting of: CH_2, $CH(C_{1-4}$ alkyl), $C(C_{1-4}$ alkyl$)_2$, CO, O, S, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), $-N(C_{1-4}$ alkyl$)CH_2-$,

-N(CO_2(C_{1-4} alkyl))CH_2-, -N(CH_2CO_2(C_{1-4} alkyl))CH_2-, -CONH-, -NHCO-, -CONHCH_2-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -OCON(C_{1-4} alkyl)-, -NHCONH-, -SO_2NH-, -NHCO_2-, and -NHSO_2-;

alternatively, L-Y is -C_{3-6} alkylene-CH=N-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, CO_2(C_{1-4} alkyl), CO(C_{1-4} alkyl), -CH_2NH_2, -$CONH_2$, -CONH(C_{1-4} alkyl), -OCH_2CO_2H, -NHCO(C_{1-4} alkyl), -NHCO_2(C_{1-4} alkyl), -NHSO_2(C_{1-4} alkyl), -SO_2NH_2, -C(=NH)NH_2, and phenyl substituted with 0-2 R^a;

R^2 is independently a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), O, and S(O)$_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a} is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, -CH_2OH, C_{1-4} alkoxy, OH, CF_3, OCF_3, CN, NH_2, CO_2H, CO_2(C_{1-4} alkyl), COC_{1-4} alkyl, -$CONH_2$, -CONH(C_{1-4} alkyl), -CON(C_{1-4} alkyl)$_2$, -SO_2(C_{1-4} alkyl), -SO_2NH_2, -SO_2NH(C_{1-4} alkyl), and -SO_2N(C_{1-4} alkyl)$_2$;

R^3 is independently selected from the group consisting of: H, =O, halogen, OH, NH_2, CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, -CH_2OH, CO_2H, CO_2(C_{1-4} alkyl), -C(O)NH_2, -C(O)NH(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)$_2$, -CH_2CO_2H, and C_{3-6} cycloalkyl;

R^4 is independently selected from the group consisting of: H, and C_{1-4} alkyl;

R^5 is, independently at each occurrence, selected from the group consisting of: H, halogen, OH, and C_{1-4} alkyl;

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, CO_2(C_{1-4} alkyl), -CH_2CO_2H, -$(CH_2)_2CO_2H$, -CH_2CO_2(C_{1-4} alkyl), -$(CH_2)_2CO_2$(C_{1-4} alkyl), NH_2, -CH_2NH_2, -NHCO(C_{1-4} alkyl), -$NHCOCF_3$, -NHCO_2(C_{1-4} alkyl), -NH$CO_2$$(CH_2)_2$O($C_{1-4}$ alkyl), -NH$CO_2$$(CH_2)_3$O($C_{1-4}$ alkyl), -NHCO_2CH_2CH(C_{1-4} alkyl)O(C_{1-4} alkyl), -NH$CO_2$$(CH_2)_2OH$, -NH$CO_2$$(CH_2)_2NH_2$, -NH$CO_2$$(CH_2)_2$N($C_{1-4}$ alkyl)$_2$,

-$NHCO_2CH_2CO_2H$, -$CH_2NHCO_2(C_{1-4}$ alkyl), -$NHC(O)NH(C_{1-4}$ alkyl), -$NHC(O)N(C_{1-4}$ alkyl)$_2$, -$NHSO_2(C_{1-4}$ alkyl), -SO_2NH_2, -$SO_2NH(C_{1-4}$ alkyl), -$SO_2NH(CH_2)_2OH$, -$SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), -$CONH_2$, -$CONH(C_{1-4}$ alkyl), -$CON(C_{1-4}$ alkyl)$_2$, -CH_2CONH_2, and -$NHCO_2(CH_2)_{0-2}R^9$;

R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, NH_2, CH_2NH_2, C_{1-4} haloalkyl, OCH_2F, $OCHF_2$, OCF_3, -$NH(C_{1-4}$ alkyl), -$N(C_{1-4}$ alkyl)$_2$, C_{1-4} alkoxy, CH_2OH, $CH_2O(C_{1-4}$ alkyl), $CH_2O(CH_2)_{1-4}O(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $CO_2(CH_2)_2O(C_{1-4}$ alkyl), $CO_2(C_{1-4}$ haloalkyl), $CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl), CH_2CO_2H, $CH_2CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, -$OCO(C_{1-4}$ alkyl), -$CH_2NH(CH_2)_2O(C_{1-4}$ alkyl), -$CONH(C_{1-4}$ alkoxy), -$CO_2(CH_2)_2O(C_{1-4}$ alkyl), -$CO_2(CH_2)_2N(C_{1-4}$ alkyl)$_2$, -$CONH(CH_2)_2O(C_{1-4}$ alkyl), -$CONH(CH_2)_2N(C_{1-4}$ alkyl)$_2$, -$CON(C_{1-4}$ alkyl)$(CH_2)_2O(C_{1-4}$ alkyl), -$CON(C_{1-4}$ alkyl)$(CH_2)_2N(C_{1-4}$ alkyl)$_2$, C_{1-4} alkyl, -CONHBn, -CONH(OBn), -$(CO)_{0-1}(CH_2)_{0-3}$-C_{3-6} carbocycle, and -$(CH_2)_{0-1}$-$(CO)_{0-1}$-$(W)_{0-1}$-$(CH_2)_{0-2}$-(4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$); wherein said carbocycle and heterocycle are substituted with 0-2 R^8;

R^8 is, independently at each occurrence, selected from the group consisting of: halogen, OH, CHF_2, CF_3, C_{1-4} alkoxy, CH_2OH, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, and C_{1-4} alkyl;

R^9 is a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), O, and $S(O)_p$;

R^a is, independently at each occurrence, selected from the group consisting of: halogen, OH, CF_3, C_{1-4} alkoxy, and C_{1-4} alkyl;

W is independently selected from the group consisting of: O, NH and $N(C_{1-4}$ alkyl); and

p is, independently at each occurrence, selected from the group consisting of: 0, 1, and 2.

2. The compound of claim 1, wherein:

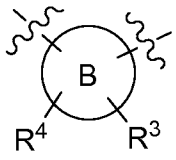
ring A is independently a 6-membered carbocycle, a 9- to 10-membered carbocycle, or a 5- to 10-membered heterocycle comprising: carbon atoms and 1-3 heteroatoms selected from N, NH, $N(C_{1-4}$ alkyl), O, and $S(O)_p$;

ring B is independently selected from the group consisting of: imidazole, oxazole, oxadiazole, triazole, pyridine, pyridazine, pyrimidine, and benzene; and

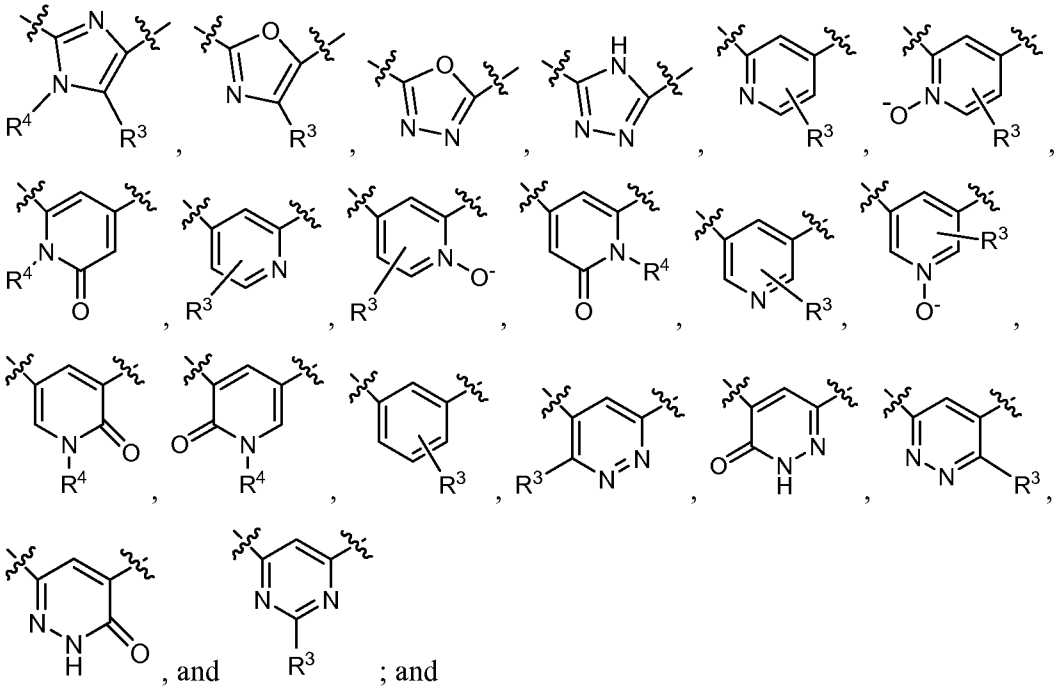
ring C is independently selected from the group consisting of: benzene, pyridine, indazole, indole, benzimidazole, quinoline, isoquinoline, tetrahydroquinoline, tetrahydroisoquinoline, and quinazoline.

3. The compound of claim 2, wherein:

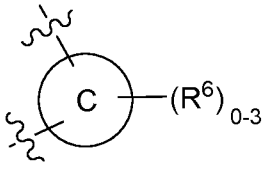
ring A is independently selected from the group consisting of: benzene, cyclohexane, indane, tetrahydronaphthalene, naphthalene, isoxazoline, isoxazole, pyrazole, imidazole, triazole, piperidine, pyridine, indazole, indole, benzimidazole, quinoline, isoquinoline, tetrahydroquinoline, and tetrahydroisoquinoline;



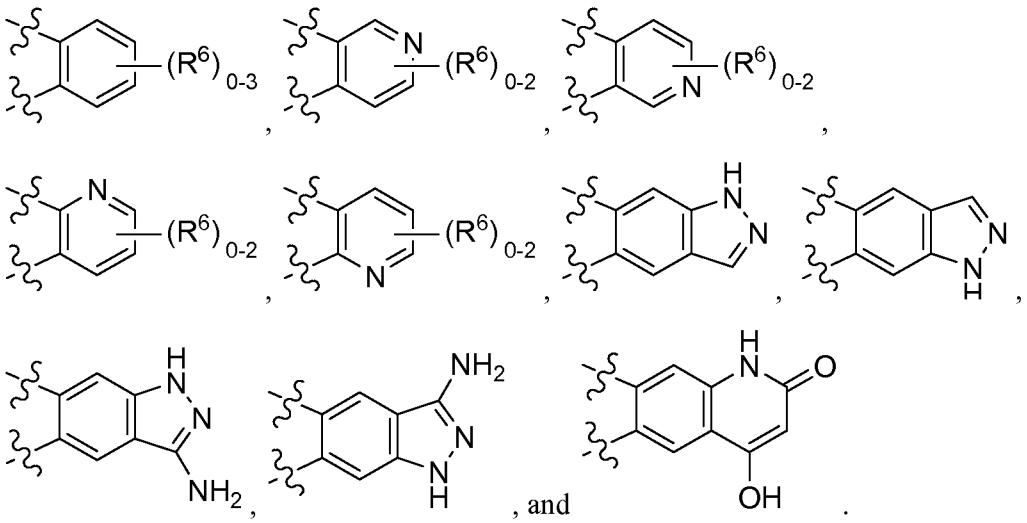
is independently selected from the group consisting of:



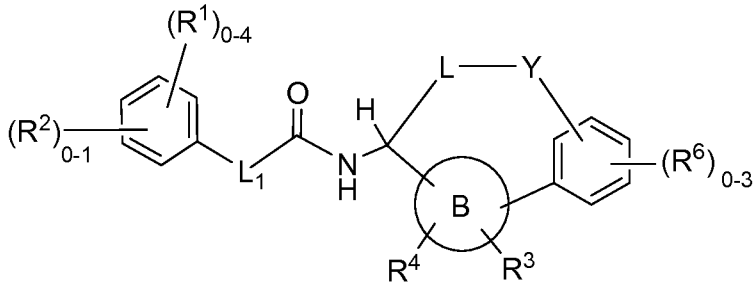
, and ; and



is independently selected from the group consisting of:

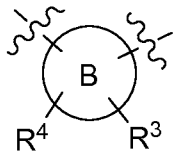


4. A compound of Formula (II):

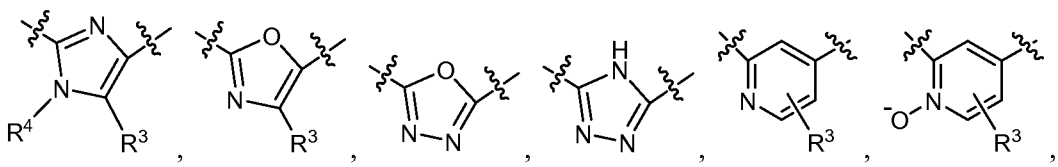


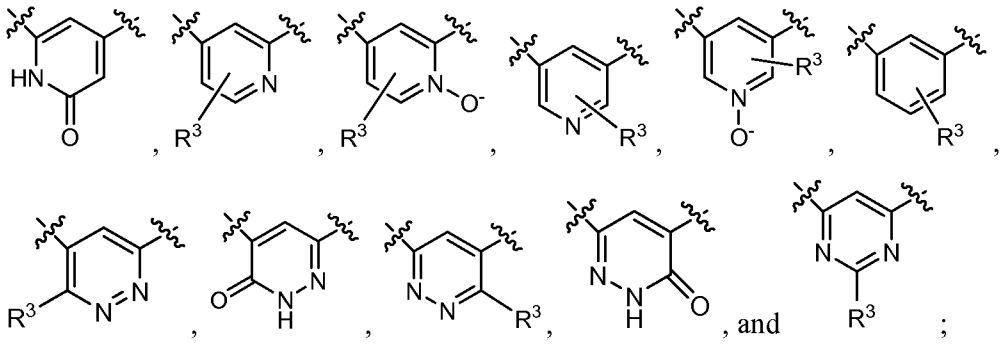
(II)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:



is independently selected from the group consisting of:





L_1 is independently selected from the group consisting of: a bond, -CHR^5CHR^5-, -CR^5=CHR^5-, -C≡C-, -OCH_2-, -CHR^5NH-, -CH_2O-, -SCH_2-, -SO_2CH_2-, -CH_2NH-, and -CR^5R^5-;

L is independently selected from the group consisting of: C_{3-8} alkylene and C_{3-8} alkenylene; wherein said alkylene and alkenylene are substituted with 0-2 R^7 and optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, CO, S, NH, N(C_{1-4} alkyl), CONH-, NHCO, OCONH, SO_2NH, or CON(C_{1-4} alkyl);

Y is independently selected from the group consisting of: CH_2, CO, CH(C_{1-4} alkyl), C(C_{1-4} alkyl)$_2$, O, S, NH, N(C_{1-4} alkyl), N(CO_2(C_{1-4} alkyl)), -N(C_{1-4} alkyl)CH_2-, -N(CO_2(C_{1-4} alkyl))CH_2-, -N(CH_2CO_2(C_{1-4} alkyl))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(C_{1-4} alkyl)CH_2-, -OCONH-, -OCON(C_{1-4} alkyl)-, -NHCONH-, and -SO_2NH-;

alternatively, L-Y is -C_{3-6} alkylene-CH=N-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} haloalkyl, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, CO_2(C_{1-4} alkyl), CO(C_{1-4} alkyl), -OCH_2CO_2H, -CH_2NH_2, -$CONH_2$, -CONH(C_{1-4} alkyl), -SO_2NH_2, and -C(=NH)NH_2;

R^2 is independently a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, O, and S(O)$_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a} is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, -CH_2OH, C_{1-4} alkoxy, OH, CF_3, CN, NH_2, CO_2H, CO_2(C_{1-4} alkyl),

COC_{1-4} alkyl, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), and $-CON(C_{1-4}$ alkyl)$_2$;

R^3 is independently selected from the group consisting of: H, halogen, OH, NH_2, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $-CH_2OH$, CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)$_2$, $-CH_2CO_2H$, and C_{3-6} cycloalkyl;

R^4 is independently selected from the group consisting of: H and C_{1-4} alkyl;

R^5 is, independently at each occurrence, selected from the group consisting of: H, halogen, OH, and C_{1-4} alkyl;

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl)$_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH(CH_2)_2O(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, $-CH_2CONH_2$, $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-NHCOCF_3$, and $-NHCO_2(CH_2)_{0-1}R^9$;

R^7 is, independently at each occurrence, selected from the group consisting of: halogen, OH, C_{1-4} haloalkyl, C_{1-4} alkoxy, CH_2OH, $CH_2O(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $CO_2(CH_2)_2O(C_{1-4}$ alkyl)), $CO_2CH_2CF_3$, $CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl), CH_2CO_2H, $CH_2CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, $-OCO(C_{1-4}$ alkyl), $-CH_2NH(CH_2)_2O(C_{1-4}$ alkyl), $-CO_2(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-CONH(CH_2)_2O(C_{1-4}$ alkyl), $-CONH(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-CON(C_{1-4}$ alkyl)$(CH_2)_2O(C_{1-4}$ alkyl), $-CONH(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-CON(C_{1-4}$ alkyl)$(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-CONH(C_{1-4}$ alkoxy), -CONHBn, -CONH(OBn), $-(CH_2)_{1-3}$Ph, C_{1-4} alkyl, and $-(CH_2)_{0-1}-(CO)_{0-1}-(W)_{0-1}-(CH_2)_{0-2}-$(4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), O, and S(O)$_p$); wherein said heterocycle is substituted with 0-2 R^8;

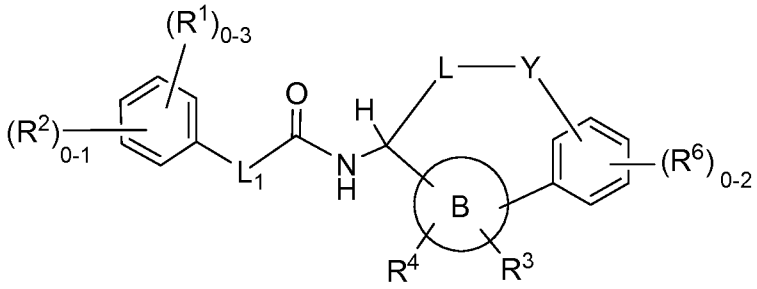
R^8 is, independently at each occurrence, selected from the group consisting of: halogen, OH, CHF_2, CF_3, C_{1-4} alkoxy, and C_{1-4} alkyl;

R^9 is a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NH, N(C_{1-4} alkyl), N(CO_2(C_{1-4} alkyl)), O, and S(O)$_p$;

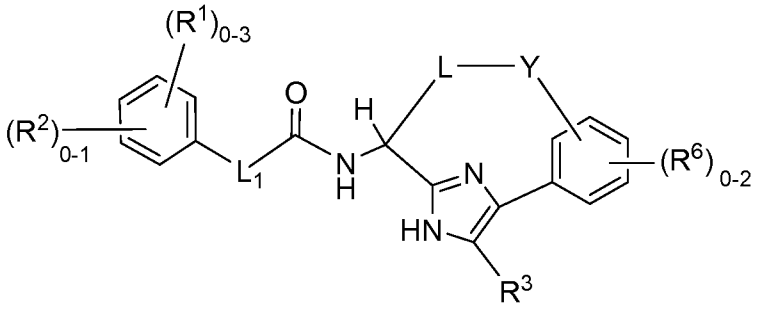
W is independently selected from the group consisting of: O and NH; and

p is, independently at each occurrence, selected from the group consisting of: 0, 1, and 2.

5. A compound of claim 4 having Formula (IIa) or Formula (IIb):



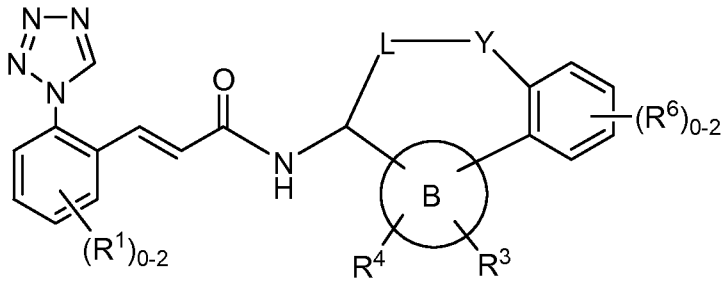
(IIa)



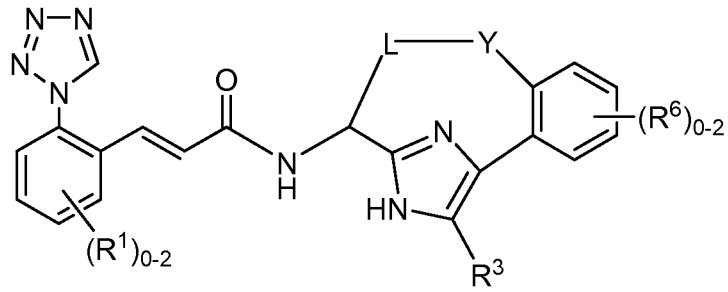
(IIb)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

6. The compound of claim 4 having Formula (IIc) or Formula (IId):



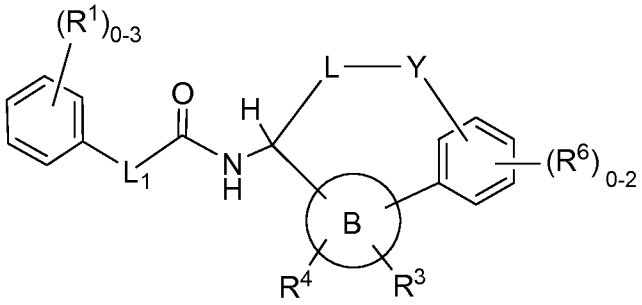
(IIc)



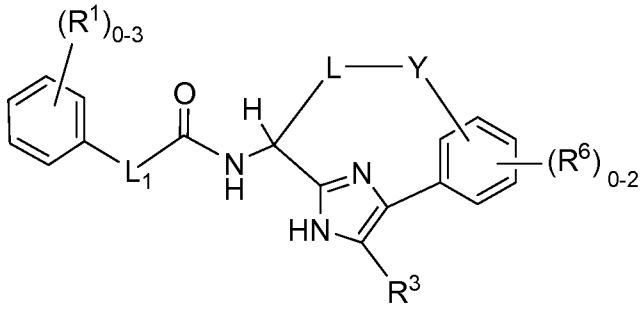
(IId)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

7. The compound of claim 4 having Formula (IIe) or Formula (IIf):



(IIe)



(IIf)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate.

8. The compound of any one of claims 1-7, wherein:

L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$, -CH=CH-, -C(Me)=CH-, -C≡C-, and $-CH_2NH-$ in Formula (I), (II), (IIa), (IIb), (IIe) or (IIf);

L is independently selected from the group consisting of: C_{3-7} alkylene and C_{3-7} alkenylene; wherein said alkylene and alkenylene are substituted with 0-2 R^7 and optionally one or two of the carbon atoms of said alkylene and alkenylene may be replaced by O, CO, NH, $N(C_{1-4}$ alkyl), CONH, NHCO, or $CON(C_{1-4}$ alkyl);

Y is independently selected from the group consisting of: CH_2, CO, $CH(C_{1-4}$ alkyl), $C(C_{1-4}$ alkyl)$_2$, O, S, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), $-N(C_{1-4}$ alkyl)CH_2-, $-N(CO_2(C_{1-4}$ alkyl))CH_2-, $-N(CH_2CO_2(C_{1-4}$ alkyl))CH_2-, -CONH-, -NHCO-, $-CONHCH_2$-, $-CON(C_{1-4}$ alkyl)CH_2-, -OCONH-, -NHCONH-, and $-SO_2NH$-;

alternatively, L-Y is $-(CH_2)_{3-6}$-CH=N-;

R^1 is, independently at each occurrence, selected from: halogen, CN, OH, OCH_2F, $OCHF_2$, OCF_3, C_{1-4} haloalkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$, and $-SO_2NH_2$;

R^3 is independently selected from the group consisting of: H, halogen, OH, NH_2, CN, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $-CH_2OH$, CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)NH_2$, $-C(O)NH(C_{1-4}$ alkyl), $-C(O)N(C_{1-4}$ alkyl)$_2$, $-CH_2CO_2H$, and C_{3-6} cycloalkyl; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), $-(CH_2)_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_3O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHC(O)NH(C_{1-4}$ alkyl), $-NHC(O)N(C_{1-4}$ alkyl)$_2$, $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl)$_2$, $-NHCOCF_3$, and $-NHCO_2(CH_2)_{0-1}R^9$.

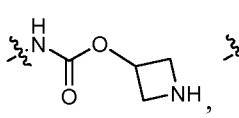
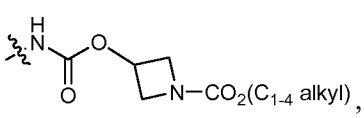
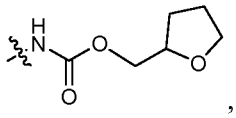
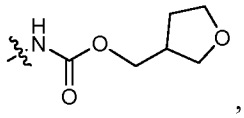
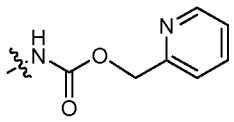
9. The compound of any one of claims 1-7, wherein:

L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2$- and -CH=CH- in Formula (I), (II), (IIa), (IIb), (IIe) or (IIf);

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, CN, C_{1-4} alkyl, OH, C_{1-4} alkoxy, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, $CO(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl)$_2$, $N(C_{1-4}$ alkyl)$_2$, $-CH_2NH_2$, and $-C(=NH)NH_2$;

R^3 is independently selected from the group consisting of: H, halogen, CN, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), C_{1-4} alkyl, $CONH_2$, $CON(C_{1-4}$ alkyl)$_2$, and C_{3-6} cycloalkyl; and

R^6 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, CN, OH, CF_3, CO_2H, $CO_2(C_{1-4}$ alkyl), $-CH_2CO_2H$, $-CH_2CO_2(C_{1-4}$ alkyl), NH_2, $-CH_2NH_2$, $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-NHCOCF_3$,


,

,

,

,

.

10. The compound of any one of claims 1-7, wherein:

L_1 is independently selected from the group consisting of: a bond and -CH=CH- in Formula (I), (II), (IIa), (IIb), (IIe) or (IIf);

L is independently selected from the group consisting of: $-(CH_2)_{3-6}-$, $-(CH_2)_{2-4}CH(C_{1-4}$ alkyl$)(CH_2)_{0-2}-$, $-(CH_2)_{1-2}-CH=CH-(CH_2)_{0-3}-$, $-CH_2-CH=C(C_{1-4}$ alkyl$)-(CH_2)_{1-2}-$, $-CH_2-C(C_{1-4}$ alkyl$)=CH-(CH_2)_{1-2}-$, $-CH_2-CH=CH-CH_2CH(C_{1-4}$ alkyl$)-$, $-CH_2-CH=CH-CH(C_{1-4}$ alkyl$)-(CH_2)_{0-2}-$, $-CH_2-CH=CH-CH_2C(halo)_2-$, $-CH_2-CH=CH-(CH_2)_{1-2}CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(halo)-$, $-(CH_2)_{3-4}C(halo)_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_{3-4}CH(C_{1-4}$ alkoxy$)-$, $-(CH_2)_4CH(CH_2(C_{1-4}$ alkoxy$))-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_{4-5}CH(CO_2(C_{1-4}$ alkyl$))-$, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}$ alkyl$))-$, $-(CH_2)_4CH(CO_2CH_2CF_3)-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl$))-$, $-(CH_2)_4C(C_{1-4}$ alkyl$)(CO_2(C_{1-4}$ alkyl$))-$, $-(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl$))-$, $-(CH_2)_4CH(CONH_2))-$, $-(CH_2)_4CH(CONH(C_{1-4}$ alkyl$))-$, $-(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)-$, $-(CH_2)_3CH(C_{1-4}$ alkyl$)CH(CONH_2)-$, $-(CH_2)_4CH(CO_2(CH_2)_2O(C_{1-4}$ alkyl$))-$, $-(CH_2)_4CH(CH_2NH(CH_2)_2O(C_{1-4}$ alkyl$))-$, $-(CH_2)_4CH(CONH(C_{1-4}$ alkoxy$))-$,

-$(CH_2)_4CH(CONH(OBn))$-, -$(CH_2)_4CH((CH_2)_3Ph)$-,

-$(CH_2)_4CH(CO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-, -$(CH_2)_4CH(CONH(CH_2)_2O(C_{1-4}$ alkyl$))$-,

-$(CH_2)_4CH(CONH(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-,

-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2O(C_{1-4}$ alkyl$))$-,

-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-,

-$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_{4-5}CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-,

-$(CH_2)_{1-3}CH(OH)(CH_2)_{1-2}$-, -$CH_2CH(OH)CH(OH)CH_2$-,

-$(CH_2)_3CH(OCO(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_3C(O)CH_2$-,

-$CH_2O(CH_2)_{2-4}$-, -$CH_2NH(CH_2)_{2-4}$-, -$(CH_2)_{2-3}NH(CH_2)_{1-2}$-,

-$(CH_2)_{2-4}N(C_{1-4}$ alkyl$)(CH_2)_{0-2}$-, -$CH_2CONH(CH_2)_{2-4}$-,

-$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_{2-4}$-, -$CH_2NHCOC(halo)_2CH_2$-,

-$(CH_2)_4CH(3$-C_{1-4} alkyl-oxetan-3-yl)-, -$(CH_2)_4CH($thiazol-4-yl$)$-,

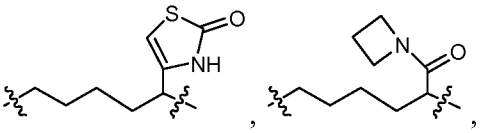
-$(CH_2)_4CH(4$-C_{1-4} alkyl-thiazol-2-yl)-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-imidazol-2-yl)-,

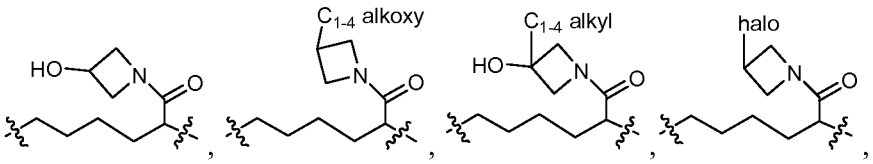
-$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-3-yl)-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-5-yl)-,

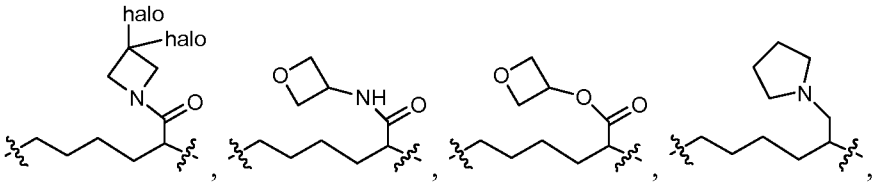
-CH_2-CH=CH-$CH_2CH(1$-C_{1-4} alkyl-pyrazol-5-yl)-,

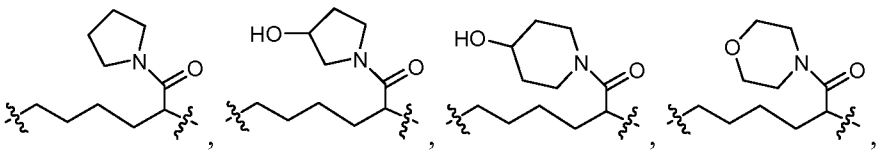
-$(CH_2)_4CH(1$-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)-,

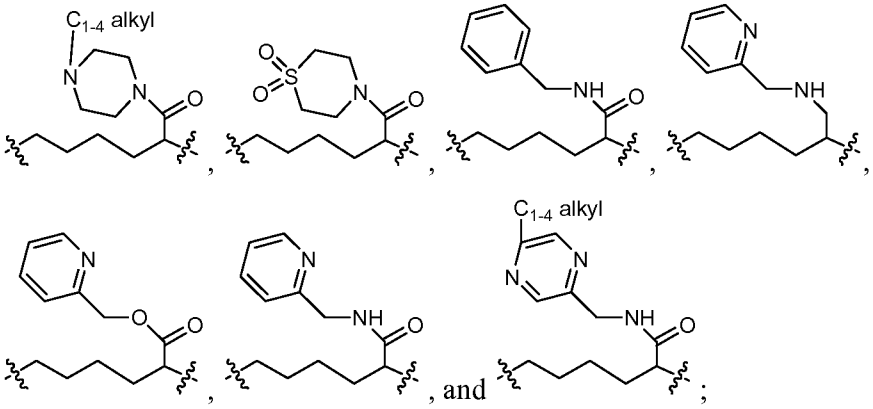
-$(CH_2)_4CH(1$-C_{1-4} alkyl-4-halo-pyrazol-3-yl)-,











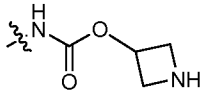
Y is independently selected from the group consisting of: CH_2, CO, O, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), $-N(C_{1-4}$ alkyl)CH_2-, $-N(CO_2(C_{1-4}$ alkyl))CH_2-, $-N(CH_2CO_2(C_{1-4}$ alkyl))CH_2-, -CONH-, -NHCO-, $-CONHCH_2$-, $-CON(C_{1-4}$ alkyl)CH_2-, -OCONH-, -NHCONH-, and $-SO_2NH$-; and

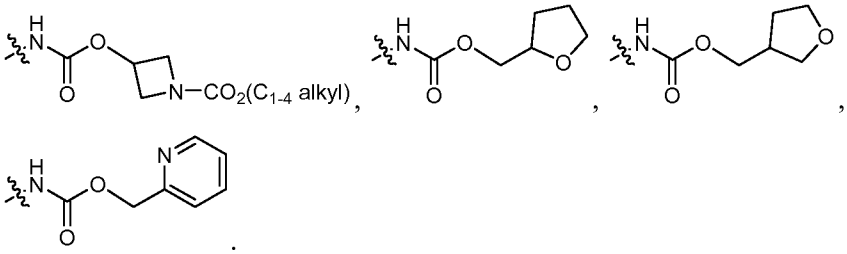
alternatively, L-Y is $-(CH_2)_{3-6}$-CH=N-;

R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, OH, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), CN, CH_2F, CHF_2, CF_3, $OCHF_2$, NH_2, $N(C_{1-4}$ alkyl$)_2$, $-CH_2NH_2$, and $-C(=NH)NH_2$;

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and C_{3-6} cycloalkyl; and

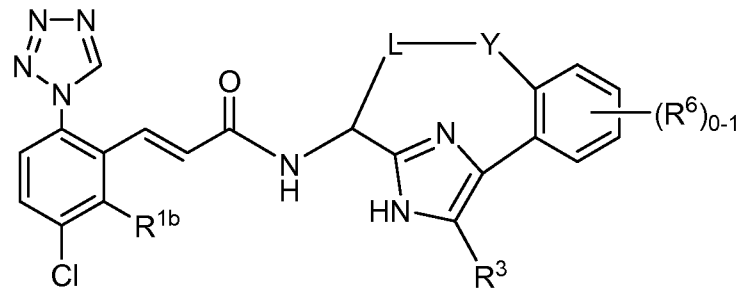
R^6 is, independently at each occurrence, selected from the group consisting of: halogen, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-NHCOCF_3$,



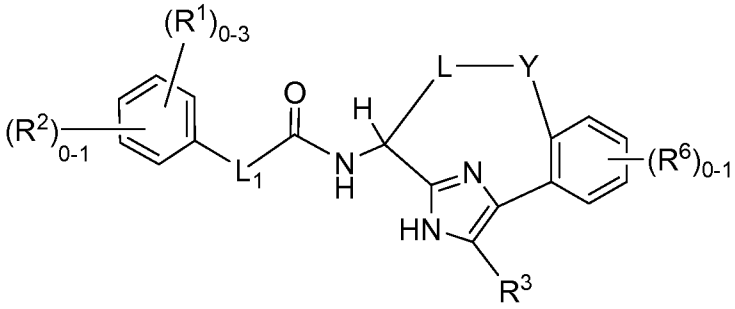


.

11. A compound of Formula (III) or Formula (IIIa):



(III)



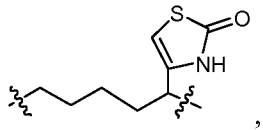
(IIIa)

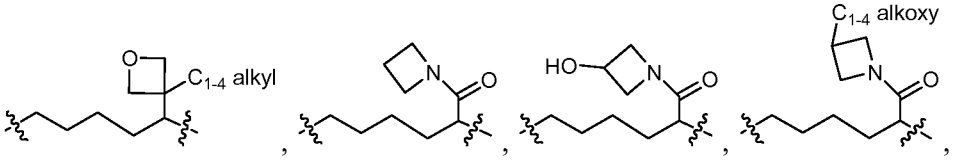
or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

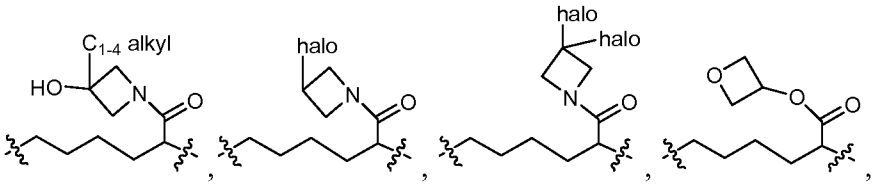
L_1 is independently selected from the group consisting of: a bond and -CH=CH- in Formula (IIIa);

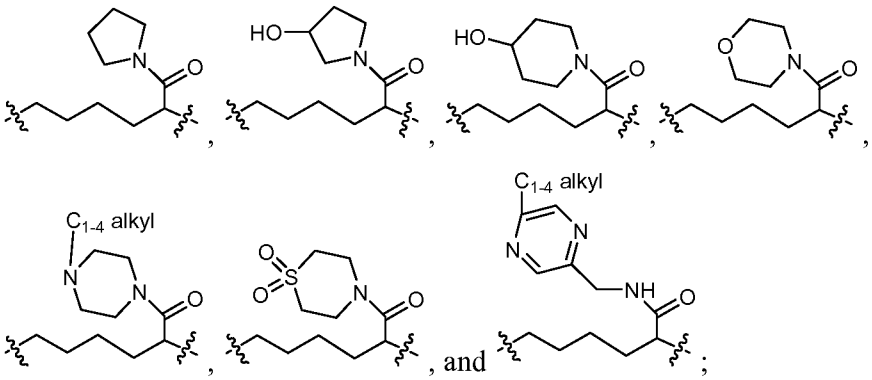
L is independently selected from the group consisting of: $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})-$, $-(CH_2)_4CH(C_{1-4}\text{ alkyl})-$, $-(CH_2)_2CH(C_{1-4}\text{ alkyl})CH_2-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})CH_2-$, $-(CH_2)_2CH(C_{1-4}\text{ alkyl})(CH_2)_2-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})(CH_2)_2-$, $-(CH_2)_4CH(C_{1-4}\text{ alkyl})CH_2-$, $-(CH_2)_4CH(C_{1-4}\text{ alkyl})(CH_2)_2-$, $-(CH_2)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(C_{1-4}\text{ alkyl})-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CH(C_{1-4}\text{ alkyl})-$, $-CH_2-CH=CH-CH(C_{1-4}\text{ alkyl})CH_2-$, $-CH_2-CH=CH-CH_2C(halo)_2-$, $-CH_2-CH=CH-CH_2CH(CF_3)-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(halo)-$, $-(CH_2)_3C(halo)_2-$, $-(CH_2)_4C(halo)_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_3CH(C_{1-4}\text{ alkoxy})-$, $-(CH_2)_4CH(CH_2(C_{1-4}\text{ alkoxy}))-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_4CH(CO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CO_2CH_2CF_3)-$,

-$(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl))-, -$(CH_2)_5CH(CO_2(C_{1-4}$ alkyl))-,
-$(CH_2)_4C(C_{1-4}$ alkyl)$(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl))-,
-$(CH_2)_4CH(CONH_2)$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl))-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CH(CONH_2)$-,
-$(CH_2)_4CH(CONH(C_{1-4}$ alkoxy))-, -$(CH_2)_4CH(CONH(OBn))$-, -$(CH_2)_4CH((CH_2)_3Ph)$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2O(C_{1-4}$ alkyl))-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-,
-$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-,
-$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-,
-$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_3C(O)CH_2$-,
-$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-,
-$(CH_2)_2N(C_{1-4}$ alkyl$)CH_2$-, -$(CH_2)_2N(C_{1-4}$ alkyl$)(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-,
-$CH_2CONH(CH_2)_3$-, -$CH_2CONH(CH_2)_4$-, -$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_2$-,
-$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_3$-, -$(CH_2)_4CH$(thiazol-4-yl)-,
-$(CH_2)_4CH(4\text{-}C_{1-4}$ alkyl-thiazol-2-yl)-, -$(CH_2)_4CH(1\text{-}C_{1-4}$ alkyl-imidazol-2-yl)-,
-$(CH_2)_4CH(1\text{-}C_{1-4}$ alkyl-pyrazol-3-yl)-, -$(CH_2)_4CH(1\text{-}C_{1-4}$ alkyl-pyrazol-5-yl)-,
-CH_2-CH=CH-$CH_2CH(1\text{-}C_{1-4}$ alkyl-pyrazol-5-yl)-,
-$(CH_2)_4CH(1\text{-}C_{1-4}$ alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)-,
-$(CH_2)_4CH(1\text{-}C_{1-4}$ alkyl-4-halo-pyrazol-3-yl)-,









Y is independently selected from the group consisting of: CH_2, CO, O, NH, $N(C_{1-4}$ alkyl), $N(CO_2(C_{1-4}$ alkyl)), $-N(C_{1-4}$ alkyl)CH_2-, $-N(CO_2(C_{1-4}$ alkyl))CH_2-, $-N(CH_2CO_2(C_{1-4}$ alkyl))CH_2-, -CONH-, -NHCO-, $-CONHCH_2$-, $-CON(C_{1-4}$ alkyl)CH_2-, -OCONH-, -NHCONH-, and $-SO_2NH$-;

alternatively, L-Y is $-(CH_2)_4$-CH=N-;

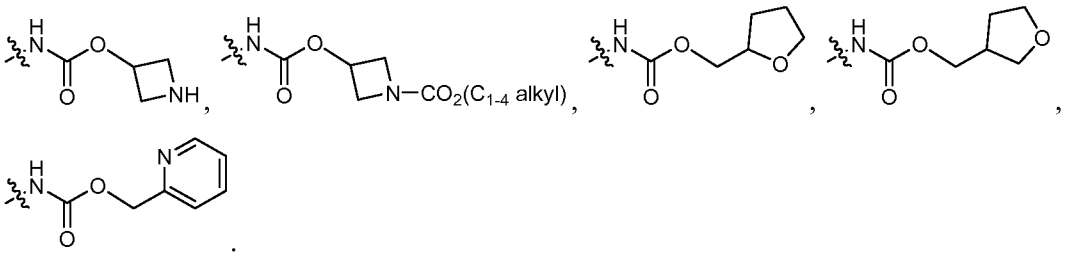
R^1 is, independently at each occurrence, selected from the group consisting of: halogen, C_{1-4} alkyl, OH, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), CN, CH_2F, CHF_2, CF_3, $OCHF_2$, NH_2, $N(C_{1-4}$ alkyl$)_2$, $-CH_2NH_2$, and $-C(=NH)NH_2$ in Formula (IIIa);

R^{1b} is independently selected from the group consisting of: H and halogen in Formula (III);

R^2 is independently a 5-membered heterocycle selected from: triazolyl and tetrazolyl in Formula (IIIa);

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and C_{3-6} cycloalkyl; and

R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, $CO_2(C_{1-4}$ alkyl), $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CO_2H$, $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2N(C_{1-4}$ alkyl$)_2$, $-NHCOCF_3$,



.

12. The compound of claim 11, wherein:

L is independently selected from the group consisting of: -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)-, -$(CH_2)_4CH(C_{1-4}$ alkyl)-, -$(CH_2)_2CH(C_{1-4}$ alkyl)CH_2-,

-$(CH_2)_3CH(C_{1-4}$ alkyl)CH_2-, -$(CH_2)_2CH(C_{1-4}$ alkyl)$(CH_2)_2$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)$(CH_2)_2$-, -$(CH_2)_4CH(C_{1-4}$ alkyl)CH_2-, -$(CH_2)_4CH(C_{1-4}$ alkyl)$(CH_2)_2$-, -$(CH_2)_2$-CH=CH-, -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C(C_{1-4} alkyl)-$(CH_2)_2$-, -CH_2-CH=CH-$CH_2CH(C_{1-4}$ alkyl)-, -CH_2-CH=CH-CH(C_{1-4} alkyl)CH_2-, -CH_2-CH=CH-$CH_2C(halo)_2$-, -CH_2-CH=CH-$CH_2CH(CF_3)$-, -CH_2-CH=CH-$(CH_2)_2CH(CF_3)$-, -CH_2-CH=CH-CH(OH)CH_2-, -$(CH_2)_3CH(halo)$-, -$(CH_2)_3C(halo)_2$-, -$(CH_2)_4C(halo)_2$-, -$(CH_2)_4CH(CH_2OH)$-, -$(CH_2)_4CH(CH_2(C_{1-4}$ alkoxy))-, -$(CH_2)_3CH(C_{1-4}$ alkoxy)-, -$(CH_2)_4CH(C_{1-4}$ alkoxy)-, -$(CH_2)_4CH(CO_2H)$-, -$(CH_2)_4CH(CH_2CO_2H)$-, -$(CH_2)_4CH(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4CH(CH_2CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4CH(CO_2CH_2CF_3)$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl))-, -$(CH_2)_5CH(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4C(C_{1-4}$ alkyl)$(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4CH(CONH_2)$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl))-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)$CH(CONH_2)$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkoxy))-, -$(CH_2)_4CH(CONH(OBn))$-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl)$(CH_2)_2O(C_{1-4}$ alkyl))-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl)$(CH_2)_2N(C_{1-4}$ alkyl$)_2)$-, -$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-, -$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-, -$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl))CH_2-, -$(CH_2)_3C(O)CH_2$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-, -$(CH_2)_2N(C_{1-4}$ alkyl)CH_2-, -$(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-, -$CH_2CONH(CH_2)_3$-, -$CH_2CONH(CH_2)_4$-, -$CH_2CON(C_{1-4}$ alkyl)$(CH_2)_2$-,

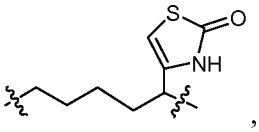
$-CH_2CON(C_{1-4}$ alkyl$)(CH_2)_3-$, $-(CH_2)_4CH$(thiazol-4-yl)-,

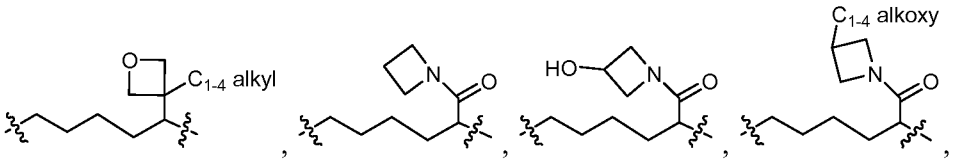
$-(CH_2)_4CH(4-C_{1-4}$ alkyl-thiazol-2-yl)-, $-(CH_2)_4CH(1-C_{1-4}$ alkyl-imidazol-2-yl)-,

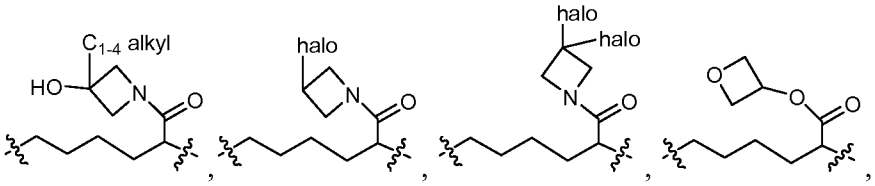
$-(CH_2)_4CH(1-C_{1-4}$ alkyl-pyrazol-3-yl)-, $-(CH_2)_4CH(1-C_{1-4}$ alkyl-pyrazol-5-yl)-,

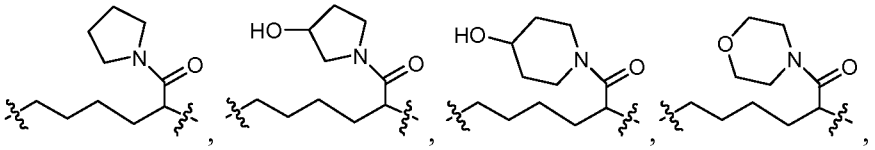
$-CH_2-CH=CH-CH_2CH(1-C_{1-4}$ alkyl-pyrazol-5-yl)-,

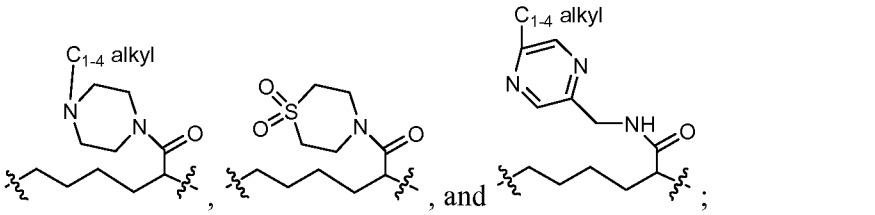
$-(CH_2)_4CH(1-C_{1-4}$ alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)-,

$-(CH_2)_4CH(1-C_{1-4}$ alkyl-4-halo-pyrazol-3-yl)-,  ,

 ,

 ,

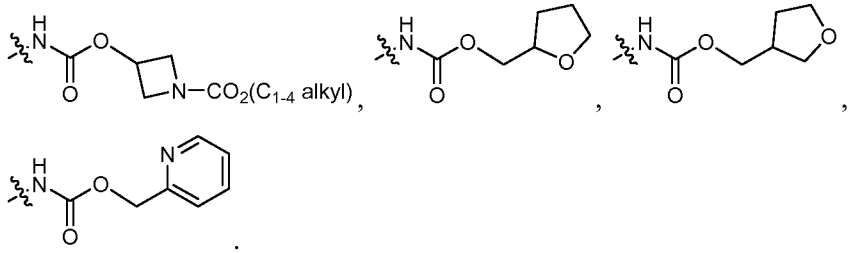
 ,

 , and ;

Y is independently selected from the group consisting of: CH_2, O, NH, -CONH-, -NHCO-, $-CONHCH_2-$, $-CON(C_{1-4}$ alkyl$)CH_2-$, $-N(C_{1-4}$ alkyl$)CH_2-$, $-N(CO_2(C_{1-4}$ alkyl$))CH_2-$, $-N(CH_2CO_2(C_{1-4}$ alkyl$))CH_2-$, -OCONH-, -NHCONH-, and $-SO_2NH-$;

alternatively, L-Y is $-(CH_2)_4-CH=N-$; and

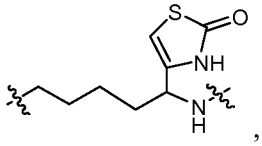
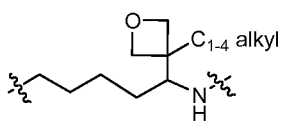
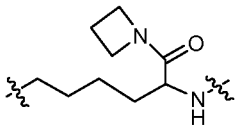
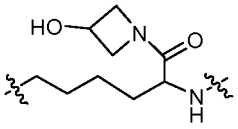
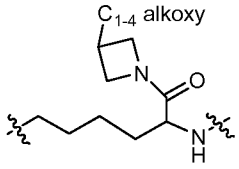
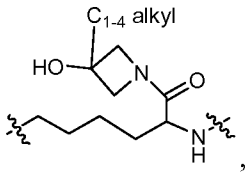
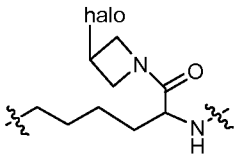
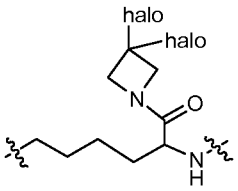
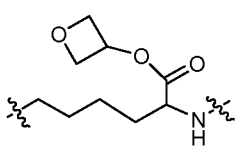
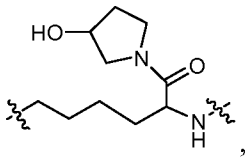
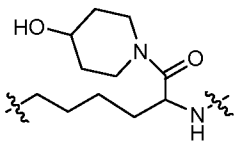
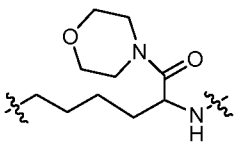
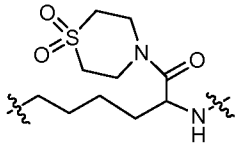
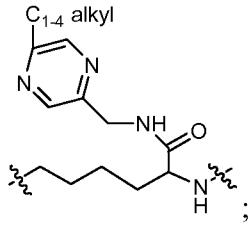
R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, $-NHCO_2(C_{1-4}$ alkyl$)$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl$)$, $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl$)$, $-NHCO_2CH_2CO_2H$,



13. The compound of claim 11 having Formula (III), wherein:

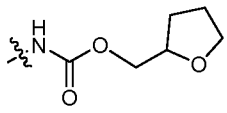
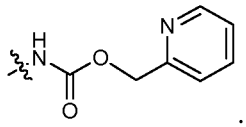
L-Y is independently selected from the group consisting of: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2(C_{1-4}$ alkyl))CH_2-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl))CH_2-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl)$_2)CH_2$-, -$(CH_2)_4CF_2CO$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=CH-$(CH_2)_4$-, -$CH_2CON(C_{1-4}$ alkyl)$(CH_2)_3$-, -$CH_2CON(C_{1-4}$ alkyl)$(CH_2)_4$-, -$(CH_2)_4N(C_{1-4}$ alkyl)CH_2-, -$(CH_2)_4N(CO_2(C_{1-4}$ alkyl))CH_2-, -$(CH_2)_4N(CH_2CO_2(C_{1-4}$ alkyl))CH_2-, -$(CH_2)_5O$-, -$(CH_2)_6O$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)$(CH_2)_2O$-, -$(CH_2)_4CH(C_{1-4}$ alkyl)CH_2O-, -$CH_2CONH(CH_2)_2O$-, -$CH_2NH(CH_2)_4O$-, -CH_2-CH=CH-$(CH_2)_2O$-, -CH_2-CH=CH-$(CH_2)_3O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CH_2NH-, -$(CH_2)_4CH(C_{1-4}$ alkyl)NH-, -$(CH_2)_4CH(C_{1-4}$ alkyl)CH_2NH-, -$(CH_2)_4CH(CH_2OH)NH$-, -$(CH_2)_4CH(CH_2(C_{1-4}$alkoxy))NH-, -$(CH_2)_4CH(CO_2H)NH$-, -$(CH_2)_4CH((CH_2)_3Ph)NH$-, -$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2(C_{1-4}$ alkyl))NH-, -$(CH_2)_4CH(CO_2(C_{1-4}$ alkyl))NH-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl))NH-, -$(CH_2)_5CH(CO_2(C_{1-4}$ alkyl))NH-, -$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl))NH-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)NH$-, -$(CH_2)_4C(C_{1-4}$ alkyl)$(CO_2(C_{1-4}$ alkyl))NH-, -$(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl))NH-, -$(CH_2)_3CH(C_{1-4}$ alkyl)$CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkoxy))NH-, -$(CH_2)_4CH(CONH(OBn))NH$-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl)$(CH_2)_2O(C_{1-4}$ alkyl))NH-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl)$(CH_2)_2N(C_{1-4}$ alkyl$)_2)NH$-, -CH_2-CH=CH-$(CH_2)_2NH$-, -CH_2-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-,

-$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_5CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-, -CH_2-CH=CH-$CH_2CH(CF_3)NH$-, -CH_2-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-, -$CH_2NHCOCF_2CH_2NH$-, -$CH_2CONH(CH_2)_4NH$-, -$(CH_2)_4CH$(CO-pyrrolidin-1-yl)NH-, -$(CH_2)_4CH$(thiazol-4-yl)NH-, -$(CH_2)_4CH$(4-C_{1-4} alkyl-thiazol-2-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-imidazol-2-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-3-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_4CH$(1-C_{1-4} alkyl-4-halo-pyrazol-3-yl)NH-, -CH_2-CH=CH-CH_2CH(1-C_{1-4} alkyl-pyrazol-5-yl)NH-, -$(CH_2)_6N(C_{1-4}$ alkyl)-, -$(CH_2)_5N(CO_2(C_{1-4}$ alkyl))-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CONH-, -$(CH_2)_4CH(C_{1-4}$ alkyl)CONH-, -$(CH_2)_2CH(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_2CH(C_{1-4}$ alkyl)$(CH_2)_2CONH$-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2CONH$-, -CH_2-CH=CH-$(CH_2)_3CONH$-, -CH_2-CH=CH-$CH_2CH(C_{1-4}$ alkyl)CONH-, -CH_2-CH=CH-CH(C_{1-4} alkyl)CH_2CONH-, -CH_2-CH=C(C_{1-4} alkyl)$(CH_2)_2CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl)CONH-, -$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3CH(CF_3)CONH$-, -$CH_2CH(OH)(CH_2)_2CONH$-, -$(CH_2)_2CH(OH)CH_2CONH$-, -$(CH_2)_3CH(OH)CH_2CONH$-, -$CH_2CH(OH)CH(OH)CH_2CONH$-, -CH_2-CH=CH-CH(OH)CH_2CONH-, -$(CH_2)_3CH(C_{1-4}$ alkoxy)CONH-, -$(CH_2)_3CH(OCO(C_{1-4}$ alkyl))CH_2CONH-, -$(CH_2)_3C(O)CH_2CONH$-, -$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-, -$CH_2NH(CH_2)_2CONH$-, -$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2CONH$-, -$(CH_2)_5NHCO$-, -CH_2-CH=CH-$(CH_2)_2NHCO$-, -$(CH_2)_3OCONH$-, -$(CH_2)_4OCONH$-, -CH_2-CH=CH-CH_2OCONH-, -CH_2-CH=CH-$CH_2NHCONH$-, -$(CH_2)_4SO_2NH$-, -CH_2-CH=CH-CH_2SO_2NH-,

-$(CH_2)_4$-CH=N-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

R^{1b} is independently selected from the group consisting of: H and halogen;

R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and C_{3-6} cycloalkyl; and

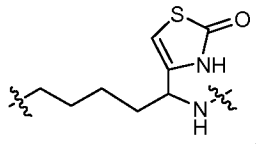
R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, -$NHCO_2(C_{1-4}$ alkyl), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), -$NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl),  , and  .

14. The compound of claim 11 having Formula (III), wherein:

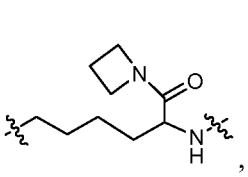
L-Y is independently selected from the group consisting of: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)CH_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=CH-$(CH_2)_4$-, -$CH_2CON(C_{1-4}$ alkyl$)(CH_2)_3$-, -$(CH_2)_5O$-, -$(CH_2)_6O$-,

-$(CH_2)_3CH(C_{1-4}$ alkyl$)(CH_2)_2O$-, -$(CH_2)_4CH(C_{1-4}$ alkyl$)CH_2O$-, -$CH_2NH(CH_2)_4O$-,
-CH_2-CH=CH-$(CH_2)_3O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CH_2NH$-,
-$(CH_2)_4CH(C_{1-4}$ alkyl$)NH$-, -$(CH_2)_4CH(C_{1-4}$ alkyl$)CH_2NH$-, -$(CH_2)_4CH(CH_2OH)NH$-,
-$(CH_2)_4CH(CH_2(C_{1-4}$ alkoxy$))NH$-, -$(CH_2)_4CH(CO_2H)NH$-,
-$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2(C_{1-4}$ alkyl$))NH$-,
-$(CH_2)_4CH(CO_2(C_{1-4}$ alkyl$))NH$-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-,
-$(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}$ alkyl$))NH$-, -$(CH_2)_5CH(CO_2(C_{1-4}$ alkyl$))NH$-,
-$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(C_{1-4}$ alkyl$))NH$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)_2)NH$-, -$(CH_2)_4C(C_{1-4}$ alkyl$)(CO_2(C_{1-4}$ alkyl$))NH$-,
-$(CH_2)_4C(CF_3)(CO_2(C_{1-4}$ alkyl$))NH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CH(CONH_2)NH$-,
-$(CH_2)_4CH(CONH(C_{1-4}$ alkoxy$))NH$-, -$(CH_2)_4CH(CONH(OBn))NH$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2O(C_{1-4}$ alkyl$))NH$-,
-$(CH_2)_4CH(CON(C_{1-4}$ alkyl$)(CH_2)_2N(C_{1-4}$ alkyl$)_2)NH$-,
-CH_2-CH=CH-$(CH_2)_2NH$-, -CH_2-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-,
-$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_5CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-,
-CH_2-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-,
-$(CH_2)_4CH(3$-C_{1-4} alkyl-oxetan-3-yl$)NH$-, -$(CH_2)_4CH($CO-pyrrolidin-1-yl$)NH$-,
-$(CH_2)_4CH($thiazol-4-yl$)NH$-, -$(CH_2)_4CH(4$-C_{1-4} alkyl-thiazol-2-yl$)NH$-,
-$(CH_2)_4CH(1$-C_{1-4} alkyl-imidazol-2-yl$)NH$-, -$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-3-yl$)NH$-,
-$(CH_2)_4CH(1$-C_{1-4} alkyl-pyrazol-5-yl$)NH$-,
-$(CH_2)_4CH(1$-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl$)NH$-,
-$(CH_2)_4CH(1$-C_{1-4} alkyl-4-halo-pyrazol-3-yl$)NH$-,
-CH_2-CH=CH-$CH_2CH(1$-C_{1-4} alkyl-pyrazol-5-yl$)NH$-, -$(CH_2)_4N(CO_2(C_{1-4}$ alkyl$))CH_2$-,
-$(CH_2)_4N(CH_2CO_2(C_{1-4}$ alkyl$))CH_2$-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-,
-$(CH_2)_3CH(C_{1-4}$ alkyl$)CONH$-, -$(CH_2)_4CH(C_{1-4}$ alkyl$)CONH$-,
-$(CH_2)_2CH(C_{1-4}$ alkyl$)CH_2CONH$-, -$(CH_2)_3CH(C_{1-4}$ alkyl$)CH_2CONH$-,
-$(CH_2)_2CH(C_{1-4}$ alkyl$)(CH_2)_2CONH$-, -$(CH_2)_2$-CH=CH-CONH-,
-CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2CONH$-,
-CH_2-CH=CH-$(CH_2)_3CONH$-, -CH_2-CH=CH-$CH_2CH(C_{1-4}$ alkyl$)CONH$-,

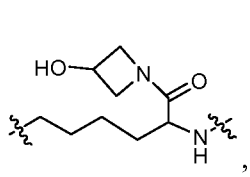
-CH_2-CH=CH-CH(C_{1-4} alkyl)CH_2CONH-, -CH_2-CH=C(C_{1-4} alkyl)-$(CH_2)_2CONH$-, -$(CH_2)_3$CH(C_{1-4} alkyl)CONH-, -$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -$CH_2CH(OH)(CH_2)_2CONH$-, -$(CH_2)_2CH(OH)CH_2CONH$-, -$(CH_2)_3CH(OH)CH_2CONH$-, -$CH_2CH(OH)CH(OH)CH_2CONH$-, -CH_2-CH=CH-$CH(OH)CH_2CONH$-, -$(CH_2)_3$CH(C_{1-4} alkoxy)CONH-, -$(CH_2)_3$CH(OCO(C_{1-4} alkyl))CH_2CONH-, -$(CH_2)_3C(O)CH_2CONH$-, -$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-, -$CH_2NH(CH_2)_2CONH$-, -$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(C_{1-4}$ alkyl)CH_2CONH-, -$(CH_2)_2N(C_{1-4}$ alkyl)$(CH_2)_2CONH$-, -$(CH_2)_5NHCO$-, -CH_2-CH=CH-$(CH_2)_2NHCO$-, -CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4OCONH$-, -CH_2-CH=CH-$CH_2NHCONH$-, -$(CH_2)_4SO_2NH$-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,



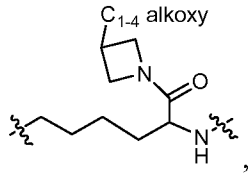
,



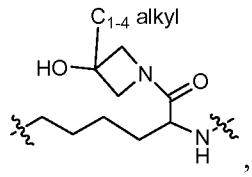
,



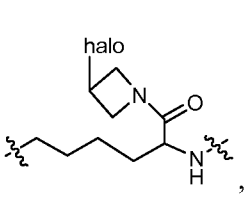
,



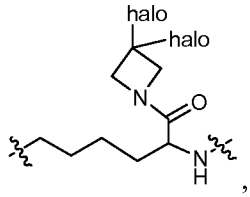
,



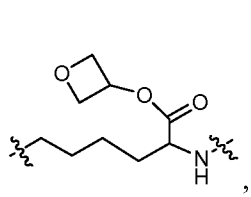
,



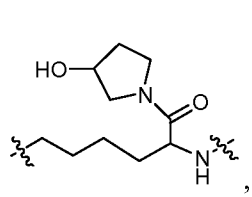
,



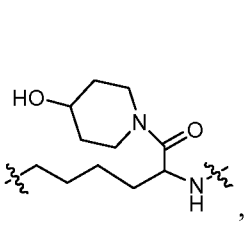
,



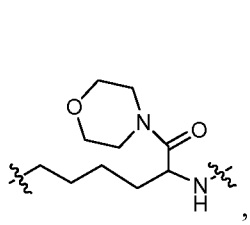
,



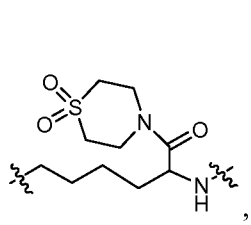
,



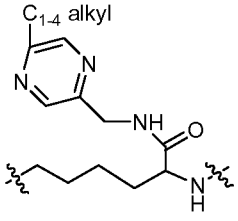
,



,



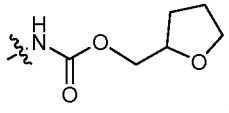
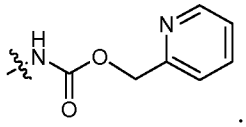
, and



;

R^{1b} is independently selected from the group consisting of: H and halogen;

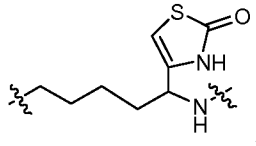
R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl)$_2$, and cyclopropyl; and

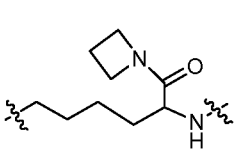
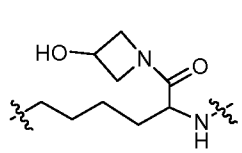
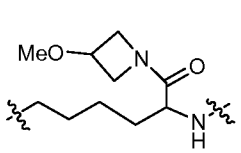
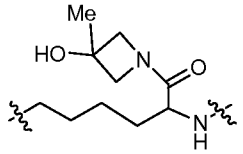
R^6 is independently selected from the group consisting of: halogen, NH_2, CO_2H, $CONH_2$, -$NHCO_2(C_{1-4}$ alkyl), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), -$NHCO_2CH_2CH(C_{1-4}$ alkyl)$O(C_{1-4}$ alkyl), and  , and  .

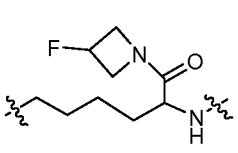
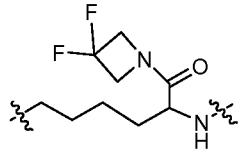
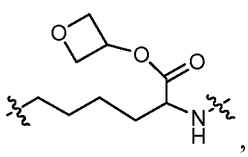
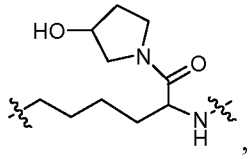
15. The compound of claim 11 having Formula (III), wherein:

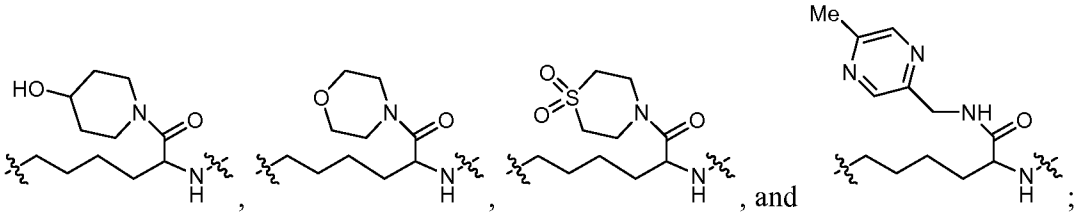
L-Y is independently selected from the group consisting of: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2Me)CH_2$-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONHMe)CH_2$-, -$(CH_2)_4CH(CON(Me)_2)CH_2$-, -$CH_2$-CH=CH-$(CH_2)_3$-, -$CH_2$-CH=CH-$(CH_2)_4$-, -$CH_2CON(CH_3)(CH_2)_3$-, -$(CH_2)_4N(CO_2Me)CH_2$-, -$(CH_2)_4N(CH_2CO_2Et)CH_2$-, -$(CH_2)_5O$-, -$(CH_2)_6O$-, -$(CH_2)_3CH(Me)(CH_2)_2O$-, -$(CH_2)_4CH(Me)CH_2O$-, -$CH_2NH(CH_2)_4O$-, -$CH_2$-CH=CH-$(CH_2)_3O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_3CH(Me)CH_2NH$-, -$(CH_2)_4CH(Me)NH$-, -$(CH_2)_4CH(Me)CH_2NH$-, -$(CH_2)_4CH(CH_2OH)NH$-, -$(CH_2)_4CH(CH_2OMe)NH$-, -$(CH_2)_4CH(CO_2H)NH$-, -$(CH_2)_4CH(CO_2Me)NH$-, -$(CH_2)_4CH(CO_2Et)NH$-, -$CH_2CONH(CH_2)_4NH$-, -$(CH_2)_4CH(CO_2(i\text{-}Pr))NH$-, -$(CH_2)_4CH(CO_2(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH$-, -$(CH_2)_5CH(CO_2Me)NH$-, -$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2Me)NH$-, -$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(Me))NH$-, -$(CH_2)_4CH(CONH(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CON(Me)_2)NH$-, -$(CH_2)_4CH(CONH(OMe))NH$-, -$(CH_2)_4CH(CONH(OBn))NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH$-, -$(CH_2)_4C(Me)(CO_2Me)NH$-, -$(CH_2)_4C(CF_3)(CO_2Me)NH$-, -$(CH_2)_3CH(Me)CH(CONH_2)NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH$-, -$CH_2$-CH=CH-$(CH_2)_2NH$-, -$CH_2$-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-, -$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_5CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-, -$CH_2$-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-, -$(CH_2)_4CH$(3-Me-oxetan-3-yl)NH-, -$(CH_2)_4CH$(CO-pyrrolidin-1-yl)NH-,

-$(CH_2)_4$CH(thiazol-4-yl)NH-, -$(CH_2)_4$CH(4-Me-thiazol-2-yl)NH-,
-$(CH_2)_4$CH(1-Me-imidazol-2-yl)NH-, -$(CH_2)_4$CH(1-Me-pyrazol-3-yl)NH-,
-$(CH_2)_4$CH(1-(n-Pr)-pyrazol-3-yl)NH-, -$(CH_2)_4$CH(1-Me-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1,3-di-Me-pyrazol-5-yl)NH-, -$(CH_2)_4$CH(1-Me-4-Cl-pyrazol-3-yl)NH-,
-CH_2-CH=CH-CH_2CH(1-Me-pyrazol-5-yl)NH-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-,
-$(CH_2)_6$CONH-, -$(CH_2)_3$CH(Me)CONH-, -$(CH_2)_4$CH(Me)CONH-,
-$(CH_2)_2$CH(Me)CH_2CONH-, -$(CH_2)_3$CH(Me)CH_2CONH-,
-$(CH_2)_2$CH(Me)$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-,
-CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-,
-CH_2-CH=CH-CH_2CH(Me)CONH-, -CH_2-CH=CHCH(Me)CH_2CONH-,
-CH_2-CH=CHCH(Et)CH_2CONH-, -CH_2-CH=C(Me)-$(CH_2)_2$CONH-,
-$(CH_2)_3$CH(Et)CONH-, -$(CH_2)_3$CH(i-Pr)CONH-, -$(CH_2)_3$CHFCONH-,
-$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-,
-$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-,
-$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-
CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OMe)CONH-, -$(CH_2)_3$CH(OCOMe)CH_2CONH-,
-$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-,
-$CH_2NH(CH_2)_2$CONH-, -$CH_2NH(CH_2)_3$CONH-, -$(CH_2)_2$N(Me)CH_2CONH-,
-$(CH_2)_2$N(Me)$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-,
-CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-,
-$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,


,


,

,

,

,

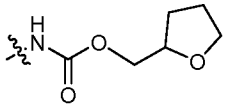
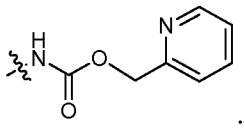

,

,

,

,



, , , and ;

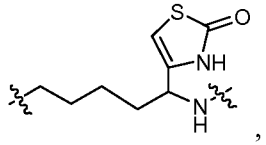
R^{1b} is independently selected from the group consisting of: H and F;

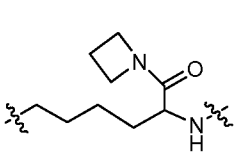
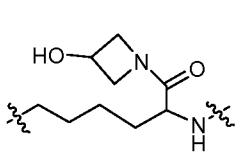
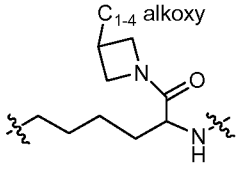
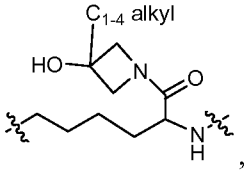
R^3 is independently selected from the group consisting of: H, F, Cl, Br, CH_3, CN, CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$, and cyclopropyl; and

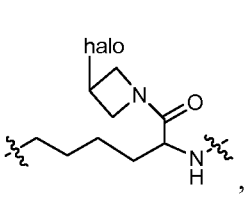
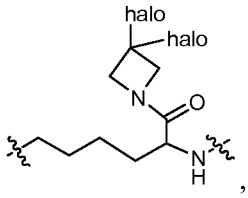
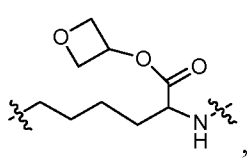
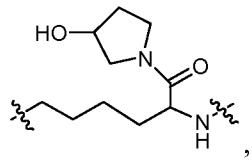
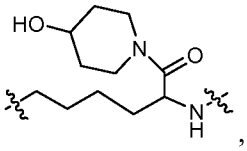
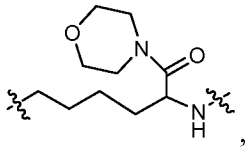
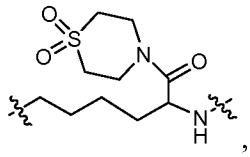
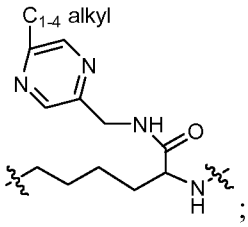
R^6 is independently selected from the group consisting of: F, NH_2, CO_2H, $CONH_2$, $-NHCO_2Me$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2OMe$, $-NHCO_2(CH_2)_2OEt$, $-NHCO_2CH_2CH(Et)OMe$, and  , and  .

16. The compound of claim 11 having Formula (III), wherein:

L-Y is independently selected from the group consisting of: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2(C_{1-4}\ alkyl))CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(C_{1-4}\ alkyl)(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_4CH(C_{1-4}\ alkyl)NH-$, $-(CH_2)_3CH(C_{1-4}\ alkyl)CH_2NH-$, $-(CH_2)_4CH(C_{1-4}\ alkyl)CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2(C_{1-4}\ alkoxy))NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_5CH(CO_2(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)_2)NH-$, $-(CH_2)_4CH(CONH(C_{1-4}\ alkoxy))NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)(CH_2)_2O(C_{1-4}\ alkyl))NH-$, $-(CH_2)_4CH(CON(C_{1-4}\ alkyl)(CH_2)_2N(C_{1-4}\ alkyl)_2)NH-$, $-CH_2-CH=CH-(CH_2)_2NH-$,

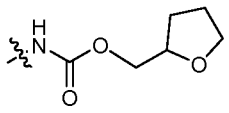
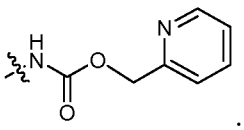
-CH_2-CH=CH-$(CH_2)_3$NH-, -$(CH_2)_4$CH(CHF_2)NH-, -$(CH_2)_4$CH(CF_3)NH-,
-$(CH_2)_3CF_2CH_2$NH-, -CH_2-CH=CH-$(CH_2)_2$CH(CF_3)NH-,
-$(CH_2)_4$CH(3-C_{1-4} alkyl-oxetan-3-yl)NH-, -$(CH_2)_4$CH(CO-pyrrolidin-1-yl)NH-,
-$(CH_2)_4$CH(thiazol-4-yl)NH-, -$(CH_2)_4$CH(4-C_{1-4} alkyl-thiazol-2-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-imidazol-2-yl)NH-, -$(CH_2)_4$CH(1-C_{1-4} alkyl-pyrazol-3-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-3-C_{1-4} alkyl-pyrazol-5-yl)NH-,
-$(CH_2)_4$CH(1-C_{1-4} alkyl-4-halo-pyrazol-3-yl)NH-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-,
-$(CH_2)_6$CONH-, -$(CH_2)_3$CH(C_{1-4} alkyl)CONH-, -$(CH_2)_4$CH(C_{1-4} alkyl)CONH-,
-$(CH_2)_2$CH(C_{1-4} alkyl)CH_2CONH-, -$(CH_2)_3$CH(C_{1-4} alkyl)CH_2CONH-,
-$(CH_2)_2$CH(C_{1-4} alkyl)$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-
CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-
CH=CH-CH_2CH(C_{1-4} alkyl)CONH-, -CH_2-CH=CH-CH(C_{1-4} alkyl)CH_2CONH-,
-CH_2-CH=C(C_{1-4} alkyl)-$(CH_2)_2$CONH-, -$(CH_2)_3$CH(C_{1-4} alkyl)CONH-,
-$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-,
-CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-,
-$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-,
-CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH_2CONH-,
-$(CH_2)_3$CH(C_{1-4} alkoxy)CONH-, -$(CH_2)_3$CH(OCO(C_{1-4} alkyl))CH_2CONH-,
-$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-,
-CH_2NH$(CH_2)_2$CONH-, -CH_2NH$(CH_2)_3$CONH-, -$(CH_2)_2$N(C_{1-4} alkyl)CH_2CONH-,
-$(CH_2)_2$N(C_{1-4} alkyl)$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-,
-CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-,
-$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,  ,

 ,  ,  ,  ,

R^{1b} is independently selected from the group consisting of: H and halogen;

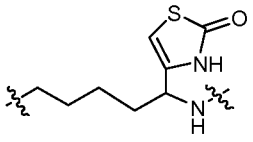
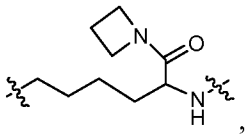
R^3 is independently selected from the group consisting of: H, halogen, C_{1-4} alkyl, CN, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CON(C_{1-4}$ alkyl$)_2$, and cyclopropyl; and

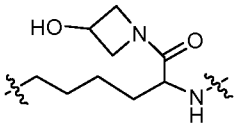
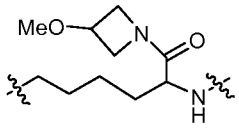
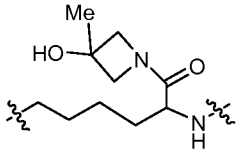
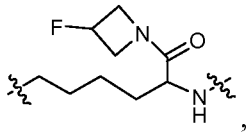
R^6 is independently selected from the group consisting of: F, NH_2, CO_2H, $-NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), $-NHCO_2CH_2CH(C_{1-4}$ alkyl$)O(C_{1-4}$ alkyl), and  , and  .

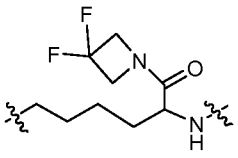
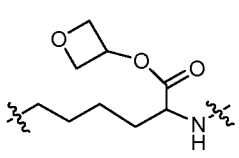
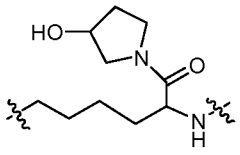
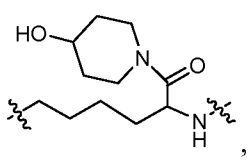
17. The compound of claim 11 having Formula (III), wherein:

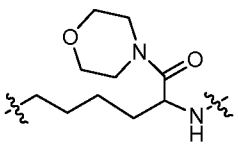
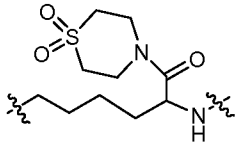
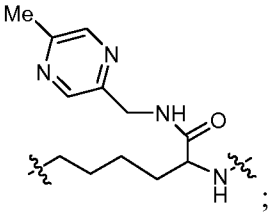
L-Y is independently selected from the group consisting of: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2Me)CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONHMe)CH_2-$, $-(CH_2)_4CH(CON(Me)_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2Me)CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(Me)(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_4CH(Me)NH-$, $-(CH_2)_3CH(Me)CH_2NH-$, $-(CH_2)_4CH(Me)CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2OMe)NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CO_2Me)NH-$, $-(CH_2)_4CH(CO_2Et)NH-$, $-(CH_2)_4CH(CO_2(i\text{-}Pr))NH-$, $-(CH_2)_4CH(CO_2(t\text{-}Bu))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH-$, $-(CH_2)_5CH(CO_2Me)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2Me)NH-$, $-(CH_2)_4CH(CONH_2)NH-$,

-$(CH_2)_4CH(CONH(Me))NH$-, -$(CH_2)_4CH(CONH(t\text{-}Bu))NH$-,
-$(CH_2)_4CH(CON(Me)_2)NH$-, -$(CH_2)_4CH(CONH(OMe))NH$-,
-$(CH_2)_4CH(CONH(OBn))NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH$-,
-$(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH$-, -$CH_2$-CH=CH-$(CH_2)_2NH$-,
-CH_2-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-, -$(CH_2)_4CH(CF_3)NH$-,
-$(CH_2)_3CF_2CH_2NH$-, -CH_2-CH=CH-$(CH_2)_2CH(CF_3)NH$-,
-$(CH_2)_4CH$(3-Me-oxetan-3-yl)NH-, -$(CH_2)_4CH$(CO-pyrrolidin-1-yl)NH-,
-$(CH_2)_4CH$(thiazol-4-yl)NH-, -$(CH_2)_4CH$(4-Me-thiazol-2-yl)NH-,
-$(CH_2)_4CH$(1-Me-imidazol-2-yl)NH-, -$(CH_2)_4CH$(1-Me-pyrazol-3-yl)NH-,
-$(CH_2)_4CH$(1-(n-Pr)-pyrazol-3-yl)NH-, -$(CH_2)_4CH$(1-Me-pyrazol-5-yl)NH-,
-$(CH_2)_4CH$(1,3-di-Me-pyrazol-5-yl)NH-, -$(CH_2)_4CH$(1-Me-4-Cl-pyrazol-3-yl)NH-,
-$(CH_2)_4N(CO_2Me)CH_2$-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-,
-$(CH_2)_3CH(Me)CONH$-, -$(CH_2)_4CH(Me)CONH$-, -$(CH_2)_2CH(Me)CH_2CONH$-,
-$(CH_2)_3CH(Me)CH_2CONH$-, -$(CH_2)_2CH(Me)(CH_2)_2CONH$-, -$(CH_2)_2$-CH=CH-CONH-,
-CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2CONH$-,
-CH_2-CH=CH-$(CH_2)_3CONH$-, -CH_2-CH=CH-$CH_2CH(Me)CONH$-,
-CH_2-CH=CH-$CH(Me)CH_2CONH$-, -CH_2-CH=$CHCH(Et)CH_2CONH$-,
-CH_2-CH=C(Me)-$(CH_2)_2CONH$-, -$(CH_2)_3CH(Me)CONH$-, -$(CH_2)_3CH(Et)CONH$-,
-$(CH_2)_3CH$(i-Pr)CONH-, -$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-
,
-CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3CH(CF_3)CONH$-, -$CH_2CH(OH)(CH_2)_2CONH$-,
-$(CH_2)_2CH(OH)CH_2CONH$-, -$(CH_2)_3CH(OH)CH_2CONH$-,
-$CH_2CH(OH)CH(OH)CH_2CONH$-, -CH_2-CH=CH-$CH(OH)CH_2CONH$-,
-$(CH_2)_3CH(OMe)CONH$-, -$(CH_2)_3CH(OCOMe)CH_2CONH$-, -$(CH_2)_3C(O)CH_2CONH$-,
-$CH_2O(CH_2)_3CONH$-, -$CH_2O(CH_2)_4CONH$-, -$CH_2NH(CH_2)_2CONH$-,
-$CH_2NH(CH_2)_3CONH$-, -$(CH_2)_2N(Me)CH_2CONH$-, -$(CH_2)_2N(Me)(CH_2)_2CONH$-,
-$(CH_2)_5NHCO$-, -CH_2-CH=CH-$(CH_2)_2NHCO$-, -CH_2-CH=CH-CH_2OCONH-,
-$(CH_2)_4OCONH$-, -CH_2-CH=CH-$CH_2NHCONH$-, -$(CH_2)_4SO_2NH$-,

-CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,  ,  ,

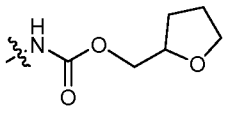
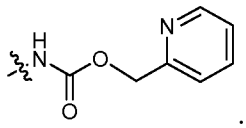
 ,  ,  ,  ,

 ,  ,  ,  ,

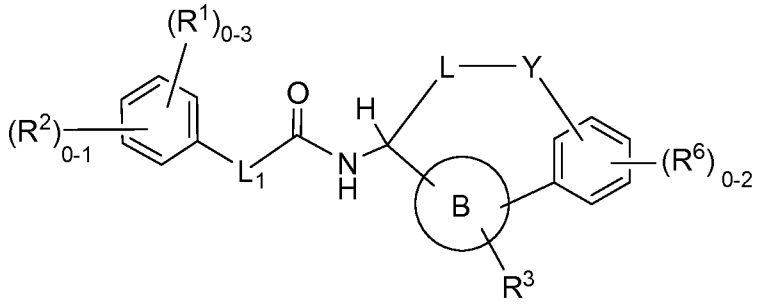
 ,  , and  ;

R^{1b} is independently selected from the group consisting of: H and F;

R^3 is independently selected from the group consisting of: H, F, Cl, Br, CH_3, CN, CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$, and cyclopropyl; and

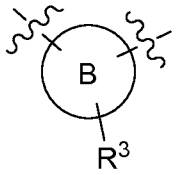
R^6 is independently selected from the group consisting of: F, NH_2, CO_2H, -$NHCO_2Me$, -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2OMe$, -$NHCO_2(CH_2)_2OEt$, -$NHCO_2CH_2CH(Et)OMe$, and  , and  .

18. A compound of any one of claims 1-7 having Formula (IV):

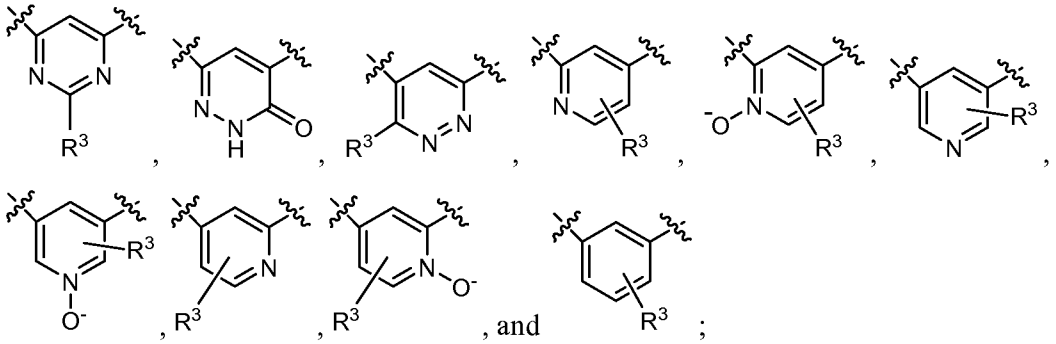


(IV)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:



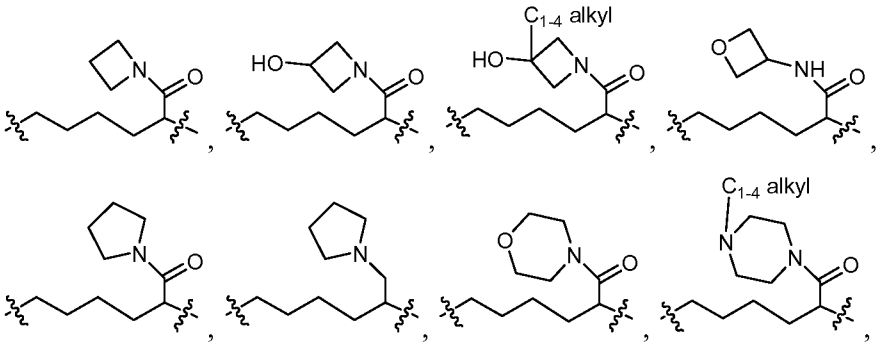
is independently selected from the group consisting of:

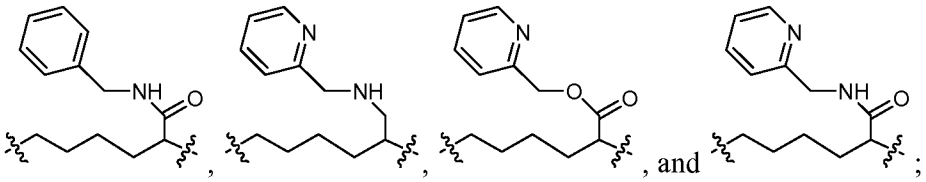


, and ;

L_1 is independently selected from the group consisting of: a bond, $-CH_2CH_2-$ and -CH=CH-;

L is independently selected from the group consisting of: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_3CH(C_{1-4}\text{ alkyl})-$, $-CH_2-CH=CH-CH_2CH(CF_3)-$, $-(CH_2)_4CH(CF_3)-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CO_2(C_{1-4}\text{ alkyl}))-$, $-CH_2CONH(CH_2)_2-$, $-(CH_2)_4CH(CO_2(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CH_2NH(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CO_2(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2O(C_{1-4}\text{ alkyl}))-$, $-(CH_2)_4CH(CON(C_{1-4}\text{ alkyl})(CH_2)_2N(C_{1-4}\text{ alkyl})_2)-$,





Y is independently -CONH-, O, or NH;

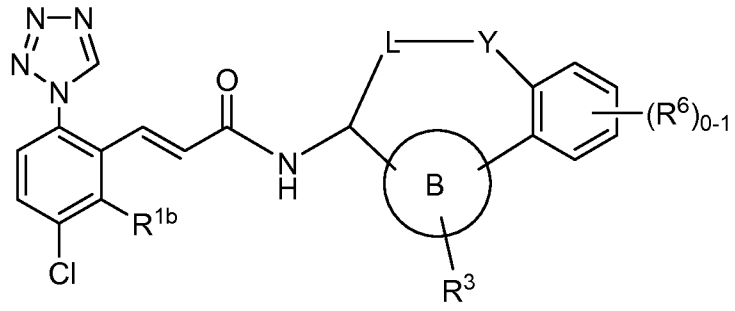
R^1 is, independently at each occurrence, selected from: halogen, CN, OCF_3, CHF_2, CF_3, C_{1-4} alkyl, C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl), NH_2, $-C(=NH)NH_2$, $-C(O)NH_2$, and $-CH_2NH_2$;

R^2 is independently a 5-membered heterocycle selected from: pyrazolyl, imidazolyl, triazolyl, and tetrazolyl;

R^3 is independently selected from the group consisting of: H, halogen, and C_{1-4} alkyl; and

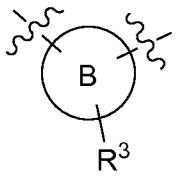
R^6 is, independently at each occurrence, selected from the group consisting of: H, halogen, CN, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl), CO_2H, and $CONH_2$.

19. The compound of claim 18 having Formula (IVa):

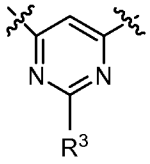
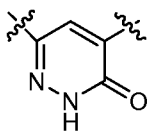
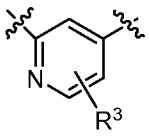
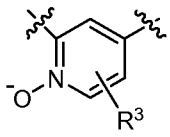
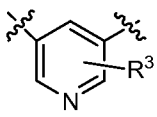
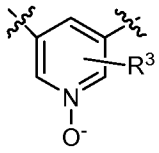
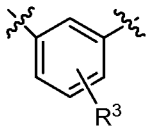


(IVa)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:



is independently selected from the group consisting of:

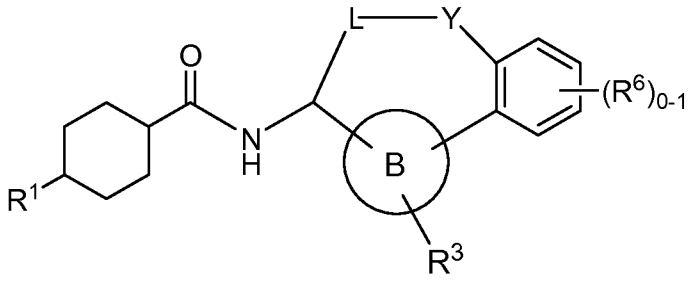






, and

;

Y is independently -CONH- or NH;

R^3 is independently selected from the group consisting of: H, F, Cl, and C_{1-4} alkyl; and

R^6 is independently selected from the group consisting of: F, $-NHCO_2(C_{1-4}$ alkyl), $-CH_2NHCO_2(C_{1-4}$ alkyl), CO_2H, $CONH_2$, and $-NHCO_2(CH_2)_2O(C_{1-4}$ alkyl).

20. The compound of any one of claims 1-3 having Formula (V):


(V)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

ring B is independently selected from the group consisting of: imidazole and pyridine; and

R^1 is independently selected from the group consisting of: C_{1-4} alkyl and CH_2NH_2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/024305

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/08 C07D498/08
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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/15530 A1 (ABBOTT LAB [US]) 1 April 1999 (1999-04-01) page 1, paragraph 1 page 5; compound claims -----	1-20
A	WO 2008/079836 A2 (SQUIBB BRISTOL MYERS CO [US]; WURTZ NICHOLAS RONALD [US]; PRIESTLEY EL) 3 July 2008 (2008-07-03) page 3, paragraph 8 - paragraph 11 page 3; compound (I) page 67, lines 22,23 examples page 474; table 1 -----	20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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
20 April 2011	03/05/2011

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	Hoepfner, Wolfgang

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/024305

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9915530 A1	01-04-1999	AT 297398 T	15-06-2005
		AU 745576 B2	21-03-2002
		AU 9581998 A	12-04-1999
		BG 64955 B1	31-10-2006
		BG 104316 A	29-12-2000
		BR 9812305 A	05-09-2000
		CA 2303934 A1	01-04-1999
		CN 1271361 A	25-10-2000
		CO 5070656 A1	28-08-2001
		CZ 20001014 A3	12-07-2000
		DE 69830502 D1	14-07-2005
		DE 69830502 T2	11-05-2006
		DK 1015459 T3	10-10-2005
		EP 1015459 A1	05-07-2000
		ES 2244087 T3	01-12-2005
		HK 1030771 A1	07-04-2006
		HU 0004556 A2	28-10-2001
		IL 134607 A	10-04-2006
		JP 3790424 B2	28-06-2006
		JP 2001517671 T	09-10-2001
		KR 20060071092 A	26-06-2006
		KR 20070086925 A	27-08-2007
		NO 20001438 A	26-05-2000
		NZ 502896 A	21-12-2001
		NZ 514778 A	28-01-2005
		PL 339455 A1	18-12-2000
		PT 1015459 E	30-09-2005
		SI 1015459 T1	31-10-2005
		SK 4172000 A3	14-08-2000
		TR 200000778 T2	21-07-2000
		TW 557297 B	11-10-2003
		ZA 9808750 A	01-04-1999
WO 2008079836 A2	03-07-2008	AR 064471 A1	01-04-2009
		AU 2007337025 A1	03-07-2008
		CA 2673598 A1	03-07-2008
		CL 37182007 A1	11-07-2008
		EP 2102176 A2	23-09-2009
		JP 2010514681 T	06-05-2010
		PE 17752008 A1	18-12-2008
		US 2010113488 A1	06-05-2010

MACROCICLOS COMO INHIBIDORES DEL FACTOR DE COAGULACION (FXIA)

Campo de la Invención

La presente invención se refiere en general a compuestos macrocíclicos y a análogos de los mismos, que son inhibidores del Factor XIa y/o de la calicreína plasmática, a composiciones que los contienen y a métodos para su uso, por ejemplo, para el tratamiento o la profilaxis de trastornos tromboembólicos.

Antecedentes de la Invención

Las enfermedades tromboembólicas permanecen como la causa principal de muerte en los países desarrollados a pesar de la disponibilidad de anticoagulantes tales como warfarina (COUMADIN®), heparina, heparinas de bajo peso molecular (por sus siglas en inglés, LMWH), y pentasacáridos sintéticos y antiagregantes plaquetarios tales como aspirina y clopidogrel (PLAVIX®). El anticoagulante oral warfarina, inhibe la maduración postraduccional de los Factores de coagulación VII, IX, X y de protrombina, y ha demostrado ser eficaz tanto en trombosis venosa como en trombosis arterial. Sin embargo, su uso es limitado debido a su índice terapéutico estrecho, aparición lenta del efecto terapéutico, numerosas interacciones dietéticas y de fármacos y la necesidad de seguimiento y de ajuste de dosis. Así, descubrir y desarrollar anticoagulantes orales inocuos y eficaces para la prevención y el tratamiento

de un amplio abanico de trastornos tromboembólicos ha llegado a tener una importancia creciente.

Un enfoque es inhibir la generación de trombina dirigiéndose a la inhibición del Factor de coagulación XIa (FXIa). El Factor XIa es una proteasa serina de plasma implicada en la regulación de la coagulación sanguínea, que se inicia *in vivo* mediante la unión del Factor tisular (por sus siglas en inglés, TF) al Factor VII (FVII) para generar el Factor VIIa (FVIIa). El complejo TF:FVIIa resultante activa el Factor IX (FIX) y el Factor X (FX), lo que conduce a la producción del Factor Xa (FXa). Los FXa generados catalizan la transformación de protrombina en cantidades pequeñas de trombina antes de que esta ruta se cierre mediante el inhibidor de la vía del Factor tisular (por sus siglas en inglés, TFPI). Los procesos de coagulación se propagan adicionalmente después por medio de la activación por retroalimentación de los Factores V, VIII y XI mediante cantidades catalíticas de trombina. (Gailani, D. y col., *Arterioscler. Thromb. Vasc. Biol.*, 27:2507-2513 (2007).) La ruptura de trombina resultante convierte el fibrinógeno en fibrina que se polimeriza para formar el armazón estructural de un coágulo sanguíneo, y activa plaquetas, que son un componente celular clave de la coagulación, M., Blood Reviews 17:S1-S5 (2003)). Por lo tanto, el Factor XIa cumple un papel clave en la propagación de este bucle de amplificación y es, así, un objetivo atractivo

para la terapia antitrombótica.

Breve Descripción de la Invención

La presente invención proporciona compuestos macrocíclicos novedosos, sus análogos, incluidos estereoisómeros, tautómeros, sales farmacéuticamente aceptables o sus solvatos, que son útiles como inhibidores selectivos de enzimas proteasa serina, especialmente Factor XIa y/o calicreina en plasma.

La presente invención también proporciona procesos e intermediarios para la preparación de compuestos de la presente invención.

La presente invención también proporciona composiciones farmacéuticas que comprenden un vehículo farmacéuticamente aceptable y al menos uno de los compuestos de la presente invención o estereoisómeros, tautómeros, sales farmacéuticamente aceptables o solvatos de los mismos.

Los compuestos de la invención pueden usarse en el tratamiento y/o la profilaxis de trastornos tromboembólicos.

Los compuestos de la presente invención pueden usarse en terapia.

Los compuestos de la presente invención pueden usarse para la fabricación de un medicamente para el tratamiento y/o la profilaxis de un trastorno tromboembólico.

Los compuestos de la invención pueden usarse solos, en combinación con otros compuestos de la presente invención

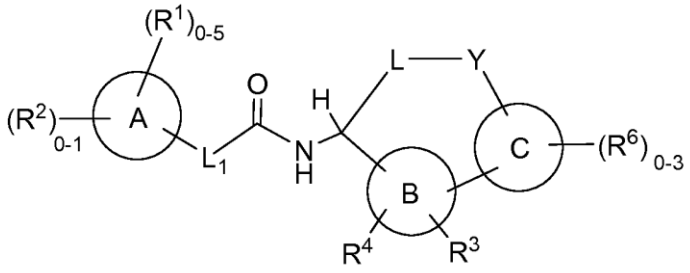
o en combinación con un agente distinto o con varios agentes distintos, preferentemente con uno o dos.

Estas y otras características de la invención se exponen de forma ampliada al avanzar la descripción.

Descripción Detallada de la Invención

I. COMPUESTOS DE LA INVENCIÓN

En un primer aspecto, la presente invención proporciona, entre otras cosas, un compuesto de fórmula (I):



(I)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco del mismo, en la que:

el anillo A es independientemente un carbociclo C_{3-10} o un carbociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, NH, N(alquilo C_{1-4}), O y S(O)p;

el anillo B es independientemente un anillo de benceno o un heteroarilo de 5 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y S(O)p;

el anillo C es independientemente un anillo de benceno o un heterociclo de 5 a 10 miembros que comprende:

átomos de carbono y 1-4 heteroátomos seleccionados del N, NH, N(alquilo C_{1-4}), O y $S(O)_p$;

L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CHR^5-$, $-CHR^5CHR^5-$, $-CR^5=CR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR_5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CN_2NH-$ y $-CR^5R^5-$;

L se selecciona independientemente del grupo constituido por: alquileno C_{3-8}, alquenileno C_{3-8} y alquinileno C_{4-8}, en donde el alquileno, alquenileno y alquinileno están sustituidos con 0-2 R^7 y opcionalmente uno o varios de los átomos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, S, NH, N(alquilo C_{1-4}), CO, CONH, NHCO, OCONH, $NHCO_2$, -NHCONH-, SO_2NH, $NHSO_2$, CON(alquilo C_{1-4}) o N(alquilo C_{1-4})CO;

Y se selecciona independientemente del grupo constituido por: CH_2, CH(alquilo C_{1-4}), C(alquilo $C_{1-4})_2$, CO, O, S, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4}), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, $-CONHCH_2-$, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -OCON(alquilo C_{1-4})-, -NHCONH-, $-SO_2NH-$, $-NHCO_2-$ y $-NHSO_2-$;

alternativamente, L-Y es alquileno C_{3-6}-CH=N-;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, haloalquilo C_{1-4}, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(alquilo C_{1-4}), N(alquilo $C_{1-4})_2$,

$-CO_2$(alquilo C_{1-4}), $-CO$(alquilo C_{1-4}), $-CH_2NH_2$, $-CONH_2$, $-CONH$(alquilo C_{1-4}), $-OCH_2CO_2H$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-C(=NH)NH_2$ y fenilo sustituido con 0-2 R^a;

R^2 es independientemente un heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados del N, NH, N(alquilo C_{1-4}), O, y $S(O)_p$, en el heterociclo está sustituido con 0-2 R^{2a};

R^{2a}, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, $-CH_2OH$, alcoxi C_{1-4}, OH, CF_3, OCF_3, CN, NH_2, CO_2H, CO_2(alquilo C_{1-4}), COalquilo C_{1-4}, $-CONH_2$, $-CONH$(alquilo C_{1-4}), $-CON$(alquilo $C_{1-4})_2$, $-SO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-SO_2NH$(alquilo C_{1-4}) y $-SO_2N$(alquilo $C_{1-4})_2$;

R^3 se selecciona independientemente del grupo constituido por: H, =O, halógeno, OH, NH_2, CN, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, $-CH_2OH$, CO_2H, CO_2(alquilo C_{1-4}), $-C(O)NH_2$, $-C(O)NH$(alquilo C_{1-4}), $-C(O)N$(alquilo $C_{1-4})_2$, $-CH_2CO_2H$ y cicloalquilo C_{3-6};

R^4 se selecciona independientemente del grupo constituido por: H y alquilo C_{1-4};

R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H, halógeno, OH y alquilo C_{1-4};

R^6, en cada aparición, se selecciona

independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), $-NHCOCF^3$, $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2$(alquilo C_{1-4}), -NHC(O)NH(alquilo C_{1-4}), -NHC(O)N(alquilo C_{1-4})$_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-SO_2NH$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $-CONH_2$, -CONH(alquilo C_{1-4}), -CON(alquilo C_{1-4})$_2$, $-CH_2CONH_2$ y $-NHCO_2(CH_2)_{0-2}R^9$;

R^7, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, NH_2, CH_2NH_2, haloalquilo C_{1-4}, OCH_2F, $OCHF_2$, OCF_3, -NH(alquilo C_{1-4}), -N(alquilo C_{1-4})$_2$, alcoxi C_1-$_4$, CH_2OH, CH_2O(alquilo C_{1-4}), $CH_2O(CH_2)_{1-4}O$(alquilo C_{1-4}), CO_2H, CO_2(alquilo C_{1-4}), $CO_2(CH_2)_2O$(alquilo C_{1-4}), CO_2(haloalquilo C_{1-4}), $CO_2(CH_2)_2SO_2$(alquilo C_{1-4}), CH_2CO_2H, CH_2CO_2(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, -OCO(alquilo C_{1-4}), $-CH_2NH_2(CH_2)_2O$(alquilo C_{1-4}), -CONH(alcoxi C_{1-4}), $-CO_2(CH_2)_2O$(alquilo C_{1-4}), $-CO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-CONH(CH_2)_2O$(alquilo C_{1-4}), $-CONH(CH_2)_2N$(alquilo C_{1-4})$_2$, -CON(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}), -CON(alquilo C_{1-4})$(CH_2)_2N$(alquilo C_{1-4})$_2$, alquilo C_1-$_4$, -CONHBn, -CONH(OBn), -

$(CO)_{0-1}(CH_2)_{0-3}$-carbociclo C_{3-6} y $-(CH_2)_{0-1}-(CO)_{0-1}-(W)_{0-1}-(CH_2)_{0-2}-$(heterociclo de 4 a 6 miembros que comprende átomos de carbonos y 1-4 hetoroátomos seleccionados de entre N, NH, N(alquilo C_{1-4}), O y $S(O)_p$); en donde el carbociclo y heterociclo están sustituidos con 0-2 R^8;

R^8, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CHF_2, CF_3, alcoxi C_1-$_4$, CH_2OH, CO_2H, CO_2(alquilo C_{1-4}), $CONH_2$ y alquilo C1-$_4$;

R^9 es un heterociclo de 4 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4})), O y $S(O)_p$;

R^a, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CF_3, alcoxi C_{1-4} y alquilo C_{1-4};

W se selecciona independientemente del grupo constituido por: O, NH y N(alquilo C_{1-4}); y

p, en cada aparición, se selecciona independientemente del grupo constituido por: 0, 1 y 2.

En un segundo aspecto, la presente invención proporciona compuestos de fórmula (I), o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco de los mismos, dentro del alcance del primer aspecto, en donde:

el anillo A es independientemente un carbociclo de

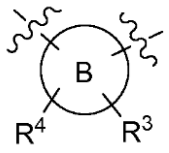
6 miembros, un carbociclo de 9 a 10 miembros o un heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-3 heteroátomos seleccionados de N, NH, N(alquilo C_{1-4}), O y $S(O)_p$;

el anillo B se selecciona independientemente del grupo constituido por: imidazol, oxazol, oxadiazol, triazol, piridina, piridazina, pirimidina y benceno y

el anillo C se selecciona independientemente del grupo constituido por: benceno, piridina, indazol, indol, bencimidazol, quinolina, isoquinolina, tetrahidroquinolina, tetrahidroisoquinilina y quinazolina.

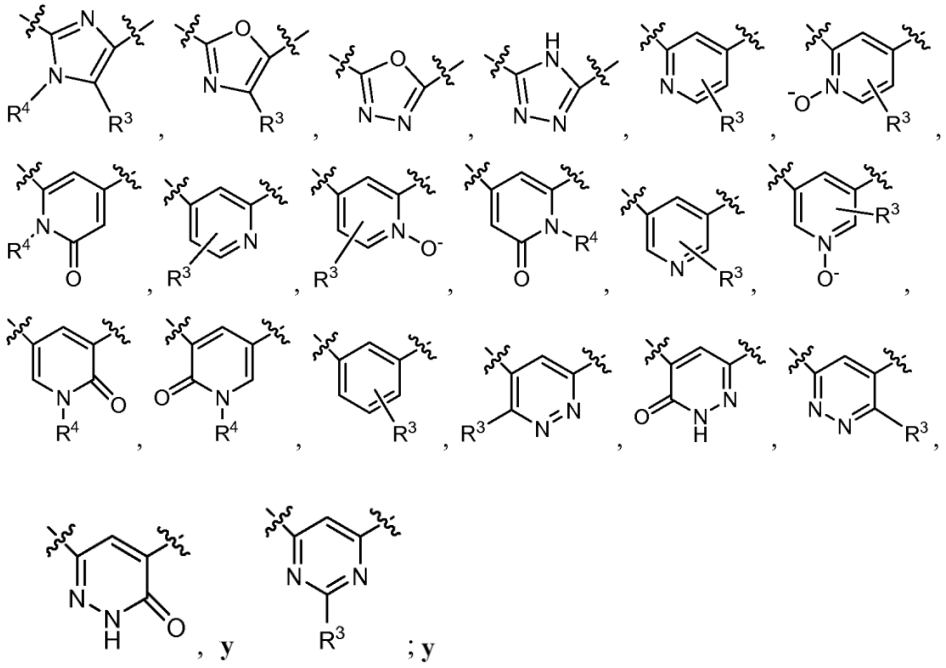
En un tercer aspecto, la presente invención proporciona compuestos de fórmula (I), o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco del mismo, dentro del alcance del primer o segundo aspectos, en donde:

el anillo A se selecciona independientemente del grupo constituido por: benceno, ciclohexano, indano, tetrahidronaftaleno, naftaleno, isoxazolina, isoxazol, pirazol, imidazol, triazol, piperidina, piridina, indazol, indol, bencimidazol, quinolina, isoquinolina, tetrahidroquinolina y tetrahidroisoquinolina;

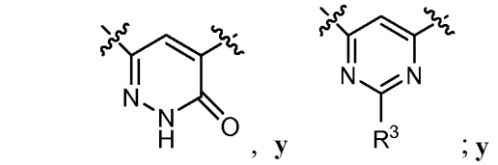


se selecciona independientemente del grupo

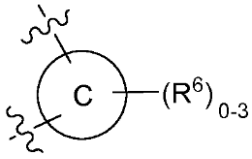
constituido por:



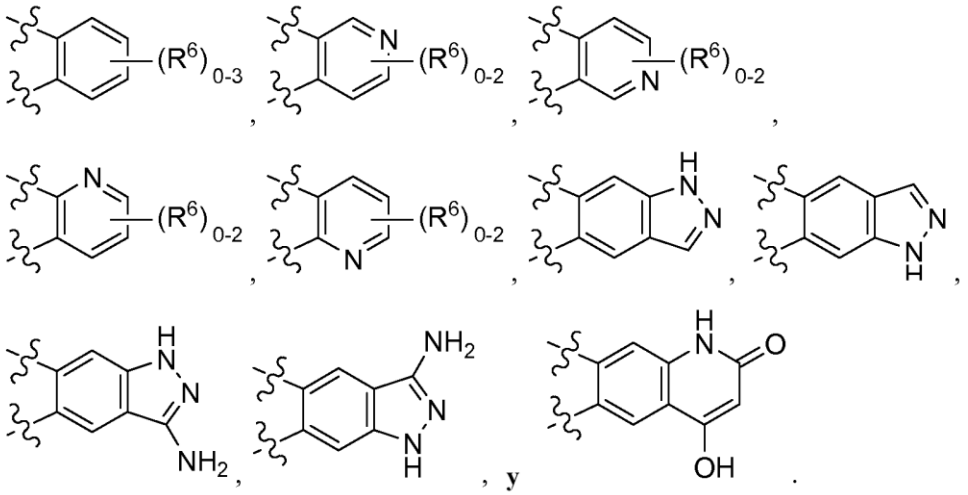
y



; y

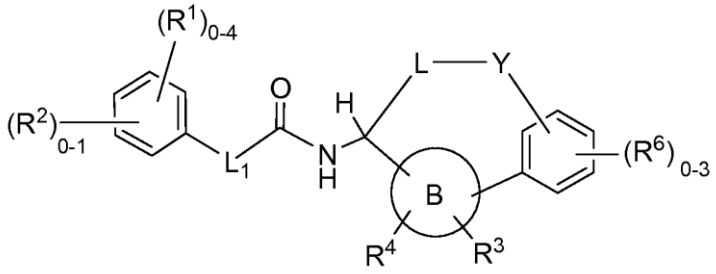


se selecciona independientemente del grupo constituido por:



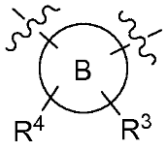
En un cuarto aspecto, la presente invención

proporciona compuestos de fórmula (II):

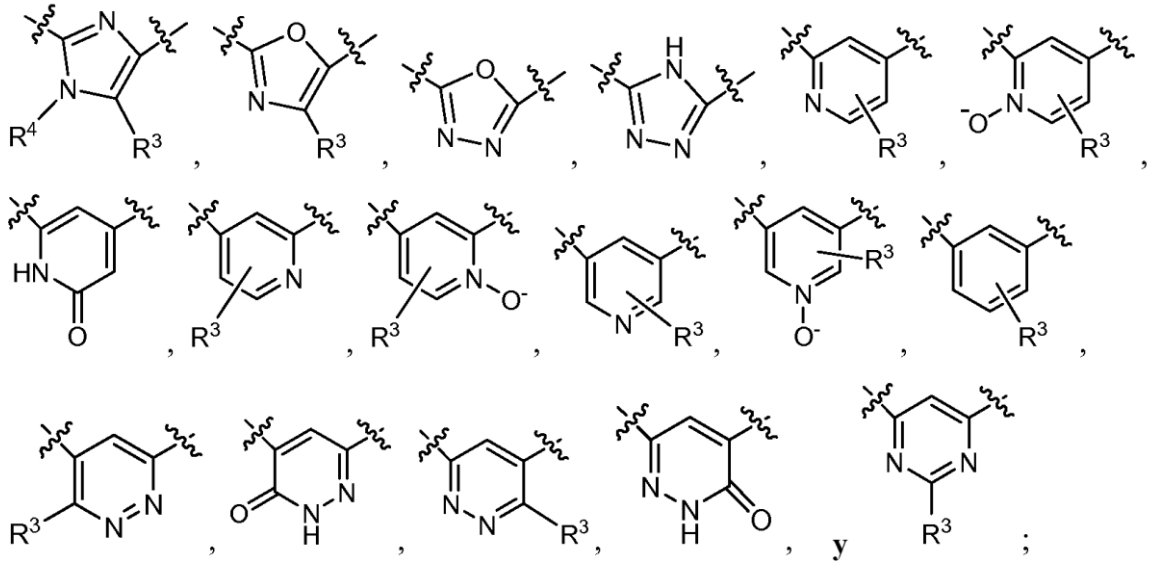


(II)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:



se selecciona independientemente del grupo constituido por:



L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CHR^5CHR^5-$, $-CR^5=CHR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR^5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CN_2NH-$ y $-CR^5R^5-$;

L se selecciona independientemente del grupo constituido por: alquileno C_{3-8} y alquenileno C_{3-8}; en el alquileno y alquenileno están sustituidos con 0-2 R^7 y opcionalmente uno o dos de los átomos de carbono del alquileno y alquenileno pueden estar reemplazados por O, CO, S, NH, N(alquilo C_{1-4}), CONH-, NHCO, OCONH, SO_2NH o CON(alquilo C_{1-4});

Y se selecciona independientemente del grupo constituido por: CH_2, CO, CH(alquilo C_{1-4}), C(alquilo C_{1-4})$_2$, O, S, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4}), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -OCON(alquilo C_{1-4})-, -NHCONH- y -SO_2NH-;

alternativamente, L-Y es –alquileno C_{3-6}-CH=N-;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, haloalquilo C_{1-4}, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(alquilo C_{1-4})$_2$, N(alquilo C_{1-4})$_2$, CO_2(alquilo C_{1-4}), CO(alquilo C_{1-4}), -OCH_2CO_2H, -CH_2NH_2, -$CONH_2$, -CONH(alquilo C_{1-4}), -SO_2NH_2 y -C(=NH)NH_2;

R^2 es independientemente un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y S(O)$_p$, en los que el heterocilo está sustituido con 0-2 R^{2a};

R^{2a}, en cada aparición, se selecciona

independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, $-CH_2OH$, alcoxi C_{1-4}, OH, CF_3, CN, NH_2, CO_2H, CO_2(alquilo C_{1-4}), COalquilo C_{1-4}, $-CONH_2$, -CONH(alquilo C_{1-4}) y $-CON(\text{alquilo } C_{1-4})_2$;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, OH, NH_2, CN, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, $-CH_2OH$, CO_2H, CO_2(alquilo C_{1-4}), $-C(O)NH_2$, $-C(O)NH(\text{alquilo } C_{1-4})$, $-C(O)N(\text{alquilo } C_{1-4})_2$, $-CH_2CO_2H$ y cicloalquilo C_{3-6};

R^4 se selecciona independientemente del grupo constituido por: H y alquilo C_{1-4};

R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H, halógeno, OH y alquilo C_{1-4};

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O(\text{alquilo } C_{1-4})$, $-NHCO_2(CH_2)_3O(\text{alquilo } C_{1-4})$, $-NHCO_2CH_2CH(\text{alquilo } C_{1-4})O(\text{alquilo } C_{1-4})$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(\text{alquilo } C_{1-4})$, $-NHC(O)NH(\text{alquilo } C_{1-4})$, $-NHC(O)N(\text{alquilo } C_{1-4})_2$, $-NHSO_2(\text{alquilo } C_{1-4})$, $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(\text{alquilo } C_{1-4})$, $-CONH(CH_2)_2O(\text{alquilo } C_{1-4})$, $CONH_2$, CONH(alquilo C_{1-4}),

$CON(alquilo\ C_{1-4})_2$, $-CH_2CONH_2$ $-NHCO_2(CH_2)_2N(alquilo\ C_{1-4})_2$, $-NHCOCF_3$ y $-NHCO_2(CH_2)_{0-1}R^9$;

R^7, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, haloalquilo C_{1-4}, OH, alcoxi C_1-$_4$, CH_2OH, $CH_2O(alcoxi\ C_{1-4})$, CO_2H, $CO_2(alquilo\ C_{1-4})$, $CO_2(CH_2)_2O(alquilo\ C_{1-4}))$, $CO_2CH_2CF_3$, $CO_2(CH_2)_2SO_2(alquilo\ C_{1-4})$, CH_2CO_2H, $CH_2CO_2(alquilo\ C_{1-4})$, $CONH_2$, $CONH(alquilo\ C_{1-4})$, $CON(alquilo\ C_{1-4})_2$, $-OCO(alquilo\ C_{1-4})$, $-CH_2NH(CH_2)_2O(alquilo\ C_{1-4})$, $-CO_2(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CONH(CH_2)_2O(alquilo\ C_{1-4})$, $-CONH(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CON(alquilo\ C_{1-4})(CH_2)_2O(alquilo\ C_{1-4})$, $-CONH(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CON(alquilo\ C_{1-4})(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CONH(alcoxi\ C_{1-4})$, -CONHBn, $-CONH(OBn)$, $-(CH_2)_{1-3}Ph$, alquilo C_1-$_4$ y $-(CH_2)_{0-1}-(CO)_{0-1}-(W)_{0-1}-(CH_2)_{0-2}-$(heterociclo de 4 a 6 miembros que comprende átomos de crbono y 1-4 heteroátomos seleccionados de entre N, NH, $N(alquilo\ C_{1-4})$, O y $S(O)_p$); en los que el heterociclo está sustituido con 0-2 R^8;

R^8, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CHF_2, CF_3, alcoxi C_{1-4} y alquilo C_{1-4};

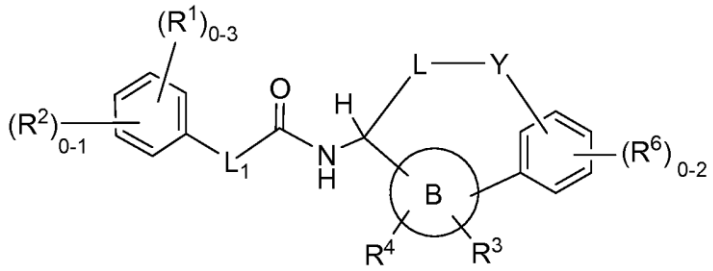
R^9 es un heterociclo de 4 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, NH, $N(alquilo\ C_{1-4})$, $N(CO_2(alquilo\ C_{1-4}))$, O y $S(O)_p$;

W se selecciona independientemente del grupo

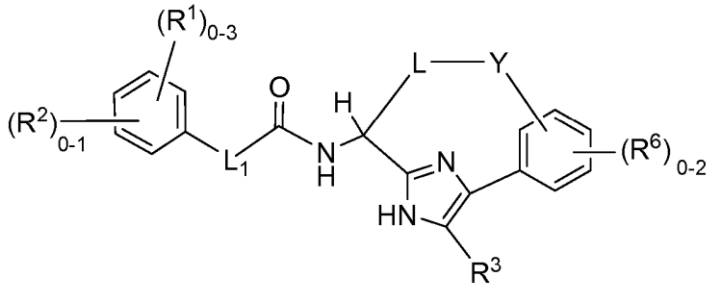
constituido por: O y NH; y

p, en cada aparición, se selecciona independientemente del grupo constituido por: 0, 1 y 2.

En un quinto aspecto, la presente invención proporciona compuestos de fórmula (IIa) o fórmula (IIb):



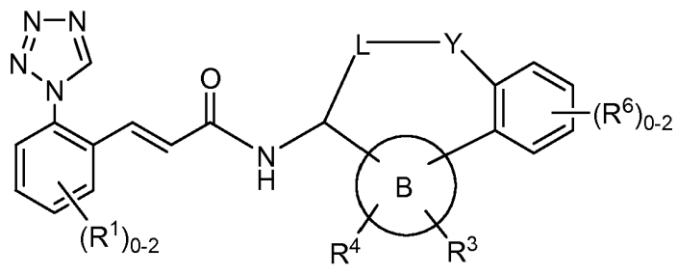
(IIa)



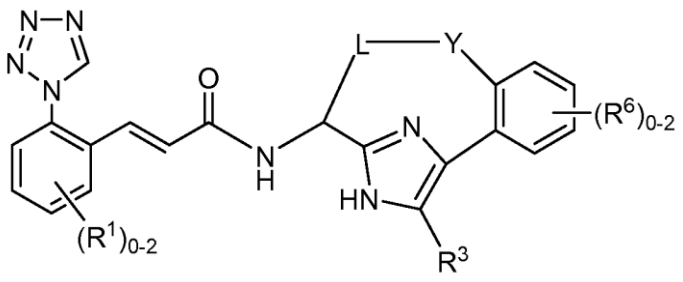
(IIb)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance del cuarto aspecto.

En un sexto aspecto, la presente invención proporciona compuestos de fórmula (IIc) o fórmula (IId):



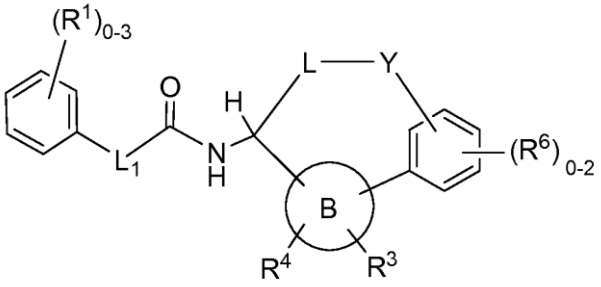
(IIc)



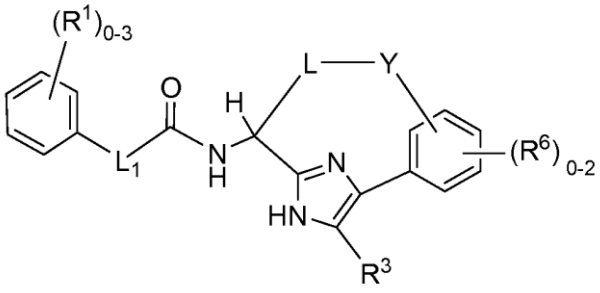
(IId)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance del cuarto aspecto.

En un séptimo aspecto, la presente invención proporciona compuestos de fórmula (IIe) o fórmula (IIf):



(IIe)



(IIf)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance del cuarto aspecto.

En un octavo aspecto, la presente invención incluye compuestos de fórmula (I), (II), (IIa), (IIb), (IIc), (IId),

(IIe) o (IIf) un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance de uno cualquiera de los aspectos anteriores, en donde:

L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CH_2CH_2-$, CH=CH-, -C(Me)=CH-, -C≡C- y $-CN_2NH-$ en la fórmula (I), (II), (IIa), (IIb), (IIe) o (IIf);

L se selecciona independientemente del grupo constituido por: alquileno C_{3-7} y alquenileno C_{3-7}, en donde el alquileno y alquenileno están sustituido con 0-2 R^7 y opcionalmente uno o dos de los átomos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, CO, NH, N(alquilo C_{1-4}), CONH, NHCO o CON(alquilo C_{1-4});

Y se selecciona independientemente del grupo constituido por: CH_2, CO, CH(alquilo C_{1-4}), C(alquilo $C_{1-4})_2$, O, S, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4}), -N(alquilo $C_{1-4})CH_2-$, $-N(CO_2$(alquilo $C_{1-4}))CH_2-$, $-N(CH_2CO_2$(alquilo $C_{1-4}))CH_2-$, -CONH-, -NHCO-, $CONHCH_2-$, -CON(alquilo $C_{1-4})CH_2-$, -OCONH-, -NHCONH- y $-SO_2NH-$;

alternativamente, L-Y es $-(CH_2)_{4-6}-CH=N-$;

R^1, en cada aparición, se selecciona independientemente de entre: halógeno, CN, OH, OCH_2F, $OCHF_2$, OCF_3, haloalquilo C_{1-4}, alquilo C_{1-4}, alcoxi C_{1-4}, CO(alquilo C_{1-4}), NH_2, NH(alquilo C_{1-4}), N(alquilo $C_{1-4})_2$, $-C(=NH)NH_2$, -

$C(O)NH_2$, $-CH_2NH_2$ y $-SO_2NH_2$;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, OH, NH_2, CN, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, $-CH_2OH$, CO_2H, CO_2(alquilo C_{1-4}), $-C(O)NH_2$, $-C(O)NH$(alquilo C_{1-4}), $-C(O)N$(alquilo $C_{1-4})_2$ y $-CH_2CO_2H$ y cicloalquilo C_{3-6}; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHC(O)NH$(alquilo C_{1-4}), $-NHC(O)N$(alquilo $C_{1-4})_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo $C_{1-4})_2$, $-NHCO_2(CH_2)_2N$(alquilo $C_{1-4})_2$, $-NHCOCF_3$ y $-NHCO_2(CH_2)_{0-1}R^9$.

En un noveno aspecto, la presente invención incluye compuestos de fórmula (I), (II), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance de uno cualquiera de los aspectos anteriores, en donde:

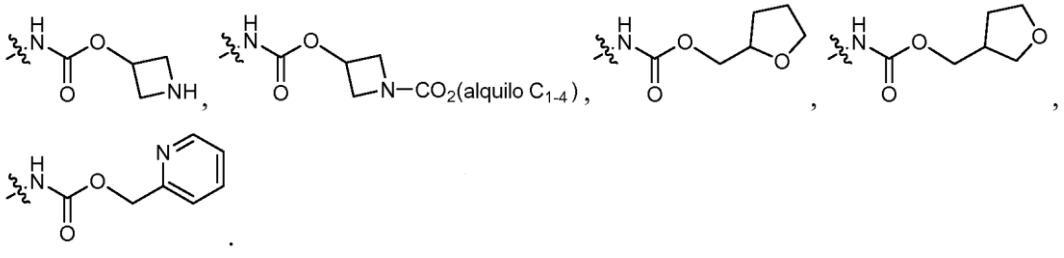
L_1 se selecciona independientemente del grupo

constituido por: un enlace, $-CH_2CH_2-$ y $-CH=CH-$ en la fórmula (I), (II), (IIa), (IIb), (IIe) o (IIf);

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CN, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, CO(alquilo C_{1-4}), NH_2, NH(alquilo C_{1-4})$_2$, N(alquilo C_{1-4})$_2$, $-CH_2NH_2$ y $-C(=NH)NH_2$;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, CN, CF_3, CO_2H, CO_2(alquilo C_{1-4}), alquilo C_{1-4},$CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6}; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2CH_2CO_2H$, $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-NHCOCF_3$,



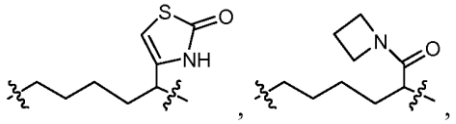
En un décimo aspecto, la presente invención incluye compuestos de fórmula (I), (II), (IIa), (IIb), (IIc), (IId),

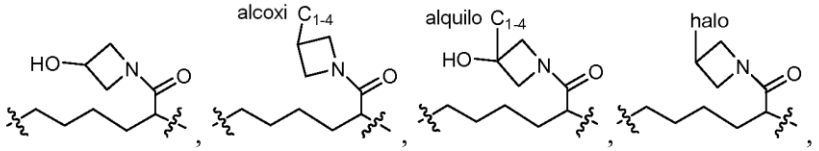
(IIe) o (IIf) o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance de uno cualquiera de los aspectos anteriores, en donde:

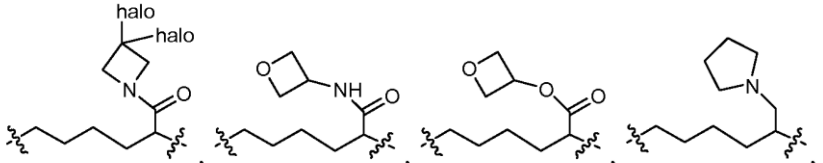
L_1 se selecciona independientemente del grupo constituido por: un enlace y -CH=CH- en la fórmula (I), (II), (IIa), (IIb), (IIe) o (IIf);

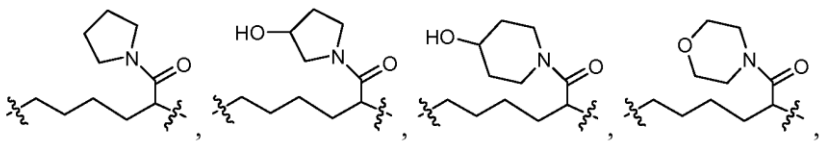
L se selecciona independientemente del grupo constituido por: $-(CH_2)_{3-6}-$, $-(CH_2)_{2-4}CH(\text{alquilo } C_{1-4})(CH_2)_{0-2}-$, $-(CH_2)_{1-2}-CH=CH-(CH_2)_{0-3}-$, $-CH_2-CH=C(\text{alquilo } C_{1-4})-(CH_2)_{1-2}-$, $-CH_2-C(\text{alquilo } C_{1-4})=CH-(CH_2)_{1-2}-$, $-CH_2-CH=CH-CH_2CH(\text{alquilo } C_{1-4})-$, $-CH_2-CH=CH-CH(\text{alquilo } C_{1-4})-(CH_2)_{0-2}-$, $-CH_2-CH=CH-CH_2C(\text{halo})_2-$, $-CH_2-CH=CH-(CH_2)_{1-2}CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(\text{halo})-$, $-(CH_2)_{3-4}C(\text{halo})_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_{3-4}CH(\text{alcoxi } C_{1-4})-$, $-(CH_2)_4CH(CH_2(\text{alcoxi } C_{1-4}))-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_{4-5}CH(CO_2(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4CH(CH_2CO_2(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4CH(CO_2CH_2CF_3)-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4C(\text{alquilo } C_{1-4})(CO_2(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4C(CF_3)(CO_2(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4CH(CONH_2))-$, $-(CH_2)_4CH(CONH(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4CH(CON(\text{alquilo } C_{1-4})_2)-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})CH(CONH_2)-$, $-(CH_2)_4CH(CO_2(CH_2)_2O(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4CH(CH_2NH(CH_2)_2O(\text{alquilo } C_{1-4}))-$, $-(CH_2)_4CH(CONH(\text{alcoxi } C_{1-4}))-$, $-(CH_2)_4CH(CONH(OBn))-$, $-(CH_2)_4CH((CH_2)_3Ph)-$, $-(CH_2)_4CH(CO_2(CH_2)_2N(\text{alquilo } C_{1-4})_2)-$, -

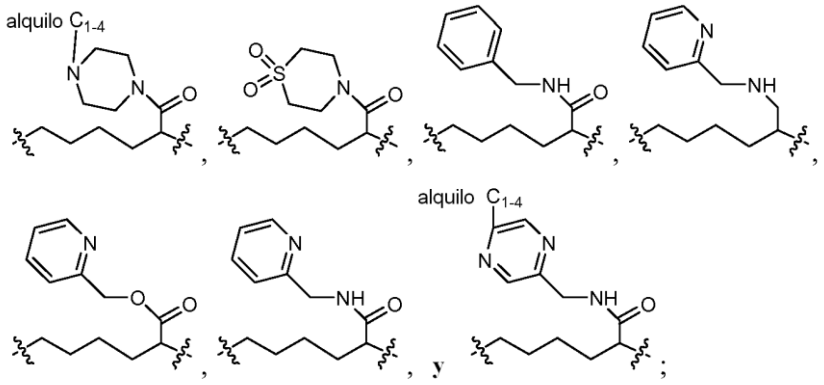
$(CH_2)_4CH(CONH(CH_2)_2O(alquilo\ C_{1-4}))-$, $-(CH_2)_4CH(CONH(CH_2)_2N(alquilo\ C_{1-4})_2)-$, $-(CH_2)_4CH(CON(alquilo\ C_{1-4})(CH_2)_2O(alquilo\ C_{1-4}))-$, $-(CH_2)_4CH(CON(alquilo\ C_{1-4})(CH_2)_2N(alquilo\ C_{1-4})_2)-$, $-(CH_2)_4CH(CH(halo)_2)-$, $-(CH_2)_{4-5}CH(CF_3)-$, $-(CH_2)_3C(halo)_2CH_2-$, $-(CH_2)_{1-3}CH(OH)(CH_2)_{1-2}-$, $-CH_2CH(OH)CH(OH)CH_2-$, $-(CH_2)_3CH(OCO(alquilo\ C_{1-4}))CH_2-$, $-(CH_2)_3C(O)CH_2-$, $-CH_2O(CH_2)_{2-4}-$, $-CH_2NH(CH_2)_{2-4}-$, $-(CH_2)_{2-3}NH(CH_2)_{1-2}-$, $-(CH_2)_{2-4}N(alquilo\ C_{1-4})(CH_2)_{0-2}-$, $-CH_2CONH(CH_2)_{2-4}-$, $-CH_2CON(alquilo\ C_{1-4})(CH_2)_{2-4}-$, $-CH_2NHCOC(halo)_2CH_2-$, $-(CH_2)_4CH(3\text{-alquilo } C_{1-4}\text{-oxetan-3-il})-$, $-(CH_2)_4CH(tiazol\text{-}4\text{-il})-$, $-(CH_2)_4CH(4\text{-alquilo } C_{1-4}\text{-tiazol-2-il})-$, $-(CH_2)_4CH(1\text{-alquilo } C_{1-4}\text{-imidazol-2-il})-$, $-(CH_2)_4CH(1\text{-alquilo } C_{1-4}\text{-pirazol-3-il})-$, $-(CH_2)_4CH(1\text{-alquilo } C_{1-4}\text{-pirazol-5-il})-$, $-CH_2-CH=CH-CH_2CH(1\text{-alquilo } C_{1-4}\text{-pirazol-5-il})-$, $-(CH_2)_4CH(1\text{-alquilo } C_{1-4}\text{-3-alquilo } C_{1-4}\text{-pirazol-5-il})-$; $-(CH_2)_4CH(1\text{-alquilo } C_{1-4}\text{-4-halo-pirazol-3-il})-$,











y

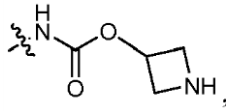
Y se selecciona independientemente del grupo constituido por: CH_2, CO, O, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4})), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -NHCONH- y -SO_2NH-; y

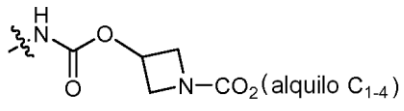
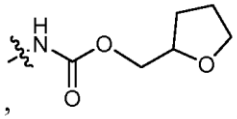
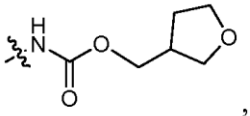
alternativamente, L-Y es -$(CH_2)_{3-6}$-CH=N-;

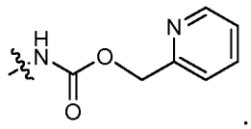
R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CO(alquilo C_{1-4}), CN, CH_2F, CHF_2, $OCHF_2$, CF_3, NH_2, N(alquilo C_{1-4})$_2$, -CH_2NH_2 y -C(=NH)NH_2;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6}; y

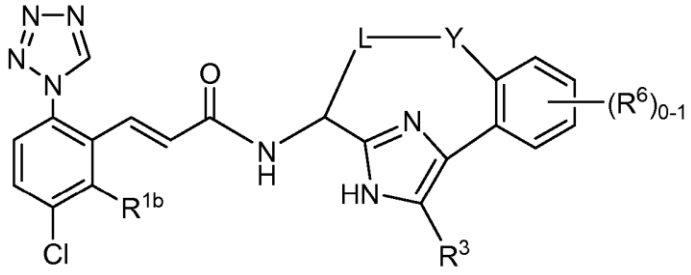
R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, CO_2(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, NHCO2(alquilo C_{1-4}), -CH_2NHCO_2(alquilo C_{1-4}), -$NHCO_2CH_2CO_2H$, -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -

$NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-NHCOCF_3$,  ,

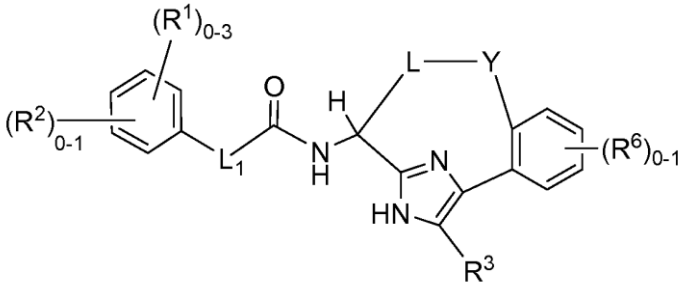
 ,  ,  , y

 .

En un undécimo aspecto, la presente invención incluye compuestos de fórmula (III) o fórmula (IIIa):



(III)



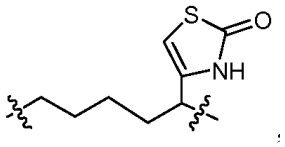
(IIIa)

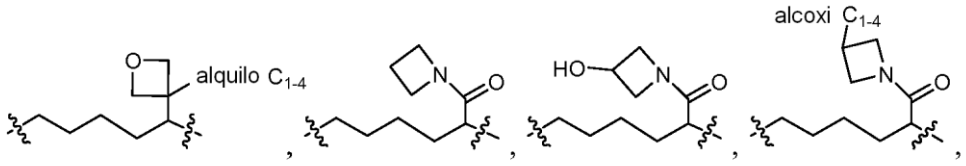
o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco de los mismos, en donde:

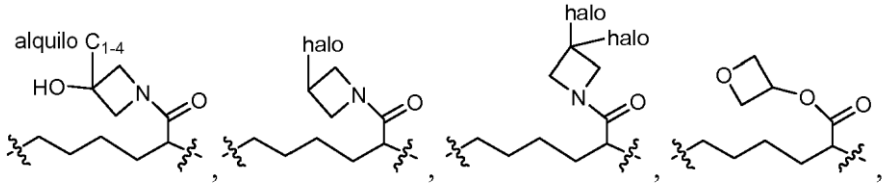
L_1 se selecciona independientemente del grupo constituido por: un enlace y -CH=CH- en la fórmula (IIIa);

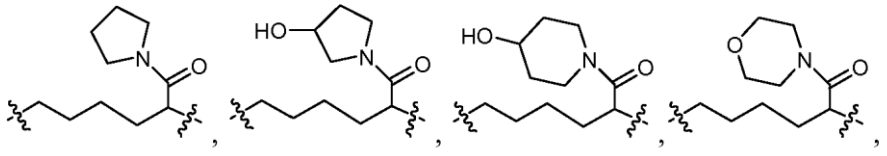
L se selecciona independientemente del grupo constituido por: $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_3CH$(alquilo C_{1-4})-, $-(CH_2)_4CH$(alquilo C_{1-4})-, $-(CH_2)_2CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_2CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_4CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_4CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C$(alquilo C_{1-4})$-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CH$(alquilo C_{1-4})-, $-CH_2-CH=CH-CH$(alquilo C_{1-4})CH_2-, $-CH_2-CH=CH-CH_2C(halo)_2-$, $-CH_2-CH=CH-CH2CH(CF_3)-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(halo)-$, $-(CH_2)_3C(halo)_2-$, $-(CH_2)_4C(halo)_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_3CH$(alcoxi C_{1-4})-, $-(CH_2)_4CH(CH_2$(alcoxi C_{1-4}))-, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4}))-, $-(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4}))-, $-(CH_2)_4CH(CO_2CH_2CF_3)-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))-, $-(CH_2)_5CH(CO_2$(alquilo C_{1-4}))-, $-(CH_2)_4C$(alquilo C_{1-4})$(CO_2$(alquilo C_{1-4}))-, $-(CH_2)_4C(CF_3)(CO_2$(alquilo C_{1-4}))-, $-(CH_2)_4CH(CONH_2)-$, $-(CH_2)_4CH(CONH$(alquilo C_{1-4}))-, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$_2)-$, $-(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)-$, $-(CH_2)_4CH(CONH$(alcoxi C_{1-4}))-, $-(CH_2)_4CH(CONH(OBn))-$, $-(CH_2)_4CH((CH_2)_3Ph)-$, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))-, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo C_{1-4})$_2)-$, $-(CH_2)_4CH(CH(halo)_2)-$, $-(CH_2)_4CH(CF_3)-$, $-(CH_2)_5CH(CF_3)-$, $-(CH_2)_3C(halo)_2CH_2-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$, $-(CH_2)_3CH(OH)CH_2-$, $-CH_2CH(OH)CH(OH)CH_2-$, $-(CH_2)_3CH(OCO$(alquilo

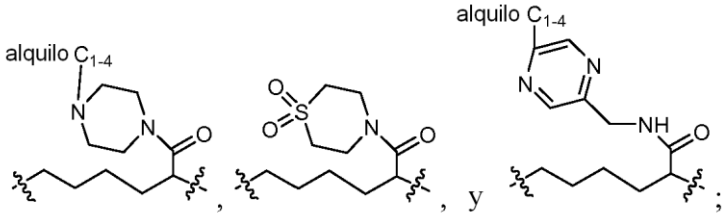
$C_{1-4}))CH_2-$, $-(CH_2)_3C(O)CH_2-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2N$(alquilo C_{1-4})CH_2-, $-(CH_2)_2N$(alquilo C_{1-4})$(CH_2)_2-$, $-CH_2CONH(CH_2)_2-$, $-CH_2CONH(CH_2)_3-$, $-CH_2CONH(CH_2)_4-$, $-CH_2CON$(alquilo C_{1-4})$(CH_2)_2-$, $-CH_2CON$(alquilo C_{1-4})$(CH_2)_3-$, $-(CH_2)_4CH$(tiazol-4-il)-, $-(CH_2)_4CH$(4-alquilo C_{1-4}-tiazol-2-il)-, $-(CH_2)_4CH$(1-alquilo C_{1-4}-imidazol-2-il)-, $-(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-3-il)-, $-(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-5-il)-, $-CH_2-CH=CH-CH_2CH$(1-alquilo C_{1-4}-pirazol-5-il)-, $-(CH_2)_4CH$(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)-, $-(CH_2)_4CH$(1-alquilo C_{1-4}-4-halo-pirazol-3-il)-,











y

Y se selecciona independientemente del grupo

constituido por: CH_2, CO, O, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4})), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -NHCONH- y -SO_2NH-;

alternativamente, L-Y es -$(CH_2)_4$-CH=N-;

L_1 se selecciona independientemente del grupo constituido por: un enlace y -CH=CH-;

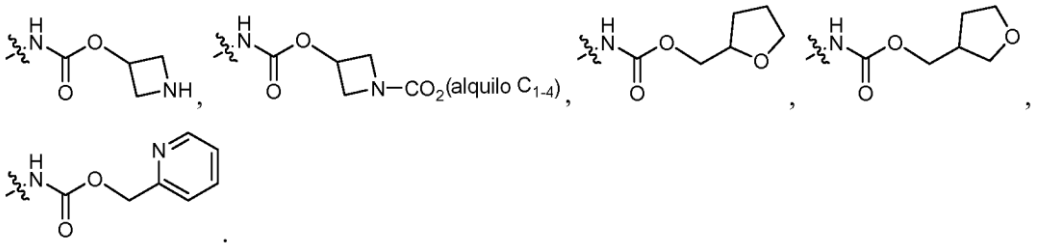
R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CO(alquilo C_{1-4}), CN, CH_2F, CHF_2, CF_3, $OCHF_2$, NH_2, N(alquilo C_{1-4})$_2$, $-CH_2NH_2$ y -C(=NH)NH_2 en la fórmula (IIIa);

R^{1b} se selecciona independientemente del grupo constituido por: H y halógeno en la fórmula (IIIa);

R^2 es independientemente un heteroarilo de 5 miembros seleccionado de entre: triazolilo y tetrazolilo en la fórmula (IIIa);

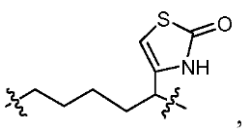
R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6}; y

R^6 se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, CO_2(alquilo C_{1-4}), -$NHCO_2$(alquilo C_{1-4}), -$NHCO_2(CH_2)_2OH$, $NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -$NHCO_2CH_2CO_2H$, $NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}) -$NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, -$NHCOCF_3$,

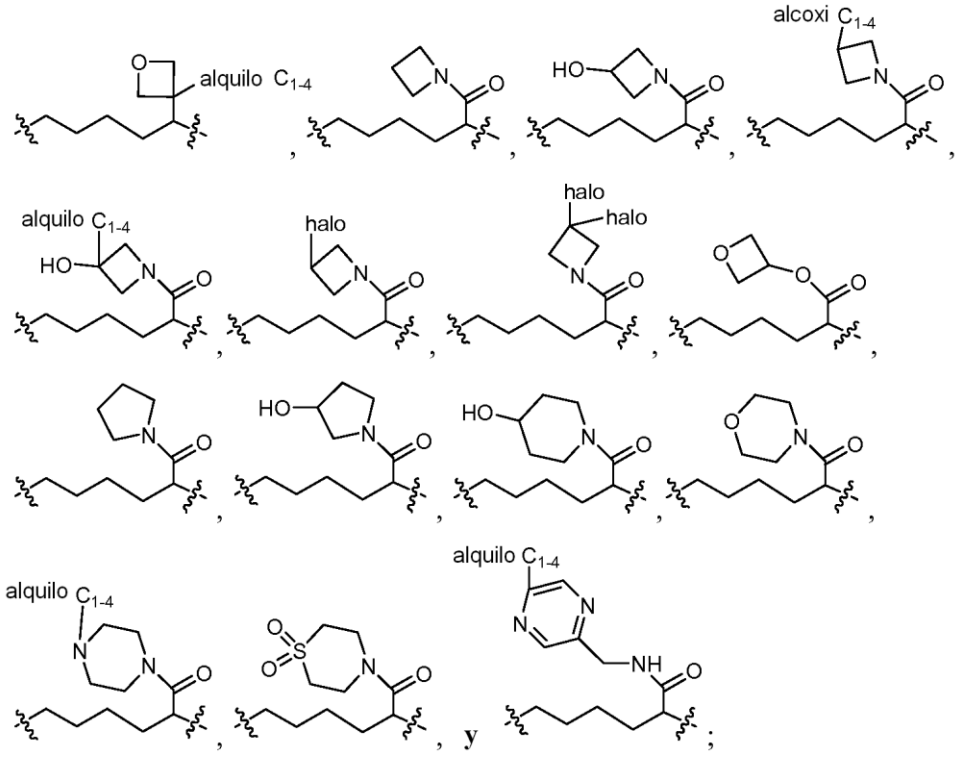


En un 12° aspecto, la presente invención incluye compuestos de fórmula (III) o fórmula (IIIa) o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco de los mismos, en donde, dentro del alcance del undécimo aspecto, en donde:

L se selecciona independientemente del grupo constituido por: $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_3CH$(alquilo C_{1-4})-, $-(CH_2)_4CH$(alquilo C_{1-4})-, $-(CH_2)_2CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_2CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_4CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_4CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C$(alquilo C_{1-4})$-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CH$(alquilo C_{1-4})-, $-CH_2-CH=CH-CH$(alquilo C_{1-4})CH_2-, $-CH_2-CH=CH-CH_2CH(halo)_2-$, $-CH_2-CH=CH-CH_2CH(CF_3)-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(halo)-$, $-(CH_2)_3C(halo)_2-$, $-(CH_2)_4C(halo)_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_4CH(CH_2$(alcoxi C_{1-4}))-, $-(CH_2)_3CH$(alcoxi C_{1-4})-, $-(CH_2)_4CH$(alcoxi C_{1-4})-, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4}))-, $-(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4}))-,

-$(CH_2)_4CH(CO_2CH_2CF_3)$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))-, -$(CH_2)_5CH(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4C$(alquilo C_{1-4})$(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4C(CF_3)(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CONH_2)$-, -$(CH_2)_4CH(CONH$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CON$(alquilo $C_{1-4})_2$)-, -$(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)$-, -$(CH_2)_4CH(CONH$(alcoxi C_{1-4}))-, -$(CH_2)_4CH(CONH(OBn))$-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo $C_{1-4})_2$)-, -$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-, -$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-, -$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO$(alquilo C_{1-4}))CH_2-, -$(CH_2)_3C(O)CH_2$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-, -$(CH_2)_2N$(alquilo C_{1-4})CH_2-, -$(CH_2)_2N$(alquilo C_{1-4})$(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-, -$CH_2CONH(CH_2)_3$-, -$CH_2CONH(CH_2)_4$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_2$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_3$-, -$(CH_2)_4CH$(tiazol-4-il)-, -$(CH_2)_4CH$(4-alquilo C_{1-4}-tiazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-imidazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-3-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-5-il)-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-4-halo-pirazol-3-il)-, 

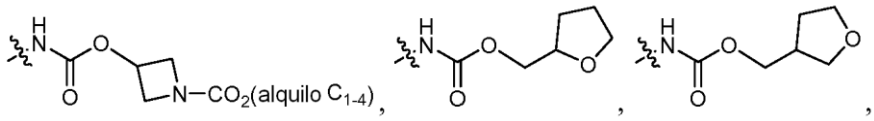
,

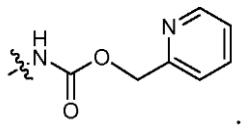


Y se selecciona independientemente del grupo constituido por: CH_2, O, NH, -CONH-, NHCO-, $-CONHCH_2-$, $-CON(alquilo\ C_{1-4})CH_2-$, $-N(alquilo\ C_{1-4})CH_2-$, $-N(CO_2(alquilo\ C_{1-4}))CH_2-$, $-N(CH_2CO_2(alquilo\ C_{1-4}))CH_2-$, -OCONH-, -NHCONH- y $-SO_2NH-$;

alternativamente, L-Y es $-(CH_2)4-CH=N-$; y

R^{6a} se selecciona independiente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, $-NHCO_2(alquilo\ C_{1-4})$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(alquilo\ C_{1-4})$, $-NHCO_2CH_2CH(alquilo\ C_{1-4})O(alquilo\ C_{1-4})$, $-NHCO_2CH_2CO_2H$,





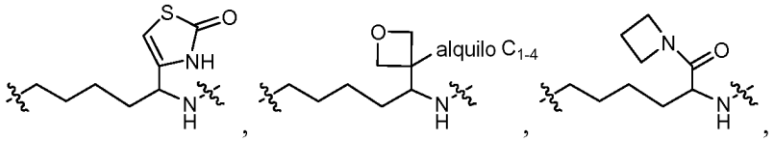
.

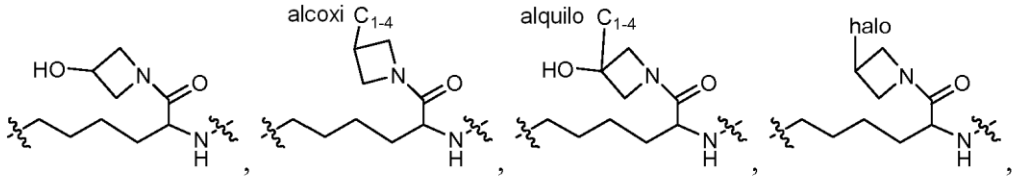
En un 13° aspecto, la presente invención incluye compuestos de fórmula (III), o un esteroisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

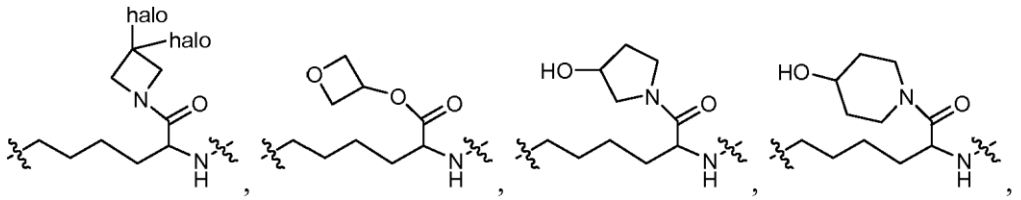
L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4CH(CON(\text{alquilo } C_{1-4})_2)CH_2-$, $-(CH_2)_4CF_2CO-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=CH-(CH_2)_4-$, $-CH_2CON(\text{alquilo } C_{1-4})(CH_2)_3-$, $-CH_2CON(\text{alquilo } C_{1-4})(CH_2)_4-$, $-(CH_2)_4N(\text{alquilo } C_{1-4})CH_2-$, $-(CH_2)_4N(CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4N(CH_2CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_5O-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})(CH_2)_2O-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})CH_2O-$, $-CH_2CONH(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-CH_2-CH=CH-(CH_2)_2O-$, $-CH_2-CH=CH-(CH_2)_3O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})CH_2NH-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})NH-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2(\text{alcoxi } C_{1-4}))NH-$, $-(CH_2)_4CH(CO2H)NH-$, $-(CH_2)_4CH((CH_2)_3Ph)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_5CH(CO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CON(\text{alquilo } C_{1-4})_2)NH-$, $-(CH_2)_4C(\text{alquilo}$

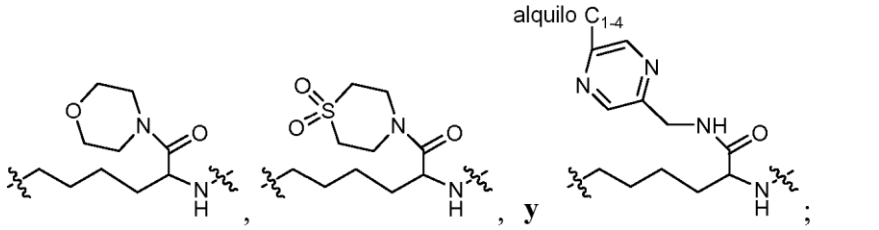
C_{1-4})(CO_2(alquilo C_{1-4}))NH-, -$(CH_2)_4$C(CF_3)(CO_2(alquilo C_{1-4}))NH-, -$(CH_2)_3$CH(alquilo C_{1-4})CH($CONH_2$)NH-, -$(CH_2)_4$CH(CONH(alcoxi C_{1-4}))NH-, -$(CH_2)_4$CH(CONH(OBn))NH-, -$(CH_2)_4$CH(CON(alquilo C_{1-4})$(CH_2)_2$O (alquilo C_{1-4}))NH-, -$(CH_2)_4$CH(CON(alquilo C_{1-4})$(CH_2)_2$N(alquilo $C_{1-4})_2$)NH-, -CH_2-CH=CH-$(CH_2)_2$NH-, -CH_2-CH=CH-$(CH_2)_3$NH-, -$(CH_2)_4$CH(CHF_2)NH-, -$(CH_2)_4$CH(CF_3)NH-, -$(CH_2)_5$CH(CF_3)NH-, -$(CH_2)_3CF_2CH_2$NH-, -CH_2-CH=CH-CH_2CH(CF_3)NH-, -CH_2-CH=CH-$(CH_2)_2$CH(CF_3)NH-, -$CH_2CONH(CH_2)_2$NH-, -$CH_2CONH(CH_2)_3$NH-, -$CH_2NHCOCF_2CH_2$NH-, -$CH_2CONH(CH_2)_4$NH-, -$(CH_2)_4$CH(CO-pirrolidin-1-il)NH-, -$(CH_2)_4$CH(tiazol-4-il)NH-, -$(CH_2)_4$CH(4-alquilo C_{1-4}-tiazol-2-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-imidazol-2-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-pirazol-3-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-4-halo-pirazol-3-il)NH-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_6$N(alquilo C_{1-4})-, -$(CH_2)_5$N(CO_2(alquilo C_{1-4}))-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_4$CH(alquilo C_{1-4})CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})$(CH_2)_2CONH$-, -$(CH_2)_2$-CH=CH-CONH-, -CH2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2CONH$-, -CH_2-CH=CH-$(CH_2)_3CONH$-, -CH_2-CH=CH-CH_2CH(alquilo C_{1-4})CONH-, -CH_2-CH=CH-CH(alquilo C_{1-4})CH_2CONH-, -CH_2-CH=C(alquilo C_{1-4})$(CH_2)_2CONH$-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_3CHFCONH$-, -$(CH_2)_3CF_2CONH$-, -$(CH_2)_4CF_2CONH$-, -CH_2-CH=CH-CH_2CF_2CONH-, -

$(CH_2)_3CH(CF_3)CONH-$, $-CH_2CH(OH)(CH_2)_2CONH-$, $-(CH_2)_2CH(OH)CH_2CONH-$, $-(CH_2)_3CH(OH)CH_2CONH-$, $-CH_2CH(OH)CH(OH)CH_2CONH-$, $-CH_2-CH=CH-CH(OH)CH_2CONH-$, $-(CH_2)_3CH$(alcoxi C_{1-4})$CONH-$, $-(CH_2)_3CH$(OCO(alquilo C_{1-4}))CH_2CONH-, $-(CH_2)_3C(O)CH_2CONH-$, $-CH_2O(CH_2)_3CONH-$, $-CH_2O(CH_2)_4CONH-$, $-CH_2NH(CH_2)_2CONH-$, $-CH_2NH(CH_2)_3CONH-$, $-(CH_2)_2N$(alquilo C_{1-4})CH_2CONH-, $-(CH_2)_2N$(alquilo C_{1-4})$(CH_2)_2CONH-$, $-(CH_2)_5NHCO-$, $-CH_2-CH=CH-(CH_2)_2NHCO-$, $-(CH_2)_3OCONH-$, $-(CH_2)_4OCONH-$, $-CH_2-CH=CH-CH_2OCONH-$, $-CH_2-CH=CH-CH_2NHCONH-$, $-(CH_2)_4SO_2NH-$, $-CH_2-CH=CH-CH_2SO_2NH-$, $-(CH_2)_4-CH=N-$,









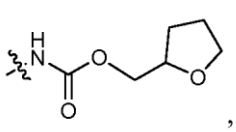
y;

R^{1b} se selecciona independientemente del grupo

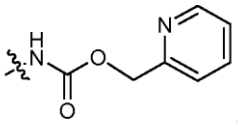
constituido por: H y halógeno;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6};

R^6 se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}),



, y



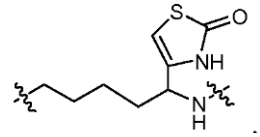
.

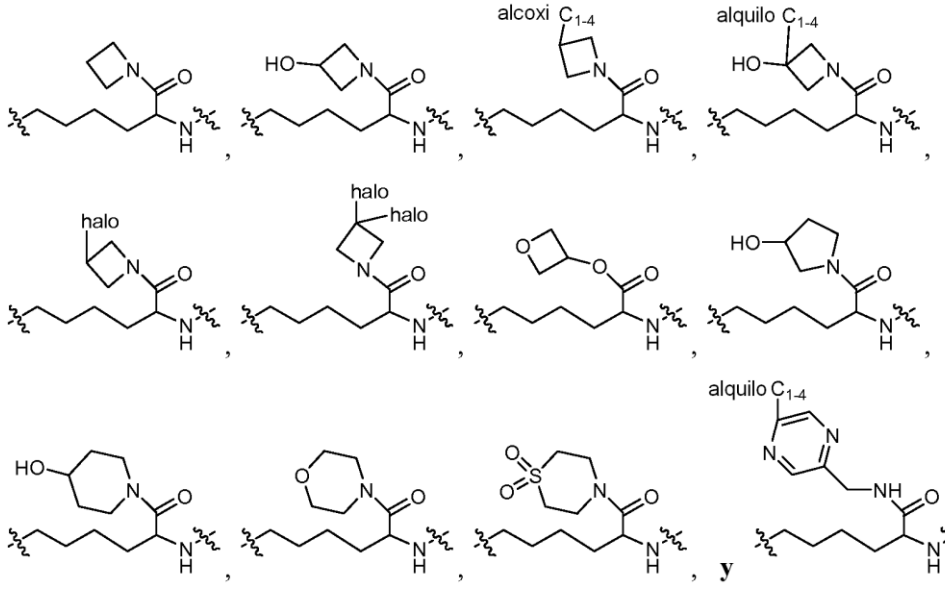
En un 14° aspecto, la presente invención incluye compuestos de fórmula (III), o un esteroisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4}))CH_2-, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH$(alquilo C_{1-4}))CH_2-, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=CH-(CH_2)_4-$, $-CH_2CON$(alquilo C_{1-4})$(CH_2)_3-$, $-(CH_2)_5O-$, $-(CH_2)_6O-$, $-(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2O-$, $-(CH_2)_4CH$(alquilo C_{1-4})CH_2O-, $-CH_2NH(CH_2)_4O-$, $-CH_2-CH=CH-(CH_2)_3O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2NH-, $-(CH_2)_4CH$(alquilo C_{1-4})$NH-$, $-(CH_2)_4CH$(alquilo C_{1-4})CH_2NH-, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2$(alcoxi C_{1-4}))$NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-$

$(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4}))$NH-$, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4}))$NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))$NH-$, $-(CH_2)_5CH(CO_2$(alquilo C_{1-4}))$NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH$(alquilo C_{1-4}))$NH-$, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$_2)NH-$, $-(CH_2)_4C$(alquilo C_{1-4})$(CO_2$(alquilo C_{1-4}))$NH-$, $-(CH_2)_4C(CF_3)(CO_2$(alquilo C_{1-4}))$NH-$, $-(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH$(alcoxi C_{1-4}))$NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))$NH-$, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo C_{1-4})$_2)NH-$, $-CH_2-CH=CH-(CH_2)_2NH-$, $-CH_2-CH=CH-(CH_2)_3NH-$, $-(CH_2)_4CH(CHF_2)NH-$, $-(CH_2)_4CH(CF_3)NH-$, $-(CH_2)_5CH(CF_3)NH-$, $-(CH_2)_3CF_2CH_2NH-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH-$, $-CH_2CONH(CH_2)_2NH-$, $-CH_2CONH(CH_2)_3NH-$, $-(CH_2)_4CH(3$-alquilo C_{1-4}-oxetan-3-il)$NH-$, $-(CH_2)_4CH(CO$-pirrolidin-1-il)$NH-$, $-(CH_2)_4CH$(tiazol-4-il)$NH-$, $-(CH_2)_4CH(4$-alquilo C_{1-4}-tiazol-2-il)$NH-$, $-(CH_2)_4CH(1$-alquilo C_{1-4}-imidazol-2-il)$NH-$, $-(CH_2)4CH(1$-alquilo C_{1-4} -pirazol-3-il)$NH-$, $-(CH_2)_4CH(1$-alquilo C_{1-4}-pirazol-5-il)$NH-$, $-(CH_2)_4CH(1$-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)$NH-$, $-(CH_2)_4CH(1$-alquilo C_{1-4}-4-halo-pirazol-3-il)$NH-$, $-CH_2-CH=CH-CH_2CH(1$-alquilo C_{1-4}-pirazol-5-il)$NH-$, $-(CH_2)_4N(CO_2$(alquilo C_{1-4}))CH_2-, $-(CH_2)_4N(CH_2CO_2$(alquilo C_{1-4}))CH_2-, $-(CH_2)_4CONH-$, $-(CH_2)_5CONH-$, $-(CH_2)_6CONH-$, $-(CH_2)_3CH$(alquilo C_{1-4})$CONH-$, $-(CH_2)_4CH$(alquilo C_{1-4})$CONH-$, $-(CH_2)_2CH$(alquilo C_{1-4})CH_2CONH-, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2CONH-, $-(CH_2)_2CH$(alquilo C_{1-4})$(CH_2)_2CONH-$, $-(CH_2)_2-CH=CH-CONH-$, $-CH2-CH=CH-CH_2CONH-$, $-CH_2-CH=CH-(CH_2)_2CONH-$, $-CH_2-CH=CH-(CH_2)_3CONH-$, $-CH_2-$

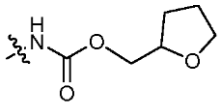
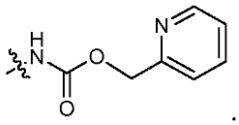
CH=CH-CH_2CH(alquilo C_{1-4})CONH-, -CH_2-CH=CH-CH(alquilo C_{1-4})CH_2CONH-, -CH_2-CH=C(alquilo C_{1-4})-$(CH_2)_2$CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH_2CONH-, -$(CH_2)_3$CH(alcoxi C_{1-4})CONH-, -$(CH_2)_3$CH(OCO(alquilo C_{1-4}))CH_2CONH-, -$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-, -$CH_2NH(CH_2)_2$CONH-, -$CH_2NH(CH_2)_3$CONH-, -$(CH_2)_2$N(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$N(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-, -CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-, -$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-,

-$(CH_2)_4$-CH=N-, 



R^{1b} se selecciona independientemente del grupo constituido por: H y halógeno;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y ciclopropilo; y

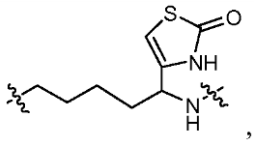
R^6 se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}) y  , y  .

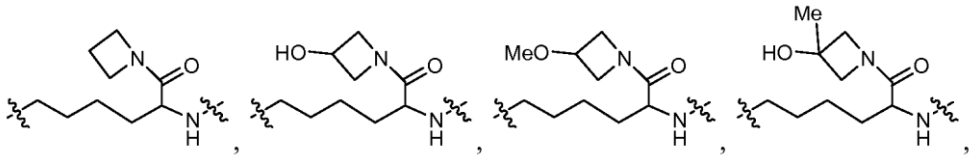
En un 15° aspecto, la presente invención incluye compuestos de fórmula (III), o un esteroisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

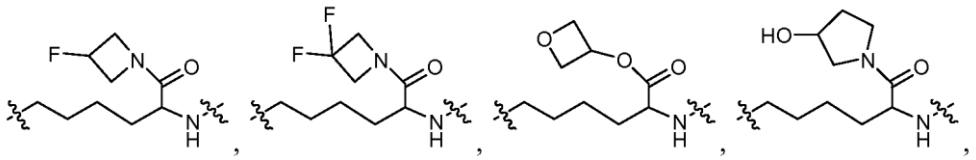
L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2Me)CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONHMe)CH_2-$, $-(CH_2)_4CH(CON(Me)_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=CH-(CH_2)_4-$, $-CH_2CON(CH_3)(CH_2)_3-$, $-(CH_2)_4N(CO_2Me)CH_2-$, $-(CH_2)_4N(CH_2CO_2Et)CH_2-$, $-(CH_2)_5O-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(Me)(CH_2)_2O-$, $-(CH_2)_4CH(Me)CH_2O-$, $-CH_2NH(CH_2)_4O-$, $-CH_2-CH=CH-(CH_2)_3O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_3CH(Me)CH_2NH-$, $-(CH_2)_4CH(Me)NH-$, $-(CH_2)_4CH(Me)CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2OMe)NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CO_2Me)NH-$, -

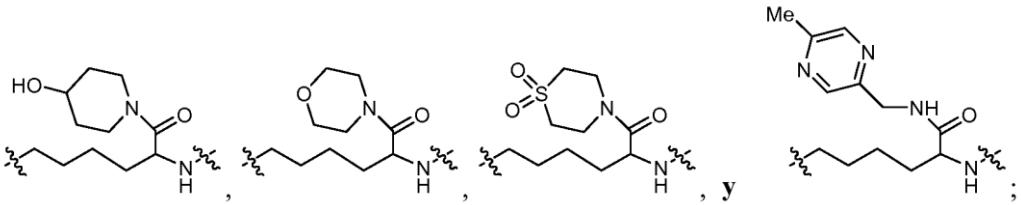
$(CH_2)_4CH(CO_2Et)NH-$, $-CH_2CONH(CH_2)_4NH-$, $-(CH_2)_4CH(CO_2(i-Pr))NH-$, $-(CH_2)_4CH(CO_2(t-Bu))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH-$, $-(CH_2)_5CH(CO_2Me)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2Me)NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(Me))NH-$, $-(CH_2)_4CH(CONH(t-Bu))NH-$, $-(CH_2)_4CH(CON(Me)_2)NH-$, $-(CH_2)_4CH(CONH(OMe))NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH-$, $-(CH_2)_4C(Me)(CO_2Me)NH-$, $-(CH_2)_4C(CF_3)(CO_2Me)NH-$, $-(CH_2)_3CH(Me)CH(CONH_2)NH-$, $-(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH-$, CH2-CH=CH-$(CH_2)_2NH-$, $-CH_2-CH=CH-(CH_2)_3NH-$, $-(CH_2)_4CH(CHF_2)NH-$, $-(CH_2)_4CH(CF_3)NH-$, $-(CH_2)_5CH(CF_3)NH-$, $-(CH_2)_3CF_2CH_2NH-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH-$, $-CH_2CONH(CH_2)_2NH-$, $-CH_2CONH(CH_2)_3NH-$, $-(CH_2)_4CH$(3-Me-oxetan-3-il)NH-, $-(CH_2)_4CH$(CO-pirrolidin-1-il)NH-, $-(CH_2)_4CH$(tiazol-4-il)NH-, $-(CH_2)_4CH$(4-Me-tiazol-2-il)NH-, $-(CH_2)_4CH$(1-Me-imidazol-2-il)NH-, $-(CH_2)_4CH$(1-Me-pirazol-3-il)NH-, $-(CH_2)_4CH$(1-(n-Pr)-pirazol-3-il)NH-, $-(CH_2)_4CH$(1-Me-pirazol-5-il)NH-, $-(CH_2)_4CH$(1,3-di-Me-pirazol-5-il)NH-, $-(CH_2)_4CH$(1-Me-4-Cl-pirazol-3-il)NH-, $-CH_2-CH=CH-CH_2CH$(1-Me-pirazol-5-il)NH-, $-(CH_2)_4CONH-$, $-(CH_2)_5CONH-$, $-(CH_2)_6CONH-$, $-(CH_2)_3CH(Me)CONH-$, $-(CH_2)_4CH(Me)CONH-$, $-(CH_2)_2CH(Me)CH_2CONH-$, $-(CH_2)_3CH(Me)CH_2CONH-$, $-(CH_2)_2CH(Me)(CH_2)_2CONH-$, $-(CH_2)_2-CH=CH-CONH-$, -CH2-CH=CH-CH_2CONH-, $-CH_2-CH=CH-(CH_2)_2CONH-$, $-CH_2-CH=CH-(CH_2)_3CONH-$, $-CH_2-CH=CH-CH_2CH(Me)CONH-$, $-CH_2-CH=CHCH(Me)CH_2CONH-$, $-CH_2-CH=CHCH(Et)CH_2CONH-$, $-CH_2-CH=C(Me)-(CH_2)_2CONH-$, -

$(CH_2)_3CH(Et)CONH-$, $-(CH_2)_3CH(i-Pr)CONH-$, $-(CH_2)_3CHFCONH-$, $-(CH_2)_3CF_2CONH-$, $-(CH_2)_4CF_2CONH-$, $-CH_2-CH=CH-CH_2CF_2CONH-$, $-(CH_2)_3CH(CF_3)CONH-$, $-CH_2CH(OH)(CH_2)_2CONH-$, $-(CH_2)_2CH(OH)CH_2CONH-$, $-(CH_2)_3CH(OH)CH_2CONH-$, $-CH_2CH(OH)CH(OH)CH_2CONH-$, $-CH_2-CH=CH-CH(OH)CH_2CONH-$, $-(CH_2)_3CH(OMe)CONH-$, $-(CH_2)_3CH(OCOMe)CH_2CONH-$, $-(CH_2)_3C(O)CH_2CONH-$, $-CH_2O(CH_2)_3CONH-$, $-CH_2O(CH_2)_4CONH-$, $-CH_2NH(CH_2)_2CONH-$, $-CH_2NH(CH_2)_3CONH-$, $-(CH_2)_2N(Me)CH_2CONH-$, $-(CH_2)_2N(Me)(CH_2)_2CONH-$, $-(CH_2)_5NHCO-$, $-CH_2-CH=CH-(CH_2)_2NHCO-$, $-CH_2-CH=CH-CH_2OCONH-$, $-(CH_2)_4OCONH-$, $-CH_2-CH=CH-CH_2NHCONH-$, $-(CH_2)_4SO_2NH-$, $-CH_2-CH=CH-CH_2SO_2NH-$, $-(CH_2)_4-CH=N-$,









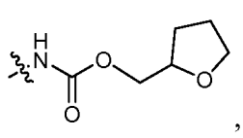
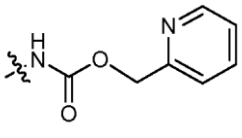
y

;

R^{1b} se selecciona independientemente del grupo constituido por: H y F;

R^3 se selecciona independientemente del grupo constituido por: H, F, Cl, Br, CH_3, CN, CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$ y ciclopropilo; y

R^6 se selecciona independiente del grupo constituido por: F, NH_2, CO_2H, $CONH_2$, $-NHCO_2Me$, $-NHCO_2(CH_2)2OH$, $-NHCO_2(CH_2)_2OMe$, $-NHCO_2(CH_2)_2OEt$, $-NHCO_2CH_2CH(Et)OMe$,

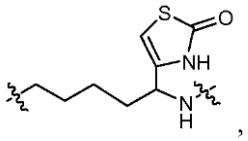

, y

.

En un 16° aspecto, la presente invención incluye compuestos de fórmula (III), o un esteroisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

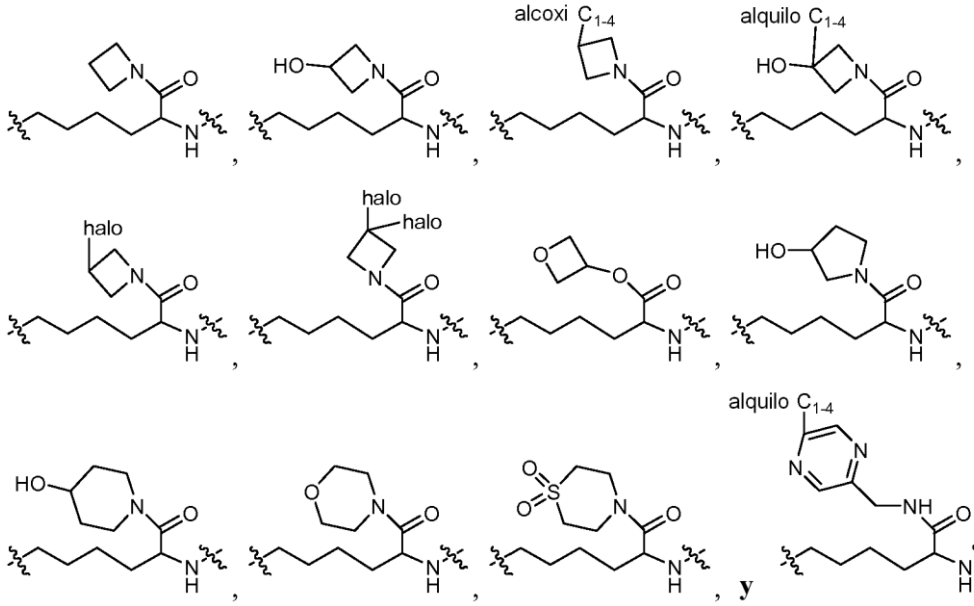
L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4CH(CON(\text{alquilo } C_{1-4})_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})NH-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})CH_2NH-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2(\text{alcoxi } C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_5CH(CO_2(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(\text{alquilo } C_{1-4}))NH-$, $-(CH_2)_4CH(CON(\text{alquilo } C_{1-4})_2)NH-$, $-(CH_2)_4CH(CONH(\text{alcoxi}$

C_{1-4}))NH-, -$(CH_2)_4$CH(CONH(OBn))NH-, -$(CH_2)_4$CH(CON(alquilo C_{1-4})$(CH_2)_2$O(alquilo C_{1-4}))NH-, -$(CH_2)_4$CH(CON(alquilo C_{1-4})$(CH_2)_2$N(alquilo $C_{1-4})_2$)NH-, -CH_2-CH=CH-$(CH_2)_2$NH-, -CH_2-CH=CH-$(CH_2)_3$NH-, -$(CH_2)_4$CH(CHF_2)NH-, -$(CH_2)_4$CH(CF_3)NH-, -$(CH_2)_3CF_2CH_2$NH-, -CH_2-CH=CH-$(CH_2)_2$CH(CF_3)NH-, -$(CH_2)_4$CH(3-alquilo C_{1-4}-oxetan-3-il)NH-, -$(CH_2)_4$CH(CO-pirrolidin-1-il)NH-, -$(CH_2)_4$CH(tiazol-4-il)NH-, -$(CH_2)_4$CH(4-alquilo C_{1-4}-tiazol-2-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-imidazol-2-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-pirazol-3-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-4-halo-pirazol-3-il)NH-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-, -$(CH_2)_6$CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_4$CH(alquilo C_{1-4})CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-CH=CH-CH_2CH(alquilo C_{1-4})CONH-, -CH_2-CH=CH-CH(alquilo C_{1-4})CH_2CONH-, -CH_2-CH=C(alquilo C_{1-4})-$(CH_2)_2$CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH2CONH-, -$(CH_2)_3$CH(alcoxi C_{1-4})CONH-, -$(CH_2)_3$CH(OCO(alquilo C_{1-4}))CH_2CONH-, -$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-, -$CH_2NH(CH_2)_2$CONH-, -

$CH_2NH(CH_2)_3CONH-$, $-(CH_2)_2N(\text{alquilo } C_{1-4})CH_2CONH-$, $-(CH_2)_2N(\text{alquilo } C_{1-4})(CH_2)_2CONH-$, $-(CH_2)_5NHCO-$, $-CH_2-CH=CH-(CH_2)_2NHCO-$, $-CH_2-CH=CH-CH_2OCONH-$, $-(CH_2)_4OCONH-$, $-CH_2-CH=CH-CH_2NHCONH-$, -



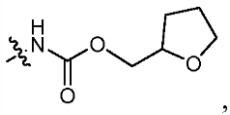
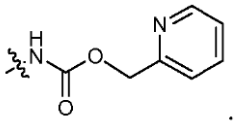
, $(CH_2)_4SO_2NH-$, $-CH_2-CH=CH-CH_2SO_2NH-$, $-(CH_2)_4-CH=N-$,



R^{1b} se selecciona independientemente del grupo constituido por: H y halógeno;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, $CO_2(\text{alquilo } C_{1-4})$, $CONH_2$, $CON(\text{alquilo } C_{1-4})_2$ y ciclopropilo;

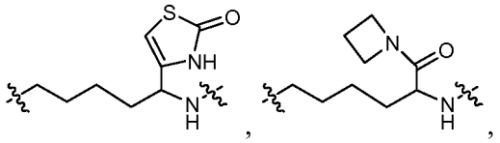
R^6 se selecciona independientemente del grupo constituido por: F, NH_2, CO_2H, $-NHCO_2(\text{alquilo } C_{1-4})$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O(\text{alquilo } C_{1-4})$, $-NHCO_2CH_2CH(\text{alquilo}$

C_{1-4})O(alquilo C_{1-4}),  , y  .

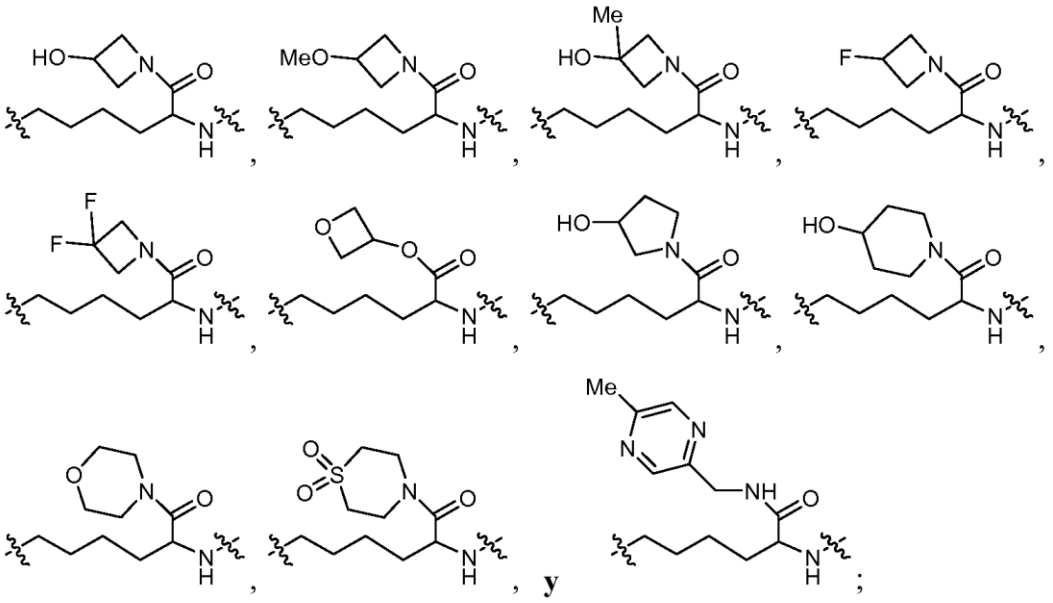
En un 17° aspecto, la presente invención incluye compuestos de fórmula (III), o un esteroisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2Me)CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONHMe)CH_2-$, $-(CH_2)_4CH(CON(Me)_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2Me)CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(Me)(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_4CH(Me)NH-$, $-(CH_2)_3CH(Me)CH_2NH-$, $-(CH_2)_4CH(Me)CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2OMe)NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CO_2Me)NH-$, $-(CH_2)_4CH(CO_2Et)NH-$, $-(CH_2)_4CH(CO_2(i\text{-}Pr))NH-$, $-(CH_2)_4CH(CO_2(t\text{-}Bu))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH-$, $-(CH_2)_5CH(CO_2Me)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2Me)NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(Me))NH-$, $-(CH_2)_4CH(CONH(t\text{-}Bu))NH-$, $-(CH_2)_4CH(CON(Me)_2)NH-$, $-(CH_2)_4CH(CONH(OMe))NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH-$, $-(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH-$, $-CH_2-CH=CH-(CH_2)_2NH-$, $-CH_2-CH=CH-(CH_2)_3NH-$, $-(CH_2)_4CH(CHF_2)NH-$, $-(CH_2)_4CH(CF_3)NH-$, $-(CH_2)_3CF_2CH_2NH-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH-$, $-(CH_2)_4CH(3\text{-Me-oxetan-3-il})NH-$, $-(CH_2)_4CH(CO\text{-pirrolidin-1-il})NH-$, -

$(CH_2)_4CH$(tiazol-4-il)NH-, $-(CH_2)_4CH$(4-Me-tiazol-2-il)NH-, $-(CH_2)_4CH$(1-Me-imidazol-2-il)NH-, $-(CH_2)_4CH$(1-Me-pirazol-3-il)NH-, $-(CH_2)_4CH$(1-(n-Pr)-pirazol-3-il)NH-, $-(CH_2)_4CH$(1-Me-pirazol-5-il)NH-, $-(CH_2)_4CH$(1,3-di-Me-pirazol-5-il)NH-, $(CH_2)_4CH$(1-Me-4-Cl-pirazol-3-il)NH-, $-(CH2)_4N(CO_2Me)CH_2$-, $-(CH_2)_4CONH$-, $-(CH_2)_5CONH$-, $-(CH_2)_6CONH$-, $-(CH_2)_3CH(Me)CONH$-, $-(CH_2)_4CH(Me)CONH$-, $-(CH_2)_2CH(Me)CH_2CONH$-, $-(CH_2)_3CH(Me)CH_2CONH$-, $-(CH_2)_2CH(Me)(CH_2)_2CONH$-, $-(CH_2)_2$-CH=CH-CONH-, $-CH_2$-CH=CH-CH_2CONH-, $-CH_2$-CH=CH-$(CH_2)_2CONH$-, $-CH_2$-CH=CH-$(CH_2)_3CONH$-, $-CH_2$-CH=CH-$CH_2CH(Me)CONH$-, $-CH_2$-CH=CH-$CH(Me)CH_2CONH$-, $-CH_2$-CH=CH$CH(Et)CH_2CONH$-, $-CH_2$-CH=C(Me)-$(CH_2)_2CONH$-, $-(CH_2)_3CH(Me)CONH$-, $-(CH_2)_3CH(Et)CONH$-, $-(CH_2)_3CH(i-Pr)CONH$-, $-(CH_2)_3CHFCONH$-, $-(CH_2)_3CF_2CONH$-, $-(CH_2)_4CF_2CONH$-, $-CH_2$-CH=CH-CH_2CF_2CONH-, $-(CH_2)_3CH(CF_3)CONH$-, $-CH_2CH(OH)(CH_2)_2CONH$-, $-(CH_2)_2CH(OH)CH_2CONH$-, $-(CH_2)_3CH(OH)CH_2CONH$-, $-CH_2CH(OH)CH(OH)CH_2CONH$-, $-CH_2$-CH=CH-$CH(OH)CH_2CONH$-, $-(CH_2)_3CH(OMe)CONH$-, $-(CH_2)_3CH(OCOMe)CH_2CONH$-, $-(CH_2)_3C(O)CH_2CONH$-, $-CH_2O(CH_2)_3CONH$-, $-CH_2O(CH_2)_4CONH$-, $-CH_2NH(CH_2)_2CONH$-, $-CH_2NH(CH_2)_3CONH$-, $-(CH_2)_2N(Me)CH_2CONH$-, $(CH_2)2N(Me)(CH_2)_2CONH$-, $-(CH_2)_5NHCO$-, $-CH_2$-CH=CH-$(CH_2)_2NHCO$-, $-CH_2$-CH=CH-CH_2OCONH-, $-(CH_2)_4OCONH$-, $-CH_2$-CH=CH-$CH_2NHCONH$-, $-(CH_2)_4SO_2NH$-, $-CH_2$-CH=CH-CH_2SO_2NH-, $-(CH_2)_4$-CH=N-,



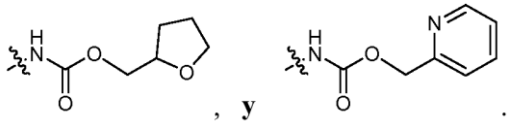
,
,



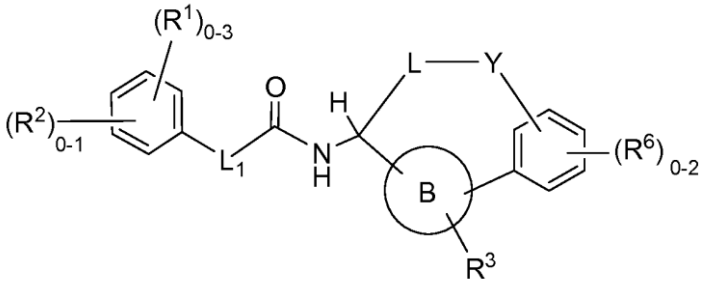
R^{1b} se selecciona independientemente del grupo constituido por: H y F;

R^3 se selecciona independientemente del grupo constituido por: H, F, Cl, Br, CH_3, CN CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$ y ciclopropilo;

R^6 se selecciona independientemente del grupo constituido por: F, NH_2, CO_2H, $NHCO_2Me$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2OMe$, $-NHCO_2(CH_2)_2OEt$, $NHCO_2CH_2CH(Et)OMe$ y

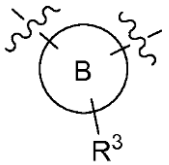


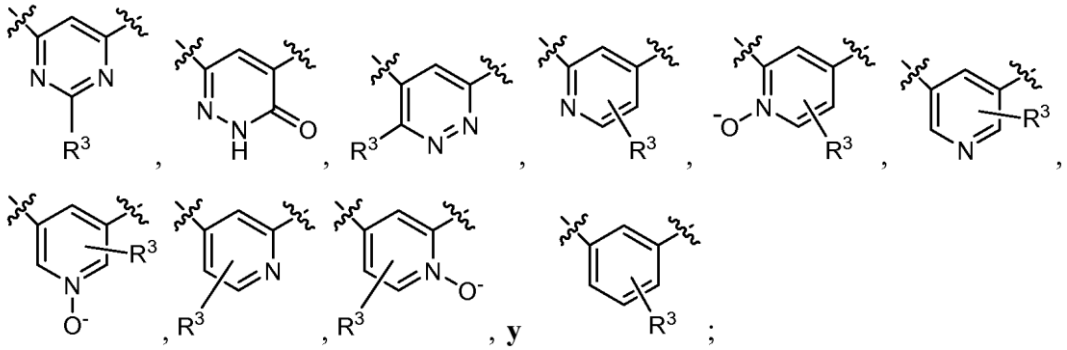
En un 18° aspecto, la presente invención incluye compuestos de fórmula (IV):



(IV)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance de uno cualquiera de los

aspectos primero a décimo, en  se selecciona independientemente del grupo constituido por:



L1 se selecciona independientemente del grupo constituido por: un enlace, $-CH_2CH_2-$ y $-CH=CH-$;

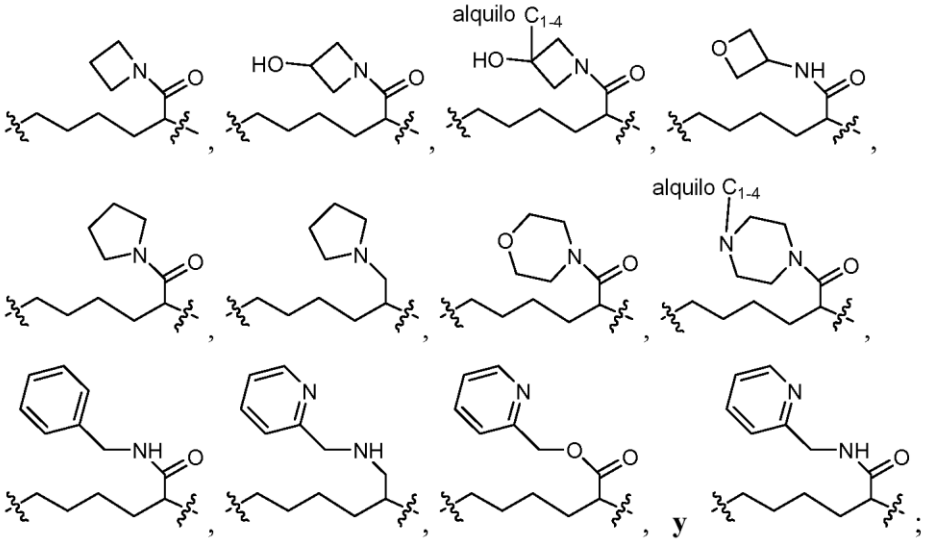
L se selecciona independientemente del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_3CH$(alquilo C_{1-4})-, $-CH_2-CH=CH-CH_2CH(CF_3)-$, $-(CH_2)_4CH(CF_3)-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4}))-, $-CH_2CONH(CH_2)_2-$,

-$(CH_2)_4CH(CO_2(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CH_2NH(CH_2)_2O$(alquilo C_{1-4}))-,

-$(CH_2)_4CH(CO_2(CH_2)_2N$(alquilo C_{1-4})$_2$)-,

-$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))-,

-$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo C_{1-4})$_2$)-,



Y es independientemente -CONH-, O o NH;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CN, OCF_3, CHF_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, CO(alquilo C_{1-4}), NH_2, $-C(=NH)NH_2$, $-C(O)NH_2$ y $-CH_2NH_2$;

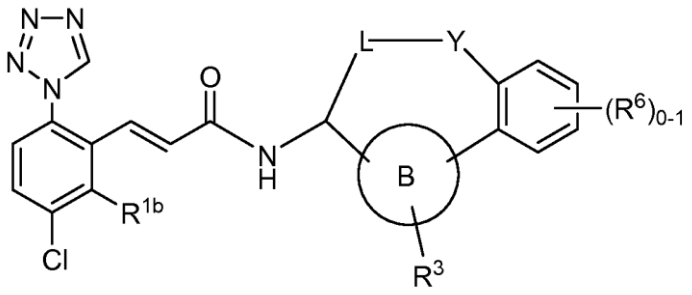
R^2 es independientemente un heterociclo de 5 miembros seleccionado de entre: pirazolilo, imidazolilo, triazolilo y tetrazolilo;

R^3 se selecciona independientemente del grupo constituido por: H y halógeno y alquilo C_{1-4}; y

R^6 se selecciona independientemente del grupo

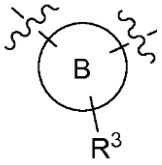
constituido por: H, halógeno, CN, $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), CO_2H y $CONH_2$.

En un 19° aspecto, la presente invención incluye compuestos de fórmula (IVa):

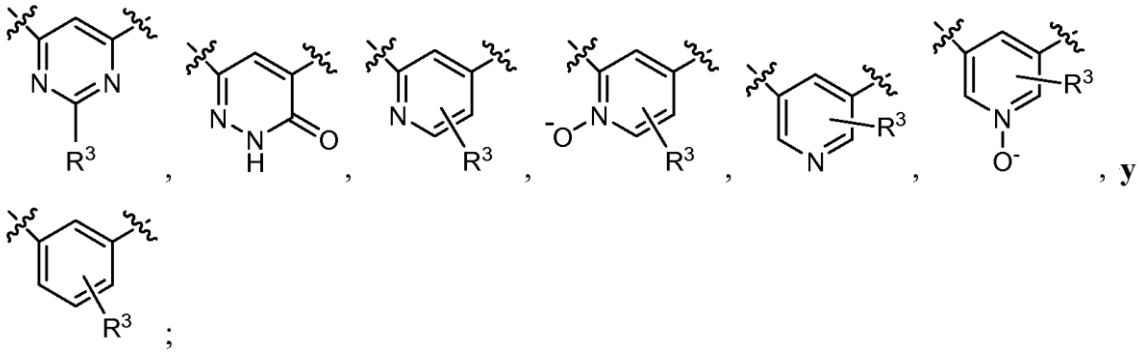


(IVa)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco del mismo, dentro del alcance del 18° aspecto, en donde:



se selecciona independientemente del grupo constituido por:



;

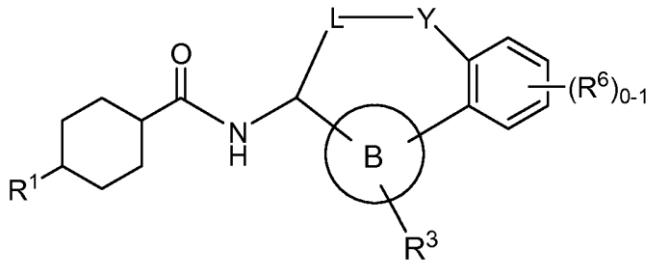
Y es independientemente -CONH- o NH;

R^3 se selecciona independientemente del grupo

constituido por: H, F, Cl y alquilo C_{1-4}; y

R^{6a} se selecciona independientemente del grupo constituido por: F, $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), CO_2H, $CONH_2$ y $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}).

En un 20° aspecto, la presente invención incluye compuestos de fórmula (V):



(V)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato de los mismos, dentro del alcance del primer, segundo o tercer aspecto, en donde:

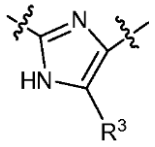
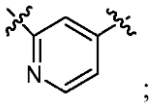
el anillo B se selecciona independientemente del grupo constituido por: imidazol y piridina; y

R^1 se selecciona independientemente del grupo constituido por: alquilo C_{1-4} y CH_2NH_2.

En otro aspecto, la presente invención incluye compuestos de fórmula (V): o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

el anillo B se selecciona independientemente

del

grupo constituido por:  y  ;

L se selecciona independientemente del grupo constituido por: $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CF_2-$, $-(CH_2)_4-$ y $-(CH_2)_4CH(CF_3)-$.

Y se selecciona independientemente del grupo constituido por: $-CH_2-$, -CONH- y NH;

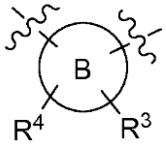
R^3 se selecciona independientemente del grupo constituido por: H, F, Cl, y Me; y

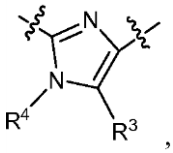
R^{6a} se selecciona independientemente del grupo constituido por: H y $-NHCO_2Me$.

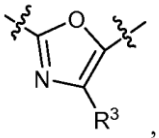
En un 21° aspecto, la presente invención proporciona un compuesto seleccionado a partir de los ejemplos ejemplificados o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo.

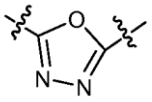
En otro aspecto, la presente invención proporciona un compuesto seleccionado de cualquier lista de subgrupo de compuestos dentro del alcance del 24° aspecto.

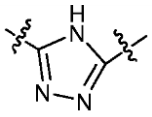
En otro aspecto la presente invención proporciona compuestos de formula (I), (II), (IIa), (IIc) o (IIe), o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, dentro del alcance del cuarto aspecto, en donde:

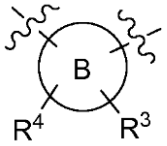


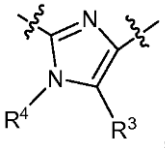
se selecciona independientemente del grupo constituido por: 

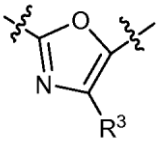
, 

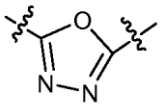
, 

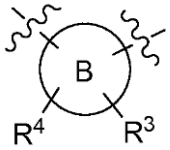
y 

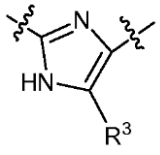
. En otro aspecto en el que: 

se selecciona independientemente del grupo constituido por: 

, 

y 

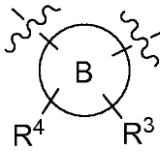
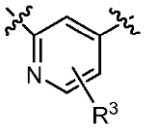
. En otro aspecto, en el que: 

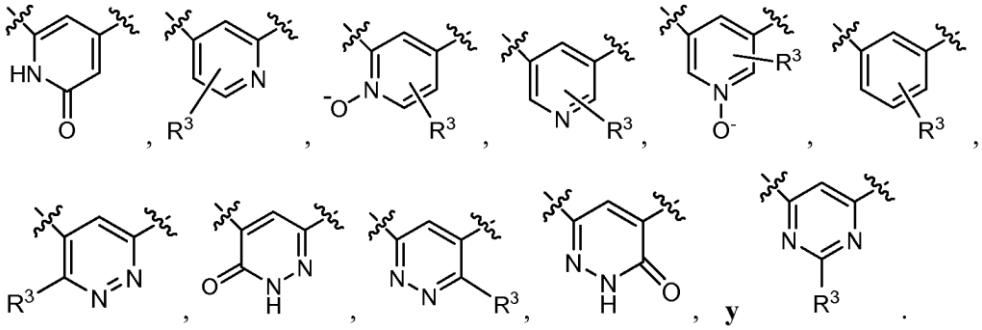
es 

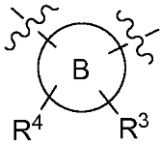
.

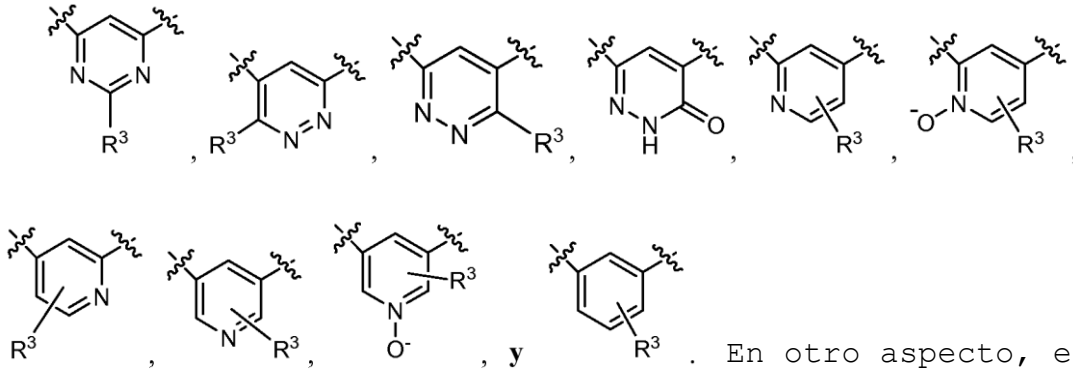
En otro aspecto, la presente invención proporciona compuestos de fórmula (I), (II), (IIa), (IIc) o (IIe), o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco del mismo, dentro del

alcance del cuarto aspecto, en donde:

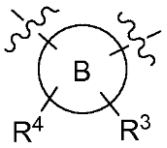
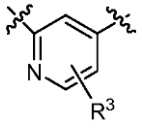
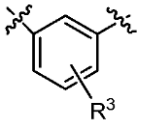
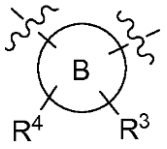
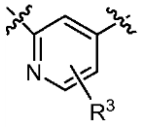
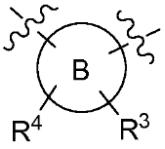
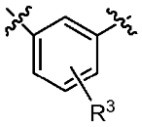
 se selecciona independientemente del grupo constituido por:  ,



En otro aspecto, en donde:  se selecciona independientemente del grupo constituido por:



En otro aspecto, en

donde:  se selecciona independientemente del grupo consitituido por  y  . En otro aspecto en donde  es  . En otro aspecto en donde  es  .

En otro aspecto, la presente invención incluye compuestos de fórmula (I) o de fórmula (I), (II), (IIa) o (IIb), o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato de los mismos, dentro del alcance de uno cualquiera de los aspectos anteriores, en donde:

R^2 es independientemente un heterociclo de 5 miembros sustituido con 0-1 R^{2a}, en donde el heterociclo se selecciona de entre: pirazolilo, imidazolilo, triazolilo y tetrazolilo; y

R^{2a}, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, NH_2, CH_2OH, CO_2H, alquilo C_{1-4}, $-CONH_2$, -CONH(alquilo C_{1-4}) y -CON(alquilo C_{1-4})$_2$.

En otro aspecto, la presente invención incluye compuestos de fórmula (I), (II), (IIa) o (IIb), un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato de los mismos, dentro del alcance de uno cualquiera de los aspectos anteriores, en donde:

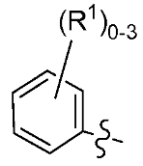
R^2 se selecciona independientemente del grupo constituido por: triazolilo y tetrazolilo.

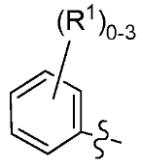
En otra modalidad, el anillo A se selecciona independientemente del grupo constituido por: fenilo, ciclohexilo y 5,6,7,8-tetrahidroisoquinolinilo.

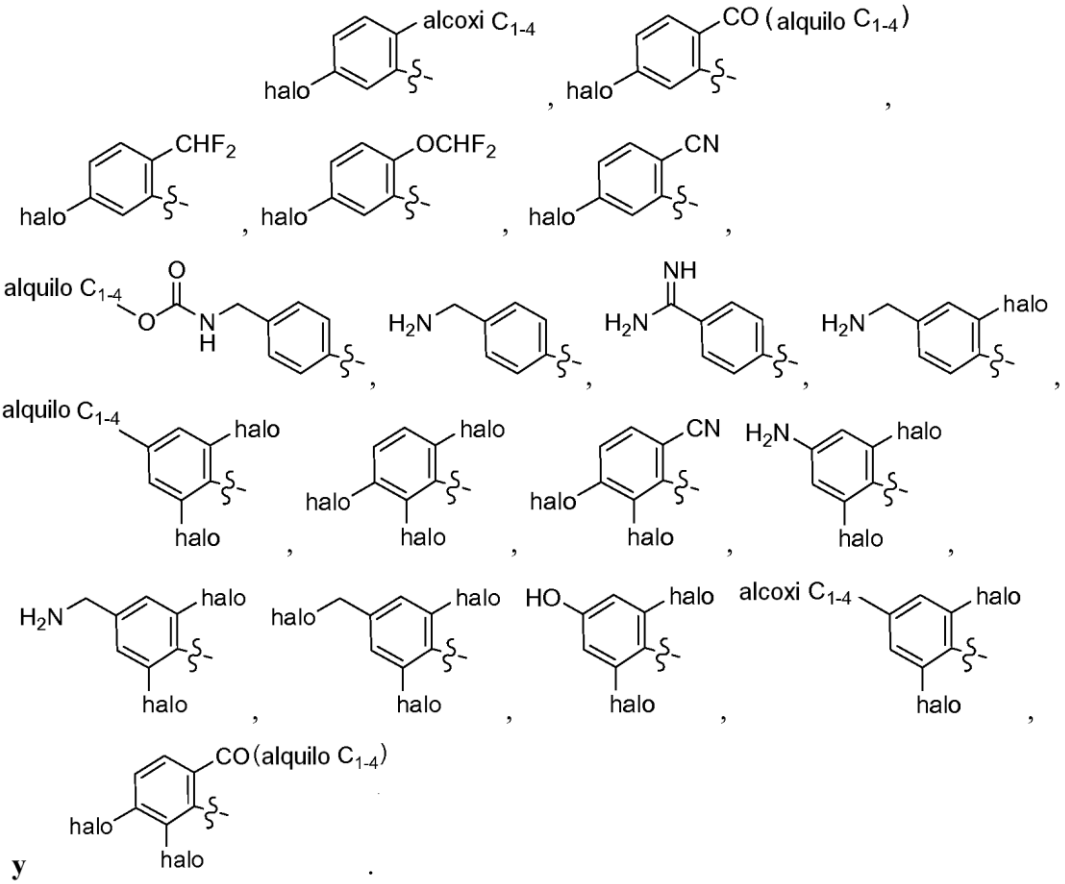
En otra modalidad, el anillo A es fenilo.

En otra modalidad, el anillo A es ciclohexilo.

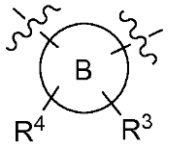
En otra modalidad, el anillo A es tetrahidroisoquinolina.

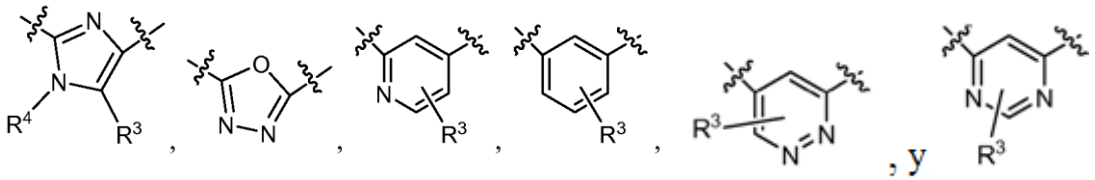
En otro aspecto, el anillo A es  , en donde R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CO(alquilo C_{1-4}), CN, CH_2F, CHF_2, $OCHF_2$, NH_2, N(alquilo C_{1-4})$_2$, $-CH_2NH_2$, $-CH_2NHCO_2$(alquilo C_{1-4}) y $-C(=NH)NH_2$.

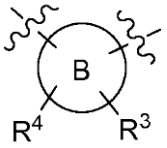
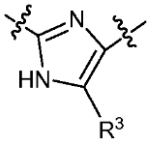
En otro aspecto, el anillo A es  , que se selecciona independientemente del grupo constituido por:

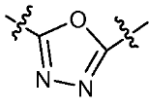


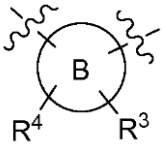
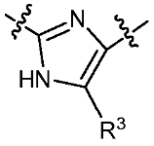
En otra modalidad, el anillo B se selecciona independientemente del grupo constituido por: imidazol, oxadiazol, piridina, piridazina y benceno.

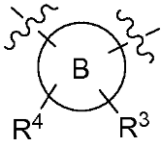
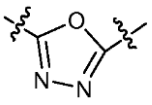
En otra modalidad,  se selecciona independientemente del grupo constituido por:

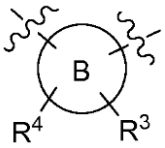


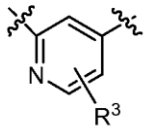
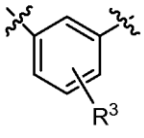
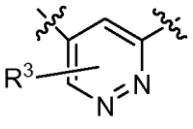
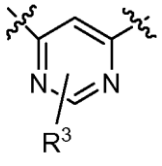
En otra modalidad,  se selecciona independientemente del grupo constituido por: 

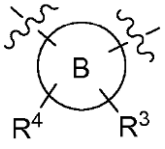
y  .

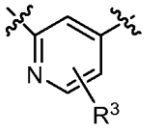
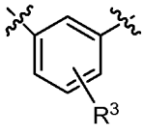
En otra modalidad,  es  .

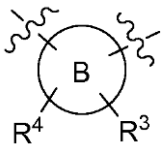
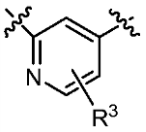
En otra modalidad,  es  .

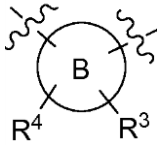
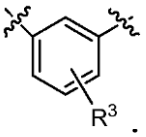
En otra modalidad,  se selecciona independientemente del grupo constituido por:

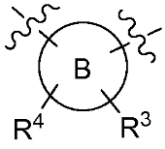
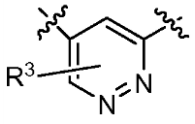
 ,  ,  , y  .

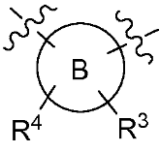
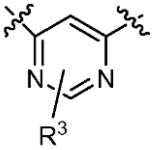
En otra modalidad,  se selecciona independientemente del grupo constituido por:

 y  .

En otra modalidad,  es  .

En otra modalidad,  es  .

En otra modalidad,  es  .

En otra modalidad,  es  .

En otra modalidad, L_1 se selecciona independientemente del grupo constituido por: un enlace, -CH_2CH_2- , -CH=CH-, -C(Me)=CH-, -C≡C- y -CN_2NH-.

En otra modalidad, L_1 se selecciona independientemente del grupo constituido por: un enlace, -CH_2CH_2-, -CH=CH- y -C(Me)=CH.

En otra modalidad, L_1 se selecciona independientemente del grupo constituido por: un enlace, -CH_2CH_2- y -CH=CH-.

En otra modalidad, L_1 es un enlace.

En otra modalidad, L_1 es -CH=CH-.

En otra modalidad, L se selecciona independientemente del grupo constituido por: alquileno C_{3-7} y alquenileno C_{3-7}; en donde el alquileno y alquenileno están sustituido con 0-2 R^7 y opcionalmente uno o dos de los átomos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, NH, N(alquilo C_{1-4}), CONH, NHCO o CON(alquilo C_{1-4}).

En otra modalidad, L se selecciona independientemente del grupo constituido por: alquileno C_{3-7} y alquenileno C_{4-7}; en donde el alquileno y alquenileno están opcionalmente sustituidos con 1-2 R^7; opcionalmente uno o dos de los átomos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, NH, N(alquilo C_{1-4}), CONH o CON(alquilo C_{1-4}).

En otra modalidad, L es alquileno C_{3-7}, en el alquileno está opcionalmente sustituido con 1-2 R^7; opcionalmente uno o dos de los átomos de carbono del alquileno pueden estar reemplazados por O, NH, N(alquilo C_{1-4}), CONH, o CON(alquilo C_{1-4}).

En otra modalidad, L es alquenileno C_{4-7}, en donde el alquenileno está opcionalmente sustituido con 1-2 R^7; opcionalmente uno o dos de los átomos de carbono del alquenileno pueden estar reemplazados por O, NH, N(alquilo C_{1-4}), CONHo CON(alquilo C_{1-4}).

En otra modalidad, Y se selecciona independientemente del grupo constituido por: $-CH_2-$, O, NH, N(alquilo C_{1-4}), $-NHCO-$, $-CONH-$, $-CONHCH_2-$, $-CON$(alquilo C_{1-4})CH_2-, $-OCONH-$, $-NHCONH-$ y $-SO_2NH-$.

En otra modalidad, Y se selecciona independientemente del grupo constituido por: $-CH_2-$, O, NH, NMe, $-CONH-$, $-NHCO-$, $-CONHCH_2-$, $-CONMeCH_2-$, $-OCONH-$, $-NHCONH-$ y $-SO_2NH-$.

En otra modalidad, Y es $-CONH-$.

En otra modalidad, R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, OH, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(alquilo $C_{1-4})_2$, N(alquilo $C_{1-4})_2$, CO_2(alquilo C_{1-4}), CO(alquilo C_{1-4}), $-OCH_2CO_2H$, $-CH_2NH_2$, $-CONH_2$, $-CONH$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-SO_2NH_2$ y $-C(=NH)NH_2$.

En otra modalidad, R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, OH, CHF_2, CF_3, OCF_3, CN, NH_2, CO_2(alquilo C_{1-4}), CO(alquilo C_{1-4}), $-OCH_2CO_2H$, $-CH_2NH_2$, $-CONH_2$, $-CONH$(alquilo C_{1-4}), $-SO_2NH_2$ y $-C(=NH)NH_2$.

En otra modalidad, R^1, en cada aparición, se selecciona independientemente de entre: halógeno, CN, OH, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, alquilo C_{1-4}, alcoxi C_{1-4},

CO(alquilo C_{1-4}), NH_2, NH(alquilo C_{1-4})$_2$, N(alquilo C_{1-4})$_2$, -C(=NH)NH_2, -C(O)NH_2, $-CH_2NH_2$, $-CH_2NHCO_2$(alquilo C_{1-4}) y $-SO_2NH_2$.

En otra modalidad, R^1, en cada aparición, se selecciona independientemente de entre: halógeno, CN, OH, OCF_3, CHF_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, CO(alquilo C_{1-4}), NH_2, -C(=NH)NH_2, -C(O)NH_2, $-CH_2NH_2$ y $-SO_2NH_2$.

En otra modalidad, R^1 se selecciona del grupo constituido por: halógeno, alquilo C_{1-4}, CHF_2 y CO(alquilo C_{1-4}).

En otra modalidad, R^2 es un heterociclo de 5 miembros sustituido con 0-1 R^{2a}, en donde el heterociclo se selecciona independientemente de entre: pirazolilo, imidazolilo, triazolilo y tetrazolilo.

En otra modalidad, R^2 se selecciona independientemente del grupo constituido por: triazolilo y tetrazolilo.

En otra modalidad, R^2 es tetrazolilo.

En otra modalidad, R^3 se selecciona independientemente del grupo constituido por: H, alquilo C_{1-4}, halógeno, CN, CO_2(alquilo C_{1-4}), $CONH_2$ y ciclopropilo.

En otra modalidad, R^3 se selecciona independientemente del grupo constituido por: H, alquilo C_{1-4} y halógeno.

En otra modalidad, R^3 se selecciona independientemente del grupo constituido por: H y halógeno.

En otra modalidad, R^3 se selecciona independientemente del grupo constituido por: H y Cl.

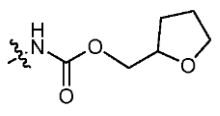
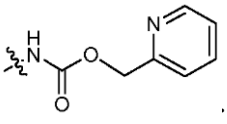
En otra modalidad, R^3 es H.

En otra modalidad, R^3 es Cl.

En otra modalidad, R^4 es H.

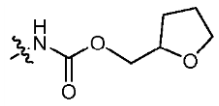
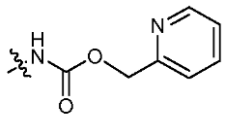
En otra modalidad, R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H y alquilo C_{1-4}.

En otra modalidad, R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H y metilo.

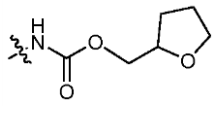
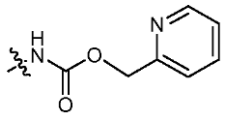
En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2$(alquilo C_{1-4}), -NHC(O)NH(alquilo C_{1-4}), $-NHC(O)N$(alquilo C_{1-4})$_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $-C(O)NH(CH_2)_2O$(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, $-CH_2CONH_2$,  y  .

En otra modalidad, R^6, en cada aparición, se

selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-CH_2NHCO_2$(alquilo C_{1-4}), -NHC(O)NH(alquilo C_{1-4}), $-NHC(O)N$(alquilo $C_{1-4})_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}) y $-CONH_2$.

En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-CONH_2$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2CH_2CO_2H$, $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}),  y  .

En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, CO_2(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo $C_{1-4})_2$, $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHCO_2CH_2CO_2H$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo

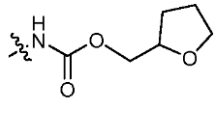
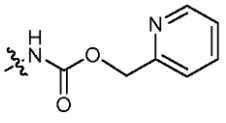
C_{1-4}),  y  .

En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), -CH_2CO_2H, -CH_2CO_2(alquilo C_{1-4}), NH_2, -CH_2NH_2, -NHCO(alquilo C_{1-4}), -$NHCO_2$(alquilo C_{1-4}), -CH_2NHCO_2(alquilo C_{1-4}) y -$CONH_2$.

En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CO_2H, CO_2(alquilo C_{1-4}), NH_2, $NHCO_2$(alquilo C_{1-4}) y -CH_2NHCO_2(alquilo C_{1-4}).

En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, NH_2, $NHCO_2$(alquilo C_{1-4}) y -CH_2NHCO_2(alquilo C_{1-4}).

En otra modalidad, R^6, en cada aparición, se selecciona independientemente del grupo constituido por: F, NH_2, $NHCO_2Me$ y -CH_2NHCO_2Me.

En otra modalidad, R^{6a} se selecciona independientemente del grupo constituido por: H, halógeno, NH_2, CO_2H, $CONH_2$, -$NHCO_2$(alquilo C_{1-4}), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -$NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}),  y  .

En otra modalidad, R^{6a} se selecciona independientemente del grupo constituido por: H, halógeno,

NH(alquilo C_{1-4}) y $NHCO_2$(alquilo C_{1-4}).

En otra modalidad, R^{6a} se selecciona independientemente del grupo constituido por: H, halógeno y $NHCO_2$(alquilo C_{1-4}).

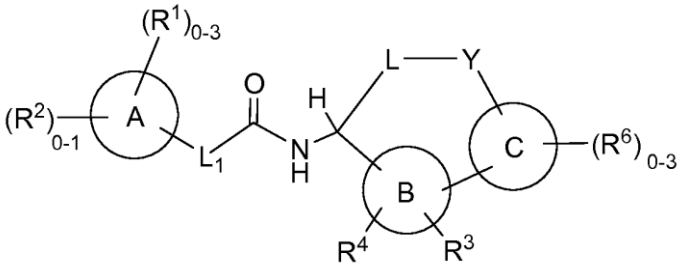
En otra modalidad, R6a es R^{6a} se selecciona independientemente del grupo constituido por: H, F y $NHCO_2Me$.

En otra modalidad, R^7, en cada aparición se selecciona independientemente del grupo constituido por: halógeno, OH, CHF_2, CF_3, alcoxi C1-$_4$, CH_2OH, CH_2O(alquilo C_{1-4}), CO_2H, CO_2(alquilo C_{1-4}), CH_2CO_2H, CH_2CO_2(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo $C_{1-4})_2$, -OCO(alquilo C_{1-4}), -CON(alquilo C_{1-4})$(CH_2)_2$N(alquilo $C_{1-4})_2$, -CONH(alcoxi C_{1-4}), alquilo C1-$_4$, y -$(CO)_{0-1}$-(heterociclo de 4 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de entre N, NH, N(alquilo C_{1-4}), O y $S(O)_p$); en el heterociclo está sustituido con 0-2 R^8.

En otra modalidad, R^7 se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4} y N(alquilo $C_{1-4})_2$.

En otra modalidad, R^7 se selecciona independientemente del grupo constituido por: halógeno y alquilo C_{1-4}.

En otro aspecto, la presente invención proporciona, entre otras cosas, un compuesto de fórmula (I-1):



(I-1)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco del mismo, en donde:

el anillo A es un carbociclo C_{3-10} o un heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y $S(O)_p$;

el anillo B es un anillo de benceno o un heterociclo de 5 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y $S(O)_p$;

el anillo C es un anillo de benceno o un heterociclo de 5-10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y $S(O)_p$;

L_1 se selecciona del grupo constituido por: un enlace, $-CHR^5CHR^5-$, $-CR^5=CR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR^5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CN_2NH-$ y $-CR^5R^5-$;

L se selecciona del grupo constituido por: alquileno C_{3-8}, alquenileno C_{4-8} y alquinileno C_{4-8}; en el alquileno, alquenileno y alquinileno están opcionalmente sustituidos con 1-2 R^7; opcionalmente uno o varios de los

átomos de carbono del alquileno y alquenileno pueden estar reemplazados por O, S, NH, N(alquilo C_{1-4}), CO, CONH, NHCO, OCONH, SO_2NH, o CON(alquilo C_{1-4});

Y se selecciona entre el grupo constituido por: O, S, NH, N(alquilo C_{1-4}), CH_2, CH(alquilo C_{1-4}), C(alquilo $C_{1-4})_2$, -CONH-, -NHCO-, $-CONHCH_2-$, -CON(alquilo $C_{1-4})CH_2-$, -OCONH-, -OCON(alquilo C_{1-4})-, -NHCONH-, $-SO_2NH-$, $-NHCO_2-$ y $-NHSO_2-$;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, OH, CHF_2, CF_3, OCF_3, CN, NH_2, $-CO_2$(alquilo C_{1-4}), -CO(alquilo C_{1-4}), $-CH_2NH_2$, $-CONH_2$, -CONH(alquilo C_{1-4}), $-OCH_2CO_2H$, -NHCO(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH_2$ y $-C(=NH)NH_2$;

R^2 es un heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y $S(O)_p$, en el heterociclo está sustituido con 0-2 R^{2a};

R^{2a}, en cada aparición, se selecciona independientemente del grupo constituido por: alquilo C_{1-4}, $-CH_2OH$, alcoxi C_{1-4}, OH, CF_3, OCF_3, CN, NH_2, CO_2H, CO_2(alquilo C_{1-4}), COalquilo C_{1-4}, $-CONH_2$, -CONH(alquilo C_{1-4}), -CON(alquilo $C_{1-4})_2$, $-SO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-SO_2NH$(alquilo C_{1-4}) y $-SO_2NH$(alquilo $C_{1-4})_2$;

R^3 se selecciona del grupo constituido por: H, halógeno, OH, NH_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, $-CH_2OH$, CO_2H,

CO_2(alquilo C_{1-4}), $-C(O)NH_2$, $-C(O)NH$(alquilo C_{1-4}), $-C(O)N$(alquilo $C_{1-4})_2$ y $-CH_2CO_2H$;

R4 se selecciona del grupo constituido por: H y alquilo C_{1-4};

R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H, halógeno, OH y alquilo C_{1-4};

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHC(O)NH$(alquilo C_{1-4}), $-NHC(O)N$(alquilo $C_{1-4})_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-SO_2NH$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $-CONH_2$, $-CONH$(alquilo C_{1-4}), $-CON$(alquilo $C_{1-4})_2$ y $-CH_2CONH_2$;

R^7, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, NH_2, $-CH_2NH_2$, CHF_2, CF_3, $-NH$(alquilo C_{1-4}), $-N$((alquilo $C_{1-4})_2$, alcoxi C_{1-4} y alquilo C_{1-4}; y

p, en cada aparición, se selecciona independientemente del grupo constituido por: 0, 1 y 2.

En otro aspecto, la presente invención proporciona

compuestos de fórmula (I-1) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

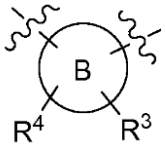
el anillo A es un carbociclo de 6 miembros o 5,6,7,8-tetrahidroisoquinolina;

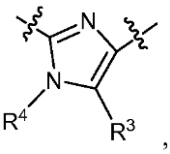
el anillo B se selecciona del grupo constituido por: imidazol, oxadiazol, piridina, piridazina, pirimidina y benceno; y

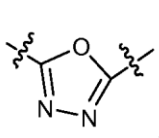
el anillo C se selecciona del grupo constituido por: benceno y piridina.

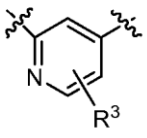
En otro aspecto, la presente invención proporciona compuestos de fórmula (Ia) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

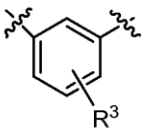
el anillo A se selecciona del grupo constituido por: benceno, ciclohexano y 5,6,7,8-tetrahidroisoquinolina;

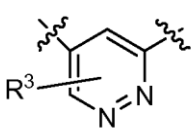


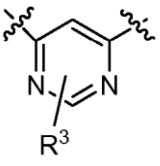
se selecciona del grupo constituido por:


,


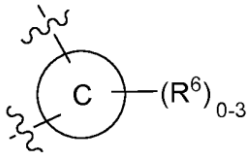
,


,


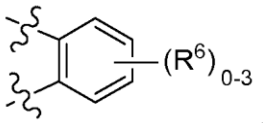
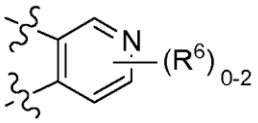
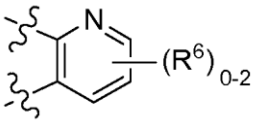
,


, y


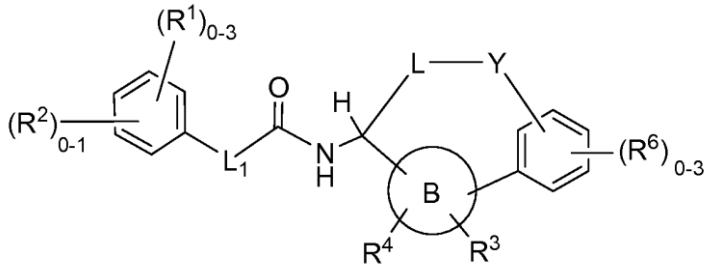
; y



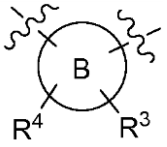
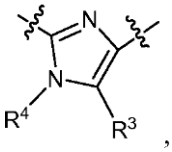
se selecciona del grupo constituido por:

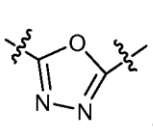
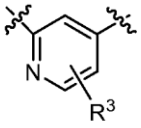
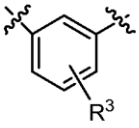
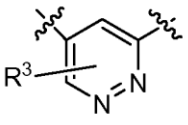
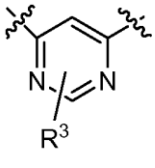

, 
, y 
.

En otro aspecto, la presente invención proporciona compuestos de fórmula (II-1):


(II-1)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:


se selecciona del grupo constituido por: 
,


, 
, 
, 
, y 
;

L_1 se selecciona del grupo constituido por: un enlace, $-CHR^5CHR^5-$, $-CR^5=CHR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR^5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CN_2NH-$ y $-CR^5R^5-$;

L se selecciona del grupo constituido por: alquileno C_{3-8} y alquenileno C_{4-8}, en donde el alquileno, alquenileno y piridinileno están opcionalmente sustituidos

con 1-2 R^7; opcionalmente uno o dos de los átmos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, S, NH, N(alquilo C_{1-4}), CONH-, o CON(alquilo C_{1-4});

Y se selecciona del grupo constituido por: CH_2, CH(alquilo C_{1-4}), C(alquilo C_{1-4})$_2$, O, S, NH, N(alquilo C_{1-4}), -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, OCONH-, -OCON(alquilo C_{1-4})-, -NHCONH- y -SO_2NH-;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, OH, CHF_2, CF_3, OCF_3, CN, NH_2, CO_2(alquilo C_{1-4}), CO(alquilo C_{1-4}), -OCH_2CO_2H, -CH_2NH_2, -$CONH_2$, -CONH(alquilo C_{1-4}), -SO_2NH_2 y -C(=NH)NH_2;

R^2 es un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y S(O)$_p$, en donde el heterociclo está sustituido con 0-2 R^{2a}.

R^{2a}, en cada aparición, se selecciona independientemente del grupo constituido por: alquilo C_{1-4}, -CH_2OH, alcoxi C_{1-4}, OH, CF_3, CN, NH_2, CO_2H, CO_2(alquilo C_{1-4}), COalquilo C_{1-4}, -$CONH_2$, -CONH(alquilo C_{1-4}) y -CON(alquilo C_{1-4})$_2$;

R^3 se selecciona del grupo constituido por: H, halógeno, OH, NH_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, -CH_2OH, CO_2H, CO_2(alquilo C_{1-4}), -$C(O)NH_2$, -C(O)NH(alquilo C_{1-4}), -C(O)N(alquilo C_{1-4})$_2$ y -CH_2CO_2H;

R^4 se selecciona del grupo constituido por: H y alquilo C_{1-4};

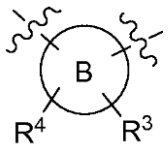
R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H, halógeno, OH y alquilo C_{1-4};

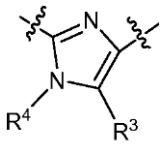
R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHC(O)NH$(alquilo C_{1-4}), $-NHC(O)N$(alquilo C_{1-4})$_2$, $-NHSO_2-$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $-CONH_2$, $-C(O)NH(CH_2)_2O$(alquilo C_{1-4}) y $-CH_2CONH_2$;

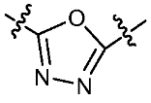
R^7, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CF_3, alcoxi C_{1-4} y alquilo C_{1-4}; y

p, en cada aparición, se selecciona independientemente del grupo constituido por: 0, 1 y 2.

En otro aspecto, la presente invención proporciona compuestos de fórmula (I), (II), (IIa), (IIc) o (IIe), o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

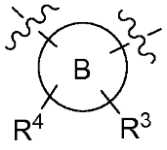


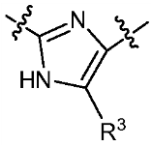
se selecciona del grupo constituido por: 

y 

.

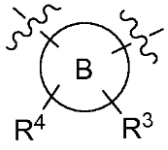
En otro aspecto, la presente invención proporciona compuestos de fórmula (I-1), (II-1), (IIa), (IIc) o (IIe), o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:



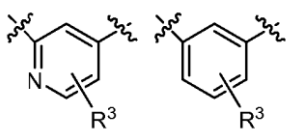
es 

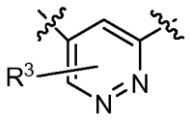
.

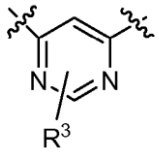
En otro aspecto, la presente invención proporciona compuestos de fórmula (I-1), (II-1), (IIa), (IIc) o (IIe), o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:



se selecciona del grupo constituido por:



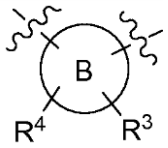
, 

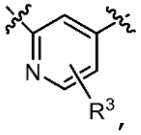
, y 

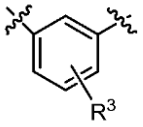
.

En otro aspecto, la presente invención proporciona

compuestos de fórmula (I-1), (II-1), (IIa), (IIc) o (IIe), o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

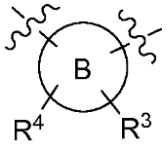


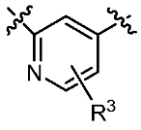
se selecciona del grupo constituido por: 

, 

.

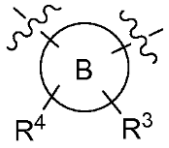
En otro aspecto, la presente invención proporciona compuestos de fórmula (I-1), (II-1), (IIa), (IIc) o (IIe), o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

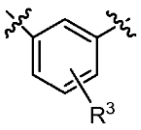


es 

.

En otro aspecto, la presente invención proporciona compuestos de fórmula (I-1), (II-1), (IIa), (IIc) o (IIe), o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:



es 

.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa) o (IIb), un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

R^2 es un heterociclo de 5 miembros sustituido con 0-1 R^{2a}, en el heterociclo se selecciona de entre: pirazolilo, imidazolilo, triazolilo y tetrazolilo; y

R^{2a} en cada aparición, se selecciona independientemente del grupo constituido por: OH, NH_2, CH_2OH, CO_2H, alquilo C_{1-4}, $-CONH_2$, -CONH(alquilo C_{1-4}) y -CON(alquilo $C_{1-4})_2$.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa) o (IIb), un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

R^2 se selecciona del grupo constituido por: triazolilo y tetrazolilo.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf), un estereosiómero, un tautómero, una

sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L_1 se selecciona del grupo constituido por: un enlace, $-CH_2CH_2-$, $-CH=CH-$, $-C(Me)=CH-$, $-C\equiv C-$ y $-CN_2NH-$;

L se selecciona del grupo constituido por: alquileno C_{3-7}, alquenileno C_{4-7}; en el alquileno y alquenileno están opcionalmente sustituidos con 1-2 R^7; opcionalmente uno o dos de los átomos de carbono del alquileno y alquenileno pueden reemplazarse por O, NH, N(alquilo C_{1-4}), CONH o CON(alquilo C_{1-4});

Y se selecciona del grupo constituido por: CH_2, CH(alquilo C_{1-4}), C(alquilo C_{1-4})$_2$, O, S, NH, N(alquilo C_{1-4}), $-CONH-$, $-NHCO-$, $-CONHCH_2-$, $-CON$(alquilo C_{1-4})CH_2-, $-OCONH-$, $-NHCONH-$ y $-SO_2NH-$;

R^1, en cada aparición, se selecciona independientemente de entre: halógeno, CN, OH, OCF_3, CHF_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, CO(alquilo C_{1-4}), NH_2, $-C(=NH)NH_2$, $-C(O)NH_2$, $-CH_2NH_2$ y $-SO_2NH_2$;

R^3 se selecciona del grupo constituido por: H, halógeno, OH, NH_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, $-CH_2OH$, CO_2H, CO_2(alquilo C_{1-4}), $-C(O)NH_2$, $-C(O)NH$(alquilo C_{1-4}), $-C(O)N$(alquilo C_{1-4})$_2$ y $-CH_2CO_2H$; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, -

$(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHC(O)NH$(alquilo C_{1-4}), $-NHC(O)N$(alquilo $C_{1-4})_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}) y $-CONH_2$.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L_1 se selecciona del grupo constituido por: un enlace, $-CH_2CH_2-$ y $-CH=CH-$;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CN, alquilo C_{1-4}, CHF_2, CF_3, CO(alquilo C_{1-4}), NH_2, $-CH_2NH_2$ y $-C(=NH)NH_2$;

R^3 se selecciona del grupo constituido por: H, halógeno, CF_3, CO_2H, CO_2(alquilo C_{1-4}) y alquilo C_{1-4}; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}) y $-CONH_2$.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L_1 se selecciona del grupo constituido por: un enlace, $-CH_2CH_2-$ y $-CH=CH-$;

L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(\text{alquilo } C_{1-4})-(CH_2)_2-$, $-CH_2-CH=CH-CH(\text{alquilo } C_{1-4})-CH_2-$, $-CH_2-C(\text{alquilo } C_{1-4})=CH-(CH_2)_2-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})CH_2-$, $-(CH_2)_2CH(\text{alquilo } C_{1-4})(CH_2)_2-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})(CH_2)_2-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(\text{alquilo } C_{1-4})CH_2-$, $-(CH_2)_2N(\text{alquilo } C_{1-4})(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CONH(\text{alquilo } C_{1-4})-(CH_2)_2-$, $-CH_2-CONH(\text{alquilo } C_{1-4})-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$ y $-CH_2CH(OH)CH(OH)CH_2-$;

Y se selecciona del grupo constituido por: $-CH_2-$, O, NH, $N(\text{alquilo } C_{1-4})$, -NHCO-, -CONH-, $-CONHCH_2-$, $-CON(\text{alquilo } C_{1-4})CH_2-$, -OCONH-, -NHCONH- y SO_2NH-;

R^3 se selecciona del grupo constituido por: H, alquilo C_{1-4} y halógeno; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CO_2H, CO_2(alquilo C_{1-4}), NH_2, $NHCO_2$(alquilo C_{1-4}) y CH_2NHCO_2(alquilo C_{1-4}).

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C$(alquilo C_{1-4})$-(CH_2)_2-$, $-CH_2-CH=CH-CH$(alquilo C_{1-4})$-CH_2-$, $-CH_2-C$(alquilo C_{1-4})$=CH-(CH_2)_2-$, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_3CH$(alquilo C_{1-4})$-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N$(alquilo C_{1-4})CH_2-, $-(CH_2)_2N$(alquilo C_{1-4})$(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON$(alquilo C_{1-4})$-(CH_2)_2-$, $-CH_2-CON$(alquilo C_{1-4})$-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$ y $-CH_2CH(OH)CH(OH)CH_2-$;

Y se selecciona del grupo constituido por: CH_2, O, NH, N(alquilo C_{1-4}), -NHCO-, -CONH-, $-CONHCH_2-$, $-CON$(alquilo C_{1-4})CH_2-, -OCONH-, -NHCONH- y $-SO_2NH-$;

R^1 se selecciona del grupo constituido por:

halógeno, alquilo C_{1-4}, CHF_2, CN y CO(alquilo C_{1-4});

R^3 se selecciona del grupo constituido por: H, alquilo C_{1-4} y halógeno; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, NH_2, $NHCO_2$(alquilo C_{1-4}) y $-CH_2NHCO_2$(alquilo C_{1-4}).

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_3CH(CH_3)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, $-CH_2-CON(CH_3)-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$ y $-CH_2CH(OH)CH(OH)CH_2-$;

Y se selecciona del grupo constituido por: CH_2, O, NH, NMe, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH- y $-SO_2NH-$;

R^1 se selecciona del grupo constituido por: H, F, Cl, Me, COMe y CHF_2;

R^3 se selecciona del grupo constituido por: H, Me y Cl; y

R6, en cada aparición, se selecciona independientemente del grupo constituido por: F, NH_2, $NHCO_2Me$ y $-CH_2NHCO_2Me$.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

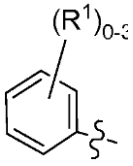
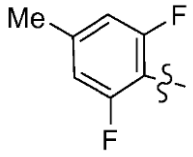
L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$,$-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$ y $-CH_2CH(OH)CH(OH)CH_2-$;

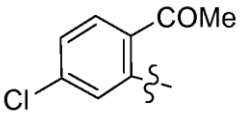
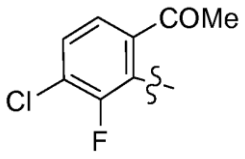
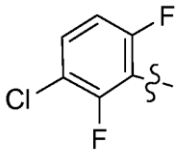
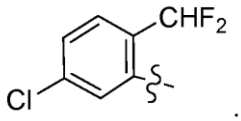
Y se selecciona del grupo constituido por: CH_2, O, NH, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH- y $-SO_2NH-$; y

R^3 se selecciona del grupo constituido por: H y Cl.

En otro aspecto, la presente invención incluye

compuestos de fórmula (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:


se selecciona del grupo constituido por:  ,

 ,  ,  , y  .

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_3CH(CH3)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, $-CH_2-CON(CH_3)-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$ y -

$CH_2CH(OH)CH(OH)CH_2$-;

Y se selecciona del grupo constituido por: CH_2, O, NH, NMe, -CONH-, -NHCO-, $-CONHCH_2$-, $-CONMeCH_2$-, -OCONH-, -NHCONH- y $-SO_2NH$-;

R^1 se selecciona del grupo constituido por: H, F, Cl, Me, COMe y CHF_2;

R^3 se selecciona del grupo constituido por: H, Me y Cl; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: F, NH2, $NHCO_2Me$ y $-CH_2NHCO_2Me$.

En otro aspecto, la presente invención incluye compuestos de fórmula (I-1), (II-1), (IIa), (IIb), (IIc), (IId), (IIe) o (IIf) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

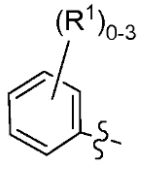
L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2$-, $-CH_2-CH=CH-(CH_2)_2$-, $-CH_2-CH=CH-(CH_2)_3$-, $-CH_2-CH=C(CH_3)-(CH_2)_2$-, $-CH_2-CH=CH-CH(CH_3)CH_2$-, $-(CH_2)_3CH(CH_3)CH_2$-, $-(CH_2)_2CH(CH_3)(CH_2)_2$-, $-(CH_2)_4$-, $-(CH_2)_5$-, $-(CH_2)_6$-, $-CH_2O(CH_2)_3$-, $-CH_2O(CH_2)_4$-, $-(CH_2)_4CF_2$-, $-CH_2-CH=CH-CH_2CF_2$-, $-CH_2NH(CH_2)_2$-, $-CH_2NH(CH_2)_3$-, $-(CH_2)_2N(CH_3)CH_2$-, $-(CH_2)_2N(CH_3)(CH_2)_2$-, $-CH_2-CONH-(CH_2)_3$-, $-CH_2-CONH-(CH_2)_4$-, $-CH_2-CON(CH_3)-(CH_2)_2$- y $-CH_2CH(OH)CH(OH)CH_2$;

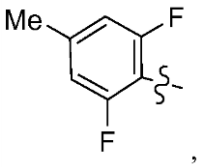
Y se selecciona entre el grupo constituido por:

CH_2, O, NH, -CONH-, -NHCO-, -$CONHCH_2$-, -$CONMeCH_2$-, -OCONH-, -NHCONH- y -SO_2NH-; y

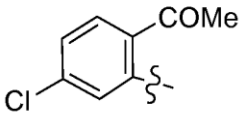
R^3 se selecciona del grupo constituido por: H y Cl.

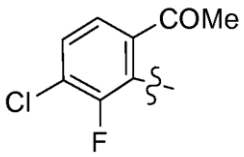
En otro aspecto, la presente invención incluye compuestos de fórmula (IIe) o (IIf) oun estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco de los mismos, en donde:



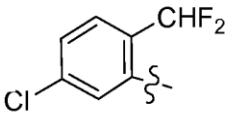
se selecciona del grupo constituido por:


,



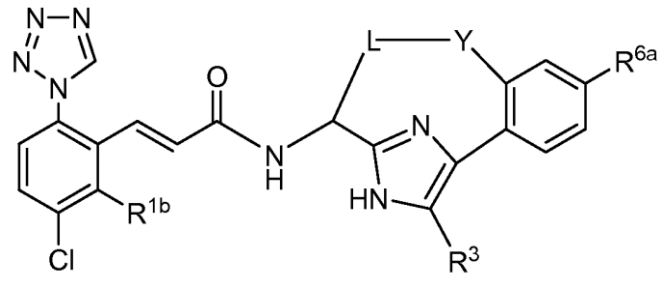
,


,


, y


.

En otro aspecto, la presente invención incluye compuestos de fórmula (III):



(III)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L se selecciona del grupo constituido por: -CH_2-

$CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, $-(CH_2)_2CH(CH_3)(CH_2)_2-$, $-(CH_2)_3CH(CH_3)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2O(CH_2)_3-$, $-CH_2O(CH_2)_4-$, $-(CH_2)_4CF_2-$, $-(CH_2)_4CH(CF_3)-$, $-CH_2-CH=CH-CH_2CF_2-$, $-CH_2NHCOCF_2CH_2-$, $-CH_2NH(CH_2)_2-$, $-CH_2NH(CH_2)_3-$, $-CH_2NH(CH_2)_4-$, $-(CH_2)_2NHCH_2-$, $-(CH_2)_2N(CH_3)CH_2-$, $-(CH_2)_2N(CH_3)(CH_2)_2-$, $-CH_2-CONH-(CH_2)_2-$, $-CH_2-CONH-(CH_2)_3-$, $-CH_2-CONH-(CH_2)_4-$, $-CH_2-CON(CH_3)-(CH_2)_2-$, $-CH_2-CON(CH_3)-(CH_2)_3-$, $-CH_2CH(OH)(CH_2)_2-$, $-(CH_2)_2CH(OH)CH_2-$ y $-CH_2CH(OH)CH(OH)CH_2-$;

Y se selecciona del grupo constituido por: CH2, O, NH, NMe, -CONH-, -NHCO-, $-CONHCH_2-$, $-CONMeCH_2-$, -OCONH-, -NHCONH- y $-SO_2NH-$;

R^{1b} se selecciona del grupo constituido por: H y F;

R^3 se selecciona del grupo constituido por: H, Me y Cl; y

R^{6a} se selecciona del grupo constituido por: H, F, NH_2 y $NHCO_2Me$.

En otro aspecto, la presente invención incluye compuestos de fórmula (III) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C(CH_3)-(CH_2)_2-$, $-CH_2-CH=CH-CH(CH_3)CH_2-$, $-(CH_2)_3CH(CH_3)CH_2-$, -

$(CH_2)_2CH(CH_3)(CH_2)_2$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$(CH_2)_4CF_2$-, -CH_2-CH=CH-CH_2CF_2-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$(CH_2)_2N(CH_3)CH_2$-, -$(CH_2)_2N(CH_3)(CH_2)_2$-, -CH_2-CONH-$(CH_2)_3$-, -CH_2-CONH-$(CH_2)_4$-, -CH_2-CON(CH_3)-$(CH_2)_2$- y -$CH_2CH(OH)CH(OH)CH_2$-;

Y se selecciona del grupo constituido por: CH_2, O, NH, -CONH-, -NHCO-, -$CONHCH_2$-, -$CONMeCH_2$-, -OCONH-, -NHCONH- y -SO_2NH-;

R^{1b} se elecciona del grupo constituido por: H y F;

R^3 se selecciona del grupo constituido por: H y Cl; y

R^{6a} se selecciona del grupo constituido por: H, F, NH_2 y $NHCO_2Me$.

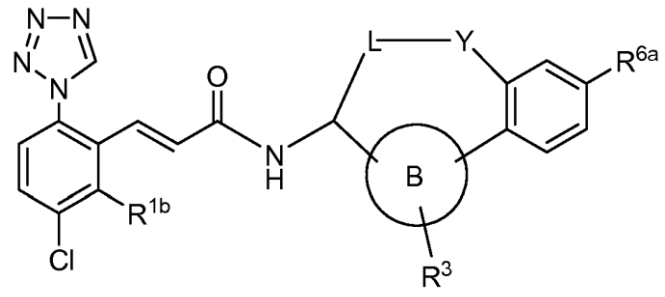
En otro aspecto, la presente invención incluye compuestos de fórmula (III) o un estereosiómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco de los mismos, en donde:

L se selecciona del grupo constituido por: -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C(CH_3)-$(CH_2)_2$-, -CH_2-CH=CH-CH$(CH_3)CH_2$-, -$(CH_2)_3CH(CH_3)$-, -$(CH_2)_3CH(CH_3)CH_2$-, -$(CH_2)_2CH(CH_3)(CH_2)_2$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$(CH_2)_4CF_2$-, -$(CH_2)_4CH(CF_3)$-, -CH_2-CH=CH-CH_2CF_2-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-, -$(CH_2)_2N(CH_3)CH_2$-, -$(CH_2)_2N(CH_3)(CH_2)_2$-, -$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$- y -$CH_2CH(OH)CH(OH)CH_2$-;

Y se selecciona del grupo constituido por: CH_2, O, NH, -CONH-, -NHCO-, -OCONH-, -NHCONH-, $-CONHCH_2-$ y $-SO_2NH-$; y

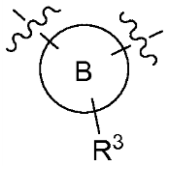
R^3 se selecciona del grupo constituido por: H y Cl.

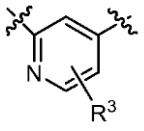
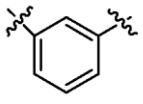
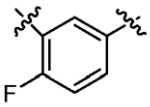
En otro aspecto, la presente invención incluye compuestos de fórmula (IV):



(IV)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco del mismo, dentro del alcance de uno cualquiera de los aspectos anteriores, en donde:



se selecciona del grupo constituido por:  ,  y  ;

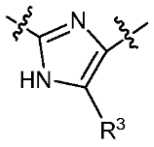
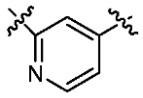
L se selecciona del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-(CH_2)_4-$ y $-(CH_2)_5-$;

Y es -CONH-;

R^3 se selecciona del grupo constituido por: H y Cl; y

R^{6a} se selecciona del grupo constituido por: H, F, -$NHCO_2Me$, y -CH_2NHCO_2Me.

En otro aspecto, la presente invención incluye compuestos de fórmula (V): o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco de los mismos, en donde:

el anillo B se selecciona del grupo constituido por:  y  ;

L se selecciona del grupo constituido por: -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-CH_2CF_2- y -$(CH_2)_4$-;

Y se selecciona del grupo constituido por: CH_2 y -CONH-;

R^3 se selecciona del grupo constituido por: H y Cl; y

R^{6a} se selecciona del grupo constituido por: H y -$NHCO_2Me$.

En otra modalidad, los compuestos de la presente invención tienen valores de Ki del Factor XIa ≤ 10 μM.

En otra modalidad, los compuestos de la presente invención tienen valores de Ki del Factor XIa ≤ 1 μM.

En otra modalidad, los compuestos de la presente invención tienen valores de Ki del Factor XIa ≤ 0.5 μM.

En otra modalidad, los compuestos de la presente

invención tienen valores de Ki del Factor XIa ≤ 0.1 μM.

II. OTRAS MODALIDADES DE LA INVENCIÓN

En otra modalidad, la presente invención proporciona una composición que comprende al menos uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende al menos un vehículo farmacéuticamente aceptable y al menos uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende: un vehículo farmacéuticamente aceptable y una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo.

En otra modalidad, la presente invención proporciona un proceso para fabricar un compuesto de la presente invención.

En otra modalidad, la presente invención proporciona un intermediario para fabricar un compuesto de la presente invención.

En otra modalidad, la presente invención

proporciona una composición farmacéutica que comprende además agente(s) terapéutico(s) adicional(es). En una modalidad preferida, la presente invención proporciona una composición farmacéutica, en donde el/los agente(s) terapéutico(s) adicional(es) es/son un antiagregante plaquetario o una combinación de los mismos. Preferiblemente, el/los antiagregante(s) plaquetario(s) son clopidogrel y/o aspirina, o una combinación de los mismos.

En otra modalidad, la presente invención proporciona un método para el tratamiento o la profilaxis de un trastorno tromboembólico que comprende: administrar a un paciente que necesita tal tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo.

En otra modalidad, la presente invención proporciona un compuesto de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo, para usar en terapia.

En otra modalidad, la presente invención proporciona un compuesto de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo, para su uso en terapia para el tratamiento y/o la profilaxis de un trastorno

tromboembólico.

En otra modalidad, la presente invención también proporciona el uso de un compuesto de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo, para la elaboración de un medicamento para el tratamiento y/o la profilaxis de un trastorno tromboembólico.

En otra modalidad, la presente invención proporciona un método para el tratamiento y/o la profilaxis de un trastorno tromboembólico, que comprende: administrar a un paciente que lo necesita una cantidad terapéuticamente eficaz de un primer y de un segundo agente terapéutico, en donde el primer agente es un compuesto de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo, y el segundo agente terapéutico es al menos un agente seleccionado de entre un segundo inhibidor del Factor Xa, un agente anticoagulante, un antiagregante plaquetario, un agente inhibidor de trombina, un agente trombolítico y un agente fibrinolítico. preferentemente, el segundo agente terapéutico es al menos un agente seleccionado de warfarina, heparina no fraccionada, heparina de bajo peso molecular, pentasacárido sintético, hirudina, argatrobanas, aspirina, ibuprofeno, naproxeno, sulindaco, indometacina, mefenamato, droxicam, diclofenaco, sulfinpirazona, piroxicam,

ticlopidina, clopidogrel, tirofibán, eptifibatida, abciximab, melagatrán, disulfatohirudina, activador de plasminógeno tisular, activador de plasminógeno tisular modificado, anistreplasa, urocinasa y estreptocinasa. Preferentemente, el segundo agente terapéutico es al menos un antiagregante plaquetario. Preferiblemente, el/los antiagregante(s) plaquetario(s) son clopidogrel y/o aspirina, o una combinación de los mismos.

El trastorno tromoembolítico incluye trastornos tromboembolíticos cardiovasculares arteriales, trastornos tromboembólicos cardiovasculares venosos, trastornos tromboembólicos cerebrovasculares arteriales y trastornos tromboembólicos cerebrovasculares venosos. Los ejemplos de trastornos tromboembólicos incluyen, pero no están limitados a, angina inestable, síndrome coronario agudo, fibrilación atrial, primer infarto de miocardio, infarto de miocardio recurrente, muerte súbita isquémica, ataque isquémico transitorio, apoplejía, aterosclerosis, enfermedad arterial oclusiva periférica, trombosis venosa, trombosis venosa profunda, tromboflebitis, embolia arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolia cerebral, embolia renal, embolia pulmonar, y trombosis provocada por implantes, disposivos o procedimientos médicos en donde la sangre se expone a una superficie artificial que promueve la trombosis.

En otra modalidad, la presente invención proporciona un método para el tratamiento y/o la profilaxis de un trastorno inflamatorio que comprende: administrar a un paciente que necesita tal tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo. Los ejemplos de trastornos inflamatorios incluyen, pero no están limitados a, septicemia, síndrome de dificultad respiratoria aguda y síndrome de respuesta inflamatoria sistémica.

En otra modalidad, la presente invención proporciona una preparación combinada de un compuesto de la presente invención y agente(s) terapéutico(s) adicional(es) para uso simultáneo, separado o secuencial en terapia.

En otra modalidad, la presente invención proporciona una preparación combinada de un compuesto de la presente invención y agente(s) terapéutico(s) adicional(es) para uso simultáneo, separado o secuencial en tratamiento y/o profilaxis de un trastorno tromboembólico.

La presente invención puede realizarse en otras formas específicas sin apartarse del espíritu o de los atributos esenciales de la misma. Esta invención comprende todas las combinaciones de aspectos preferidos de la invención indicadas en el presente documento. Se entiende

que cualquiera y todas las modalidades de la presente invención se pueden tomar junto con cualquier otra modalidad o modalidades para describir modalidades adicionales. Se entenderá también que cada elemento individual de las modalidades es su propia modalidad independiente. Además, se pretende que cualquier elemento de una modalidad se combine con cualquiera y con todos los otros elementos de cualquier modalidad para describir una modalidad adicional.

III. QUÍMICA

En toda la descripción y las reivindicaciones adjuntas, una fórmula o una denominación química dada comprende todos los estereoisómeros y todos los isómeros ópticos y racematos de la misma donde existan tales isómeros. A menos que se indique lo contrario, todas las formas quirales (enantiómeras y diastereómeras) y racémicas están dentro del alcance de la invención. Pueden presentarse también en los compuestos muchos isómeros geométricos de los dobles enlaces C=C, dobles enlaces C=N, sistemas de anillos y similares, y están contemplados en la presente invención todos los isómeros estables. Los isómeros geométricos cis y trans (o E y Z) de los compuestos de la presente invención se describen y se pueden aislar como una mezcla de isómeros o como formas isómeras separadas. Los presentes compuestos se pueden aislar en formas ópticamente activas o racémicas. Las formas ópticamente se pueden preparar mediante resolución de

formas racémicas o mediante síntesis de materiales de partida ópticamente activos. Se considera que son parte de la presente invención todos los procesos usados para preparar compuestos de la presente invención y los intermediarios fabricados en la misma. Cuando se preparan productos enantiómeros o diastereómeros, pueden separarse mediante métodos convencionales, por ejemplo, mediante cromatografía o mediante cristalización fraccional. Dependiendo de las condiciones de procesamiento los productos finales de la presente invención se obtienen bien en forma libre (neutra) o bien en forma de sal. Tanto las formas libre como las sales de estos productos finales están dentro del alcance de la invención. Si se desea, una forma de un compuesto se puede convertir en otra forma. Una base o ácido se puede convertir en una sal, una sal se puede convertir en el compuesto libre o en otra sal; una mezcla de compuestos isómeros de la presente invención se puede separar en los isómeros individuales. Los compuestos de la presente invención, forma libre y sales de los mismos, pueden existir en formas tautómeras múltiples, en donde los átomos de hidrógeno se transponen a otras partes de las moléculas y los enlaces de hidrógeno entre los átomos de las moléculas se reordenan consecuentemente. Se entendería que todas las formas tautómeras, en la medida en que ellas puedan existir, se incluyen dentro de la invención.

El término "estereoisómero" se refiere a isómeros de constitución idéntica que difieren en la disposición de sus átomos en el espacio. Ejemplos de estereoisómeros son enantiómeros y diastereómeros. El término "enantiómero" se refiere a uno de un par de especies moleculares que son imágenes especulares entre sí y no son superponibles. El término "diastereómero" se refiere a estereoisómeros que no son imágenes especulares. El término "racemato" o "mezcla racémica" se refiere a una composición compuesta de cantidades equimolares de dos especies enantiómeras, estando la composición desprovista de actividad óptica.

Los símbolos "R" y "S" representan la configuración de sustituyentes alrededor de un(os) átomo(s) de carbono quiral. Los descriptores isómeros "R" y "S" se usan, tal como se describe en el presente documento, para indicar la configuración atómica o las configuraciones atómicas con respecto a una molécula central y se pretende que se usen tal como se define en la bibliografía (*IUPAC Recommendations 1996, Pure and Applied Chemistry*, 68, 2193-2222 (1996)).

El término "quiral" se refiere a la estructura característica de una molécula que imposibilita la superposición a su imagen especular. El término "homoquiral" se refiere a un estado de pureza enantiómera. El término "actividad óptica" se refiere a un grado en donde una molécula homoquiral o mezcla no racémica de moléculas

quirales gira un planto de luz polarizada.

Tal como se usan en el presente documento, se pretende que el término "alquilo" o "alquileno" incluya grupos de hidrocarburos alifáticos saturados tanto ramificados como de cadena lineal que tengan el número especificado de átomos de carbono. Por ejemplo, "alquilo C1 a C_{10}" o "alquilo C_{1-10}" (o alquileno), se pretende que incluya grupos alquilo de C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 y C_{10}. Adicionalmente, por ejemplo, "alquilo C_1 a C_6" o "alquilo C_1-C_6" indica un alquilo que tiene de 1 a 6 átomos de carbono. Los grupos alquilo pueden estar no sustituidos o sustituidos con al menos un hidrógeno que está reemplazado por otro grupo químico. Los ejemplos de grupos alquilo incluyen, pero no se limitan a, metilo (Me), etilo (Et), propilo (por ejemplo, n-propilo e isopropilo), butilo (por ejemplo, n-butilo, isobutilo, t-butilo) y pentilo (por ejemplo, n-pentilo, isopentilo, neopentilo). Cuando se usa "alquilo C_0" o "alquileno C_0" se pretende indicar un enlace directo.

"Alquenilo" o "alquenileno" se pretende que incluyan cadenas de hidrocarburos tanto de configuración lineal como de configuración Ramificada que tengan el número de átomos de carbono especificado y uno o más, preferentemente uno o dos, dobles enlaces carbono-carbono, que pueden estar presentes en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquenilo C_2 a C_6"

"alquenilo C_{2-6}" (o alquenileno), se pretende que incluya grupos alquenilo C_2, C_3, C_4, C_5 y C_6. Los ejemplos de alquenilo incluyen, pero no se limitan a, etenilo, 1-propenilo, 2-propenilo, 2-butenilo, 3-butenilo, 2-pentenilo, 3, pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 2-metil-2-propenilo y 4-metil-3-pentenilo.

"Alquinilo" o "alquinileno" se pretende que incluyan cadenas de hidrocarburos tanto de configuración ramificada como de configuración lineal que tengan uno o más trilples enlaces carbono-carbono, que pueden estar presentes en cualquier punto estable a lo largo de la cadena. Por ejemplo, "alquinilo C_2 a C_6" o "alquinilo C_{2-6}" (o alquinileno), se pretende que incluya grupos alquinilo C_2, C_3, C_4, C_5 y C_6; tales como etinilo, propinilo, butinilo, pentinilo y hexinilo.

El término "alcoxi" o "alquiloxi" se refiere a un grupo –O-alquilo. "alcoxi C_1 a C_6" o "alcoxi C_{1-6}" (o alquiloxi) se pretende que incluya grupos alcoxi C_1, C_2, C_3, C_4, C_5 y C_6. Los ejemplos de grupos alcoxi incluyen, pero no se limitan a, metoxi, etoxi, propoxi (por ejemplo, n-propoxi e isopropoxi) y t-butoxi. De forma similar, "alquiltio" o "tioalcoxi" representan un grupo alquilo tal como se ha definido anteriormente con el número indicado de átomos de carbono unidos a través de un puente de azufre; por ejemplo metil-S- y etil-S-.

"Halo" o "halógeno" incluye fluoro, cloro, bromo y yodo. "Haloalquilo" se pretende que incluya grupos hidrocarburo alifáticos tanto de cadena ramificada como de cadena lineal que tengan el número especificado de átomos de carbono, sustituidos con 1 o más halógenos. Los ejemplos de haloalquilo incluyen, pero no se limitan a, fluorometilo, difluorometilo, trifluorometilo, triclorometilo, pentafluoroetilo, pentacloroetilo, 2,2,2-trifluoroetilo, heptafluoropropilo y heptacloropropilo. Ejemplos de haloalquilo también incluyen "fluoroalquilo" que se pretende qe incluya grupos hidrocarburo alifáticos tanto de cadena Ramificada como de cadena lineal quie tienen el número especificado de átomos de carbono, sustituidos con 1 o más átomos de flúor.

"Haloalcoxi" o "haloalquiloxi" representa un grupo haloalquilo tal como se ha definido anteriormente con el número de átomos de carbono indicados unidos a través de un puente de oxígeno. Por ejemplo, "haloalcoxi C_1 a C_6" o "haloalcoxi C_{1-6}" se pretende que incluya grupos haloalcoxi C_1, C_2, C_3, C_4, C_5 y C_6. Los ejemplos de haloalcoxi incluyen, pero no se limitan a, trifluorometoxi, 2,2,2-trifluoroetoxi y pentafluoroetoxi. De forma similar, "haloalquiltio" o "tiohaloalcoxi" representan un grupo haloalquilo tal como se ha definido anteriormente con el número indicado de átomos de carbono unidos a través de un puente de azufre; por ejemplo

trifluorometil-S- y pentafluoroetil-S-.

El término "cicloalquilo" se refiere a grupos alquilo ciclados, incluyendo sistemas de anillos mono, bi o policíclicos. "Cicloalquilo C_3 a C_7" o "cicloalquilo C_{3-7}" se pretende que incluyan grupos cicloalquilo C_3, C_4, C_5, C_6 y C_7. Los ejemplos de grupos cicloalquilo incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y norbornilo. Los grupos cicloalquilo Ramificados tales como 1-metilciclopropilo y 2-metilciclopropilo están incluidos en la definición de "cicloalquilo".

Tal como se usa en el presente documento, "carbociclo" o "resto carbocíclico" se pretende que signifique cualquier anillo monocíclico o bicíclico de 3, 4, 5, 6, 7 u 8 miembros estable o cualquier anillo bicíclico o tricíclico de 7, 8, 9, 10, 11, 12 ó 13 miembros estable, cualquiera de los cuales puede estar saturado, parcialmente insaturado, insaturado o ser aromático. Ejemplos de tales carbociclos incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclobutenilo, ciclopentilo, ciclopentenilo, ciclohexilo, cicloheptenilo, cicloheptilo, cicloheptenilo, adamantilo, ciclooctilo, ciclooctenilo, ciclooctadienilo, [3.3.0]biciclooctano, [4.3.0]biciclononano, [4.4.0]biciclodecano (decalina), [2.2.2]biciclooctano, fluorenilo, fenilo, naftilo, indanilo, adamantilo,

antracenilo y tetrahidronaftilo (tetralina). Tal como se ha mostrado anteriormente, los anillos dotados de puentes están incluidos en la definición de carbociclo (por ejemplo [2.2.2]biciclooctano). Los carbociclos preferidos, a menos que se especifique otra cosa, son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo e indanilo. Cuando se usa el término "carbociclo", se pretende que incluya"arilo". Un anillo dotado de puentes se da cuando uno o más átomos de carbono enlazan dos átomos no adyacentes. Los puentes preferidos son uno o dos átomos de carbono. Nótese que un puente siempre convierte un anillo monocíclico en un anillo tricíclico. Cuando un anillo está dotado de puentes, los sustituyentes enumerados para el anillo pueden estar también presentes en el enlace.

Tal como se usa en el presente documento, el término "carbociclo bicíclico" o "grupo carbociclo bicíclico" se pretende que signifique un sistema anular carbocíclico estable de 9 ó 10 miembros que contiene dos anillos condensados y está constituido por átomos de carbono. De los dos anillos condensados, un anillo es un anillo benzo condensado a un segundo anillo; y el segundo anillo es un anillo de carbono de 5 ó 6 miembros que está saturado, parcialmente insaturado o insaturado. El grupo carbocílico bicíclico puede estar unido a su grupo lateral en cualquier átomo de carbono que dé como resultado una estructura

estable. El grupo carbocíclico bicíclico descrito en el presente documento puede estar sustituido en cualquier carbono si el compuesto resultante es estable. Ejemplos de un grupo carbocíclico bicíclico son, pero no se limitan a, naftilo, 1,2-dihidronaftilo, 1,2,3,4-tetrahidronaftilo e indanilo.

Grupos "arilo" se refiere a hidrocarburos aromáticos monocíclicos o policíclicos, incluidos, por ejemplo, fenilo, naftilo y fenantranilo. Los restos arilo son bien conocidos y se describen, por ejemplo, en *Hawley's Condensed Chemical Dictionary* (13ª edición), Lewis, R.J., ed., J. Wiley & Sons, Inc., Nueva York (1997). "Arilo C_6 o C_{10}" o "arilo C_{6-10}" se refiere a fenilo y naftilo. A menos de que se especifique lo contrario, el "arilo", "arilo C_6 o C_{10}" o "arilo C_{6-10}" o "resto aromático" puede estar no sustituido o sustituido con 1 a 5 grupos, preferentemente con 1 a 3 grupos, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H y CO_2CH_3.

El término "bencilo", tal como se usa en el presente documento, se refiere a un grupo metilo en donde uno de los átomos de hidrógeno está reemplazado por un grupo fenilo, en el grupo fenilo puede estar opcionalmente sustituido con 1 a 5 grupos, preferentemente con 1 a 3 grupos, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$,

CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H y CO_2CH_3.

Tal como se usa en el presente documento, el término “heterociclo” o “grupo heterociclíco” se pretende que signifique un anillo estable monocíclico o bicíclico de 3, 4, 5, 6 ó 7 miembros o un anillo estable heterocíclico policíclico de 7, 8, 9, 10, 11, 12, 13 ó 14 miembros que está saturado, parcialmente insaturados o totalmente insaturado, y que contiene átomos de carbono y 1, 2, 3 ó 4 heteroátomos seleccionados independientemente del grupo constituido por N, O y S; y que incluye cualquier grupo policíclico en donde cualquiera de los anillos definidos anteriormen te está fusionado a un anillo de benceno. Los heteroátomos nitrógeno y azufre pueden estar opcionalmente oxidados (es decir, N→O y S(O)p, en donde p es 0, 1 ó 2). El átomo de nitrógeno puede estar sustituido o no sustituido (es decir, N o NR, en donde R es H o cualquier sustituyente, si está definido). El anillo heterocíclico puede estar unido a su grupo lateral a traves de cualquier heteroátomo o átomo de carbono que dé como resultado una estructura estable. Los anillos heterocíclicos descritos en el presente documento pueden estar sustituidos en un átomo de carbono o de nitrógeno si el compuesto resultante es estable. Un nitrógeno en el heterociclo puede estar opcionalmente cuaternizado. Es preferente que cuando el número total de átomos de S y de O

en el heterociclo exceda de 1, estos heteroátomos no sean entonces adyacentes uno a otro. Es preferente que el número total de átomos S y O en el heterociclo no sea superior a 1. Si se usa el término "heterociclo", se pretende que incluya heteroarilo.

Ejemplos de heterociclos incluyen, pero no se limitan a, acridinilo, azetidinilo, azocinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzoxazolinilo, benztiazolilo, benztriazolilo, benztetrazolilo, bencisoxazolilo, bencisotiazolilo, bencimidazolinilo, carbazolilo, 4aH-carbazolilo, carbolinilo, cromanilo, cromenilo, cinnolinilo, decahidroquinolinilo, 2H,6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]tetrahidrofurano, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, imidazolopiridinilo, indolenilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isatinoílo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolopiridinilo, isoxazolilo, isoxazolopiridinilo, metilenodioxifenilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxazolopiridinilo, oxazolidinilpirimidinilo, oxindolilo, pirimidinilo,

fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, piperidonilo, 4-piperidonilo, piperonilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolopiridinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2-pirrolidonilo, 2H-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrazolilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolilo, tienilo, tiazolopiridinilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo. También están incluidos compuestos de anillos condensados y compuestos espiro que contienen, por ejemplo, los heterociclos anteriores.

Los ejemplos de los heterociclos de 5 a 10 miembros incluyen, pero no se limitan a, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxadiazolilo, oxazolidinilo, tetrahidrofuranilo,

tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo, triazolilo, bencimidazolilo, 1H-indazolilo, benzofuranilo, benzotiofuranilo, benztetrazolilo, benzotriazolilo, bencisoxazolilo, benzoxazolilo, oxindolilo, benzoxazolinilo, benztiazolilo, bencisotiazolilo, isatinoílo, isoquinolinilo, octahidroisoquinolinilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, isoxazolopiridinilo, quinazolinilo, quinolinilo, isotiazolopiridinilo, tiazolopiridinilo, oxazolopiridinilo, imidazolopiridinilo y pirazolopiridinilo.

Los ejemplos de heterociclos de 5 a 6 miembros incluyen, pero no se limitan a, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxadiazolilo, oxazolidinilo, tetrahidrofuranilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo y triazolilo. También están incluidos compuestos de anillos condensados y compuestos espiro que contienen, por ejemplo, los heterociclos anteriores.

Tal como se usa en el presente documento, el término “heterociclo bicíclico” o “grupo heterocíclico bicíclico” se pretende que signifique un sistema anular heterocíclico estable de 9 ó 10 miembros que contiene dos anillos condensados y está constituido por átomos de carbono y 1, 2, 3 ó 4 heteroátomos seleccionados independientemente

del grupo constituido por N, O y S. De los dos anillos condensados, un anillo es un anillo aromáticos monocíclico de 5 ó 6 miembros que comprende un anillo de heteroarilo de 5 miembros, un anillo de heteroarilo de 6 miembros o un anillo benzo, cada uno condensado con un segundo anillo. El segundo anillo es un anillo monocíclico de 5 ó 6 miembros que está saturado, parcialmente insaturado o insaturado y comprende un heterociclo de 5 miembros, un heterociclo de 6 miembros o un carbociclo (dado que el primer anillo no es benzo si el segundo anillo es un carbociclo).

El grupo heterocíclico bicíclico puede estar unido a su grupo lateral en cualquier heteroátomo o átomo de carbono que dé como resultado una estructura estable. El grupo bicíclico heterocíclico descrito en el presente documento puede estar sustituido en un carbono o en un átomo de nitrógeno si el compuesto resultante es estable. Es preferente que cuando el número total de átomos de S y de O en el heterociclo exceda de 1, estos heteroátomos no sean entonces adyacentes uno a otro. Es preferente que el número total de átomos de S y O en el heterociclo no sea superior a 1.

Ejemplos de un grupo heterociclo bicíclico son, pero no se limitan a, quinolinilo, isoquinolinilo, ftalazinilo, quinazolinilo, indolilo, isoindolilo, indolinilo, 1H-indazolilo, bencimidazolilo, 1,2,3,4-

tetrahidroquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, 5,6,7,8-tetrahidro-quinolinilo, 2,3-dihidro-benzofuranilo, cromanilo, 1,2,3,4-tetrahidro-quinoxalinilo y 1,2,3,4-tetrahidro-quinazolinilo.

Tal como se usa en el presente documento, el término "grupo heterocíclico aromático" o "heteroarilo" se pretende que signifique hidrocarburos aromáticos monocíclicos y policíclicos estables que incluyen al menos un heteroátomo miembro de anillo tal como azufre, oxígeno o nitrógeno. Los grupos heteroarilo incluyen, sin limitación, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, furilo, quinolilo, isoquinilo, tienilo, imidazolilo, tiazolilo, indolilo, pirrolilo, oxazolilo, benzofurilo, benzotienilo, benztiazolilo, isoxazolilo, pirazolilo, triazolilo, tetrazolilo, indazolilo, 1,2,4-tiadiazolilo, isotiazolilo, purinilo, carbazolilo, benzimidazolilo, indolinilo, benzodioxolanilo y benzodioxano. Los grupos heteroarilo están sustituidos o no sustituidos. El átomo de nitrógeno está sustituido o no sustituido (es decir, N o NR, en donde R es H o cualquier sustituyente, si está definido). Los heteroátomos nitrógeno y azufre pueden estar opcionalmente oxidados (es decir, N→O y $S(O)_p$, en donde p es 0, 1 ó 2).

Los anillos dotados de puentes también están incluidos en la definición de heterociclo. Un anillo puenteado se presenta cuando uno o más átomos (es decir, C,

O, N o S) enlazan dos átomos de carbono o de nitrógeno no adyacentes. Ejemplos de anillos puenteados incluyen, pero no se limitan a, un átomo de carbono, dos átomos de carbono, un átomo de nitrógeno, dos átomos de nitrógeno y un grupo carbono-nitrógeno. Debe indicarse que un puente siempre convierte un anillo monocíclico en un anillo tricíclico. Cuando un anillo está puenteado, los sustituyentes enumerados para el anillo pueden estar también presentes en el puente.

El término "contraión" se usa para representar una especie cargada negativamente tal como cloruro, bromuro, hidróxido, acetato y sulfato.

Cuando se usa un anillo de puntos dentro de una estructura de anillo, se indica que la estructura de anillo puede estar saturada, parcialmente saturada o insaturada.

Tal como se refiere en el presente documento, el término "sustituido" significa que al menos un átomo de hidrógeno está reemplazado por un grupo que no es hidrógeno, siempre que las valencias normales se mantengan y la sustitución dé como resultado un compuesto estable. Cuando un sustituyente es ceto (es decir, =O), entonces están reemplazados 2 hidrógenos en el átomo. Los sustituyentes ceto no están presentes en restos aromáticos. Si se dice que un sistema anular (por ejemplo, carbocíclico o heterocíclico) está sustituido con un grupo carbonilo o un doble enlace, se pretende que el grupo carbonilo o el doble enlace sea parte

(es decir, esté dentro) del anillo. Los enlaces anulares dobles, tal como se usan en el presente documento, son dobles enlaces que se forman entre dos átomos de anillo adyacentes (por ejemplo, C=C, C=N o N=N).

En casos en donde hay átomos de nitrógeno (por ejemplo, aminas) en compuestos de la presente invención, éstos se pueden convertir a N-óxidos mediante tratamiento con un agente oxidante (por ejemplo, mCPBA y/o peróxidos de hidrógeno) para proporcionar otros compuestos de la presente invención. Así, los átomos de nitrógeno mostrados y reivindicados se considera que cubren tanto el nitrógeno mostrado como su derivado N-óxido (N→O).

Cuando una variable aparece más de una vez en cualquier constituyente o fórmula para un compuesto, su definición en cada aparición es independiente de su definición en cualquier otra aparición. Así, por ejemplo, si un grupo se muestra que está sustituido con 0-3 grupos R, el grupo puede estar opcionalmente sustituido con hasta tres grupos R y en cada aparición R se selecciona independientemente de la definición de R. También, están permitidas las combinaciones de sustituyentes y/o variables sólo si las combinaciones dan como resultado compuestos estables.

Cuando se muestra que un enlace a un sustituyente cruza un enlace que conecta dos átomos de un anillo, entonces

el sustituyente puede estar unido a cualquier átomo en el anillo. Cuando un sustituyente se enumera sin indicar el átomo en donde tal sustituyente está unido al resto del compuesto de una fórmula dada, entonces el sustituyente puede estar unido por medio de cualquier átomo del sustituyente. Sólo están permitidas las combinaciones de sustituyentes y/o variables si tales combinaciones dan como resultado compuestos estables.

La frase "farmacéuticamente aceptable" se usa en el presente documento para hacer referencia a los compuestos, materiales, composiciones y/o formas de dosificación que son, dentro del alcance del juicio médico razonable, adecuados para usar en contacto con los tejidos de seres humanos y animales sin toxicidad, irritación, respuesta alérgica, y/u otro problema o complicación excesivos, proporcionalmente a una relación beneficio/riesgo Razonable.

Tal como se usa en el presente documento, "sales farmacéuticamente aceptables" se refiere a derivados de los compuestos descritos en donde el compuesto progenitor se modifica fabricando sales de ácidos o de bases del mismo. Los ejemplos de sales farmacéuticamente aceptables incluyen, pero no se limitan a, sales de ácidos minerales u orgánicos de grupos básicos tales como aminas; y sales alcalinas u orgánicas de grupos ácidos tales como ácidos carboxílicos. Las sales farmacéuticamente aceptables incluyen las sales no

tóxicas convencionales o las sales de amonio cuaternario del compuesto progenitor que se forman, por ejemplo, a partir de ácidos inorgánicos u orgánicos no tóxicos. Por ejemplo, tales sales no tóxicas convencionales incluyen donde se derivan de ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico y nítrico; y las sales que se preparan a partir de ácidos orgánicos tales como acético, propiónico, succínico, glicólico, esteárico, láctico, málico, tartárico, cítrico, ascórbico, pamoico, maleico, hidroximaleico, fenilacético, glutámico, benzoico, salicílico, sulfanílico, 2-acetoxibenzoico, fumárico, toluenosulfónico, metanosulfónico, etanodisulfónico, oxálico e isetiónico.

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto parental que contiene un resto ácido o básico mediante métodos químicos convencionales. Generalmente, tales sales se pueden preparar haciendo reaccionar las formas de base o ácido libre de estos compuestos con una cantidad estequiométrica de la base o del ácido apropiado en agua o en un solvente orgánico, o en una mezcla de los dos; generalmente son preferentes medios no acuosos como éter, acetato de etilo, etanol, isopropanol o acetonitrilo. La lista de las sales adecuadas se encuentra en Remington’s Pharmaceutical Sciences, 18ª edición, Mack

Publishing Company, Easton, PA, 1990, cuya descripción se incorpora en el presente documento mediante referencia.

Además, los compuestos de fórmula I puede tener formas de profármaco. Cualquier compuesto que se convierta *in vivo* proporcionando el agente bioactivo (es decir, un compuesto de fórmula I) es un profármaco dentro del alcance y del espíritu de la invención. En la técnica son conocidas varias formas de profármaco. Para ejemplos de los derivados profármacos, véase:

a) *Design of Prodrugs*, Bundgaard, H., ed., Elsevier (1985) y *Methods in Enzymology*, 112:309-396, Widder, K. y col., eds., Academic Press (1985);

b) Bundgaard, H., Capítulo 5, "Design and Application of Prodrugs," *A Textbook of Drug Design and Development*, páginas 113-191, P. Krosgaard-Larsen y col., Ed. Harwood Academic Publishers (1991); y

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. y col., *J. Pharm. Sci.*, 77:285 (1988); y

e) Kakeya, N. y col., *Chem. Pharm. Bull.*, 32:692 (1984).

Los compuestos que contienen un grupo carboxi pueden formar ésteres fisiológicamente hidrolizables que sirven como profármacos estando hidrolizados en el cuerpo

para producir compuestos de fórmula I per se. Tales profármacos se administran preferentemente por vía oral, ya que la hidrólisis, en muchos casos, tiene lugar principalmente bajo la influencia de las enzimas digestivas. La administración parenteral se puede usar donde el éster está activo *per se*, o en los casos en donde la hidrólisis tiene lugar en la sangre. Los ejemplos de ésteres fisiológicamente hidrolizables de compuestos de fórmaula I incluyen alquilo C_{1-6}, alquilo C_{1-6}-bencilo, 4-metoxibencilo, indanilo, ftalilo, metoximetilo, alcaniloxi C_{1-6}-alquilo C_{1-6} (*e.g.*, acetoximetilo, pivaloiloximetilo o propioniloximetilo), alcoxi C_{1-6}-carboniloxi-alquilo C_{1-6} (por ejemplo, metoxicarbonil-oximetilo o etoxicarboniloximetilo, gliciloximetilo, fenilgliciloximetilo, (5-metil-2-oxo-1,3-dioxolen-4-il)-metilo) y otros ésteres fisiológicamente hidrolizables bien conocidos que se usan, por ejemplo, en las técnicas de la penicilina y la cefalosporina. Los ésteres se pueden preparar usando técnicas convencionales conocidas en la técnica.

La preparación de profármacos es bien conocida en la técnica y se describe en, por ejemplo, *Medicinal Chemistry: Principles and Practice*, King, F.D., ed. The Royal Society of Chemistry, Cambridge, Reino Unido (1994); Testa, B. y col., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA y Wiley-VCH, Zurich, Suiza (2003); *The Practice of Medicinal*

Chemistry, Wermuth, C.G., ed., Academic Press, San Diego, CA, Estados Unidos (1999).

La presente invención se pretende que incluya todos los isótopos de 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 13C y 14C. Los compuestos de la invención marcados con isótopos se pueden preparar generalmente usando técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en el presente documento, usando un reactivo apropiado marcado isotópicamente en lugar del reactivo no marcado que se usa en otros casos. Los compuestos tienen una diversidad de usos potenciales, por ejemplo, como patrones y reactivos en determinar la capacidad de un compuesto farmacéutico potencial para unirse a proteínas o receptores objetivo, o para obtener imágenes de compuestos de esta invención unidos a receptores biológicos *in vivo* o *in vitro*.

"Compuesto estable" y "estructura estable" se pretende que indiquen un compuesto que es suficientemente resistente para sobrevivir al aislamiento en un grado de

pureza útil a partir de una mezcla de reacción y a la formulación en un agente terapéutico eficaz. Es preferente que los compuestos de la presente invención no contengan un grupo N-halo, S(O)2H o S(O)H.

El término "solvato" quiere decir una asociación física de un compuesto de esta invención con una o más moléculas de solvente, sean orgánico o inorgánico. Esta asociación física incluye la formación de enlaces de hidrógeno. En determinados casos será posible aislar el solvato, por ejemplo cuando una o más moléculas de solvente están incorporadas en la red cristalina del sólido cristalino. Las moléculas de solvente en el solvato pueden estar presentes en una disposición regular y/o en una disposición no ordenada. El solvato puede comprender bien una cantidad estequiométrica o bien una cantidad no estequiométrica de las moléculas de solvente. "Solvato" comprende tanto solvatos en fase de solución como solvatos aislables. Los ejemplos de solvatos incluyen, pero no se limitan a, hidratos, etanolatos, metanolatos e isopropanolatos. Los métodos de solvatación se conocen generalmente en la técnica.

Las abreviaturas, tal como se usan en el presente documento, se definen como sigue: "1 x" para una vez, "2 x" para dos veces, "3 x" para tres veces, " °C" para grados Celsius, "eq" para equivalente o

equivalentes, “g” para gramo o gramos, “mg” para miligramo o miligramos, “l” para litro o litros, “ml” para mililitro o mililitros, “µl” para microlitro o microlitros, “N” para normal, “M” para molar, “mmol” para milimol o milimoles, “min” para minuto o minutos, “h” para hora o horas, “ta” para temperatura ambiente, “TR” para tiempo de retención, “atm” para atmósfera, “psi” para libra por pulgada cuadrada, “conc.” para concentrado, “sat” o “sat’d” para saturado, “PM” para peso molecular, “pf” para punto de fusión, “ee” para exceso enantiomérico, “EM” o “espec. de masas” para espectroscopía de masas, “ESI” espectroscopia de masas por electropulverización, “AR” para alta resolución, “EMAR” para espectroscopía de masas de alta resolución, “CL-EM” para cromatografía líquida-espectroscopía de masas, “HPLC” para cromatografía líquida de alta presión, “RP-HPLC” para HPLC de fase inversa, “TLC” o “tlc” para cromatrografía de capa fina, “RMN” para espectroscopía de resonancia magnética nuclear, “nOe” para espectroscopía de efecto Overhauser nuclear, “1H” para protón, “δ” para delta, “s” para singulete, “d” para doblete, “t” para triplete, “c” para cuartete, “m” para multiplete, “ancho” para ancho, “Hz” para hercio y “α”, “β”, “R”, “S”, “E” y “Z” son denominaciones estereoquímicas familiares para un experto en la técnica.

Me	metilo
Et	etilo
Pr:	propilo
i-Pr:	isopropilo
Bu	butilo
i-Bu:	isobutilo
t-Bu:	*terc*-butilo
Ph	fenilo
Bn	bencilo
Boc	terc-butiloxicarbonilo
AcOH o HOAc	ácido acético
$AlCl_3$	cloruro de aluminio
AIBN	azobisisobutironitrilo
BBR_3	tribromuro de boro
BCl_3	tricloruro de boro
BEMP	2-terc-butilimino-2-dietilamino-1,3-dimetilperhidro-1,3,2-diazafosforina
reactivo BOP	hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio
reactivo de Burgess	metanimidato de 1-metoxi-N-trietilamoniosulfonilo
CBz	carbobenciloxi
CH_2Cl_2	diclorometano
CH_3CN o ACN	Acetonitrilo
$CDCl_3$	Deuterocloroformo

$CDCl_3$	cloroformo
mCPBA o m-CPBA	ácido metacloroperbenzoico
Cs_2CO_3	carbonato de cesio
$Cu(OAc)_2$	acetato de cobre (II)
Cy_2NMe	N-ciclohexil-N-metilciclohexanamina
DBU	1,8-diazabiciclo[5.4.0]undec-7-eno
DCE	1,2 dicloroetano
DCM	diclorometano
DEA	dietilamina
reactivo de Dess-Martin	1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benciodoxol-3-(1H)-ona
DIC o DIPCDI	diisopropilcarbodiimida
DIEA, DIPEA o base de Hunig	diisopropiletilamina
DMAP	4-dimetilaminopiridina
DME	1,2-dimetoxietano
DMF	dimetil formamida
DMSO	dimetilsulfóxido
ADNc	ADN complementario
Dppp	(R)-(+)-1,2-bis(difenilfosfino)propano
DuPhos	(+)-1,2-bis((2S,5S)-2,5-dietilfosfolano)benceno
EDC	N-(3-dimetilaminopropil)-N'-etilcarbodiimida

EDCI	clorhidrato de *N*-(3-dimetilaminopropil)-*N*´-etilcarbodiimida
EDTA	ácido etilenodiaminotetraacético
(*S*,*S*)-EtDuPhosRh(I)	trifluorometanosulfonato de (+)-1,2-bis((2S,5S)-2,5-dietilfosfolano)benceno(1,5-ciclooctadieno)rodio(I)
Et_3N o TEA	trietilamina
EtOAc	acetato de etilo
Et_2O	dietil éter
EtOH	etanol
GMF	filtro de microfibras de vidrio
Grubbs (II)	(1,3-bis(2,4,6-trimetilfenil)-2-imidazolidinilideno)dicloro(fenilmetileno)(triciclohexilfosfina)rutenio
HCl	ácido clorhídrico
HATU	hexafluorfosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio
HEPES	ácido 4-(2-hidroxietil)piperaxina-1-etanosulfónico
Hex	hexano
HOBt o HOBT	1-hidroxibenzotriazol
H_2SO_4	ácido sulfúrico
K_2CO_3	carbonato de potasio
KOAc	acetato de potasio
K_3PO_4	fosfato de potasio

LAH	hidruro de litio y aluminio
LG	grupo saliente:
LiOH	hidróxido de litio
MeOH	metanol
$MgSO_4$	sulfato de magnesio
MsOH o MSA	ácido metilsulfónico
NaCl	cloruro de sodio
NaH	hidruro de sodio
$NaHCO_3$	bicarbonato de sodio
Na_2CO_3	carbonato de sodio
NaOH	hidróxido de sodio
Na_2SO_3	sulfito de sodio
Na_2SO_4	sulfato de sodio
NBS	N-bromosuccinimida
NCS	N-clorosuccinimida
NH_3	amoniaco
NH_4Cl	cloruro de amonio
NH_4OH	hidróxido de amonio
OTf	triflato o trifluorometanosulfonato
$Pd_2(dba)_3$	tris(dibencilidenoacetona)dipaladio(0)
$Pd(OAc)_2$	acetato de paladio (II)
Pd/C	paladio en carbono
$Pd(dppf)Cl_2$	[1,1´-bis(difenilfosfino)-ferroceno]dicloropaladio(II)
Ph_3PCl_2	dicloruro de trifenilfosfina

PG	grupo protector
PL-HCO_3 MP SPE	Intercambio aniónico en fase sólida
$POCl_3$	oxicloruro de fósforo
i-PrOH o IPA	isopropanol
PS	poliestireno
SEM-Cl	cloruro de 2-(trimetilsilil)etoximetilo
SiO_2	óxido de silicio
$SnCl_2$	cloruro de estaño (II)
TBAI	yoduro de tetra-*n*-butilamonio
TEA	trietilamina
TFA	ácido trifluoroacético
THF	tetrahidrofurano
$TMSCHN_2$	trimetilsilildiazometano
T_3P	anhídrido del ácido propanofosfónico
TRIS	tris(hdroximetil) aminometano

Los compuestos de la presente invención se pueden preparar mediante varias rutas conocidas por un experto en la técnica de la síntesis orgánica. Los compuestos de la presente invención pueden sintetizarse usando los métodos descritos a continuación, conjuntamente con métodos de síntesis conocidos en la técnica de la química orgánica sintética o mediante variaciones de los mismos, como apreciarán los expertos en la técnica. Los métodos preferentes incluyen, pero no están limitados

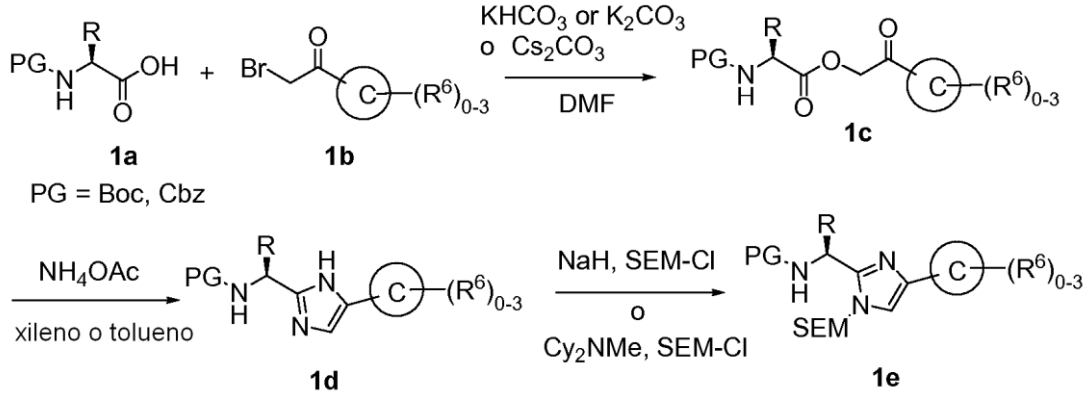
a, los descritos a continuación. Las reacciones se llevan a cabo en un solvente adecuado o en una mezcla de solventes adecuada para los reactivos y materiales usados y para las transformaciones que se efectúan. Los expertos en la técnica de síntesis orgánica entenderán que la funcionalidad presente en la molécula deberá ser consecuente con las transformaciones propuestas. Esto requerirá algunas veces sentido común para modificar el orden de las etapas de síntesis o para seleccionar un Esquema de reacción de proceso en particular en vez de otro con el fin de obtener un compuesto deseado de la invención.

Se reconocerá que otra consideración principal reconocida en la planificación de cualquier ruta de síntesis en este campo es la elección acertada del grupo protector usado para proteger los grupos funcionales reactivos presentes en los compuestos descritos en esta invención. Un informe magistral que describe las muchas alternativas para el experto es Greene y col. (*Protective Groups in Organic Synthesis*, 4ª edición., Wiley-Interscience (2006)).

Pueden sintetizarse derivados de imidazol útiles para la síntesis de los compuestos de la presente invención de acuerdo con el método general esbozado en el Esquema de reacción 1 (Contour-Galcera y col., *Bioorg. Med. Chem. Lett.*, 11(5), 741-745 (2001)). La alquilación del carboxilato de potasio o cesio de un alfa-aminoácido 1A

apropiadamente protegido o derivatizado con una alfa-bromocetona 1b adecuadamente sustituida (el anillo C es arilo o heteroarilo) proporciona el cetoéster 1c. El imidazol 1d se forma calentando el cetoéster 1c a reflujo en un solvente adecuado, tal como tolueno o xileno, en presencia de acetato de amonio en exceso usando una trampa de Dean-Stark para eliminar agua. La formación del imidazol también puede llevarse a cabo combinando el cetoéster 1c y acetato de amonio en un solvente adecuado, tal como xileno o etanol o en una combinación de solventes tal como dimetilformamida y etanol (1:1) y aplicando un calentamiento por microondas. A continuación, el imidazol 1d puede protegerse con un grupo protector adecuado. Por ejemplo, el imidazol 1d puede hacerse reaccionar con SEM-Cl, en presencia de una base, tal como hidruro de sodio o diciclohexilmetil amina, y en un solvente tal como dimetilformamida o tetrahidrofurano, dando 1e.

Esquema de reacción 1



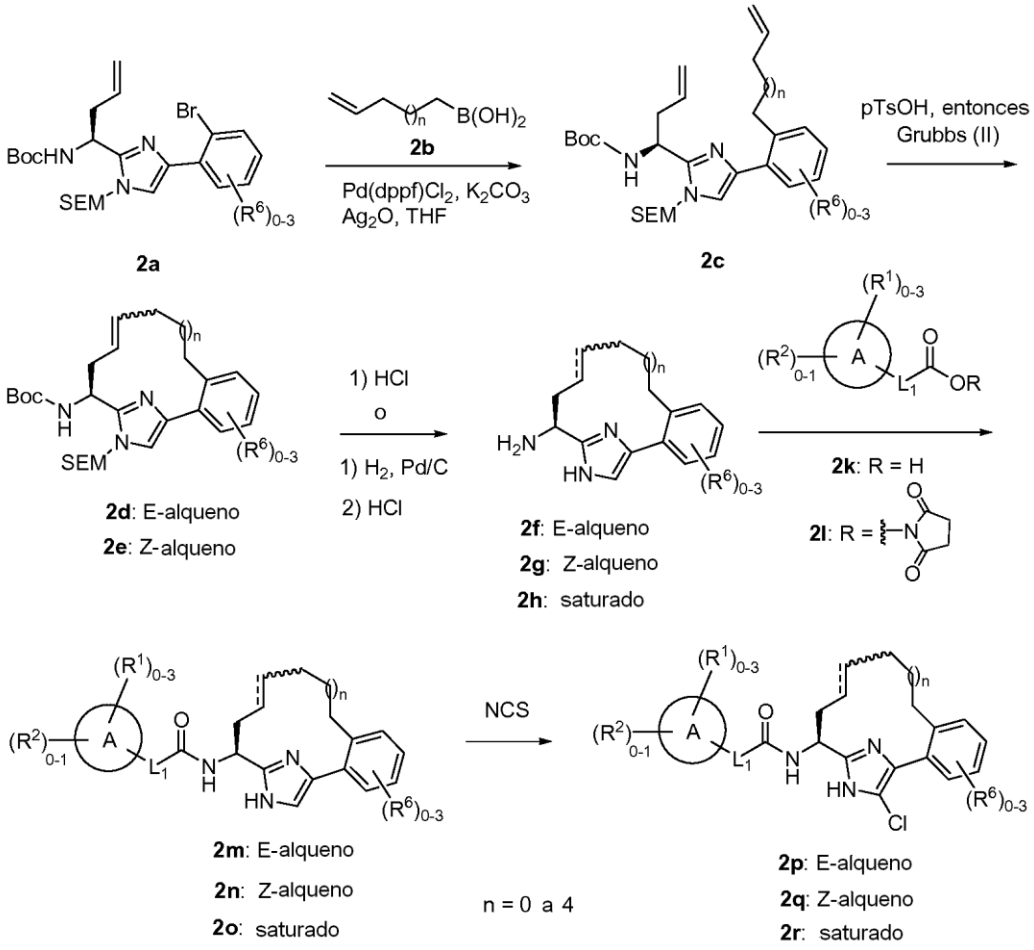
Pueden prepararse macrociclos de la presente

invención que contienen imidazol en donde Y es $-CH_2-$ de acuerdo con el Esquema de reacción 2. El acoplamiento de Suzuki-Miyaura entre 2a, preparado tal como se describe en el Esquema de reacción 1, y un ácido alquilborónico 2b sustituido adecuadamente en presencia de óxido de plata (I) y una base, tal como carbonato de potasio, usando un precatalizador tal como un complejo $Pd(dppf)Cl_2 \bullet CH_2Cl_2$, en un solvente tal como tetrahidrofurano a temperatura elevada proporciona 2c (Falck, J.R., *Tetrahedron Letters*, 42:7213 (2001)). Usando un procedimiento modificado descrito por Lovely (*Tetrahedron Letters*, 44:1379 (2003)), 2c, siguiendo un pretratamiento con ácido p-toluenosulfónico para formar el ion imidazolio, puede ciclarse mediante metátesis de cierre de anillo usando un catalizador, tal como catalizador de Grubbs (II), en un solvente adecuado, tal como diclorometano, dicloroetano o tolueno a temperatura elevado, dando el macrociclo que contiene imidazol como una mezcla de isómeros olefínicos (E-alqueno 2d y Z-alqueno 2e). Las olefinas pueden separarse y después de la desprotección de los grupos Boc y SEM con ácido clorhídrico acuoso 5 M en metanol o etanol a temperatura elevada proporciona aminas 2f y 2g. Alternativamante, la desprotección puede realizarse en

condiciones anhidras con ácido clorhídrico 4 M en dioxano a temperatura elevada. La mezcla de isómeros olefínicos (E-alqueno 2d y Z-alqueno 2e) puede reducirse con hidrógeno sobre paladio en carbono u óxido de platino y la desprotección subsiguiente tal como se ha descrito anteriormente da la amina saturada 2h. El acoplamiento amídico entre aminas 2f-h, con un ácido carboxílico sustituido apropiadamente 2k, usando reactivos de acoplamiento adecuados, tales como EDCI, HOBt, y base genera 2m-o (para reactivos de acoplamiento alternativos véase: Han, S.-Y. y col., *Tetrahedron*, 60:2447 (2004)). Alternativamente, las aminas 2f-h pueden acoplarse con un éster carboxílico activado 2l en presencia de una base tal como base de Hunig y en un solvente tal como dimetilformamida para dar 2m-o. La incorporación posterior de un grupo funcional en el anillo de imidazol puede lograrse mediante cloración del C-5 del anillo de imidazol con N-clorosuccinimida, usando un solvente adecuado tal como cloruro de metileno, acetonitrilo o cloroformo, dando compuestos 2p-r. La incorporación adicional de grupos funcionales al anillo de imidazol puede lograrse también mediante fluoración del anillo de imidazol C-5 con Accufluor, usando un solvente adecuado, tal como dimetilformamida, en presencia de

una base, tal como carbonato de sodio.

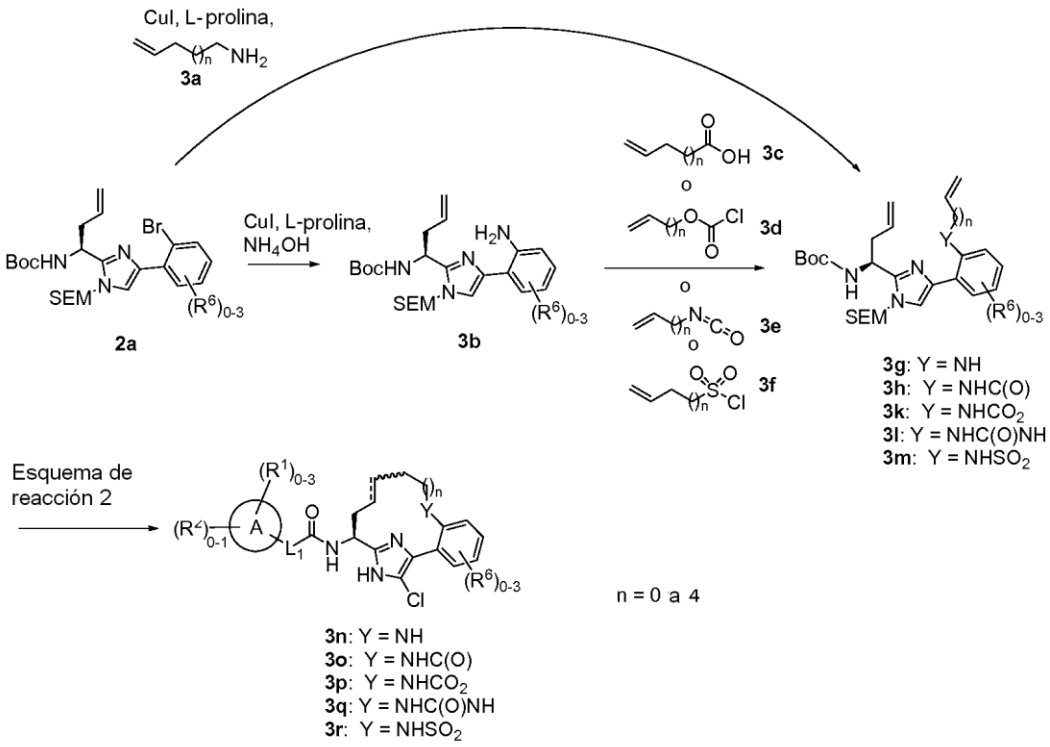
Esquema de reacción 2



Los macrociclos de la presente invención que contienen imidazol en donde Y es NH, NHC(O), $NHCO_2$, NHC(O)NH y $NHSO_2$ pueden prepararse de acuerdo con el Esquema de reacción 3. Usando un procedimiento modificado descrito por Ma (*Synthesis*, 3:496 (2005)), el bromuro 2a puede acoplarse con una amina 3A sustituida apropiadamente usando yoduro de cobre (I) y L-prolina en presencia de una base tal como

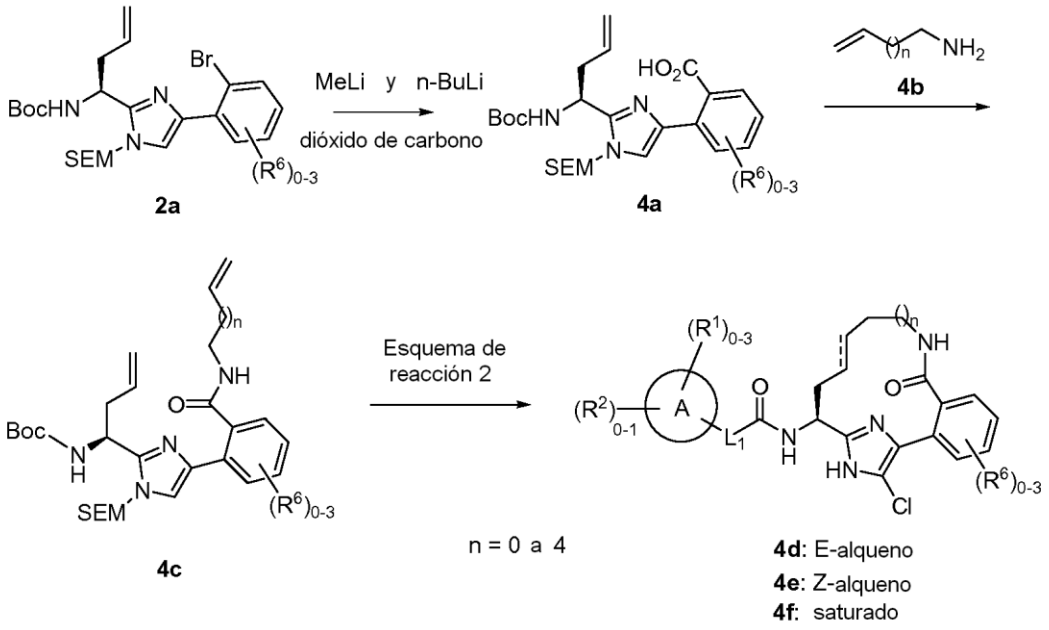
carbonato de potasio, en un solvente tal como dimetilsulfóxido a temperatura elevada, dando la anilina sustituida 3g. Alternativamente, el bromuro 2a puede convertirse en la anilina 3b no sustituida en condiciones de reacción similares (Chang, S., *Chem. Commun.*, 3052 (2008)). A continuación, la anilina 3b puede acoplarse con un ácido carboxílico 3c sustituido apropiadamente usando T3P en un solvente tal como acetato de etilo o dimetilformamida, dando la amida 3h. La anilina 3b también puede acoplarse con un cloroformiato 3d, isocianato 3e o cloruro de sulfonilo 3f sustituidos apropiadamente, dando el carbamato 3k, la urea 3l y la sulfonamida 3m, respectivamente. Los compuestos de la fórmula 3g, 3h y 3k-m pueden convertirse en los compuestos 3n-r de acuerdo con el Esquema de reacción 2. Para la preparación de compuestos de las formulas 3n, el método preferente para eliminar el Boc y el SEM, tal como se describe en el Esquema de reacción 2, usando ácido clorhídrico anhidro 4 M en dioxano a temperaturas elevadas bien con cisteína o bien con O-metil hidroxilamina como secuestrante de formaldehído.

Esquema de reacción 3



Pueden prepararse macrociclos que contienen imidazol de la presente invención en donde Y es C(O)NH de acuerdo con el Esquema de reacción 4. Sometiendo 2a a metil-litio seguido de intercambio metal-halógeno con n-butil-litio e inactivando el anión intermediario con dióxido de carbono se obtiene el ácido carboxílico 4a. El acoplamiento amídico con una amina 4b sustituido apropiadamente, tal como se ha descrito previamente para la conversión de 3b a 3h, da la amida 4c. La amida 4c puede convertirse en compuestos 4d-f de acuerdo con el Esquema de reacción 2.

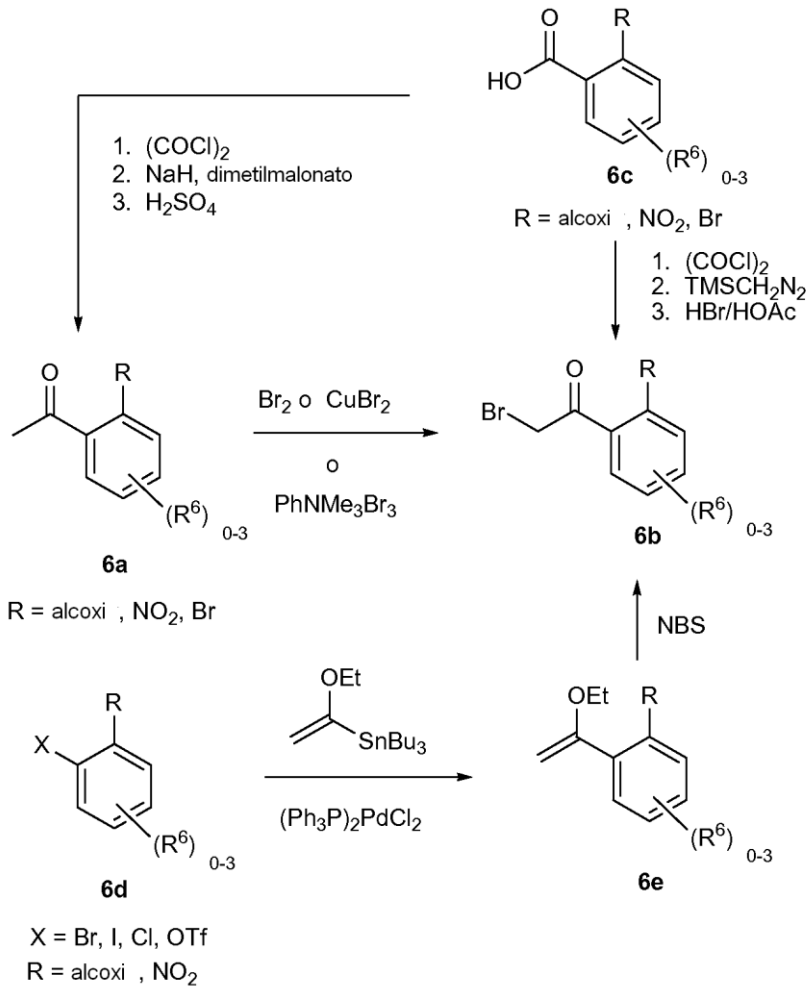
Esquema de reacción 4



Determinados análogos de 2-bromoacetofenona (1b, C = arilo) que no están disponibles comercialmente pueden sintetizarse a partir de materiales disponibles comercialmente tal como se describe en el Esquema de reacción 6. Pueden tratarse derivados de acetofenona con un reactivo de bromación tal como bromuro en un solvente tal como cloroformo, dando 6b. Alternativamente, pueden tratarse derivados de acetofenona 6b bien con bromuro de cobre (II) en un solvente tal como acetato de etilo a temperatura elevada o bien tribromuro de feniltrimetilamonio en un solvente tal como tetrahidrofurano a baja temperatura, proporcionando el 6b. Pueden tratarse

derivados de ácido benzoico secuencialmente con cloruro oxálico en un solvente adecuado, tal como diclorometano, incluyendo unas pocas gotas de DMF, y a continuación con trimetilsilildiazometano en un solvente adecuado o una combinación adecuada de solventes, tales como acetonitrilo y hexano. La diazocetona intermedia se aísla y se trata con ácido bromhídrico acuoso y diclorometano, proporcionando el 6b. Altenativamente, los derivados de ácido benzoico 6c pueden convertirse en los derivados de acetofenona 6A en tres etapas tal como se describe en el Esquema de reacción 6. Alternativamente, el acoplamiento de Stille entre un haluro o triflato de arilo sustituido adecuadamente y tributil-(1-etoxivinil)eestanato con un catalizador de paladio, tal como dicloruro de bis-(trifenilfosfina)paladio, en un solvente adecuado, tal como tolueno, a temperatura elevada, proporciona el enol éter 6e. El enol éter 6e puede convertirse en el 6b con N-bromosuccinimida.

Esquema de reacción 6



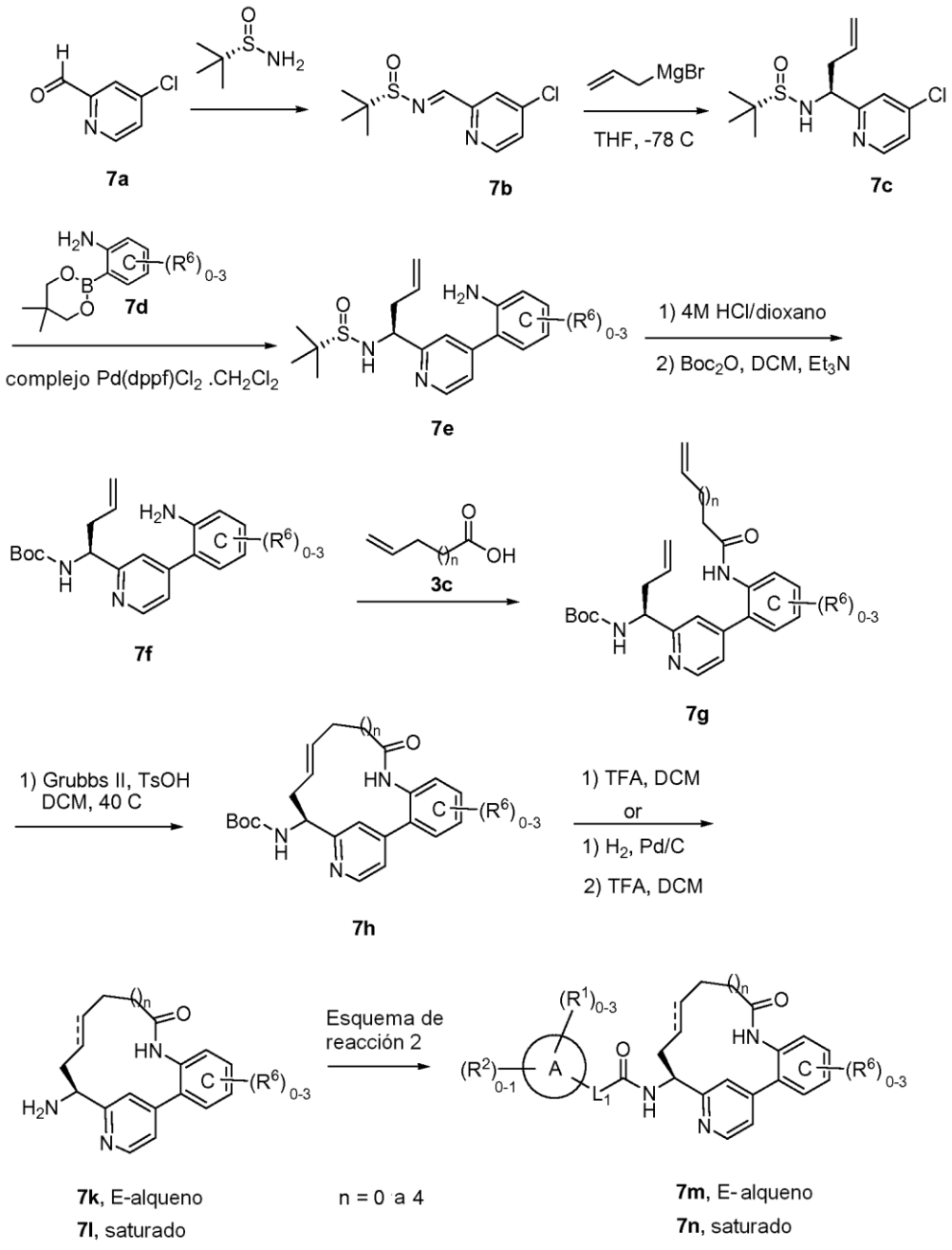
Las sintesis de ácidos carboxílicos de fórmula 2k sustituidos apropiadamente, en donde A = arilo y en donde L_1 = $-CH_2CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-OCH_2-$, $-S(O)_pCH_2-$ o CH_2NH-, útiles para la síntesis de compuestos amídicos de la presente invención tal como se esboza en el Esquema de reacción 2 se describen en la solicitud internacional PCT N° WO 2009/114677 publicada el 17/09/2009, que se incorpora al presente

documento por referencia en su totalidad. Además, el ácido 1-amino-5,6,7,8-tetrahidroisoquinolina-6-carboxílico útil para la síntesis de compuestos amídicos de la presente invención tal como se esboza en el Esquema de reacción 2 se describe en la solicitud de patente de Estados Unidos N° 2005/0282805 publicada el 22/12/2005, que se incorpora al presente documento por referencia en su totalidad.

Los macrociclos que contienen piridina representativos (anillo B = piridina) de la presente invención en donde Y es NHCO pueden prepararse tal como se muestra en el Esquema de reacción 7. La condensación del aldehído 7a, preparado de acuerdo con un procedimiento modificado descrito por Negi (*Synthesis*, 991 (1996)), con (S)-2-metilpropano-2-sulfinamida en presencia de sulfato de cobre anhidro en un solvente tal como diclorometano da la sulfinimina 7b (Ellman, J., *J. Org. Chem.*, 64:1278 (1999).) Usando un procedimiento modificado descrito por Kuduk (*Tetrahedron Letters*, 45:6641 (2004)), puede añadirse reactivos de Grignard sustituidos adecuadamente, por ejemplo bromuro de alilmagnesio, a la sulfinimina 7b, dando la sulfinamida 7c, en forma de una mezcla de diastereómeros, que pueden separarse

en varias etapas de la secuencia. El acoplamiento de Suzuki-Miyaura entre 4-cloropiridina 7c y un ácido o éster aril o heteroaril borónico 7d sustituido apropiadamente en presencia de una base tal como fosfato de potasio en una mezcla de solventes, tales como dimetilsulfóxido y agua, o dimetilformamida, usando un precatalizador tal como complejo de $Pd(dppf)_2Cl_2 \bullet CH_2Cl_2$ proporciona el 7e. La interconversión del grupo protector puede realizarse en dos etapas, dando el 7f. A continuación, la anilina 7f puede acoplarse con un ácido carboxílico 3c sustituido apropiadamente usando anhídrido de ácido propanofosfónico (T3P), dando la amida 7g. La metátesis de cierre de anillo, tal como se ha descrito previamente en el Esquema de reacción 2, proporciona el macrociclo que contiene piridina 7h, como el E-alqueno. La desprotección de Boc en 7h con TFA en diclorometano o con ácido clorhídrico 4M en dioxano da la amina 7k. Alternativamente, la hidrogenación de 7h, seguida de la desprotección de Boc con TFA en diclorometano proporciona la amina 7l. Los compuestos 7k y 7l pueden convertirse en compuestos 3m y 3n de acuerdo con el Esquema de reacción 2.

Esquema de reacción 7



Pueden prepararse macrociclos adicionales que contienen piridina (anillo B = piridina) de la presente invención en donde Y es $NHCO_2$, NHC(O)NH y

$NHSO_2$ de acuerdo con el Esquema de reacción 7 reemplazando 3c con un cloroformiato 3d, isocianato 3e o cloruro de sulfonilo 3f sustituidos apropiadamente. Pueden prepararse macrociclos adicionales que contienen unidades de piridina regioisómera como la descrita en el Esquema de reacción 7 usando una secuencia análoga.

Se conocen bien en la técnica y se han revisado ampliamente métodos para sintetizar una gran variedad de piridinas sustituidas y compuestos útiles como materiales de partida para la preparación de compuestos de la presente invención. (Para ejemplos de métodos útiles para la preparación de materiales de partida de piridina véase: Kroehnke, F., *Synthesis*, 1 (1976); "Pyridine and Its Derivatives", *The Chemistry of Heterocyclic Compounds*, 14, (Supl. 1-4), Abramovitch, R.A., ed., John Wiley & Sons, Nueva York (1974); *Comprehensive Heterocyclic Chemistry*, 2: 165-524, Boulton, A.J. y col., eds., Pergamon Press, Nueva York (1984); *Comprehensive Heterocyclic Chemistry*, 5: 1-300, McKillop, A., ed., Pergamon Press, Nueva York (1996)).

En los casos en donde los ácidos bóricos sustituidos adecuadamente no están comercialmente disponibles, se puede adoptar una modificación de este

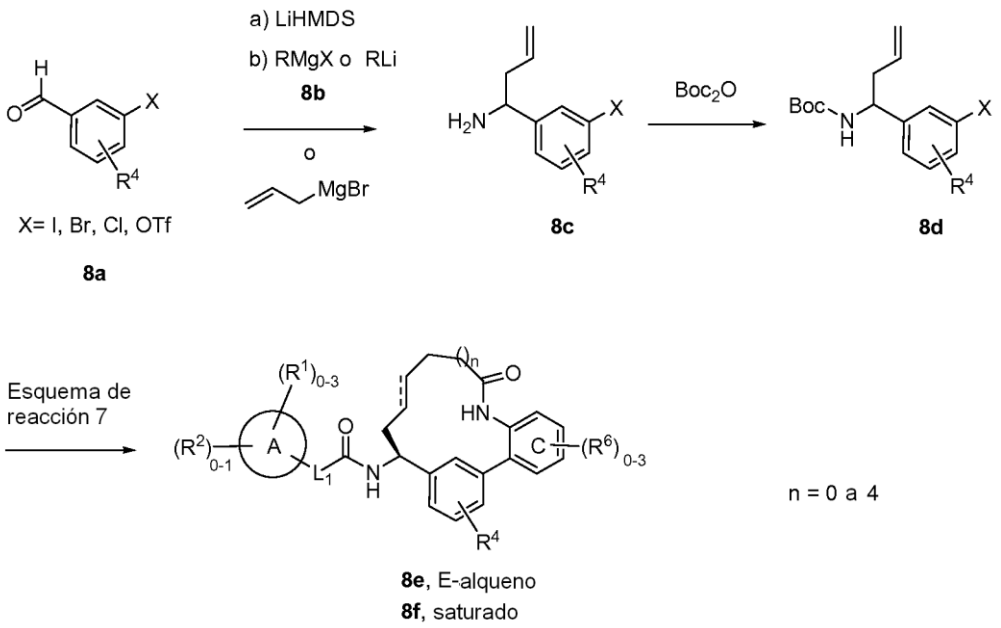
enfoque en donde un haluro de arilo se somete a un acoplamiento mediado por paladio con una especie de diboro tal como bis(pinacolato)diboro o bis(neopentilglicolato)diboro proporcionando los intermediarios 4,4,5,5-tetrametil-[1,3,2]dioxaborolano o 5,5-dimetil-[1,3,2]dioxaborolano correspondiente usando el método de Ishiyama, T. y col. (*J. Org. Chem.*, 60(23):7508-7510 (1995)). Alternativamente, este mismo intermediario puede prepararse mediante reacción del haluro intermediario con el dialcoxihidroborano correspondiente tal como se describe por Murata y col. (*J. Org. Chem.*, 62(19):6458-6459 (1997)). Los intermediarios de pinacolato de boro se pueden usar en lugar de los ácidos borónicos para el acoplamiento a los haluros o triflatos de arilo/heteroarilo o el intermediario de pinacolato de boro se puede convertir en los ácidos borónicos. Alternativamente, los ácidos borónicos correspondientes se pueden preparar mediante intercambio metal-halógeno del haluro de arilo/heteroarilo, inactivación con un reactivo de trialcoxiborato y tratamiento acuoso, proporcionando los ácidos bóricos (Miyaura, N.; Suzuki, A. *Rev.*, 95:2457 (1995)).

También se entiende que el alcance de la síntesis del intermediario puede extenderse

adicionalmente más allá del uso de la metodología del acoplamiento de Suzuki-Miyaura, ya que los haluros o triflatos de arilo precursores descritos anteriormente son también precursores para metodologías de acoplamiento cruzado del tipo Stille, Negishi, Hiyama y Kumada (Tsuji, J., *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis,* John Wiley & Sons (2000); Tsuji, J., *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, John Wiley & Sons (1996).)

Los macrociclos representativos de la presente invención que contienen fenilo (anillo B = fenilo) en donde Y es NHCO pueden prepararse tal como se muestra en el Esquema de reacción 8. Usando una modificación del procedimiento descrito por Hart (*J. Org. Chem.*, 48(3):289-294 (1983)), la generación *in situ* de N-trimetilsililaldiminas a partir de benzaldehído 8a sustituido adecuadamente y *bis*(trimetilsilil)amida de litio, seguido de la adición de reactivo de Grignard o reactivos de alquil-litio 8b, por ejemplo bromuro de alilmagnesio, da, después del tratamiento acuoso, la amina 8c. La amina puede protegerse como el Boc. Los compuestos de la fórmula 8e y 8f pueden prepararse siguiendo la secuencia descrita en el Esquema de reacción 7, reemplazando el 7c por el 8d.

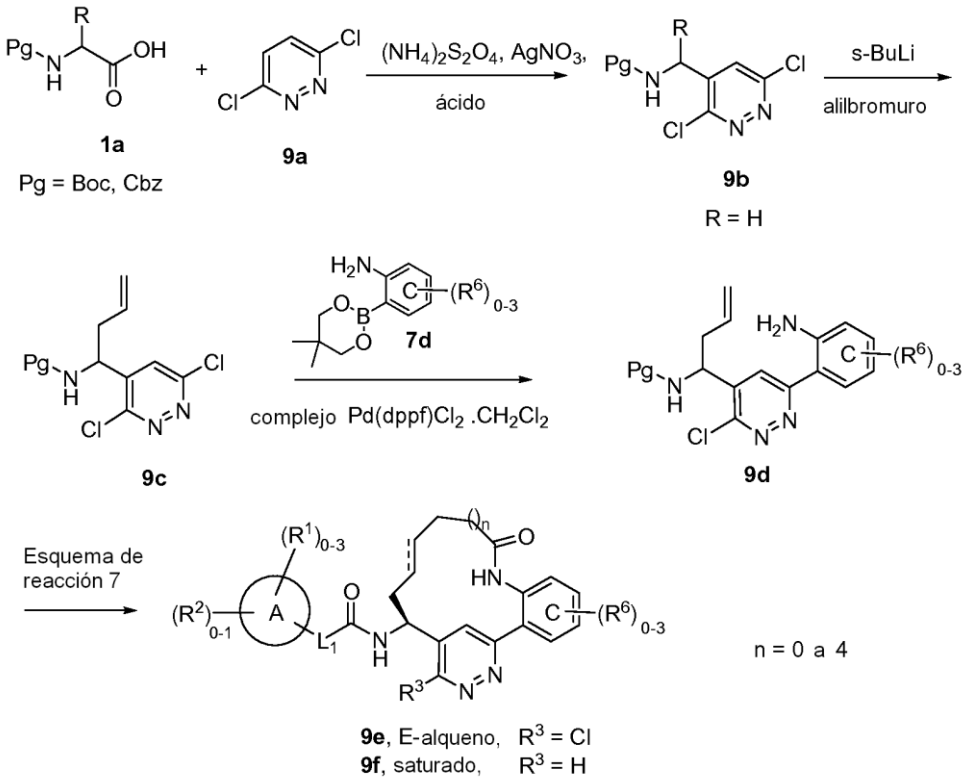
Esquema de reacción 8



Los macrociclos representativos de la presente invención que contienen piridazina (anillo B = piridazina) en donde Y es NHCO pueden prepararse tal como se muestra en el Esquema de reacción 9. Usando una modificación de la reacción de Minisci descrita por Cowden (*Org. Lett.*, 5:4497-4499 (2003)), un alfa aminoácido 1a apropiadamente protegido o derivatizado y 3,6-dicloropiridazona 9a pueden acoplarse a temperatura elevada en presencia de nitrato de plata, persulfato de amonio y un ácido, tal como ácido trifluoroacético, en un solvente, tal como agua o una mezcla de agua/dimetilformamida, dando 1c. El compuesto 9b en donde R = H, preparado usando un derivado de glicina del 1a protegido apropidadamente, puede funcionalizarse posteriormente por desprotonación con sec-BuLi y alquilación

subsiguiente con un haluro de alquilo sustituido apropiadamente, por ejemplo bromuro de alilo, dando del compuesto 9c. El acoplamiento de Suzuki-Miyaura entre cloropiridazina 9c y un ácido o éster aril o heteroaril borónico 7d sustituido apropiadamente en presencia de una base tal como fosfato de potasio en una mezcla de solventes, tal como dimetilsulfóxido y agua, o dimetilformamida, usando un precatalizador tal como complejo de $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ proporciona el 9d. Los compuestos de fórmula 9e y 9f pueden prepararse siguiendo la secuencia descrita en el Esquema de reacción 7, reemplazando el 7f por el 9d.

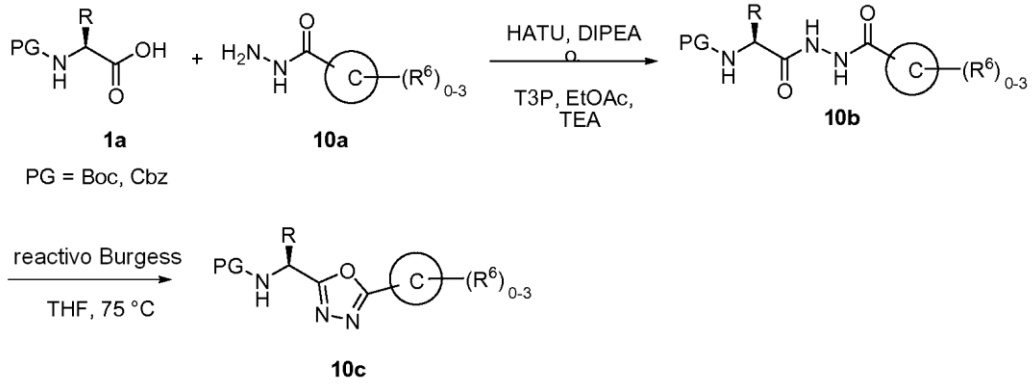
Esquema de reacción 9



Los métodos para la síntesis de una gran variedad

de piridazinas sustituidas útiles para la preparación de compuestos de la presente invención son bien conocidos en la técnica (para ejemplos de métodos útiles para la preparación de materiales de partida de pirazina véase: "Pyridazines", *The Chemistry of Heterocyclic Compounds*, Vol. 28, Castle, R.N., ed., John Wiley & Sons, Nueva York (1973); "The Pyridazines", *The Chemistry of Heterocyclic Compounds*, 57 (Supl. 1), Brown, D.J., ed., John Wiley & Sons, Nueva York (2000); *Comprehensive Heterocyclic Chemistry II*, 6: 1-93, Boulton, A.J., ed., Elsevier Science Inc., Nueva York (1996)).

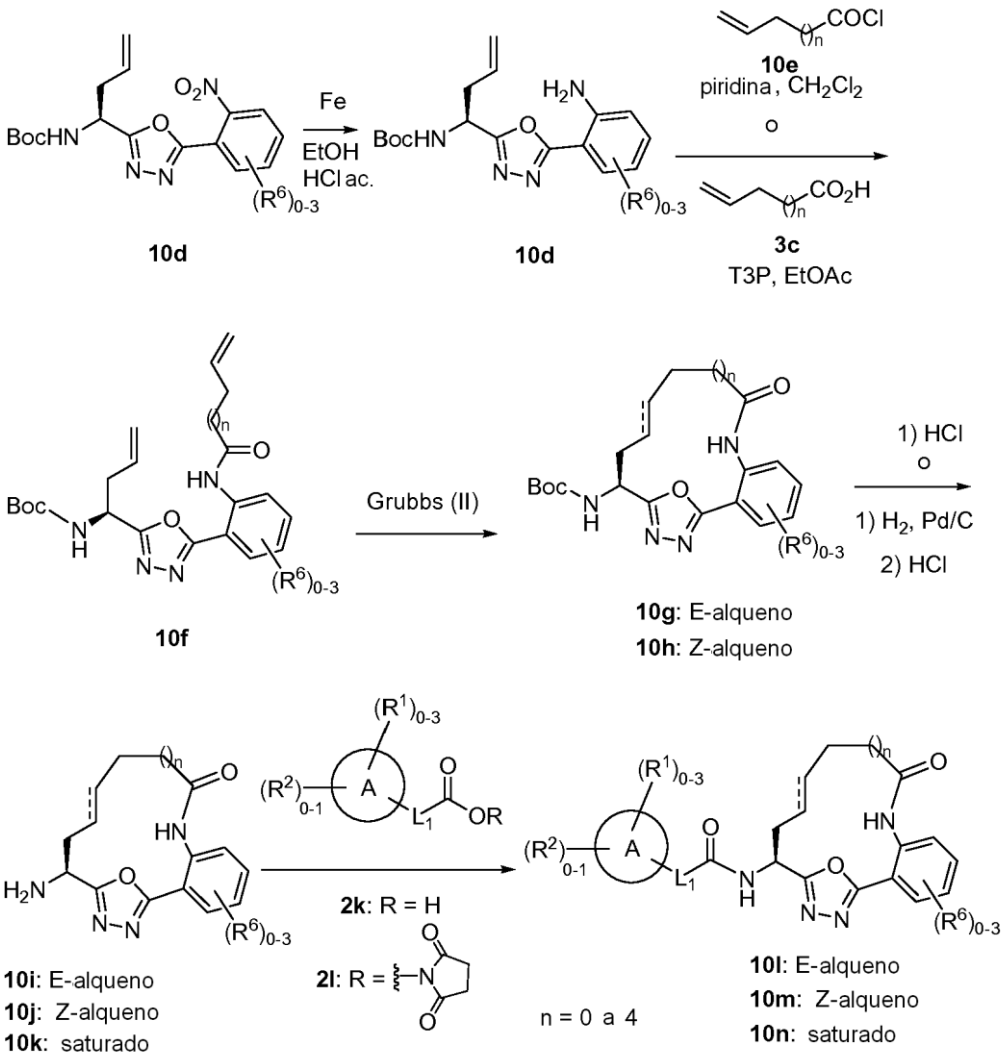
Esquema de reacción 10



Pueden sintetizarse derivados de oxadiazol útiles para la síntesis de los compuestos de la presente invención de acuerdo con el método general esbozado en el Esquema de reacción 10. Un aminoácido 1a protegido adecuadamente se acopla a una hidrazina de fórmula 10a en presencia de un reactivo de acoplamiento tal como HATU o T3P,

proporcionando la acilhidrazida 10b que se cicla dando el oxadizol 10c correspondiente mediante calentamiento en presencia de reactivo de Burgess en un solvente adecuado tal como THF.

Esquema de reacción 10a

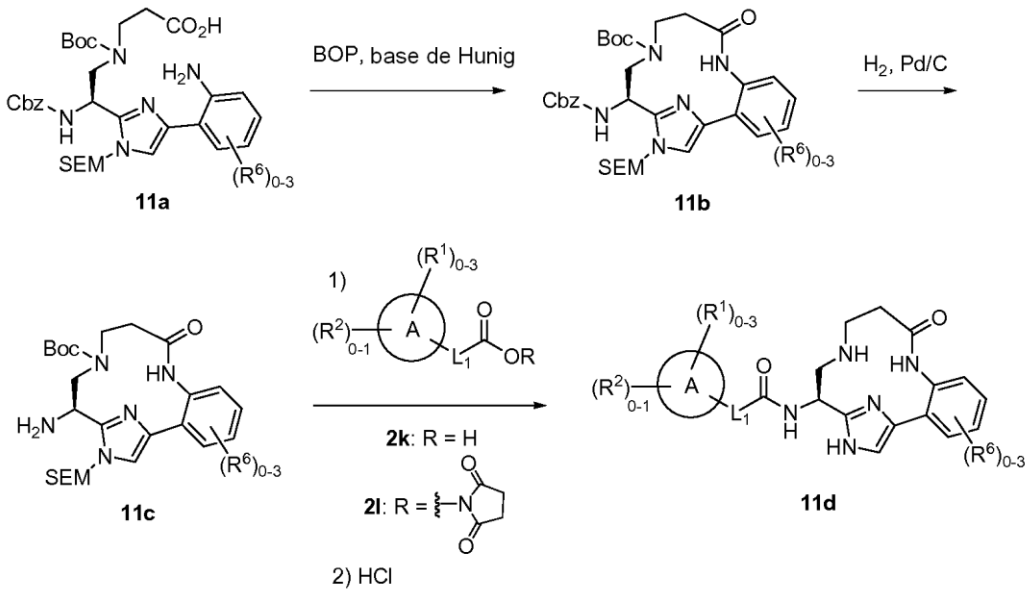


Los macrociclos representativos de la presente invención que contienen oxidiazol (anillo B = oxadiazol) en donde Y es NHCO pueden prepararse tal

como se muestra en el Esquema de reacción 10a. Así, a partir de N-Boc-alilglicina y una 2-nitrofenilhidrazina sustituida adecuadamente, pueden obtenerse compuestos de fórmula 10d y después covertirlos en compuestos macrocíclicos de la presente invención usando una química similar a la descrita anteriormente en el Esquema de reacción 7.

Un experto en la técnica de la síntesis orgánica debería reconocer que los compuestos macrocíclicos adicionales de la presente invención pueden prepararse usando estrategias alternativas de ciclación que no se limitan a la estrategia de metástesis de cierre de anillo del Esquema de reacción 2. Por ejemplo, puede usarse también macrolactamización tal como se describe en el Esquema de reacción 11. La adición lenta de una solución de 11a y base de Hunig a una solucuón de reactivo BOP en una mezcla de diclorometano y DMF proporciona el macrociclo 11b. La hidrogenólisis del Cbz proprociona la amina 11c. El acoplamiento amídico de la amina 11c con 2k o 2l, tal como se describe en el Esquema de reacción 2, y la desprotección total da 11d.

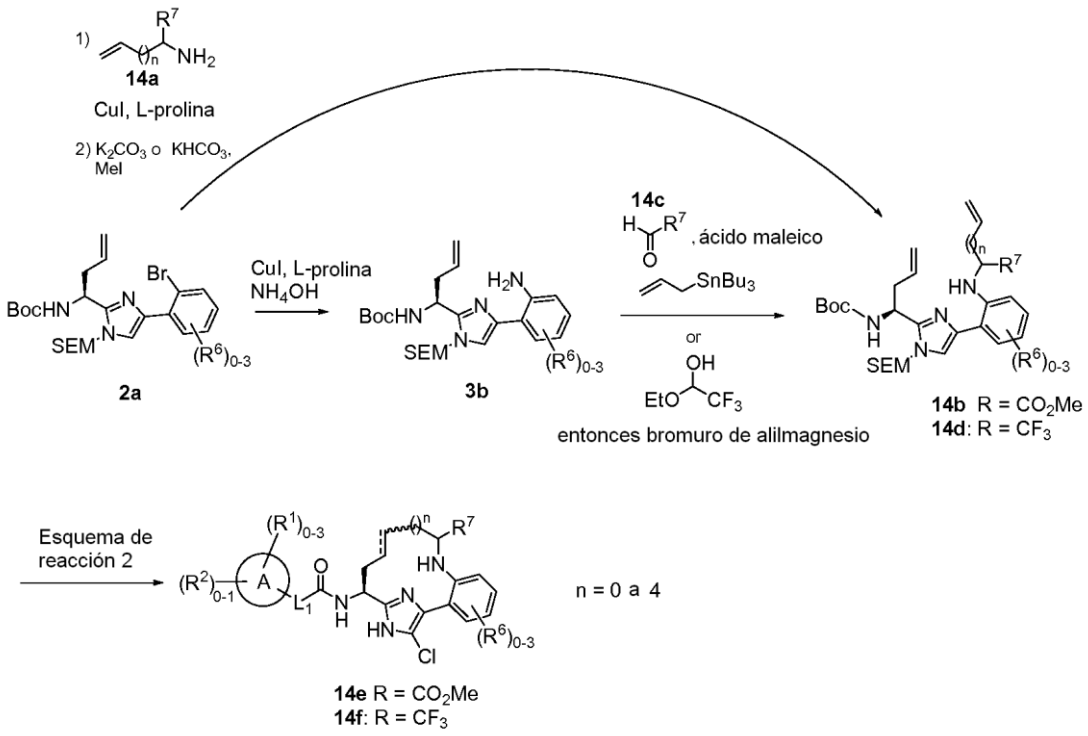
Esquema de reacción 11



Pueden prepararse macrociclos adicionales de la presente invención que contienen imidazol en donde Y es NH de acuerdo con el Esquema de reacción 14. Usando un procedimiento modificado descrito por Ma (*Synthesis*, ***3:*** 496 (2005)), el bromuro 2a puede acoplarse con una amina sustituida apropidamente o un aminoácido sustituido apropiadamente (R^7 = CO_2H) 14a usando yoduro de cobre (I) y L-prolina en presencia de una base tal como carbonato de potasio, en un solvente tal como dimetilsulfóxido a temperatura elevada, seguido de la alquilación del resto de ácido carboxílico con un yoduro de alquilo tal como yoduro de metilo dando la anilina 14b sustituida. Alternativamente, puede prepararse 14b usando un

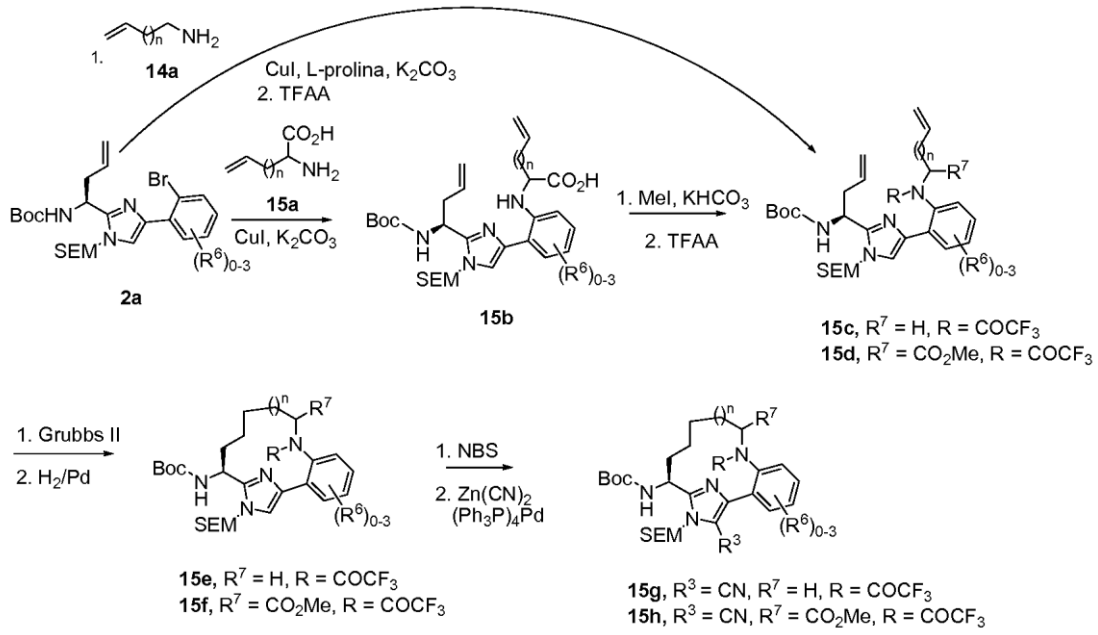
procedimiento modificado descrito por Zhao (*Synthesis*, 19: 3189 (2006)). La combinación de anilina 3b con aldehídos 14c sustituidos apropiadamente en presencia de ácido maleico y aliltributilestaño proporciona el 14b. Alternativamente, la anilina 3b puede condensarse con etil hemiacetal de trifluoroacetaldehído seguido de la adición de reactivos de Grignard, tales como bromuro de alilmagnesio, lo que da el 14d. Los compuestos de la fórmula 14b y 14d pueden convertirse en compuestos 14e y 14f de acuerdo con el Esquema de reacción 2. Para la preparación de compuestos de las fórmulas 14e y 14f, los métodos preferentes para eliminar el Boc y el SEM, tal como se describe en el Esquema de reacción 2, usan ácido clorhídrico anhidro 4 M en dioxano a temperaturas elevadas con bien cisteína o bien O-metil hidroxilamina como secuestrante de formaldehído. La manipulación adicional de grupos funcionales en R^7 usando métodos conocidos por los expertos en la técnica de la síntesis orgánica dará compuestos adicionales de la invención.

Esquema de reacción 14



Pueden prepararse macrociclos adicionales de la presente invención en donde R^3 es CN de acuerdo con el Esquema de reacción 15. La desprotección de intermediarios 15g y 15h, seguida del acoplamiento amídico, tal como se ha descrito anteriormente proporcionará a continuación compuestos adicionales de la presente invención. La posterior manipulación de los grupos funcionales R^7 y R^3 usando métodos conocidos por el experto en la técnica de la síntesis orgánica y tal como se ejemplifica en los ejemplos específicos que se dan a más adelante da compuestos adicionales de la presente invención.

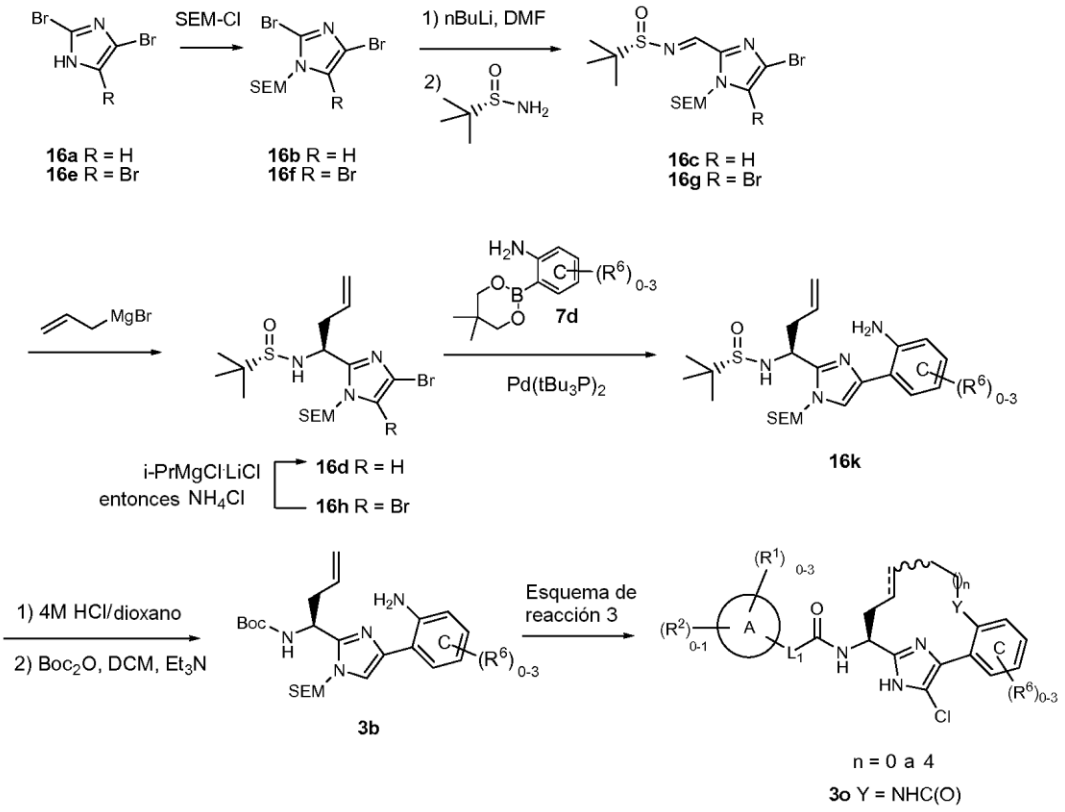
Esquema de reacción 15



Pueden prepararse macrociclos adicionales que contienen imidazol de la presente invención de acuerdo con el Esquema de reacción 16. La protección regioselectiva del 2,4-dibromo imidazol con SEM-Cl proporciona el 16b. El intercambio metal-halógeno de 16b con n-BuLi seguido de la inactivación con dimetilformamida proporciona un mezcla de aldehídos C2 y C4. La condensación del aldehído C2 con (S)-2-metilpropano-2-sulfinamida en presencia de sulfato de cobre anhidro en un solvente tal como diclorometano da la sulfinimina 16c. Pueden añadirse reactivos de Grignard sustituidos apropiadamente, por ejemplo bromuro de alilmagnesio, a la sulfinimina 16c, dando

la sulfinamina 16d, en forma de una mezcla de disastereomeros que pueden separarse en varias etapas de la secuencia. Alternativamente, el 2, 4, 5-tribromo imidazol 16e puede convertirse en 16h de acuerdo con la secuencia de cuatro etapas descrita anteriormente. El intercambio regioselectivo halógeno-magnesio de 16h con cloruro de isopropilmagnesio, seguido de la inactivación con cloruro de amonio saturado, proporciona el 16d. El acoplamiento de Suzuki-Miyaura entre bromoimidazol 16d y un ácido o ester aril o heteroaril borónico sustituido apropiadamente 7d en presencia de una base tal como carbonato de potasio en un solvente, tal como dioxano, usando un catalizador tal como $Pd(tBu_3P)_2$ proprociona el 16k. La interconversión del grupo protector puede realizarse en dos etapas, dando el 3b. El compuesto 3b puede convertirse en el compuesto 3o de acuerdo con el Esquema de reacción 3.

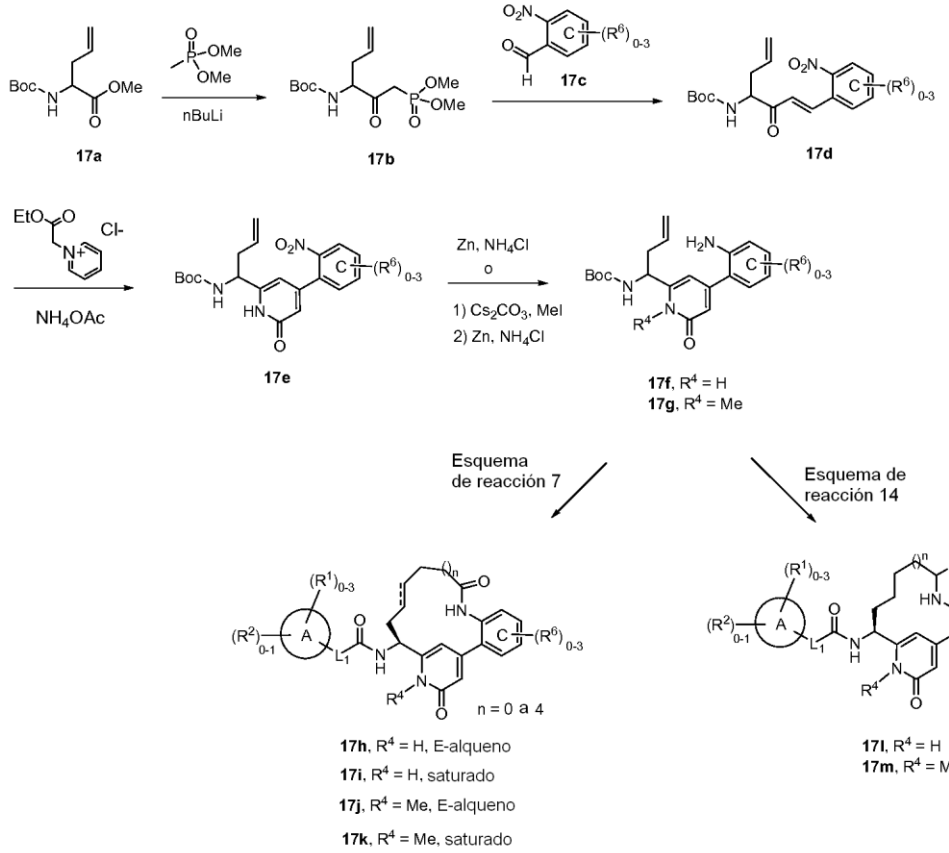
Esquema de reacción 16



Pueden prepararse macrociclos que contienen piridona representative (anillo B = piridona) tal como se muestra en el Esquema de reacción 17. El compuestos 17d puede prepararse en dos etapas de acuerdo con un procedimiento modificado descrito por Resmini (Resmini, M. y col., *Tetrahedron Asymmetry*, 15:1847 (2004)). Un aminoéster sustituido adecuadamente 17a puede convertirse en el β-cetofosfonato 17b corespondiente mediante tratamiento con dimetilmetilfosfonato de litio. La reacción de Horner-Wadsworth-Emmons de 17b y un aldehído 17c sustituido adecuadamente en presencia de una base tal como carbonato de potasio en un solvente tal como etanol o tetrahidrofurano da la cetona α,β-insaturada 17d. La condensación de 17d con cloruro de 1-

(etoxicarbonilmetil)-piridinio o cloruro de 1-(carbamoilmetil)-piridinio en presencia de acetato de amonio en un solvente tal como etanol o ácido acético glacial genera la piridona 17e. El grupo nitro puede reducirse a la aniline 17f con zinc y cloruro de amonio en metanol. Alternativamente, la alquilación de la sal de cesio de la piridona 17e con yoduro de metilo, seguida de la reducción del nitro tal como se ha descrito anteriormente, puede proporcionar el derivado de N-Me piridona 17g. Los compuestos de la fórmula 17f y 17g pueden convertirse en compuestos 17h-k, de acuerdo con el Esquema de reacción 7, o en compuestos 17l-m, de acuerdo con el Esquema de reacción 14.

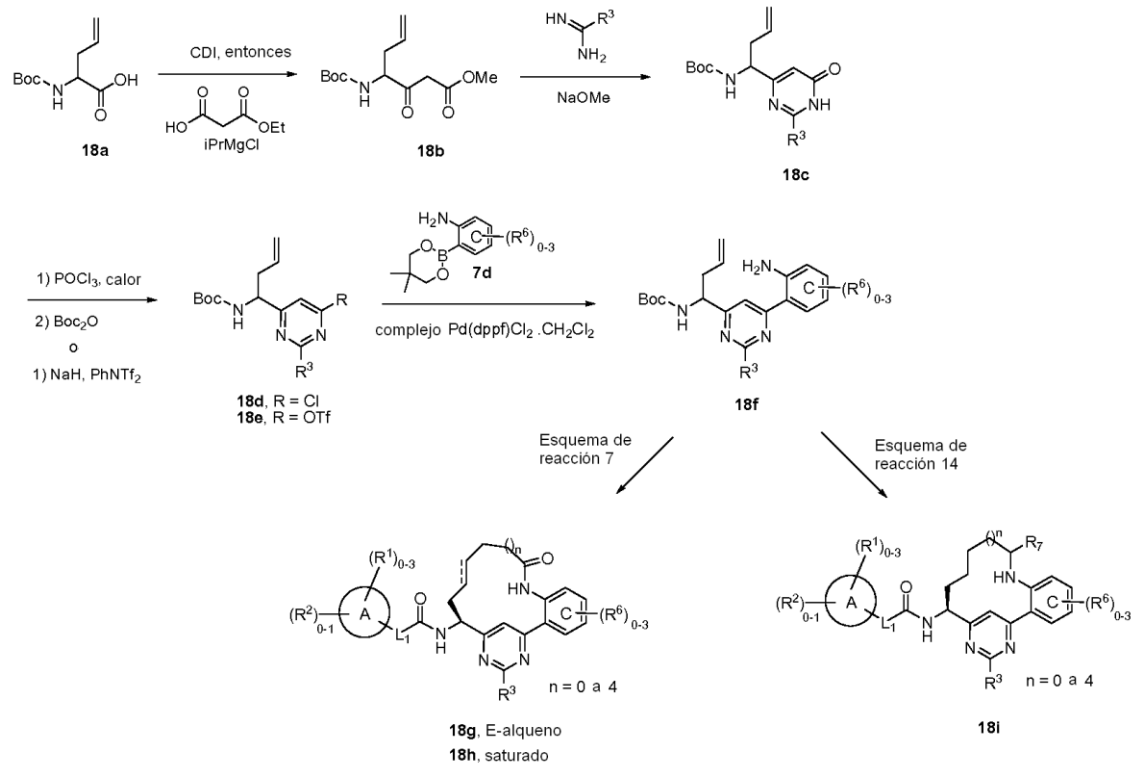
Esquema de reacción 17



Pueden prepararse macrociclos representatives

de la presente invención que contienene pirimidina (anillo B = pirimidina) tal como se muestra en el Esquema de reacción 18. La condensación del β-cetoéster 18b, preparado de acuerdo con un procedimiento modificado de Maibaum (*J. Org. Chem.*, 53:869 (1988)), con una amidina sustituida adecuadamente en condiciones básicas, tales como formamidina y metóxido de sodio en metanol, proporciona la pirimidona 18c. La pirimidona puede convertirse en la cloro pirimidina 18d en dos etapas con oxicloruro de fósforo y, a continuación, reprotección de la amina con anhídrido de Boc. Alternativamente, la pirimidona puede convertirse directamente en el triflato 18e correspondiente con hidruro de sodio y *N*-feniltrifluorometanosulfonimida. El acoplamiento de Suzuki-Miyaura entre 18d o 18e y un ácido o ester aril o heteroaril borónico 7d en presencia de una base tal como fosfato de potasio en una mezcla de solventes, tal como dimetilsulfóxido y agua, o dimetilformamida, usando un precatalizador tal como complejo $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ proprociona el 18f. Los compuestos de la formula 18f pueden convertirse en compuestos 18g-h, de acuerdo con el Esquema de reacción 7, o en compuestos 18i, de acuerdo con el Esquema de reacción 14.

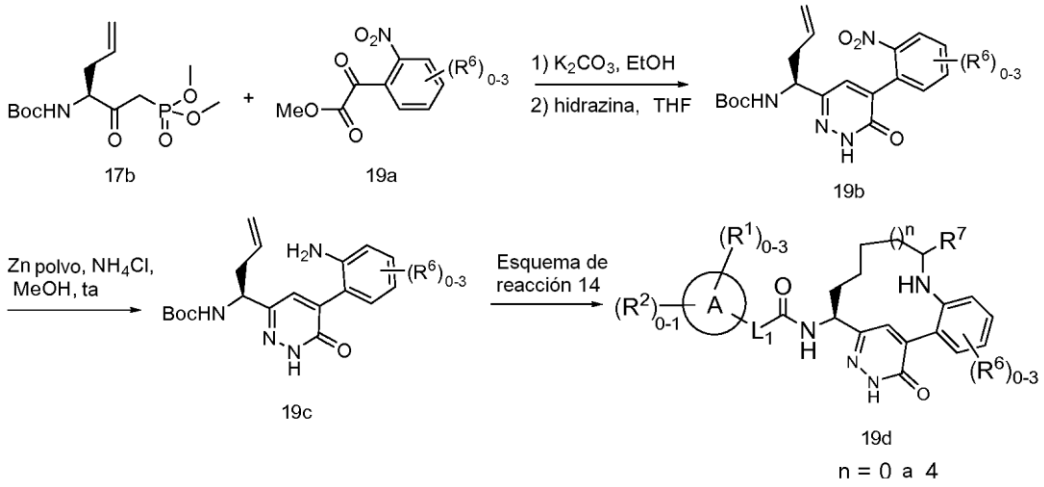
Esquema de reacción 18



Pueden prepararse macrociclos representatives de la presente invención que contienen piridazinona (anillo B = piridazinona) tal como se muestra en el Esquema de reacción 19. La condensación de la sal de potasi del 17b con un α-cetoéster 19a sustituido adecuadamente, que está disponible comercialmente o se prepara usando un procedimiento modificado descrito por Domagala (*Tetrahedron Lett.*, 21:4997-5000), en un solvente tal como tetrahidrofurano genera el derivado de cetona α,β-insaturado que puede condensarse con un derivado de hidracina sustituido adecuadamente dando la piridazinona 19b. El grupo nitro puede reducirse a la aniline 19c con zinc y cloruro de amonio en methanol. Los compuestos

de la fórmula 19c pueden convertirse en compuestos 19d de acuerdo con el Esquema de reacción 14.

Esquema de reacción 19



Se debería reconocer que las etapas de desprotección adicional y las manipulaciones de grupos funcionales de compuestos obtenidos por medio de los Esquemas de reacción 1-19 anteriores usando métodos conocidos en la técnica proporcionarán después compuestos adicionales de la presente invención.

La purificación de intermediarios y productos finales se lleva a cabo por medio de cromatografía de fase normal o inversa. La cromatografía de fase normal se llevó a cabo usando cartuchos de SiO_2 preempaquetados que eluyen o con gradientes de hexanos y acetato de etilo o de diclorometano y metanol a menos que se indique lo contrario. La HPLC preparativa en fase inversa se llevó a cabo usando columnas C18 que eluyen con gradientes de solvente A (agua al

90 %, metanol al 10 %, TFA al 0.1 %) y solvente B (agua al 10 %, metanol al 90 %, TFA al 0.1 %, UV 220 nm) o con gradientes de solvente A (agua al 90 %, acetonitrillo al 10 %, TFA al 0.1 %) y solvente B (agua al 10 %, acetonitrilo al 90 %, TFA al 0.1 %, UV 220 nm) o con gradientes de solvente A (agua al 98 %, acetonitrilo al 2 %, TFA al 0.05 %) y solvente B (acetonitrilo al 98 %, agua al 2 %, TFA al 0.05 %, UV 254 nm).

A menos que se indique lo contrario el análisis de los productos finales se llevó a cabo mediante HPLC analítica de fase inversa usando la columna de Waters SunFire (3.5 mm C18, 3.0 x 150 mm). Se usó elución de gradiente (1.0 ml/min) de solvente B al 10-100 % durante 12 min y después de solvente B al 100 % durante 3 minutos. El solvente A es (agua al 95 %, acetonitrilo al 5 %, TFA al 0.05 %) y el solvente B es (agua al 5 %, acetonitrilo al 95 %, TFA al 0.05 %, UV 254 nm). Método B: Agilent ZORBAX® (3.5 µm C18, 4.6 x 75 mm) elución a 2.5 ml/min con un gradiente de 8 min de A al 100 % a B al 100 % (A: metanol al 10 %, agua al 89.9 %, H_3PO_4 al 0.1 %; B: agua al 10 %, metanol 89.9 %, H_3PO_4 al 0.1 %, UV 220 nm). Método C: Columna Waters SunFire (3.5 µm C18, 4.6 x 150 mm) elución a 1ml/min con un gradiene de solvente B al 10-100 % durante 10 min y después del solvente B al 100 % durante 5 min. (A: NH_4HCO_3 0.01 M en agua:metanol 95:5. B: NH_4HCO_3 0.01 M en agua:metanol 5:95. UV

254 nm).

Método D: Columna Waters SunFire (3.5 µm C18, 3.0 x 150 mm). Se usó elución de gradiente (1.0 ml/min) de solvente B al 10-100 % durante 10 min y después de solvente B al 100 % durante 5 minutos. El solvente A es (agua al 95 %, acetonitrilo al 5 %, TFA al 0.05 %) y el solvente B es (agua al 5 %, acetonitrilo al 95 %, TFA al 0.05 %, UV 254 nm).

IV. BIOLOGÍA

Aunque la coagulación de la sangre es esencial para la regulación de una hemostasis del organismo, está implicada en muchas afecciones patológicas. En la trombosis, puede formarse un coágulo de sangre o trombo y obstruir la circulación localmente, causando isquemia y un daño a los órganos. Alternativamente, en un proceso conocido como embolia, el coágulo puede desplazarse y subsiguientemente quedar atrapado en un vaso distal, donde de nuevo causa isquemia y un daño a los órganos. Las enfermedades que se presentan a partir de la formación patológica de trombos se denominan colectivamente trastornos tromboembólicos e incluyen síndrome coronario agudo, angina de pecho inestable, infarto de miocardio, trombosis en la cavidad del corazón, apoplejía isquémica, trombosis venosa profunda, enfermedad arterial oclusiva periférica, ataque isquémico transitorio y embolia pulmonar. Además, la trombosis tiene lugar en superficies artificiales en contacto con sangre, incluidos

catéteres, endoprótesis vasculares, válvulas cardiacas artificiales y membranas de hemodiálisis.

Algunas afecciones contribuyen al riesgo de desarrollar trombosis. Por ejemplo, alteraciones de la pared de los vasos sanguíneos, cambios en el flujo de sangre y alteraciones en la composición del compartimento vascular. Estos factores de riesgo se conocen colectivamente como tríada de Virchow. (*Hemostasis and Thrombosis, Basic Principles and Clinical Practice*, 5ª edición, página 853, Colman, R.W. y col., eds., Lippincott Williams & Wilkins (2006)).

Los agentes antitrombóticos se administran frecuentemente a pacientes con riesgo de desarrollar una enfermedad tromboembólica debido a la presencia de uno o más factores de riesgo predisponentes de la triada de Virchow para evitar la formación de un trombo oclusivo (prevención primaria). Por ejemplo, en un ajuste ortopédico quirúrgico (por ejemplo, reemplazo de cadera y de rodilla), se administra frecuentemente un agente antitrombótico antes de un procedimiento quirúrgico. El agente antitrombótico sirve de contrapeso al estímulo protrombótico ejercido por las alteraciones del flujo vascular (estasis), al daño quirúrgico potencial a paredes de los vasos sanguíneos, así como a los cambios en la composición de la sangre debidos a la respuesta de fase aguda relacionada con cirugía. Otro ejemplo del uso

del agente antitrombótico para la prevención primaria es administrar dosis con aspirina, un inhibidor de la activación plaquetaria, en pacientes con riesgo de desarrollar una enfermedad cardiovascular trombótica. Los factores de riesgo bien reconocidos en este marco incluyen edad, sexo masculino, hipertensión, diabetes mellitus, alteraciones lipídicas y obesidad.

Los agentes antitrombóticos están indicados también para la prevención secundaria tras un episodio trombótico inicial. Por ejemplo, a los pacientes con mutaciones en el factor V (también conocido como el Factor V Leiden) y factores de riesgo adicionales (por ejemplo, embarazo), se les administra anticoagulantes para evitar la reordenación de la trombosis venosa. Otro ejemplo conlleva la prevención secundaria de eventos cardiovasculares en pacientes con un historial de infarto de miocardio agudo o de síndrome coronario agudo. En un marco clínico, puede usarse una combinación de aspirina y clopidogrel (u otras tienopiridinas) para evitar un segundo evento trombótico.

Los agentes antitrombóticos se administran también para tratar el estado de enfermedad (es decir, deteniendo su desarrollo) después de que ya haya empezado. Por ejemplo, los pacientes que presentan trombosis venosa profunda se tratan con anticoagulantes (es decir, heparina, warfarina o LMWH) para evitar el crecimiento adicional de la oclusión venosa. A

lo largo del tiempo, estos agentes también causan una regresión del estado de enfermedad debido a que el equilibrio entre factores protrombóticos y rutas anticoagulantes/profibrinolíticas se cambia en favor de las últimas. Los ejemplos del lecho vacular arterial incluyen el tratamiento de pacientes con infarto de miocardio agudo o con síndrome coronario agudo con aspirina y clopidogrel para evitar el crecimiento adicional de oclusiones vasculares y eventualmente para conducir a una regresión de las oclusiones trombóticas.

Así, se usan agentes antitrombóticos extensamente para la prevención primaria y secundaria (es decir, profilaxis o reducción del riesgo) de trastornos tromboembólicos, y como tratamiento de un proceso trombótico ya existente. Los fármacos que inhiben la coagulación sanguínea o anticoagulantes son “agentes esenciales para la prevención y el tratamiento de trastornos tromboembólicos” (Hirsh, J. y col., *Blood*, *105*:453-463 (2005)).

Una ruta alternativa de iniciación de la coagulación es operativa cuando la sangre se expone a superficies artificiales (por ejemplo, durante hemodiálisis, cirugía cardiovascular “con bomba”, injertos de vasos sanguíneos, septicemia bacteriana), en superficies celulares, receptores celulares, desechos celulares, ADN, ARN y matrices extracelulares. Este proceso se denomina también activación

por contacto. La absorción de superficie del Factor XII conduce a un cambio conformacional en la molécula del Factor XII, facilitando de este modo la activación para moléculas activas proteolíticas de Factor XII (Factor XIIa y Factor XIIf). El Factor XIIa (o XIIf) tiene varias proteínas objetivo, que incluyen precalicreína de plasma y Factor XI. La calicreína de plasma activa activa adicionalmente el Factor XII, provocando una amplificación de la activación por contacto. Alternativamente, la serina proteasa prolilcarboxilpeptidasa puede activar calicreína de plasma acomplejada con quininógeno de alto peso molecular en un complejo multiproteína formado sobre la superficie de células y matrices (Shariat-Madar y col., Blood, 108: 192-199 (2006)). La activación por contacto es un proceso mediado por superficie responsable en parte de la regulación de la trombosis y la inflamación y está mediado, al menos en parte, por rutas fibrinolítica, del complemento, de quininógeno/quinina y otras rutas humorales y celulares (para revisión, Coleman, R., Contact Activation Pathway, *Hemostasis and Thrombosis*, páginas 103-122, Lippincott Williams & Wilkins (2001); Schmaier, A.H., "Contact Activation", *Thrombosis and Hemorrhage*, páginas 105-128 (1998)). La relevancia biológica del sistema de activación por contacto para enfermedades tromboembólicas está respaldada por el fenotipo de Ratones deficientes en Factor XII. Más

específicamente, los ratones deficientes en Factor XII se protegieron de oclusiones vasculares tromboembólicas en varios modelos de trombosis y modelos de apoplejía y el fenotipo de los ratones deficientes en XII fue indéntico al de los ratones deficientes en XI (Renne y col., *J. Exp. Med.*, 202:271-281 (2005); Kleinschmitz y col., *J. Exp. Med.*, 203:513-518 (2006)). El hecho de que el Factor XI está corriente abajo del Factor XIIa, combinado con el fenotipo idéntico de los ratones deficientes en XII y XI sugiere que el sistema de activación por contacto cumple un papel principal en la activación del Factor XI *in vivo*.

El Factor XI es un zimógeno de una serina proteasa similar a tripsina y está presente en plasma en una concentración relativamente baja. La activación proteolítica de un enlace interno R369-I370 proporciona una cadena pesada (369 aminoácidos) y una cadena ligera (238 aminoácidos). La última contiene una triada catalítica similar a tripsina típica (H413, D464 y S557). La activación del Factor XI por la trombina se cree que tiene lugar en superficies cargadas negativamente, más probablemente en la superficie de plaquetas activadas. Las plaquetas contienen sitios específicos (130-500/plaqueta) de alta afinidad (0.8 nM) para el Factor XI activado. Después de la activación, el Factor XIa se mantiene unido a la superficie y reconoce al Factor IX como su sustrato macromolecular normal. (Galiani, D., *Trends*

Cardiovasc. Med., 10:198-204 (2000)).

Además de los mecanismos de activación de retroalimentación anteriormente descritos, la trombina activa el inhibidor de fibrinolisis activado por trombina (por sus siglas en inglés, TAFI), una carboxipeptidasa de plasma que escinde los restos de lisina C-terminal y de arginina en fibrina, reduciendo la capacidad de la fibrina para potenciar la activación de plasminógeno dependiente de activador de plasminógeno de tipo de tejido (por sus siglas en inglés, tPA). En presencia de anticuerpos para FXIa, la lisis de coágulos puede tener lugar más rápidamente independientemente de la concentración de TAFI en plasma. (Bouma, B.N. y col., *Thromb.* Res., 101, 329, -3542001). Así, se espera que los inhibidores del Factor XIa sean anticoagulantes y profibrinolíticos.

La evidencia adicional para los efectos antitromboembólicos del Factor XI dirigido se deriva de ratones deficientes en Factor XI. Se ha demostrado que la deficiencia completa de fXI protegió a los ratones de trombosis arterial de carótida inducida por cloruro férrico (FeCl3) (Rosen y col., Thromb. *Haemost.*, 87:774-777 (2002); Wang y coll., *J. Thromb. Haemost.*, 3:695-702 (2005)). Además, la deficiencia de Factor XI rescata el fenotipo letal perinatal de deficiencia completa de proteína C (Chan y col., *Amer. J. Pathology*, 158:469-479 (2001)). Además, anticuerpos de reacción cruzada de babuino, que bloquean la función del

Factor XI humano protegen contra la trombosis en derivaciones arterio-venosas en babuinos (Gruber y col., Blood, 102: 953-955 (2003)). La evidencia de un efecto antitrombótico de inhibidores del Factor XIa de molécula pequeña también se describe en la solicitud de patente de Estados Unidos publicada N° 2004/0180855A1. Tomados conjuntamente, estos estudios sugieren que dirigirse al Factor XI reducirá la propensión a enfermedades trombóticas y tromboembólicas.

La evidencia genética indica que no se requiere el Factor XI para la homostasis normal, implicando un perfil de seguridad superior del mecanismo del Factor XI en comparación con mecanismos antitrombóticos que competidores. En contraste con la hemofilia A (deficiencia en Factor VIII) o hemofilia B (deficiencia en Factor IX), las mutaciones del gen del Factor XI que causan deficiencia en Factor XI (hemofilia C) sólo dan como resultado una diatésis sangrante de leve a moderada caracterizada principalmente por hemorRagia postoperatoria o postraumática, pero raramente espontánea. El sangrado postoperatorio tiene lugar mayoritariamente en tejidos con altas concentraciones de actividad fibrinolítica endógena (por ejemplo, cavidad oral y sistema urogenital). La mayor parte de los casos se identifican fortuitamente mediante prolongación preoperatoria de aPTT (sistema intrínseco) sin ninguna historia de sangrado previo.

El aumento de la seguridad de inhibición de XIa

como terapia de anticoagulación esta adicionalmente respaldada por el hecho de que los ratones con el Factor XI desactivado, que no tienen proteína de Factor XI detectable, experimentan un desarrollo normal y tienen un periodo de vida normal. No se ha registrado ninguna evidencia de sangrado espontáneo. El aPTT (sistema intrínseco) se prolonga en una manera dependiente de la dosis génica. De forma interesante, incluso después de una estimulación intensa del sistema de coagulación (transección de cola), el tiempo de sangrado no se prolonga significativamente en comparación con hermanos de camada de tipo silvestre y heterocigotos. (Gailani, D., *Frontiers in Bioscience*, 6:201-207 (2001); Gailani, D. y col., *Blood Coagulation and Fibrinolysis*, 8:134-144 (1997).) Tomadas conjuntamente, estas observaciones sugieren que los niveles altos de inhibición del Factor XIa deberían tolerarse bien. Esto está en contraste con experimentos dirigidos a genes con otros factores de cogulación, excluyendo el Factor XII.

La activación *in vivo* del Factor XI se puede determinar por formación de complejos bien con inhibidor de C1 o bien con alfa 1 antitripsina. En un estudio de 50 pacientes con infarto de miocardio agudo (por sus siglas en inglés, AMI), aproximadamente el 25 % de los pacientes tuvieron valores por encima del intervalo normal superior del ELISA del complejo. Este estudio se puede ver como evidencia

de que al menos en una subpoblación de pacientes con AMI, la activación del Factor XI contribuye a la formación de trombina (Minnema, M.C. y col., *Arterioscler. Thromb. Vasc. Biol.*, 20:2489-2493 (2000)). Un segundo establece una correlación positiva entre la extensión de la arterioesclerosis coronaria y el Factor XIa en complejos con alfa 1 antitripsina. En otro estudio, los niveles de Factor XI anteriores al percentil 90° en pacientes estaban asociados con un aumento del riesgo de 2,2 veces en trombosis venosa (Meijers, J.C.M. y col., *N. Engl. J. Med.*, 342:696-701 (2000)).

La calicreína plasmática es un zimógeno de una serina proteasa similar a tripsina y está presente en plasma en 35 a 50 g/ml. La estructura génica es similar a la del Factor XI. En conjunto, la secuencia de aminoácidos de calicreína plasmática tiene una homología del 58 % con el Factor XI. La activación proteolítica mediante el Factor XIIa en un enlace I 389-R390 interno proporciona una cadena pesada (371 aminoácidos) y una cadena ligera (248 aminoácidos). El sitio activo de la calicreína de plasma está incluido en la cadena ligera. La cadena ligera de la calicreína plasmática reacciona con los inhibidores de proteasa, incluidos alfa 2 macroglobulina y el inhibidor de C1. De forma interesante, la heparina acelera significativamente la inhibición de la calicreína plasmática mediante antitrombina III en presencia de quininógeno de alto peso molecular (por sus siglas en

inglés, HMWK). En sangre, la mayor parte de la calicreína de plasma circula en complejo con el HMWK. La calicreína de plasma escinde el HMWK para liberar bradiquinina. La bradiquinina liberada da como resultado un aumento de la permeabilidad vascular y vasodilatación (para revisión, Coleman, R., Contact Activation Pathway, *Hemostasis and Thrombosis,* páginas 103-122, Lippincott Williams & Wilkins (2001); Schmaier A.H., "Contact Activation", *Thrombosis and Hemorrhage*, páginas 105-128 (1998)).

Además, es preferente encontrar nuevos compuestos con actividad aumentada en ensayos de coagulación *in vitro*, en comparación con inhibidores de serina proteasa conocidos, tales como el ensayo de tromboplastina activada a tiempo parcial (aPTT) o el ensayo de tiempo de protrombina (PT). (para una descripción de los ensayos aPTT y PT véase, Goodnight, S.H. y col., "Screening Tests of Hemostasis", *Disorders of Thrombosis and Hemostasis: A Clinical Guide*, 2ª edición., páginas **41-51**, McGraw-Hill, Nueva York (2001)).

También es deseable y preferente encontrar compuestos con características ventajosas y mejoradas en comparación con inhibidores conocidos de la serina proteasa, en una o más de las categorías siguientes que se dan como ejemplos y que no pretenden ser limitantes: (a) propiedades farmacocinéticas, incluidas biodisponibilidad oral, semivida y eliminación; (b) propiedades farmacéuticas; (c) requisitos

de dosificación; (d) factores que disminuyen las características de pico a valle de concentración en sangre ; (e) factores que aumentan la concentración de fármaco activo en el receptor; (f) factores que disminuyen la propensión por interacciones fármaco-fármaco clínicas; (g) factores que disminuyen el potencial de efectos secundarios adversos, incluida la selectividad frente a otros objetivos biológicos; y (h) factores que aumentan los costes o la viabilidad de fabricación.

Los estudios preclínicos demostraron efectos antitrombóticos significativos de inhibidores de Factor XIa de molécula pequeña en modelo de rata y modelo de conejo de trombosis arterial, a dosis que preservaron la hemostasis. (Wong P.C. y col., *American Heart Association Scientific Sessions*, Abstract (resumen) N° 6118, noviembre 12-15, 2006; Schumacher, W. y col., *J. Thromb. Haemost*, 3 (Supl. 1):P1228 (2005); Schumacher, W.A. y col., *Eur. J.Pharmacol.*, 167-174 (2007)). Además, se observó que la prolongación *in vitro* de la aPTT mediante inhibidores de XIa específicos es un buen vaticinador de eficacia en nuestros modelos de trombosis. Así, la prueba de aPTT *in vitro* se puede usar como sustituta de la eficacia *in vivo*.

Tal como se usa en el presente documento, el término “paciente” comprende todas las especies de mamíferos.

Tal como se usa en el presente documento, “tratar”

o “tratamiento” abarca el tratamiento de un estado de enfermedad en un mamífero, particularmente en un ser humano, e incluye: (a) inhibir el estado de enfermedad, es decir, detener su desarrollo y/o (b) aliviar el estado de enfermedad, es decir, causar la regresión del estado de enfermedad.

Tal como se usa en el presente documento, “profilaxis” o “prevención” abarcan el tratamiento preventivo de un estado subclínico de enfermedad en un mamífero, particularmente en un ser humano, orientado a reducir la probabilidad de la aparición de un estado clínico de enfermedad en un paciente. Se seleccionan pacientes para terapia preventiva en base a factores que se conocen por incrementar el riesgo de sufrir un estado clínico de enfermedad en comparación con la población general. Las terapias de “profilaxis” se pueden dividir en (a) prevención primaria y (b) prevención secundaria. La prevención primaria se define como tratamiento en un sujeto que no ha presentado aún un estado clínico de enfermedad, mientras que prevención secundaria se define como evitar una segunda aparición del mismo estado clínico de enfermedad o similar.

Tal como se usa en el presente documento, “reducción del riesgo” abarca terapias que disminuyen la incidencia de desarrollo de un estado clínico de enfermedad. Como tales, las terapias de prevención primaria y secundaria

son ejemplos de reducción del riesgo.

"Cantidad terapéuticamente eficaz" se pretende que incluya una cantidad de un compuesto de la presente invención que es eficaz, cuando se administra sola o en combinación, para inhibir el Factor XIa y/o calicreína plasmática y/o para evitar o tratar los trastornos enumerados en el presente documento. Cuando se aplica a una combinación, el término hace referencia a cantidades combinadas de los ingredientes activos que dan como resultado el efecto preventivo o terapéutico, si se administran en combinación, en serie o simultáneamente.

El término "trombosis", tal como se usa en el presente documento, se refiere a la formación o presencia de un trombo, una coagulación dentro de un vaso sanguíneo que puede causar una isquemia o un infarto de los tejidos a los que suministra al vaso. El término "embolia", tal como se usa en el presente documento, hace referencia a un bloqueo repentino de una arteria por un coágulo o material extraño que ha sido llevado a ese sitio de emplazamiento por la corriente sanguínea. El término "tromboembolia", tal como se usa en el presente documento, hace referencia a la obstrucción de un vaso sanguíneo con material trombótico llevado por el torrente sanguíneo a partir del sitio de origen para tapar otro vaso. El término "trastornos tromboembólicos" conlleva tanto trastornos "trombóticos" como

trastornos “embólicos” (definidos anteriormente).

El término “trastornos tromboembólicos” tal como se usa en el presente documento incluye trastornos tromboembólicos cardiovasculares arteriales, trastornos tromboembólicos cardiovasculares o cerebrovasculares venosos y trastornos tromboembólicos en las cavidades cardiacas o en la circulación periférica. El término “trastornos tromboembólicos” tal como se usa en el presente documento incluye también trastornos específicos seleccioandos de, pero no limitados a, angina inestable u otros síndromes coronarios agudos, fibrilación atrial, primer infarto de miocardio o recurrente, mueste súbita isquémica, ataque isquémico transitorio, apoplejía, ateroesclerosis, enfermedad arterial oclusiva periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolia arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolia cerebral, embolia renal, embolia pulmonar y trombosis resultante de implantes, dispositivos, o procedimientos médicos en donde la sangre está expuesta a una superficie artificial que promueve la trombosis. Los implantes o dispositivos médicos incluyen, pero no están limitados a: válvulas protésicas, válvulas artificiales, catéteres permanentes, endoprótesis vasculares, oxigenadores de la sangre, derivaciones, puertos de acceso vasculares, dispositivos de asistencia ventricular y corazones o

cavidades cardiacas artificiales e injertos vasculares. Los procedimientos incluyen, pero no están limitados a: derivaciones cardiopulmonarees, intervenciones coronarias percutáneas y hemodiálisis. En otra modalidad, el término "trastornos tromboembólicos" incluye síndrome coronario agudo, apoplejía, trombosis de vena profunda y embolia pulmonar.

En otra modalidad, la presente invención proporciona un método para el tratamiento de un trastorno tromboembólico, en donde el trastorno tromboembólico está seleccionado de entre angina de pecho inestable, un síndrome coronario agudo, fibrilación atrial, infarto de miocardio, ataque isquémico transitorio, apoplejía, ateroesclerosis, enfermedad oclusiva arterial periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolia arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolia cerebral, embolia renal, embolia pulmonar y trombosis resultante de implantes, dispositivos o procedimientos médicos en donde la sangre se expone a una superficie artificial que promueve la trombosis. En otra modalidad, la presente invención proporciona un método para el tratamiento de un trastorno tromboembólico, en donde el trastorno tromboembólico está seleccionado de entre síndrome coronario agudo, apoplejía, trombosis venosa, fibrilación atrial y trombosis resultante

de implantes y dispositivos médicos.

En otra modalidad, la presente invención proporciona un método para el tratamiento de un trastorno tromboembólico, en donde el trastorno tromboembólico está seleccionado de entre angina de pecho inestable, un síndrome coronario agudo, fibrilación atrial, infarto de miocardio, muerte súbita isquémica, ataque isquémico transitorio, apoplejía, ateroesclerosis, enfermedad oclusiva arterial periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolia arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolia cerebral, embolia renal, embolia pulmonar y trombosis resultante de implantes, dispositivos o procedimientos médicos en donde la sangre se expone a una superficie artificial que promueve trombosis. En otra modalidad, la presente invención proporciona un método para la profilaxis primaria de un trastorno tromboembólico, en donde el trastorno tromboembólico está seleccionado de entre síndrome coronario agudo, apoplejía, trombosis venosa y trombosis resultante de implantes y dispositivos médicos.

En otra modalidad, la presente invención proporciona un método para el tratamiento de un trastorno tromboembólico, en donde el trastorno tromboembólico está seleccionado de entre angina de pecho inestable, un síndrome coronario agudo, fibrilación atrial,

infarto de miocardio recurrente, ataque isquémico transitorio, apoplejía, ateroesclerosis, enfermedad oclusiva arterial periférica, trombosis venosa, trombosis de vena profunda, tromboflebitis, embolia arterial, trombosis arterial coronaria, trombosis arterial cerebral, embolia cerebral, embolia renal, embolia pulmonar, y trombosis resultante de implantes, dispositivos o procedimientos médicos en donde la sangre se expone a una superficie artificial que promueve trombosis. En otra modalidad, la presente invención proporciona un método para la profilaxis secundaria de un trastorno tromboembólico, en donde el trastorno tromboembólico está seleccionado de entre síndrome coronario agudo, apoplejía, fibrilación atrial y trombosis venosa.

El término "apoplejía", tal como se usa en el presente documento, hace referencia a apoplejía embólica o a apoplejía aterotrombótica que surge de trombosis oclusiva en las arterias carótida común, carótida interna o intracerebral.

Debe indicarse que la trombosis incluye oclusión de vasos (por ejemplo, después de una derivación) y reoclusión (por ejemplo, durante o después de la angioplastia coronaria transluminal percutánea). Los trastornos tromboembólicos pueden ser el resultado de afecciones que incluyen, pero no se limitan a, ateroesclerosis, cirugía o complicaciones

quirúrgicas, inmovilización prolongada, fibrilación arterial, trombofilia congénita, cáncer, diabetes, efectos de medicaciones u hormonas y complicaciones del embarazo.

Los trastornos tromboembólicos están asociados frecuentemente con pacientes con ateroesclerosis. Los factores de riesgo para ateroesclerosis incluyen pero no se limitan a sexo masculino, edad, hipertensión, trastornos lipídicos y diabetes mellitus. Los factores de riesgo para ateroesclerosis son al mismo tiempo factores de riesgo para complicaciones de la ateroesclerosis, es decir, trastornos tromboembólicos.

De forma similar, la fibrilación arterial está frecuentemente asociada con trastornos tromboembólicos. Los factores de riesgo para la fibrilación arterial y los trastornos tromboembólicos subsiguientes incluyen enfermedad cardiovascular, enfermedad reumática cardiaca, enfermedad de válvula mitral no reumática, enfermedad cardiovascular hipertensiva, enfermedad pulmonar crónica y una diversidad de anormalidades cardiacas variadas, así como tirotoxicosis.

La diabetes mellitus está frecuentemente asociada con ateroesclerosis y trastornos tromboembólicos. Los factores de riesgo para el tipo 2 más común incluyen, pero no se limitan a, historial familiar, obesidad, inactividad física, raza/grupo étnico, ensayo de glucosa en ayuno previamente alterada o ensayo de tolerancia a glucosa

previamente alterada, historia de diabetes mellitus gestacional o desarrollo de un “bebé grande”, hipertensión, colesterol HDL bajo y síndrome del ovario policístico.

Los factores de riesgo para la trombofilia congénita incluyen mutaciones con ganancia de función en factores de coagulación o pérdida de mutaciones de función en las rutas anticoagulantes o fibrinolíticas.

La trombosis se ha asociado con una diversidad de tipos de tumores, por ejemplo, cáncer pancreático, cáncer de mama, tumores cerebrales, cáncer de pulmón, cáncer de ovario, cáncer de próstata, tumores malignos gastrointestinales y linfoma de Hodgkins o linfoma no-Hodgkins. Estudios recientes sugieren que la frecuencia de cáncer en pacientes con trombosis refleja la frecuencia de un tipo de cáncer en particular en la población general (Levitan, N. y col., *Medicine* (Baltimore), 78(5):285-291 (1999); Levine M. y col., *N. Engl. J. Med.*, 334(11):677-681 (1996); Blom, J.W. y col., *JAMA*, 293(6):715-722 (2005)). Así, los cánceres más comunes asociados con trombosis en hombres son cáncer de próstata, cáncer colorrectal, cáncer cerebral y cáncer de pulmón, y en mujeres son cáncer de mama, cáncer de ovario y cáncer de pulmón. La proporción de tromboembolia venosa (por sus siglas en inglés, VTE) observada en pacientes de cáncer es significativa. Las proporciones variables de VTE entre diferentes tipos de tumores están relacionadas más probablemente con la selección

de la población de pacientes. Los pacientes de cáncer con riesgo de trombosis pueden poseer cualquiera de los factores de riesgo siguientes o todos ellos: (i) la etapa del cáncer (*es decir*, presencia de metástasis), (ii) presencia de catéteres venosos centrales, (iii) terapias quirúrgicas y contra el cáncer, incluida la quimioterapia, y (iv) hormonas y fármacos antiangiogénicos. Así, es práctica clínica común administrar dosis a pacientes que tienen tumores avanzados con heparina o heparina de bajo peso molecular para evitar trastornos tromboembólicos. Se ha aprobado varias preparaciones de heparina molecular por la FDA para estas indicaciones.

Existen tres situaciones clínicas principales para considerar la prevención de VTE en un paciente médico con cáncer: (i) el paciente se queda postrado en la cama durante periodos prolongados; (ii) el paciente capaz de andar está recibiendo quimioterapia o radiación; y (iii) el paciente tiene catéteres de venas centrales permanentes. La heparina no fraccionada (por sus siglas en inglés, UFH) y la heparina de bajo peso molecular (LMWH) son agentes antitrombóticos eficaces en pacientes de cáncer que se someten a cirugía. (Mismetti, P. y col., *Brit. J. Surg.*, 88:913-930 (2001).)

A. Ensayos *in vitro*

La eficacia de los compuestos de la presente invención como inhibidores de los Factores de coagulación XIa, VIIa, IXa, Xa, XIIa, calicreína plasmática o trombina,

se puede determinar usando una serina proteasa purificada relevante, respectivamente, y un sustrato sintético apropiado. La tasa de hidrólisis del sustrato cromogénico o fluorogénico mediante la serina proteasa relevante se midió tanto en la ausencia como en la presencia de compuestos de la presente invención. La hidrólisis del sustrato dio como resultado la liberación de pNA (paranitroanilina), que se monitorizó espectrofotométricamente midiendo el aumento de absorbancia a 405 nm, o la liberación de AMC (aminometilcumarina), que se monitorizó espectrofluorométricamente midiendo el aumento de emisión a 460 nm con excitación a 380 nm. Una disminución en la tasa de absorbancia o un cambio de fluorescencia en la presencia de un inhibidor es indicador de inhibición enzimática. Tales métodos son conocidos por un experto en la técnica. Los resultados de este ensayo se expresan como constante de inhibición, Ki.

Las determinaciones de Factor XIa se realizaron en amortiguador de HEPES 50 mM a pH 7.4 que contenía NaCl a 145 mM, KCl 5 mM, y PEG 8000 (polietilenoglicol; JT Baker o Fisher Scientific) al 0.1 %. Las determinaciones se realizaron usando Factor XIa humano purificado a una concentración final de 25-200 pM (Haematologic Technologies) y el sustrato sintético S-2366 (piroGlu-Pro-Arg-pNA; Chromogenix o AnaSpec) a una concentración 0.0002-0.001 M.

Las determinaciones de Factor VIIa se realizaron en cloruro de calcio 0.005 M, cloruro de sodio 0.15 M, amortiguador de HEPES 0.05 M que contenía PEG 8000 al 0.1 % a un pH de 7.5. Las determinaciones se realizaron usando Factor VIIa humano purificado (Haematologic Technologies) o Factor VIIa humano recombinante (Novo Nordisk) a una concentración de ensayo final de 0.5-10 nM, factor de tejido soluble recombinante a una concentración de 10-40 nM y el sustrato sintético H-D-Ile-Pro-Arg-pNA (S-2288; Chromogenix o BMPM-2; AnaSpec) a una concentración de 0.001-0.0075 M.

Las determinaciones de Factor IXa se realizaron en cloruro de calcio 0.005 M, cloruro de sodio 0.1 M, Refludan (Berlex) 0.0001 M, base de TRIS 0.05 M y PEG 8000 al 0.5 % a un pH de 7.4. Se añadió Refludan para inhibir pequeñas cantidades de trombina en las preparaciones comerciales de Factor IXa humano. Las determinaciones se realizaron usando Factor IXa humano purificado (Haematologic Technologies) a una concentración de ensayo final 20-100 nM y el sustrato sintético PCIXA2100-B (CenterChem) o Pefafluor IXa 3688 (H-D-Leu-Ph'Gly-Arg-AMC; CenterChem) a una concentración 0.0004-0.0005 M.

Las determinaciones de Factor Xa se realizaron

en amortiguador de fosfato de sodio 0.1 M a un pH de 7.5 que contenía cloruro de sodio 0.2 M y PEG 8000 al 0.5 %. Las determinaciones se realizaron usando Factor Xa humano purificado (Haematologic Technologies) a una concentración de ensayo final 150-1000 pM y el sustrato sintético S-2222 (Bz-Ile-Glu (gamma-OMe, 50 %)-Gly-Arg-pNA; Chromogenix) a una concentración 0.0002-0.00035 M.

Las determinaciones de Factor XIIa se realizaron en amortiguador de HEPES 50 mM a pH 7.4 que contenía NaCl 145 mM, KCl 5 mM, y PEG 8000 al 0.1 %. Las determinaciones se realizaron usando Factor XIIa humano purificado a una concentración final 4 nM (American Diagnostica) y el sustrato sintético Spectrozyme #312 (H-D-CHT-Gly-L-Arg-pNA.2AcOH; American Diagnostica) a una concentración 0.00015 M.

Las determinaciones de calicreína plasmática se realizaron en amortiguador de fosfato de sodio 0.1 M a un pH de 7.5 que contienía cloruro de sodio 0.1-0.2 M y PEG 8000 al 0.5 %. Las determinaciones se realizaron usando calicreína humana purificada (Enzyme Research Laboratories) a una concentración de ensayo final de 200 pM y el sustrato sintético S-2302 (H-(D)-Pro-Phe-Arg-pNA; Chromogenix) a una concentración 0.00008-0.0004 M. Los valores de Km que se usaron para el cálculo de Ki fueron 0.00005 a 0.00007 M.

Las determinaciones de trombina se realizaron en amortiguador de fosfato de sodio 0.1 M a un pH de 7.5 que contenía cloruro de sodio 0.2 M y PEG 8000 al 0.5 %. Las determinaciones se realizaron usando trombina alfa humana purificada (Haematologic Technologies or Enzyme Research Laboratories) a una concentración de ensayo final 200-250 pM y el sustrato sintético S-2366 (piroGlu-Pro-Arg-pNA; Chromogenix® o AnaSpec) a una concentración 0.0002-0.0004 M.

La constante de Michaelis, Km, para la hidrólisis del sustrato mediante cada proteasa, se determinó a 25 °C usando el método de Lineweaver y Burk. Los valores de Ki se determinaron permitiendo a la proteasa reaccionar con el sustrato en presencia del inhibidor. Las reacciones se dejaron progresar durante periodos de 20-180 minutos (dependiendo de la proteasa) y se midieron las velocidades (tasa de absorbancia o cambio en fluorescencia frente al tiempo). Las siguientes relaciones se usaron para calcular valores de Ki:

$(v_o-v_s)/vs = I/(K_i(1 + S/K_m))$ para un inhibidor competitivo con un sitio de unión; o

$v_s/v_o = A + ((B-A)/1 + ((CI_{50}/(I)_n)))$; y

$K_i = CI_{50}/(1 + S/K_m)$ para un inhibidor competitivo

donde:

v_o es la velocidad del control en ausencia de inhibidor;

v_s es la velocidad en presencia de inhibidor;

I es la concentración de inhibidor;

A es la actividad mínima restante (usualmente fijada a cero);

B es la actividad máxima restante (usualmente fijada a 1.0);

n es el coeficiente de Hill, una medida del número y la cooperatividad de sitios de unión de inhibidores potenciales;

CI_{50} es la concentración de inhibidor que produce inhibición del 50 % en las condiciones de ensayo;

K_i es la constante de disociación del complejo enzima:inhibidor;

S es la concentración de sustrato; y

K_m es la constante de Michaelis para el sustrato.

La selectividad de un compuesto se puede evaluar tomando la relación entre el valor de Ki para una proteasa dada y el valor de Ki para la proteasa de interés (es decir, selectividad para FXIa frente a proteasa P = Ki para la proteasa P/K_i para FXIa). Los compuestos con relaciones de selectividad >20 se consideran selectivos. Son preferentes los compuestos

con relaciones de selectividad > 100, y son más preferentes los compuestos con relaciones de selectividad > 500.

La eficacia de compuestos de la presente invención como inhibidores de la coagulación se pueden determinar usando un ensayo de coagulación estándar o modificado. Un incremento en el tiempo de coagulación de plasma en la presencia de inhibidor es indicador de anticoagulación. El tiempo de coagulación relativo es el tiempo de coagulación en presencia de un inhibidor dividido por el tiempo de coagulación en ausencia de un inhibidor. Los resultados de este ensayo se pueden expresar como CI 1.5x o CI 2x, la concentración de inhibidor requerida para incrementar el tiempo de coagulación en un 50 por ciento o en un 100 por ciento, respectivamente. La CI 1.5x o la CI 2x se encuentra por interpolación lineal a partir del tiempo de coagulación relativo frente a trazados de puntos de concentración de inhibidor que abarcan la CI 1.5x o la CI 2x.

Los tiempos de coagulación se determinan usando plasma humano normal citrado, así como plasma obtenido a partir de varias especies animales de laboratorio (por ejemplo rata o conejo). Se diluye un compuesto en plasma empezando con una solución madre de DMSO 10 mM. La concentración final de DMSO es inferior

al 2 %. Los ensayos de coagulación de plasma se llevan a cabo en un analizador de coagulación automatizado (Sysmex, Dade-Behring, Illinois, Estados Unidos). De forma similar, los tiempos de coagulación se pueden determinar a partir de especies animales de laboratorio o de seres humanos a los que se ha administrado compuestos de la invención.

El Tiempo de Tromboplastina Parcial Activado (aPTT) se determina usando ALEXIN® (Trinity Biotech, Irlanda) o ACTIN® (Dade-Behring, Illinois, Estados Unidos) siguiendo las directrices incluidas en el envase. El plasma (0.05 ml) se calienta a 37 °C durante 1 minuto. Se añade ALEXIN® o ACTIN® (0.05 ml) al plasma y se incuba durante 2 a 5 minutos adicionales. Se añade cloruro de calcio (25 mM, 0.05 ml) a la reacción para iniciar la coagulación. El tiempo de coagulación es el tiempo en segundos desde el momento en que se añade cloruro de calcio hasta que se detecta un coágulo.

El Tiempo de Protrombina (por sus siglas en inglés, PT) se determina usando tromboplastina (Thromboplastin C Plus, Dade-Behring, Illinois) siguiendo las directrices incluidas en el envase. El plasma (0.05 ml) se calienta a 37 °C durante 1 minuto. Se añade tromboplastina (0.1 ml) al plasma para iniciar la coagulación. El tiempo de coagulación es el tiempo

en segundos desde el momento en que se añade tromboplastina hasta que se detecta un coágulo.

Los ejemplos ejemplificados que se describen a continuación se ensayaron en el ensayo de Factor XIa descrito anteriormente y se encontró que tienen actividad inhibitoria del Factor XIa. Se consideró un intervalo de actividad inhibitoria del Factor XIa (valores de Ki) ≤ 10 μM (10000 nM). La tabla 1 siguiente enumera valores de Ki del Factor XIa medidos para los ejemplos siguientes.

TABLA 1

Ejemplo n°	Ki del Factor XIa (nM)
1	2983
3	6174
4	636
6	34
9	249
10	< 5
11	6
19	96
21	4515
61	< 5
89	1057
90	< 5
93	< 5
121	< 5

Ejemplo nº	Ki del Factor XIa (nM)
122	25
136	962
137	192
138	20
167	157
I-4	< 5
I-5	< 5
I-9	1872
I-10	217
I-13	311
I-14	2920
I-17	351
I-21	< 5
I-57	6.6
I-59	< 5
I-60	616
I-67	203
I-70	270
I-72	289
I-77	< 5
I-80	< 5
I-84	580
I-94	3851
I-99	1322
I-104	435
I-106	24
I-107	29

Ejemplo nº	Ki del Factor XIa (nM)
I-108	3869
I-114	296
I-115	< 5
I-121	736
I-124	< 5
I-134	< 5
I-136	183
I-137	2979
I-151	< 5
I-152	21
I-153	1652
I-183	4949
I-211	2171
I-227	< 5
I-242	456
I-251	< 5
I-258	947
I-262	675
I-265	133
I-268	9
I-270	1745
I-278	< 5
I-284	102
I-299	19
I-309	9
I-311	< 5
II-3	< 5

Ejemplo n°	Ki del Factor XIa (nM)
II-4	111
II-10	23
II-13	< 5
II-15	4156
II-18	572
II-35	< 5
II-43	938
II-58	21
II-62	< 5

B. Ensayos *in vivo*

La eficacia de compuestos de la presente invención como agentes antitrombóticos se puede determinar usando modelos de trombosis *in vivo* relevantes, incluidos modelos de trombosis de arterias carótidas inducida electricamente *in vivo* y modelos de trombosis en derivaciones arterio-venosas en conejos *in vivo*.

a. Trombosis de arterias carótidas inducida electricamente (por sus siglas en inglés, ECAT) *in vivo*

El modelo de ECAT de conejo, descrito por Wong y col. (*J. Pharmacol. Exp. Ther.*, *295*:212-218 (2000)), puede usarse en este estudio. Se anestesiaron conejos blancos de Nueva Zelanda machos con quetamina (50 mg/kg + 50 mg/kg/h IM) y xilazina (10 mg/kg + 10 mg/kg/h IM). Estos productos

anestésicos se suplementan según sea necesario. Una sonda de flujo electromagnético se sitúa en un segmento de una arteria carótida aislada para monitorizar el flujo sanguíneo. Los agentes o el vehículo de ensayo se administrarán (i.v., i.p., s.c. u oralmente) antes o después de la iniciación de la trombosis. El tratamiento de fármacos antes de la iniciación de la trombosis se usa para hacer un modelo de la capacidad de los agentes de ensayo para evitar o reducir el riesgo de la formación de trombos, mientras que la dosificación después de la iniciación se usa para hacer un modelo de la capacidad para tratar la enfermedad trombótica existente. La formación de trombos se induce mediante estimulación eléctrica de la arteria carótida durante 3 minutos a 4 mA usando un electrodo bipolar de acero inoxidable externo. El flujo sanguíneo de la carótida se mide de forma continua durante un periodo de 90 min para monitorizar la oclusión inducida por trombos. El flujo sanguíneo total de la carótida durante 90 min se calcula mediante la regla trapezoidal. El flujo medio en la carótida durante 90 min se determina a continuación convirtiendo el flujo total de sangre en la carótida durante 90 min en un porcentaje del flujo de sangre control total en la carótida, lo que daría como resultado si el flujo de sangre control se ha mantenido continuamente durante 90 min. La DE50 (dosis que aumenta el flujo de sangre medio en la carótida durante 90 min a un 50 % del control) de compuestos

se estima mediante un programa de regresión de mínimos cuadrados no linear usando la ecuación de Emax sigmoidal de Hill (DeltaGraph; SPSS Inc., Chicago, IL, Estados Unidos).

b. Modelo de trombosis en derivaciones arterio-venosas (AV) en conejos *in vivo*

El modelo de derivaciones AV en conejos, descrito por Wong y col. (Wong, P.C. y col., *J. Pharmacol. Exp. Ther. 292*:351-357 (2000)), puede usarse en este estudio. Se anestesiaron conejos blancos de Nueva Zelanda machos con quetamina (50 mg/kg + 50 mg/kg/h IM) y xilazina (10 mg/kg + 10 mg/kg/h IM). Estos productos anestésicos se suplementan según sea necesario. La arteria femoral, la vena yugular y la vena femoral se aíslan y se cateterizan. Se conecta un dispositivo de derivación AV relleno con medio salino entre las cánulas de la arteria femoral y de la vena femoral. El dispositivo de derivación AV está constituido por una pieza externa de tubería de tygon (longitud = 8 cm; diámetro interno = 7.9 mm) y por una pieza interna de tubería (longitud = 2.5 cm; diámetro interno = 4.8 mm). La derivación AV contiene también un hilo de seda 2-0 de 8 cm de longitud (Ethicon, Somerville, NJ). La sangre fluye desde la arteria femoral a través de la derivación a la vena femoral. La exposición del flujo de sangre a un hilo de seda induce la formación de un trombo significativo. Cuarenta minutos más tarde, se desconecta la derivación y se pesa el hilo de seda

cubierto con trombo. Los agentes o el vehículo de ensayo se administrarán (i.v., i.p., s.c. u oralmente) antes o después de la apertura del dispositivo de derivación AV. Se determina el porcentaje de inhibición de formación de trombos para cada grupo de tratamiento. Los valores de DI_{50} (dosis que produce la inhibición del 50 % de formación de trombos) se estiman mediante un programa de regresión de mínimos cuadrados no lineal usando la ecuación de Emáx sigmoidea de Hill (DeltaGraph; SPSS Inc., Chicago, IL).

El efecto antiinflamatorio de estos compuestos se puede demostrar en un ensayo de extravasación de tinción de Evans Blue usando ratones deficientes en inhibidores de esterasa C1. En este modelo, se administra a los ratones un compuesto de la presente invención, la tinción de Evans Blue se inyecta a través de la vena de la cola y la extravasación de la tinción azul se determina usando medios espectrofotométricos a partir de extractos de tejidos.

La capacidad de los compuestos de la presente invención para reducir o evitar el síndrome de respuesta inflamatoria sistémica, por ejemplo, como se observa durante procedimientos cardiovasculares con bomba, se pueden ensayar en sistemas de perfusión *in vitro* o mediante procedimientos quirúrgicos con bomba en mamíferos mayores, incluyendo perros y babuinos. Las lecturas para evaluar el beneficio de los compuestos de la presente invención incluyen por ejemplo

pérdida de plaquetas reducida, complejos plaquetas/leucocitos reducidos, niveles de elastasa de neutrófilos en plasma reducidos, activación reducida de factores del complemento y activación reducida y/o consumo reducido de proteínas de activación por contacto (calicreína plasmática, Factor XII, Factor XI, quininógeno de peso molecular alto, inhibidores de C1-esterasa).

Los compuestos de la presente invención pueden ser también útiles como inhibidores de serina proteasas adicionales, en particular trombina humana, calicreína plasmática humana y plasmina humana. Debido a su acción inhibidora, estos compuestos están indicados para usar en la prevención o en el tratamiento de reacciones fisiológicas, incluyendo coagulación de la sangre, fibrinolisis, regulación la presión sanguínea e inflamación, y cicatrización de heridas catalizada por la clase de enzimas citada. Específicamente, los compuestos tienen utilidad como fármacos para el tratamiento de enfermedades provocadas por la actividad elevada de trombina de las serina proteasas mencionadas, tales como infarto de miocardio, y como reactivos que se usan en el procesamiento de sangre a plasma para diagnóstico y para otros propósitos comerciales.

V. COMPOSICIONES, FORMULACIONES Y COMBINACIONES FARMACÉUTICAS.

Los compuestos de esta invención pueden

administrarse en formas de dosificación oral tales como comprimidos, cápsulas (cada una de las cuales incluye formulaciones de liberación sostenida o formulaciones de liberación sostenida cronometrada), píldoras, polvos, gránulos, elixires, tinturas, suspensiones, jarabes y emulsiones. Se pueden administrar también en forma intravenosa (inyección ultrarrápida o infusión), intraperitoneal, subcutánea o intramuscular, usando todas las formas de dosificación bien conocidas por los expertos en las técnicas farmacéuticas. Se pueden administrar solos, pero se administrarán generalmente con un vehículo farmacéutico seleccionado sobre la base de la vía de administración elegida y la práctica farmacéutica estándar.

El término "composición farmacéutica" significa una composición que comprende un compuesto de la invención en combinación con al menos un vehículo farmacéuticamente aceptable adicional. Un "vehículo farmacéuticamente aceptable" se refiere a medios generalmente aceptados en la técnica para la administración de agentes biológicamente activos a animales, en particular, mamíferos, incluidos, es decir, coadyuvante, excipiente o vehículo, tales como diluyentes, agentes conservantes, cargas, agentes de regulación de flujo, agentes disgregantes, agentes humectantes, agentes emulsionantes, agentes de suspensión, agentes edulcorantes, agentes aromatizantes, agentes

perfumantes, agentes antibacterianos, agentes antifúngicos, agentes lubricantes y agentes de administración, dependiendo de la naturaleza o del modo de administración y de las formas posológicas. Los vehículos farmacéuticamente aceptables se formulan de acuerdo con varios factores dentro del ámbito de los expertos en la técnica. Estos incluyen, sin limitación: el tipo y la naturaleza del agente activo que se está formulando; el sujeto al que se está administrando la composición que contiene agentes; la vía de administración deseada de la composición; y la indicación terapéutica a la que se dirige. Los vehículos farmacéuticamente aceptables incluyen tanto medios líquidos acuosos como medios líquidos no acuosos, así como una diversidad de formas posológicas sólidas y semisólidas. Los vehículos incluyen una serie de ingredientes y aditivos diferentes además del agente activo, tales ingredientes adicionales se incluyen en la formulación por una variedad de razones, por ejemplo, estabilización del agente activo, aglutinantes, etc., bien conocidas por los expertos en la técnica. Las descripciones de vehículos farmacéuticamente aceptables adecuados y de factores implicados en su selección se encuentran en una variedad de fuentes fácilmente disponibles tales como, por ejemplo *Remington's Pharmaceutical Sciences*, 18ª edición (1990).

El régimen de dosificación para los compuestos de la presente invención variará, lógicamente, dependiendo de

factores conocidos, tales como las características farmacodinámicas del agente particular y su modo y vía de administración; la especie, edad, sexo, salud, afección médica y peso del receptor; la naturaleza y extensión de los síntomas; la clase de tratamiento concurrente; la frecuencia de tratamiento; la vía de administración, la función renal y hepática del paciente y el efecto deseado. Un médico o veterinario puede determinar y prescribir la cantidad eficaz del fármaco para evitar, contrarrestar o detener el progreso del trastorno tromboembólico.

A modo de guía general, la dosificación oral diaria de cada ingrediente activo, cuando se usa para los efectos indicados, variará entre aproximadamente 0.001 y aproximadamente 1000 mg/kg de peso corporal, preferentemente entre aproximadamente 0.01 y aproximadamente 100 mg/kg de peso corporal por día, y del modo más preferente entre aproximadamente 0.1 y aproximadamente 20 mg/kg/día. Intravenosamente, las dosis más preferentes variarán de aproximadamente 0.001 a aproximadamente 10 mg/kg/minuto durante una infusión a velocidad constante. Los compuestos de esta invención se pueden administrar en una dosis diaria única, o la dosificación diaria total se puede administrar en dosis divididas de dos, tres o cuatro veces al día.

Los compuestos de esta invención se pueden administrar también mediante administración parenteral (por

ejemplo, intravenosa, intraarterial, intramuscular o subcutánea. Cuando se administra por vía intravenosa o intraarterial, la dosis se puede administrar de forma continua o intermitente. Además, la formulación se puede desarrollar para administración intramuscular y subcutánea que asegure una liberación gradual del ingrediente farmacéutico activo.

Los compuestos de esta invención se pueden administrar en forma intranasal por medio del uso tópico de vehículos intranasales adecuados, o por medio de vías transdérmicas, usando parches cutáneos transdérmicos. Cuando se administran en forma de un sistema de administración transdérmico, la administración de dosificación será, lógicamente, continua más que intermitente durante todo el régimen de dosificación.

Los compuestos se administran típicamente en mezcla con diluyentes, excipientes o vehículos farmacéuticos (colectivamente denominados en el presente documento vehículos farmacéuticos) adecuadamente seleccionados con respecto a la forma deseada de administración, por ejemplo, comprimidos, cápsulas, elixires y jarabes orales, y de forma consecuente con prácticas farmacéuticas convencionales.

Por ejemplo, para la administración oral en forma de un comprimido o una cápsula, el componente de fármaco activo se puede combinar con un vehículo oral, no tóxico,

farmacéuticamente aceptable, un vehículo inerte tal como lactosa, almidón, sacarosa, glucosa, metilcelulosa, estearato de magnesio, fosfato de dicalcio, sulfato de calcio, manitol, sorbitol y similares; para administración oral en forma líquida, los componentes de fármaco oral se pueden combinar con cualquier vehículo oral, no tóxico, farmacéuticamente aceptable tal como etanol, glicerol, agua y similares. 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, goma de tragacanto o alginato de sodio, carboximetilcelulosa, polietilenoglicol, ceras y similares. Los lubricantes usados en estas formas posológicas incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio y similares. Los disgregantes incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantana y similares.

Los compuestos de la presente invención se pueden administrar también en forma de sistemas de administración de liposomas, tales como vesículas unilaminares pequeñas, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas se pueden formar a partir de una diversidad de

fosfolípidos, tales como colesterol, estearilamina o fosfatidilcolinas.

Los compuestos de la presente invención se pueden acoplar también con polímeros solubles como vehículos de fármacos dirigibles. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamida-fenol, polihidroxietilaspartamidafenol u óxido de polietileno-polilisina sustituido con restos de palmitoílo. Además, los compuestos de la presente invención pueden acoplarse a una clase de polímeros biodegradables útiles para lograr la liberación controlada de un fármaco, por ejemplo, ácido poliláctico, ácido poliglicólico, copolímeros de ácido poliláctico y ácido poliglicólico, poliepsilon caprolactona, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacilatos y copolímeros en bloque reticulados o anfipáticos de hidrogeles.

Las formas posológicas (composiciones farmacéuticas) adecuadas para la administración pueden contener de aproximadamente 1 miligramo a aproximadamente 1000 miligramos de ingrediente activo por unidad de dosificación. En estas composiciones farmacéuticas el ingrediente activo estará presente normalmente en una cantidad de aproximadamente el 0.1 al 95 % en peso sobre la base del peso total de la composición.

Las cápsulas de gelatina pueden contener el ingrediente activo y los vehículos en polvo, tales como lactosa, almidón, derivados de celúlosa, estearato de magnesio, ácido esteárico y similares. Se pueden usar diluyentes similares para fabricar comprimidos prensados. Tanto los comprimidos como las cápsulas se pueden elaborar como productos de liberación mantenida para proporcionar la liberación continua de un medicamento durante un periodo de horas. Los comprimidos prensados pueden recubrirse de azúcar o recubrirse de una película para enmascarar cualquier sabor desagradable y para proteger el comprimido de la atmósfera, o pueden recubrirse entéricamente para su disgregación selectiva en el tracto gastrointestinal.

Las formas posológicas líquidas para la administración oral pueden contener colorante y aromatizante para aumentar su aceptación por parte del paciente.

En general, son vehículos adecuados para soluciones parenterales agua, un aceite adecuado, medio salino, dextrosa acuosa (glucosa) y soluciones de azúcares relacionadas y glicoles relacionados tales como propilenoglicol o polietilenoglicoles. Las soluciones para la administración parenteral contienen preferentemente una sal soluble en agua del ingrediente activo, agentes estabilizantes adecuados y, si es necesario, sustancias amortiguadoras. Los agentes antioxidantes tales como bisulfito de sodio, sulfito de sodio, o ácido

ascórbico, bien solos o bien combinados, son agentes estabilizantes adecuados. También se usan ácido cítrico y sus sales y EDTA de sodio. Además, las soluciones parenterales pueden contener conservantes, tales como cloruro de benzalconio, metilparabeno o propilparabeno, y clorobutanol.

Los vehículos farmacéuticamente aceptables se describen en *Remington's Pharmaceutical Sciences*, Mack Publishing Company, un texto de referencia estándar en este campo.

Cuando se combinan los compuestos de la presente invención con otros agentes anticoagulantes, por ejemplo, una dosificación diaria puede ser de aproximadamente 0.1 a aproximadamente 100 miligramos del compuesto de la presente invención y aproximadamente 0.1 a aproximadamente 100 miligramos por kilogramo de peso corporal del paciente. Para una forma posológica en comprimidos, los compuestos de la presente invención pueden estar presentes generalmente en una cantidad de aproximadamente 5 a aproximadamente 100 miligramos por unidad de dosificación, y el segundo anticoagulante en una cantidad de aproximadamente 1 a aproximadamente 50 miligramos por unidad de dosificación.

Cuando los compuestos de la presente invención se administran en combinación con un antiagregante plaquetario, a modo de directriz general, típicamente una dosificación diaria puede ser aproximadamente 0.01 a aproximadamente 25

miligramos del compuesto de la presente invención y aproximadamente 50 a aproximadamente 150 miligramos del antiagregante plaquetario, preferentemente aproximadamente 0.1 a aproximadamente 1 miligramo del compuesto de la presente invención y aproximadamente 1 a aproximadamente 3 miligramos de antiagregantes plaquetarios, por kilogramo de peso corporal del paciente.

Cuando los compuestos de la presente invención se administran en combinación con agente trombolítico, típicamente una dosificación diaria puede ser aproximadamente 0.1 a aproximadamente 1 miligramo del compuesto de la presente invención, por kilogramo de peso corporal del paciente y, en el caso de los agentes trombolíticos, la dosificación habitual del agente trombolítico cuando se administra solo puede reducirse en aproximadamente el 50-80 % cuando se administra con un compuesto de la presente invención.

Particularmente cuando se proporciona como una unidad de dosificación, puede existir potencialmente una interacción química entre los ingredientes activos combinados. Por esta razón, cuando el compuesto de la presente invención y un segundo agente terapéutico se combinan en una unidad de dosificación única se formulan de tal forma que aunque los ingredientes activos se combinan en una unidad de dosificación única, el contacto físico entre

los ingredientes activos está minimizado (es decir, reducido). Por ejemplo, un ingrediente activo puede estar recubierto entéricamente. Recubriendo entéricamente uno de los ingredientes activos, no sólo es posible minimizar el contacto entre los ingredientes activos combinados, sino que también es posible controlar la liberación de uno de estos componentes en el tracto gastrointestinal de tal forma que uno de estos componentes no se libera en el estómago sino que se libera más bien en los intestinos. Uno de los ingredientes activos se puede recubrir también con un material que afecta a una liberación controlada a través del tracto gastrointestinal y además sirve para minimizar el contacto físico entre los ingredientes activos combinados. Además, el componente de liberación sostenida puede recubrirse entéricamente adicionalmente de tal forma que la liberación de este componente tiene lugar sólo en el intestino. Otro enfoque más implicaría la formulación de un producto de combinación en donde el único componente está recubierto con un polímero de liberación mantenida y/o entérica, y el otro componente está recubierto también con un polímero tal como hidroxipropilmetilcelulosa (HPMC) con un grado de viscosidad bajo u otros materiales apropiados tal como se conocen en la técnica, con el fin de separar adicionalmente los componentes activos. El recubrimiento polimérico sirve para formar una barrera adicional a la interacción con el otro componente.

Éstas, así como otras maneras de minimizar el contacto entre los componentes de productos de combinación de la presente invención, si se administran en una forma posológica individual o si se administran en formas separadas pero al mismo tiempo mediante la misma manera, serán fácilmente patentes para los expertos en la técnica, una vez equipados con la presente descripción.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende adicionalmente agente(s) terapéutico(s) adicional(es) seleccionado(s) de entre abridores de canales de calcio, bloqueantes de canales de potasio, bloqueantes de canales de calcio, inhibidores de intercambiador sodio hidrógeno, agentes antiarrítmicos, agentes antiateroescleróticos, anticoagulantes, agentes antitrombóticos, agentes protrombolíticos, antagonistas de fibrinógeno, diuréticos, agentes antihipertensión, inhibidores de ATPasa, antagonistas de receptores de mineralocorticoides, inhibidores de fosfodiesterasa, agentes antidiabéticos, agentes antiinflamatorios, inhibidores de fosfodiesterasa, agentes antidiabéticos, agentes antiinflamatorios, antioxidantes, moduladores de angiogénesis, agentes antiosteoporosis, terapias de reemplazo de hormonas, moduladores de receptores de hormonas, anticonceptivos orales, agentes antiobesidad, antidepresivos, agentes antiansiedad, agentes antipsicóticos,

agentes antiproliferativos, agentes antitumorales, agentes antiúlcera y agentes de enfermedad de reflujo gastroesofágico, agentes de hormona del crecimiento y/o secretagogos de hormona del crecimiento, mimetizadores de tiroides, agentes antiinfecciosos, agentes antivirales, agentes antibacterianos, agentes antifúngicos, agentes que bajan colesterol/lípidos y terapias de perfil lipídico, y agentes que mimetizan el precondicionamiento isquémico y/o aturdimiento miocárdico o una combinación de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende adicionalmente agente(s) terapéutico(s) adicional(es) seleccionado(s) de un agente antiarrítmico, un agente antihipertensión, un agente anticoagulante, un antiagregante plaquetario, un agente inhibidor de trombina, un agente antitrombolítico, un agente fibrinolítico, un bloqueante de canales de calcio, un bloqueante de canales de potasio, un agente que disminuye colesterol/lípidos o una combinación de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica que comprende agente(s) terapéutico(s) adiciona(es) seleccionado(s) de warfarina, heparina no fraccionada, heparina de peso molecular bajo, pentasacárido sintético, hirudina, argatrobán, aspirina, ibuprofeno, naproxeno, sulindaco,

indometacina, mefenamato, dipiridamol, droxicam, diclofenaco, sulfinpirazona, piroxicam, ticlopidina, clopidogrel, tirofibán, eptifibatida, abciximab, melagatran, ximelagatrán, disulfatohirudina, activador de plasminógeno tisular, activador de plasminógeno tisular modificado, anistreplasa, urocinasa y estreptocinasa, o una combinación de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica en donde el agente terapéutico adicional es un agente antihipertensivo seleccionado de entre inhibidores de ACE, antagonistas de receptores AT-1, antagonistas de receptores beta-adrenérgicos, antagonistas de receptores ETA, antagonistas de receptores duales ETA/AT-1, inhibidores de renina (aliskiren) e inhibidores de vasopepsidasa, un agente antiarrítmico seleccionado de inhibidores de IKur, un anticoagulante seleccionado de inhibidores de trombina, activadores de antitrombina-III, activadores de cofactor-II de heparina, otros inhibidores de XIa, otros inhibidores de calicreína, antagonistas del inhibidor del activador de plasminógeno (PAI-1), inhibidores de inhibidor de fibrinolisis activado por trombina (TAFI), inhibidores de Factor VIIa, inhibidores de Factor IXa e inhibidores del Factor Xa, o un antiagregante plaquetario seleccionado de entre bloqueantes GPIIb/IIIa, bloqueantes GP Ib/IX, antagonistas de receptor 1 activado por proteasas (PAR-1), antagonistas de receptor 4 activado por

proteasas (PAR-4), antagonistas EP3 del receptor de prostaglandina E2, antagonistas de receptor de colágeno, inhibidores de fosfodiesterasa-III, antagonistas de receptor P2Y1 , antagonistas de P2Y12, antagonistas de receptor de tromboxano, inhibidores de ciclooxigenasa-1 y aspirina, o una combinación de los mismos.

En otra modalidad, la presente invención proporciona una composición farmacéutica, en donde el/los agente(s) terapéutico(s) adicional(es) es/son un antiagregante plaquetario o una combinación de los mismos.

En otra modalidad, la presente invención propociona una composición farmacéutica, en donde el agente terapéutico adicional es el antiagregante plaquetario clopidogrel.

Los compuestos de la presente invención se pueden administrar solos o en combinación con uno o más agentes terapéuticos adicionales. “Administrado en combinación” o “terapia de combinación” significa que el compuesto de la presente invención y uno o más agentes terapéuticos adicionales se administran concurrentemente al mamífero que se está tratando. Cuando se administran en combinación, cada componente se puede administrar al mismo tiempo o secuencialmente en cualquier orden en diferentes puntos temporales. Así, cada componnente se puede administrar por separado pero de forma suficientemente cercana en el tiempo para proporcionar el efecto terapéutico deseado.

Los compuestos que se pueden administrar en combinación con los compuestos de la presente invención incluyen, pero no se limitan a, anticoagulantes, agentes antitrombina, antiagregantes plaquetarios, fibrinolíticos, agentes hipolipidémicos, agentes antihipertensión y agentes antiisquémicos.

Otros agentes anticoagulantes (o agentes inhibidores de la coagulación) que se pueden usar en combinación con los compuestos de esta invención incluyen warfarina, heparina (bien heparina no fraccionada o bien cualquier heparina de peso molecular bajo comercialmente disponible, por ejemplo LOVENOX®), pentasacárido sintético, inhibidores de trombina de acción directa que incluyen hirudina y argatroban, así como otros inhibidores del Factor VIIa, inhibidores del Factor IXa, inhibidores del Factor Xa (por ejemplo, ARIXTRA®, apixabán, rivaroxabán, LY-517717, DU-176b, DX-9065A, y los descritos en los documentos WO 98/57951, WO 03/026652, WO 01/047919, y WO 00/076970), inhibidores del Factor XIa e inhibidores de TAFI y PAI-1 activados conocidos en la técnica.

El término antiagregantes plaquetarios (o agentes inhibidores de plaquetas), tal como se usa en el presente documento, denomina agentes que inhiben la función de las plaquetas, por ejemplo, inhibiendo la agregación, adhesión o secreción del contenido de gránulos de plaquetas. Tales

agentes incluyen, pero no se limitan a, los diversos fármacos antiinflamatorios no estereideos conocidos (NSAIDS, por sus siglas en inglés) tales como acetaminofeno, aspirina, codeína, diclofenaco, droxicam, fentanilo, ibuprofeno, indometacina, ketorolaco, mefenamato, morfina, naproxeno, fenacetina, piroxicam, sufentanilo, sulfinpirazona, sulindaco,y sales farmacéuticamente aceptables o profármacos de los mismos. De los NSAIDS, se prefieren aspirina (ácido acetilsalicílico o ASA) y piroxicam. Otros agentes inhibidores de plaquetas adecuados incluyen antagonistas de glicoproteína IIb/IIIa (por ejemplo, tirofibán, eptifibatida, abciximab e integrelina), antagonistas del receptor de tromboxano-A2 (por ejemplo, ifetrobán), inhibidores de tromboxano-A-sintetasa, inhibidores de fosfodiesterasa-III (PDE-III) (por ejemplo, dipiridamol, cilostazol), e inhibidores de PDE-V (tales como sildenafilo), antagonistas del receptor 1 activado por proteasas (PAR-1) (por ejemplo, E-5555, SCH-530348, SCH-203099, SCH-529153 y SCH-205831) y sales farmacéuticamente aceptables o profármacos de los mismas.

Otros ejemplos de antiagregantes plaquetarios adecuados para usar en combinación con los compuestos de la presente invención, con o sin aspirina, son antagonistas del receptor de ADP (adenosina difosfato), preferiblemente antagonistas de los receptores purinérgicos P2Y1 y P2Y12,

siendo P2Y12 incluso más preferente. Los antagonistas del receptor P2Y12 preferente incluyen clopidogrel, ticlopidina, Prasugrel, ticagrelor y cangrelor, y sales farmacéuticamente aceptables o profármacos de los mismos. La ticlopidina y el clopidogrel son también compuestos preferentes dado que se conocen por ser más suaves que la aspirina en el tracto gastrointestinal en uso. El clopidogrel es un agente incluso más preferente.

Un ejemplo preferente es una combinación triple de un compuesto de la presente invención, aspirina y de otro antiagregante plaquetario. Preferentemente, el antiagregante plaquetario es clopidogrel o Prasugrel, más preferentemente clopidogrel.

El término inhibidores de trombina (o agentes antitrombina), tal como se usa en el presente documento, designa inhibidores de la serina proteasa trombina. Inhibiendo la trombina, se desestabilizan diversos procesos mediados por trombina, tales como la activación plaquetaria mediada por trombina (esto es, por ejemplo, la agregación de plaquetas y/o los contenidos de gránulos de plaquetas incluida la serotonina) y/o la formación de fibrina. Un experto en la técnica conoce una serie de inhibidores y estos inhibidores se consideran para su uso en combinación con los compuestos presentes. Tales inhibidores incluyen, pero no se limitan a, derivados de boroarginina, boropéptidos,

heparinas, hirudina, argatrobán, dabigatrán, AZD-0837 y los descritos en los documentos WO 98/37075 y WO 02/044145, y sales farmacéuticamente aceptables y profármacos de los mismos. Los derivados de boroarginina y de boropéptidos incluyen derivados N-acetílicos y peptídicos de ácido bórico, tales como derivados de ácido a-aminobórico de lisina, ornitina, arginina, homoarginina y análogos de isotiouronio correspondientes. El término hirudina, tal como se usa en el presente documento, incluye derivados adecuados o análogos de hirudina, denominados en el presente documento hirúlogos, tales como disulfatohirudina.

El término agentes trombolíticos (o fibrinolíticos) (o trombolíticos o fibrinolíticos), tal como se usa en el presente documento, designa agentes que lisan coágulos sanguíneos (trombos). Los agentes incluyen el activador de plasminógeno tisular (TPA, natural o recombinante) y formas modificadas del mismo, anistreplasa, urocinasa, estreptocinasa, tenecteplasa (TNK), lanoteplasa (nPA), inhibidores del Factor VIIa, inhibidores de trombina, inhibidores de Factores IXa, Xa y XIa, inhibidores de PAI-I (es decir, inactivadores de inhibidores del activador de plasminógeno tisular), inhibidores de TAFI activado, inhibidores de alfa-2-antiplasmina, y complejo activador de estreptocinasa de plasminógeno anisoilado, incluidas sales farmacéuticamente aceptables o profármacos de los mismas. El

término anistreplasa, tal como se usa en el presente documento, se refiere al complejo activado de la estreptocinasa de plasminógeno anisoilado, tal como se describe, por ejemplo, en la solicitud de patente europea N° 028,489, cuya descripción se incorpora al presente documento por referencia. El término urocinasa, tal como se usa en el presente documento, se pretende que designe tanto urocinasa de cadena doble como urocinasa de cadena simple, denominándose también la última en el presente documento prourocinasa.

Los ejemplos de agentes que disminuyen colesterol/lípidos adecuados y terapias de perfil lipídico adecuadas para usar en combinación con los compuestos de la presente invención incluyen inhibidores de HMG-CoA reductasa (por ejemplo, Pravastatina, lovastatina, simvastatina, fluvastatina, atorvastatina, rosuvastatina y otras estatinas),moduladores de actividad de receptor de lipoproteína de baja densidad (LDL, por sus siglas en inglés) (por ejemplo, HOE-402, inhibidores de PCSK9), secuestrantes de ácidos biliares (por ejemplo, colestiramina y colestipol), ácido nicotínico y derivados del mismo (por ejemplo, NIASPAN®), moduladores de GPR109B (receptor de ácido nicotínico), derivados de ácido fenofíbrico (por ejemplo, gemfibrozilp, clofibrato, fenofibrato y benzafibrato) y otros moduladores alfa de receptores de proliferador activado de

peroxisomas (PPAR), moduladores de PPARdelta (por ejemplo, GW-501516), moduladores de PPARgamma (por ejemplo, rosiglitazona), compuestos que tienen funcionalidad múltiple para modular las actividades de diversas combinaciones de PParalfa, PPARgamma y PPARdelta, probucol o derivados del mismo (por ejemplo, AGI-1067), inhibidores de absorción de colesterol y/o inhibidores de transportador de Niemann-Pick similar a C1 (por ejemplo, ezetimibe), inhibidores de proteína de transferencia de éster de colesterol (por ejemplo, CP-529414), inhibidores de escualeno sintasa y/o inhibidores de escualeno epoxidasa o mezclas de los mismos, acil-coenzima A: inhibidores de acetiltransferasa de colesterilo (ACAT, por sus siglas en inglés) 1, inhibidores de ACAT2, inhibidores de ACAT1/2 duales, inhibidores de transportadores de ácido biliar ileal (o inhibidores de transportadores de ácido biliar co-dependiente sódico apical), los inhibidores de proteínas de transferencia de triglicéridos microsomales, moduladores alfa de receptor X del hígado (LXR, por sus siglas en inglés), moduladores de LXRbeta, moduladores duales de LXR alfa/beta, moduladores de FXR, ácidos grasos omega 3 (por ejemplo, 3-PUFA), estanoles de plantas y/o ésteres de ácidos grasos de estanoles de plantas (por ejemplo, éster de sitostanol usado en margarina BENECOL®), inhibidores de lipasa endotelial y mimetizadores funcionales de HDL que activan el transportador de colesterol

inverso (por ejemplo, derivados de apoAI o péptidomiméticos de apoAI).

Los compuestos de la presente invención son también útiles como patrones o compuestos de referencia, por ejemplo como un patrón de calidad o un control de calidad, en pruebas o ensayos que implican la inhibición de trombina, Factor VIIa, IXa, Xa, XIa y/o calicreína de plasma. Tales compuestos pueden proporcionarse en un kit comercial, por ejemplo, para usar en investigación farmacéutica que implica trombina, Factor VIIa, IXa, Xa, XIa y/o calicreína plasmática. Por ejemplo, un compuesto de la presente invención podría usarse como una referencia en un ensayo para comparar su actividad conocida a un compuesto con una actividad desconocida. Esto aseguraría al experimentador que el ensayo se estaba llevando a cabo apropiadamente y proporciona una base para comparación, especialmente si el compuesto de ensayo era un derivado del compuesto de referencia. Cuando se desarrollen nuevos ensayos o protocos, los compuestos de acuerdo con la presente invención se podrían usar para probar su efectividad.

Los compuestos de la presente invención se pueden usar también en ensayos diagnósticos que implican trombina, Factor VIIa, IXa, Xa, XIa y/o calicreína plasmática. Por ejemplo, la presencia de trombina, Factor VIIa, IXa, Xa XIa y/o calicreína de plasma en una muestra desconocida se

determinaría mediante la adición del sustrato cromogénico relevante, por ejemplo S2366 para Factor XIa, a una serie de soluciones que contienen el compuesto de ensayo y opcionalmente uno de los compuestos de la presente invención. Si se observa la producción de pNA en las soluciones que contienen muestra de ensayo, pero no en presencia de un compuesto de la presente invención, entonces se concluiría que el Factor XIa estaba presente.

Se pueden usar también compuestos extremadamente potentes y selectivos de la presente invención, los que tienen valores de K_i inferiores o iguales a 0.001 M frente a la proteasa objetivo y superiores o iguales a 0.1 M frente a las otras proteasas, en ensayos diagnósticos que implican la cuantificación de trombina, Factor VIIa, IXa, Xa, XIa, y/o calicreina de plasma en muestras de suero. Por ejemplo, la cantidad de Factor XIa en muestras de suero podría determinarse mediante valoración cuidadosa de la actividad de proteasa en presencia del sustrato cromogénico relevante, S2366, con un inhibidor de Factor XIa potente y selectivo de la presente invención.

La presente invención también comprende un artículo de fabricación. Tal como se usa en el presente documento, el artículo de fabricación se pretende que incluya, pero no se limita a, kits y envases. El artículo de fabricación de la presente invención comprende: (a) un primer recipiente; (b)

una composición farmacéutica localizada dentro del primer recipiente, comprendiendo la composición: un primer agente terapéutico que comprende: un compuesto de la presente invención o una forma de sal farmacéuticamente aceptable del mismo, (c) un envase que indica que la composición farmacéutica puede usarse para el tratamiento de un trastorno tromboembólico y/o inflamatorio (tal como se ha definido previamente). En otra modalidad, el envase establece que la composición farmacéutica se puede usar en combinación (tal como se ha definido previamente) con un segundo agente terapéutico para tratar un trastorno tromboembólico y/o inflamatorio. El artículo de fabricación puede comprender adicionalmente: (d) un segundo recipiente, en donde los componentes (a) y (b) están localizados dentro del segundo recipiente y el componente (c) está localizado dentro o fuera del segundo recipiente. Localizado dentro del primer y el segundo recipientes significa que el recipiente respectivo mantiene el artículo dentro de sus límites.

El primer recipiente es un receptáculo usado para mantener una composición farmacéutica. Este recipiente puede ser para fabricar, almacenar, transportar, y/o vender individualmente/en gran cantidad. El primer recipiente se pretende que abarque una botella, frasco, vial jeringa, tubo (por ejemplo, para una preparación de crema), o cualquier otro recipiente usado para fabricar, mantener, almacenar o

distribuir un producto farmacéutico.

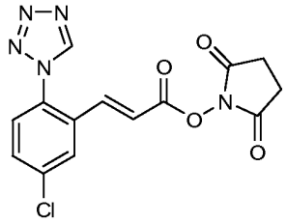
El segundo recipiente es uno usado para mantener el primer recipiente y, opcionalmente, el prospecto. Los ejemplos del segundo recipiente incluyen, pero no se limitan a, cajas (por ejemplo, caja de cartón o plástico), cajones para embalar, cartones, bolsas (por ejemplo, bolsas de papel o de plástico), bolsas pequeñas y sacos. El prospecto puede estar unido físicamente al exterior del primer recipiente por medio de cinta, cola, grapas u otro método de unión, o puede descansar dentro del segundo recipiente sin medio físico alguno de unión al primer recipiente. Alternativamente, el prospecto está ubicado en el exterior del segundo recipiente. Cuando se localiza en el exterior del segundo recipiente, es preferente que el prospecto esté unido físicamente por medio de cinta, cola, grapas u otro método de unión. Alternativamente, puede estar adyacente a o tocando el exterior del segundo recipiente sin estár físicamente unido.

El inserto de paquete es una marca, etiqueta, marcador, etc. que enumera información relativa a la composición farmacéutica ubicada dentro del primer recipiente. La información indicada se determinará habitualmente mediante la agencia reguladora que gobierna el área en donde se va a vender el artículo de elaboración (por ejemplo, la Administración para alimentos y fármacos de los

Estados Unidos). Preferentemente, el inserto de paquete específicamente enumera las indicaciones para las que se ha aprobado la composición farmacéutica. El inserto de paquete se puede hacer de cualquier material en donde una persona pueda leer la información contenida en el mismo. Preferentemente, el inserto de paquete es un material imprimible (por ejemplo, papel, plástico, cartulina, lámina, papel o plástico adhesivo en su parte trasera, etc.) en el cual se ha incluido la información deseada (por ejemplo, por impresión o aplicación).

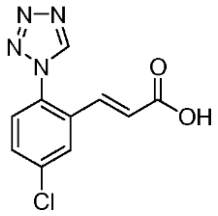
Otras características de la invención llegarán a ser patentes en el curso de las siguientes descripciones de modalidades ejemplares que se dan para ilustrar la invención y no pretenden ser limitantes de la misma. Los siguientes ejemplos se han preparado, aislado y caracterizado usando los métodos descritos en el presente documento.

Intermediario 1. 3-(5-Cloro-2-(1H-tetrazol-1-il)fenil)acrilato de (E)-2,5-dioxopirrolidin-1-ilo



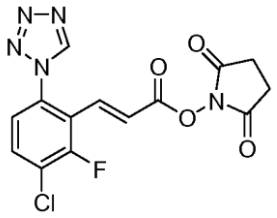
La síntesis se describió como Intermediario 1 en la solicitud internacional PCT N° WO 2009/114677 publicada el 17/09/2009.

Intermediario 2. Ácido (E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrílico



La síntesis se describe como Intermediario 1B en la solicitud internacional PCT N° WO 2009/114677 publicada el 17/09/2009.

Intermediario 3. Éster 2,5-dioxo-pirrolidin-1-ílico del ácido (E)-3-(3-cloro-2-fluoro-6-tetrazol-1-il-fenil)-acrílico

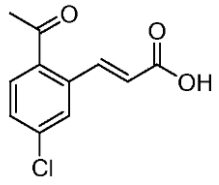


Intermediario 3A. Ácido (E)-3-(3-cloro-2-fluoro-6-(1H-tetrazol-1-il)fenil)acrílico: La síntesis del intermediario 3A se describe como Intermediario7 en la solicitud internacional WO 2009/114677 publicada el 17/09/2009.

Intermediario 3. A una mezcla ligeramente turbia del intermediario 3A (1.0 g, 3.72 mmol) en THF (18.70 ml) y DMF (1.870 ml) se añadió 1-hidroxipirrolidina-2,5-diona (0.471 g, 4.09 mmol) y DIC (0.638 ml, 4.09 mmol). La reacción

se agitó a ta y se formó con el tiempo un precipitado blanco. El sólido se recogió mediante filtración con succión y se lavó con MeOH, agua, MeOH, se secó al aire y se secó al vacío dando el intermediario 3 (0.98 g, 72.0 % de rendimiento), en forma de un sólido blanco. EM (ESI) m/z: 366.2 (M+H)+.

Intermediario 4. Ácido (E)-3-(2-acetil-5-clorofenil)acrílico

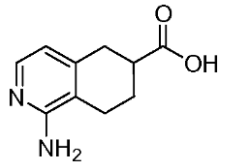


Intermediario 4A. 3-(2-Acetil-5-clorofenil)acrilato de (E)-terc-butilo: A una solución desgasificada de 1-(2-bromo-4-clorofenil)etanona (1.0 g, 4.28 mmol), tributilamina (2.041 ml, 8.57 mmol) y acrilato de terc-butilo (1.255 ml, 8.57 mmol) en DMF (10 ml) se añadió paladio sobre carbono (0.456 g, 0.428 mmol) y acetato de paladio (II) (0.096 g, 0.428 mmol). La mezcla de reacción se calentó a 100 °C. Después de 16 h, la reacción se calentó hasta ta. La reacción se filtró y el sólido se lavó con DMF. El filtrado se diluyó con EtOAc, se lavó con agua (2x), salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en fase normal proporcionó el intermediario 4A (0.760 g, 63 %) en forma de un aceite marrón. EM (ESI) m/z: 225.0 ($M-C_4H^8+H$)+.

Intermediario 4. Se agitó una solución de

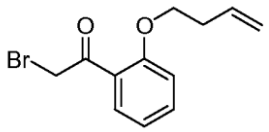
intermediario 4A (0.048 g, 0.171 mmol) en un 50 % de TFA/DCM (2 ml) a ta. Después de 1h, la reacción se concentró dando el intermediario 4 (0.038 g, 100 % de rendimiento) en forma de un sólido amarillo. El material se usó sin purificación adicional. EM (ESI) m/z: 225.1 (M+H)+.

Intermediario 5. Ácido 1-amino-5,6,7,8-tetrahidroisoquinolina-6-carboxílico



La síntesis se describió como ejemplo 147, parte E en la solicitud de patente de Estados Unidos N° 2005/0282805 publicada el 22/12/2005.

Intermediario 6. 2-Bromo-1-(2-(but-3-eniloxi)fenil)etanona

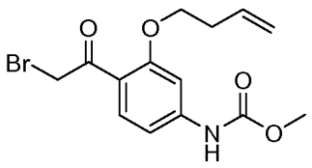


Intermediario 6A. 1-(2-But-3-eniloxi-fenil)-etanona: A una suspensión blanca de carbonato de potasio (15.2 g, 110 mmol) en acetona (29.4 ml) se añadió 5-bromobut-1-eno (3.73 mL, 36.7 mmol) y 1-(2-hidroxifenil)etanona (4.42 ml, 36.7 mmol). La suspensión blancuzca resultante se calentó a reflujo y se agitó durante la noche. La reacción se enfrió hasta ta, se filtró y el filtrado se concentró. El residuo se fraccionó entre agua y EtOAc y las capas se separaron. La capa acuosa se extrajo con EtOAc (2 x 20ml). Las fases

orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron. La purificación por cromatografía en fase normal dio 1.12 g (15 %) del intermediario 6A, en forma de un aceite violeta oscuro. EM (ESI) m/z: 205.2 (M+H)+.

Intermediario 6. Una suspensión del intermediario 6A (1.1153 g, 5.86 mmol) y bromuro de cobre (II) (2.62 g, 11.73 mmol) en EtOAc (10.47 ml) se calentó a reflujo. Después 1 h, la suspensión se enfrió hasta ta, se filtró y el filtrado se concentró dando un residuo marrón verdoso. El residuo marrón verdoso se recogió en EtOAc (100 ml) y se lavó con agua (2 x 100ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por cromatografía en fase normal dio 0.773 g (44 %) del intermediario 6, en forma de un aceite amarillo. EM (ESI) m/z: 271.1 (M+H)+.

Intermediario 7. 4-(2-Bromoacetil)-3-(but-3-eniloxi)fenilcarbamato de metilo



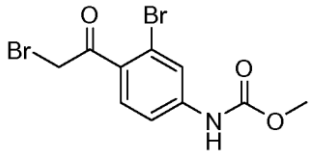
Intermediario 7A. 1-(4-Amino-2-(but-3-eniloxi)fenil)etanona: Una suspensión de 1-(4-amino-2-hidroxifenil)etanona (3 g, 19.85 mmol), 4-bromobut-1-eno (6.04 ml, 59.5 mmol) y K_2CO_3 (16.46 g, 119 mmol) en acetona

(30 ml) se calentó en un tubo sellado a 60 °C. Después de 18 h, se añadieron otros 2 eq. de 4-bromobut-1-eno y la reacción se calentó a 60 °C durante 18 h. Este proceso se repitió una vez más, y la reacción se enfrió hasta ta, se diluyó con EtOAc, se lavó con agua, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en fase normal proporcionó 1.055 g (14.24 %) del intermediario 7A, en forma de un sólido amarillo. EM (ESI) m/z: 206.0 (M+H)+.

Intermediario 7B. 4-Acetil-3-(but-3-eniloxi)fenilcarbamato de metilo: A una solución amarilla clara enfriada (0 °C) del intermediario 7A (1.055 g) en DCM (9.42 ml) y piridina (0.252 ml, 3.11 mmol) se añadió gota a gota cloroformiato de metilo (0.230 ml, 2.97 mmol). La suspensión amarilla resultante se agitó a 0 °C durante 2 h. La reacción se fraccionó entre EtOAc/bicarbonato de sodio saturado y las capas se separaron. La fase acuosa se extrajo con EtOAc (1x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron, dando un sólido amarillo. El sólido se purifico mediante valoración de DCM. El sólido se recogió usando un embudo de filtración Buchner y se enjuagó con DCM (3 x 2 ml), se secó al aire y se secó al vacío dando 0.91 g del intermediario 7B en forma de un sólido blanco. EM (ESI) m/z: 264.0 (M+H)+.

El intermediario 7 se preparó siguiendo el procedimiento descrito en el intermediario 6, reemplazando el intermediario 6A por el intermediario 7B. El material se usó sin purificación adicional. EM (ESI) m/z: 341.9 (M+H)+ y 343.9 (M+2+H)+.

Intermediario 8. Éster metílico del ácido [3-bromo-4-(2-bromo-acetil)-fenil]-carbámico



Intermediario 8A. 1-(4-Amino-2-bromofenil)etanona: (**¡Precaución, riesgo de explosión posible!**) Una solución incolora, clara, de 1-(2-bromo-4-fluorofenil)etanona (22.8 g, 0.105 mol) en DMSO (105 ml) e hidróxido de amonio (68.2 ml, 0.526 mol) se dividió en diecinueve viales de microondas de 20 ml. Los viales se sellaron, se sometieron a microondas a 150 °C durante 1.5 h y después se enfriaron a ta. Todas las reacciones se combinaron, se fraccionaron entre DCM y agua (400 ml) y las capas se separaron. La fase acuosa se extrajo con DCM (2x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron dando 35 g del intermediario 8A en forma de un aceite naranja. El material se llevó a la siguiente etapa sin purificación adicional. EM (ESI) m/z: 212.4 (M+H)+ y 214.4 $(M+2+H)^+$.

El intermediario 8 se preparó siguiendo los procedimientos descritos en el intermediario 7, reemplazando el intermediario 7A por el intermediario 8A. EM (ESI) m/z: 352.1 (M+H)+ y 354.1 $(M+2+H)^+$.

A continuación se destaca una preparación alternativa del intermediario 8

Intermediario 8A alternativo. 1-(4-Amino-2-bromofenil)etanona: a una solución del intermediario 10C (19 g, 0.077 mol) en etanol (400 ml) se añadió en porciones cloruro de estaño (II) (74 g, 0.39 mol). Seguidamente a la adición, la reacción se calentó a reflujo durante la noche. La reacción se concentró y el residuo se disolvión en hidroxido de sodio acuoso al 10 % (200 ml). La solución se extrajo con acetate de etilo (2 x 200 ml). Las capas orgánicas combinadas se lavaron con salmuera y se concentraron, proporcionando un aceite. Se añadió éter de petróleo (25 ml) dando una suspensión. El éter de petróleo se decantó y el sólido se suspendió en acetato de etilo al 20 %/éter de petróleo. El sólido se recogió proporcionando 14 g del intermediario 8A.

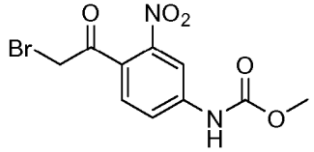
Intermediario 8B alternativo. Éster metílico del ácido (4-acetil-3-bromo-fenil)-carbámico: A una mezcla enfriada (10 °C) del intermediario 8A alternativo (14g, 0.065 mol) y base de Hunig (12.7 g, 0.098 mol) en dioxano seco (140 ml) se añadió gota a gota cloroformiato de metilo (7.4 g,

0.078 m). Después de 3 h, la reacción se inactivó con agua (100 ml) y después se extrajo con acetato de etilo (2 x150 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. La purificación por valoración a partir de isopropanol proporcionó 14 g del intermediario 8B alternativo. MS (ESI) *m/z*: 271.7 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.50 (s, 3H), 3.71 (s, 3H), 7.53 – 7.56 (m, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 10.14 (s, 1H).

Intermediario 8 alternativo. A una solución enfriada (10 °C) del intermediario 8B alternativo (90 g, 0.33 mol) en dioxano seco (900 ml) se añadió una solución de bromo (52.9 g, 0.33 mol) en dioxano (430 mL) gota a gota durante 1h. Después de 2h, se añadió agua fría (500 ml) y la reacción se extrajo con acetato de etilo (2 x 500 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron, proporcionando 110 g de producto bruto. Se calentó una suspension del producto bruto en etanol (1l) hasta 50 °C. Después de formarse una solución clara, se añadió agua (1.0 l) gota a gota y la mezcla se enfrió gradualmente hasta 35°C. El sólido precipitado se recogió por filtración, se lavó con etanol (200 ml), se seco al aire y después se secó a 50°C al vacío durante 30 min, proporcionando 70 g del

intermediario 8 alternativo.

Intermediario 9. 4-(2-Bromoacetil)-3-nitrofenilcarbamato de metilo



Intermediario 9A. 4-Yodo-3-nitrofenilcarbamato de metilo: A una suspensión amarilla enfriada (0 °C) de 4-yodo-3-nitroanilina (8.46 g, 32.0 mmol) en DCM (320 ml) y piridina (2.85 ml, 35.2 mmol) se añadió gota a gota cloroformiato de metilo (2.61 ml, 33.6 mmol). La solución amarilla clara resultante se agitó a 0 °C. Después de 1.5 h, la reacción se diluyó con DCM, se lavó con $NaHCO_3$ sat., salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se disolvió en una cantidad mínima de DCM (~100 ml) y después se añadió hexano (600ml) dando una suspensión amarilla. La suspensión se filtró y el sólido se lavó con hexano y después se secó, dando el intermediario 9A (10.3 g, 100 %) en forma de un sólido amarillo. EM (ESI) m/z: 321.3 [M-H]-.

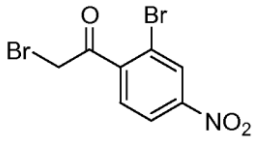
Intermediario 9B. 4-(1-Etoxivinil)-3-nitrofenilcarbamato de metilo: Una solución del intermediario 9A (6 g, 18.63 mmol), (1-etoxivinil)estanato de tributilo (7.55 ml, 22.36 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0.654 g, 0.932 mmol) en tolueno (37.3 ml) se calentó a 110 °C. Después de 2h, la reacción se enfrió a ta. La mezcla de

reacción se filtró a través de GMF de 0.45 micrómetros, lavándose con EtOAc. El filtrado se concentró. La purificación mediante cromatografía en fase normal del intermediario 9B (3.59 g, 72.4 % de rendimiento) en forma de un sólido marrón. EM (ESI) m/z: 267.4 (M+H)+.

Intermediario 9. A una mezcla ligeramente turbia del intermediario 9B (3.59 g, 13.48 mmol) en THF (20 ml) y agua (7 ml) se añadió NBS (2.400 g, 13.48 mmol). La solución amarilla, clara, resultante se agitó a ta durante 20 min y, a continuación, la reacción se fraccionó entre EtOAc/salmuera. Las capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró, proporcionando el intermediario 9 (4.28 g, 100 % de rendimiento) en forma de una espuma amarilla. Este material se usó sin purificación adicional. EM (ESI) m/z: 317.3 (M+H)+, 319.3 (M+2+H)+.

Alternativamente, el intermediario 9B puede hidrolizarse con HCl acuoso 1 N, dando la metilcetona que puede, a continuación, bromarse con bromuro de cobre (II) de acuerdo con el procedimiento descrito en el Intermediario 6.

Intermediario 10. 2-Bromo-1-(2-bromo-4-nitrofenil)etanona



Intermediario 10A. Ácido 2-bromo-4-nitro-benzoico:

A una solución caliente (80 °C) de piridina (500 ml) y agua (1.0 l) se añadió 4-nitro-2-bromo tolueno (100 g, 0.46 mol). La suspensión resultante se agitó hasta que se tornó en una solución clara. A continuación se añadió $KMnO_4$ (600 g, 3.8 mol) en porciones durante 1.5 h. La reacción se agitó durante la noche. La mezcla de reacción se enfrió hasta TA y, a continuación, se añadió hidróxido de sodio acuoso al 10 % (200 ml). Después de 15 min, la reacción se filtró para eliminar el sólido. El sólido se lavó con hidróxido de sodio acuoso al 10 % (5 x 100 ml). El filtrado se extrajo con MTBE (3 x 250 ml). La capa acuosa clara se enfrió hasta 10 °C y, a continuación, se acidificó con HCl concentrado. La capa acuosa se extrajo con MTBE (4 x 500 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, se filtraron y se concentraron, proporcionando 72 g del intermediario 10A. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7,96 (d, J = 8 Hz, 1H), 8.28 – 8.48 (m, 1H), 8.49 (d, J = 2.4 Hz, 1H), 14.1 (s ancho, 1H).

Intermediario 10B. Éster dietílico del ácido 2-(2-bromo-4-nitro-benzoil)-malónico: A una solución del intermediario 10A (50 g, 0.2 mol) en tolueno (500 ml) se añadió trietilamina (24.6 g, 0.24 mol). La reacción se enfrió hasta 15 °C y se añadió cloroformiato de etilo (24 g, 0.22 mol). Después 45 min, la solución mixta de anhídrido se enfrió hasta 0 °C.

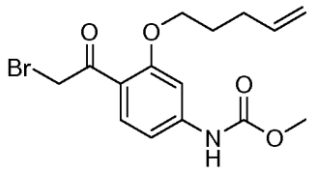
En un matraz aparte: A una suspensión de virutas de Mg (5.4 g) en éter seco (300 ml) se añadió etanol (3.0 ml), tetracloruro de carbono (2.0 ml) y malonato de dietilo (34 ml, 0.22 mol). La mezcla se agitó a 40 °C durante una hora para asegurar la completa disolución del magnesio. Después de la reacción se tornó en una solución clara, se añadió la solución enfriada del anhídrido mixto. Después de 2 h, la reacción se inactivó con ácido sulfúrico 2N (200 ml) y, a continuación, se extrajo con acetato de etilo (4 X 100 ml). Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron, proporcionando 80 g del intermediario 10B. Éste se usó en la etapa siguiente sin purificación adicional.

Intermediario 10C. 1-(2-Bromo-4-nitro-fenil)-etanona: Una mezcla de intermediario 10B (80 g, 0.2 mol) en ácido acético (400 ml) y ácido sulfúrico (400 ml) se agitó a 105 °C. Después de 3h, la reacción se enfrió a TA y, a continuación, se extrajo con acetato de etilo (2 x 500 ml). Las capas orgánicas combinadas se lavaron con hidróxido de sodio acuoso al 20 %, se secaron sobre sulfato de sodio, se filtraron y se concentraron, proporcionando 43.0 g del intermediario 10C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.66 (s, 3H), 7.57 (d, J = 8 Hz, 1H), 8.21 – 8.24 (dd, 1H), 8.48 (d, J = 2.0 Hz, 1H).

Intermediario 10. A una solución enfriada (10 °C) del intermediario 10C (43 g, 0.17 mol) en dioxano seco (430 ml) se

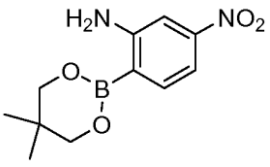
añadió gota a gota durante 1.5 h una solución de bromo (31 g) en dioxano (430 ml). La reacción se enfrió durante 30 min y después se añadió agua enfriada con hielo (150 ml). La reacción se extrajo con acetato de etilo (2 x 200 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron. La purificación mediante cromatografía en fase normal (éter de petróleo/acetato de etilo dio 30 g del intermediario 10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H), 7.62 (d, J = 8.4 Hz, 1H), 8.25 – 8.27 (dd, 1H), 8.50 (d, J = 2.4 Hz, 1H).

Intermediario 11. 4-(2-Bromoacetil)-3-(pent-4-eniloxi)fenilcarbamato de metilo



Este compuesto se preparó siguiendo los procedimientos descritos en el intermediario 7, reemplazando el 4-bromobut-1-eno con 5-bromopent-1-eno. EM (ESI) m/z: 355.9 (M+H)+, 357.9 (M+2+H)+.

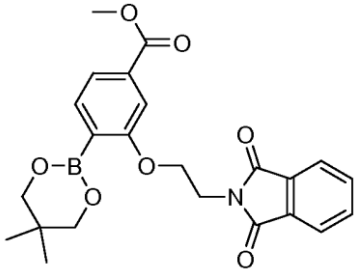
Intermediario 12. 2-(5,5-Dimetil-1,3,2-dioxaborinan-2-il)-5-nitro-fenilamina



A un recipiente secado con llama, equipado con un

condensador de reflujo, que contenía 2-bromo-5-nitroanilina (10.0 g, 46.1 mmol), bis(neopentil glicolato)diboro (13.01 g, 57.6 mmol), acetato de potasio (13.57 g, 138 mmol) y aducto $PdCl_2(dppf)-CH_2Cl_2$ (0.941 g, 1.152 mmol) se añadió DMSO (132 ml). La suspensión marrón rojiza oscura resultante se desgasificó con argón durante 30 min y, a continuación, la reacción se calentó hasta 80 °C. Después de 4 h, la reacción se detuvo y se enfrió hasta ta. La reacción se vertió lentamente en agua (300 ml) enfriada con hielo agitada vigorosamente, dando una suspensión marrón. Después de agitar durante 10 min, la suspensión se filtró para recoger el sólido. El sólido se lavó con agua (3 x 125 ml), se secó al aire y, después, se secó al vacío, dando un sólido marrón. La purificación mediante cromatografía en fase normal dio 4.36 g del intermediario 12 en forma de un sólido naranja. EM (ESI) m/z: 183.1 $(M-C_5H_8+H)+$.

Intermediario 13. Éster metílico del ácido 4-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etoxi]-benzoico

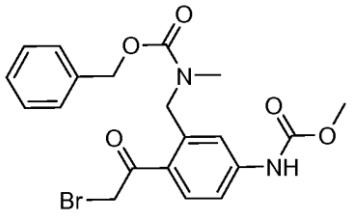


Intermediario 13A. Éster metílico del ácido 4-bromo-3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etoxi]-

benzoico: A una solución de 4-bromo-3-hidroxibenzoato de metilo (2.0 g, 8.66 mmol) y 2-(2-bromoetil)isoindolina-1,3-diona (2.419 g, 9.52 mmol) en DMF (10 ml) se añadió NaH (0.866 g, 21.64 mmol) en pequeñas porciones a 0 °C. La reacción se agitó en atmósfera de argón a 0 °C durante 2 h. La reacción se calentó a 60 °C y se agitó durante 4 h. Después de enfriar a ta, la mezcla de reacción se diluyó con EtOAc, se lavó con HCl 1 M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en fase normal dio el intermediario 13A (0.36 g, 10.3 % de rendimiento) en forma de un sólido blanco. EM (ESI) m/z: 404.0, 406.0 (M+H)+.

El intermediario 13 se preparó siguiendo el procedimiento descrito en el intermediario 12, reemplazando la 2-bromo-5-nitroanilina por el intermediario 13A y llevando a cabo la reacción en acetonitrilo a 90 °C. MS (ESI) *m/z:* 352.1 (M+H)+.

Intermediario 14. Éster metílico del ácido [3-[(benciloxicarbonil-metil-amino)-metil]-4-(2-bromo-acetil)-fenil]-carbámico

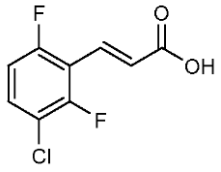


Intermediario 14A. 5-Amino-2-

bromobencil(metil)carbamato de bencilo: A una mezcla de 2-bromo-5-nitrobencil(metil)carbamato de bencilo (3.0 g, 7.91 mmol) en MeOH (60 ml) se añadió cloruro de amonio (2.116 g, 39.6 mmol) y zinc (2.59 g, 39.6 mmol) a 0 °C. La mezcla de reacción se calentó hasta ta y se agitó en atmósfera de argón durante 3 h. El sólido se separó por filtración y el solvente se eliminó, dando el intermediario 14A (2.72 g, 98 % de rendimiento) en forma de un sólido canela claro. EM (ESI) m/z: 350.8 (M+H)+.

El intermediario 14 se preparó siguiendo los procedimientos descritos en el intermediario 9, reemplazando 4-yodo-3-nitroanilina por el intermediario 14A. EM (ESI) m/z: 449.0 (M+H)+.

Intermediario 15. Ácido (E)-3-(3-cloro-2,6-difluoro-fenil)-acrílico



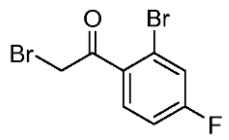
Intermediario 15A. 3-Cloro-2,6-difluorobenzaldehído: A una solución de (3-cloro-2,6-difluorofenil)metanol (1.07 g, 5.99 mmol) en CH_2Cl_2 (20 ml) se añadió periodinano de Dess-Martin (3.05 g, 7.19 mmol). Después de 2h, la reacción se concentró. La purificación mediante cromatografía en fase normal dio 15A (0.94 g, 89 % de rendimiento) en forma de un sólido blanco. EM (ESI) m/z:

177.1 (M+H).

Intermediario 15B. 3-(3-Cloro-2,6-difluorofenil)acrilato de (E)-*terc*-butilo: A una solución del intermediario15A (0.94 g, 5.32 mmol) en THF (30 ml) se añadieron 2-(dimetoxifosforil)acetato de terc-butilo (1.194 g, 5.32 mmol) y KO*t*Bu (0.896 g, 7.99 mmol). Después de 2h, la reacción se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía en fase normal proporcionó el intermediario 15B (0.866 g, 59.2 % de rendimiento) en forma de un aceite incoloro claro. EM (ESI) m/z: 219.2 (M-*t*Bu+H)+.

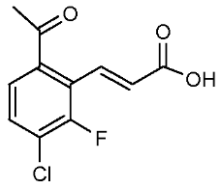
Intermediario 15. A una solución del intermediario 15B (0.866 g, 3.15 mmol) en DCM (7.0 ml) se añadió TFA (3.0 ml, 38.9 mmol). Después de 1.5 h, la reacción se concentró y el residuo se secó al vacío, dando el intermediario 15 (0.689 g, 100 % de rendimiento) en forma de un sólido blancuzco. EM (ESI) m/z: 219.1 (M+H).

Intermediario 17. 2-Bromo-1-(2-bromo-4-fluoro-fenil)-etanona



La sintesis se describe como Método A-1, página 92 en la solicitud internacional PCT N° WO 2005/014566 publcada el 17/02/2005.

Intermediario 18. Ácido (E)-3-(6-acetil-3-cloro-2-fluoro-fenil)-acrílico



Intermediario 18A. Ácido 2-bromo-4-cloro-3-fluorobenzoico: A una solución enfriada (-78 °C) de DIEA (4.9 ml, 48 mmol) en THF se añadió gota a gota n-BuLi (132 ml, 2.3 eq, solución 2.5 M). La mezcla se agitó a -30 °C durante 30 min. La mezcla de reacción se enfrió de muevo a -78°C, y se añadió solución de ácido 4-cloro-3-fluorobenzoico (25 g, 143 mmol) en THF durante 1 h. La reacción se agitó a -78°C durante la noche. El día siguiente se añadió una solución de 1,2-dibromo-1,1,2,2-tetracloroetano (87 g, 267 mmol) en THF y la reacción se agitó a -78 °C durante 2 h adicionales y, a continuación a TA durante 4 h. La reacción se inactivó con agua, las capas se separaron y la capa acuosa se lavó con Et_2O. La capa acuosa se acidificó con HCl 1.5 N y, a continuación, se extrajo en EtOAc (2 x 200 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, se filtraron y se concentraron, proporcionando el intermediario 18A (30 g, 83.3 %). EM (ESI) m/z: 252.6 [M-H] -.

Intermediario 18B. 2-((2-Bromo-4-cloro-3-fluorofenil) (hidroxi)metileno)malonato de dietilo: A una

suspensión de intermediario 18A (14.6 g, 57 mmol) en DCM (200 ml) se añadió cloruro de tionilo (6.6 ml, 88 mmol). La mezcla se agitó a reflujo durante 3 h. El solvente se retiró y el residuo se secó al vació, proporcionando el cloruro ácido en forma de un sólido marrón claro.

A una suspensión enfriada (0 °C) de hidruro de sodio (3.66 g (60 %), 91.5 mmol) en THF se añadió una solución de malonato de dietilo (0.612 g, 3.82 mmol) en THF (5 ml). Después de 10 min, se añadió lentamente (16.4 g, 60 mmol) en THF (160 ml). Después de la adición, la reacción se calentó hasta TA. Después de 30 min, el solvente se retiró y el residuo se trató con HCl 1.2 M (150 ml) (0 °C). La mezcla se extrajo con EtOAc (3 x 250 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron, dando el intermediario 18B (20 g, 87 %) en forma de un sólido. EM (ESI) m/z: 395/397 (M+H)+.

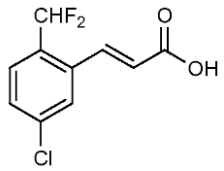
Intermediario 18C. 1-(2-Bromo-4-cloro-3-fluorofenil)-etanona: Una solución de intermediario 18B (18.6 g, 47 mmol) en ácido acético (200 ml), H_2O (150 ml) y H_2SO_4 (2.0 ml) se agitó a 110 °C durante 4 h. La mayor parte del solvente se retiró y el residuo se diluyó con EtOAc (400 ml), se lavó con agua (5 x 20 ml), $NaHCO_3$ saturado, NaOH 1 N y salmuera. El solvente se eliminó, dando el intermediario 18C (10 g, 84 %) en forma de un sólido de bajo punto de fusión.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.42 (c, *J* = 6.8, 6.4 Hz, 1 H), 7.24 (c, *J* = 6.4, 5.2 Hz, 1 H), 2.5 (s, 3H).

Intermediario 18D. 3-(6-Acetil-3-cloro-2-fluorofenil)acrilato de (E)-terc-butilo: A una mezcla de intermediario 18C (50 g, 198 mmol), acrilato de terc-butilo (50.9 g, 397 mmol) y TEA (55 ml, 397 mmol) en DMF (500 ml) se añadió Pd(OAc)2 (8.9 g, 39.7 mmol). La mezcla resultante se agitó a 90 °C durante la noche. La reacción se enfrió hasta TA, se filtró y el filtrado se concentró. La purificación mediante cromatografía en fase normal dio el intermediario 18D (30 g, 50.8 %) en forma de un sólido amarillo claro. EM (ESI) m/z: 242.7 (M+H)+.

Intermediario 18. Una solución del intermediario 18D (25 mg, 84 mmol) en DCM (330 ml) y TFA (330 ml) se agitó a TA. Después de 1.5 h, el solvente se concentró, dando el intermediario 18 (19.5 g, 97.0) en forma de un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.69 (s ancha, 1 H), 7.80-7.76 (m, 2 H), 7.62 (d, *J* = 12.1 Hz, 1 H), 6.30 (dd, *J* =2.4, 2.0 Hz, 1 H), 2.6 (s, 3H). EM (ESI) m/z: 241 (M-H)+.

Intermediario 19. Ácido (E)-3-(5-cloro-2-(difluorometil)fenil)acrílico



Intermediario 19A. 2-Bromo-4-cloro-1-

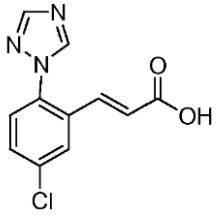
(difluorometil)benceno: A una solución de 2-bromo-4-clorobenzaldehído (1 g, 4.56 mmol) en DCM (15 ml) se añadió DAST (0.903 ml, 6.83 mmol) a 0 °C. La reacción se dejó calentar hasta ta y se agitó durante la noche. La mezcla de reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ sat y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró, dando el intermediario 19A (0.88 g, 80 % de rendimiento) en forma de un aceite claro. EM (ESI) m/z: 261.2 (M+Na)+.

Intermediario 19B. 3-(5-Cloro-2-(difluorometil)fenil)acrilato de (E)-terc-butilo: A una solución del intermediario 19A (0.88 g, 3.64 mmol) en DMF (10 ml) se añadió acrilato de terc-butilo (1.401 g, 10.93 mmol), TEA (1.270 ml, 9.11 mmol) y acetato de paladio (0.082 g, 0.364 mmol). La reacción se calentó hasta 90 °C. Después de 5h, la reacción se enfrió hasta ta y, a continuación, se retiró el sólido. El filtrado se diluyó con EtOAc, se lavó con HCl 1 M, $NaHCO_3$ sat y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía en fase normal dio el intermediario 19B (232 mg, 22 % de rendimiento) en forma de un aceite tostado. EM (ESI) m/z: 233.1(M-tBu)+.

Intermediario 19. Una solución del intermediario 19B (232 mg, 0.804 mmol) en DCM (2.0 ml) se añadió TFA (2.0 ml, 26.0 mmol). La reacción se agitó en atmósfera de argón a

ta. Después de 1 h, el solvente se retiró y el residuo se secó, dando el intermediario 19 (191mg, 100 % de rendimiento) en forma de un sólido tostadoa. ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (dt, *J* = 15.8, 1.5 Hz, 1H), 7.83 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.01 (t, *J* = 54.6 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -111.67 (s, 2F). EM (ESI) m/z: 233.1 (M+H)+.

Intermediario 20. Ácido (E)-3-(5-cloro-2-(1H-1,2,4-triazol-1-il)fenil)-acrílico



Intermediario 20A 5-Cloro-2-(1H-1,2,4-triazol-1-il)benzaldehído: Una mezcla de 5-cloro-2-fluorobenzaldehído (0.634 g, 4 mmol), 1H-1,2,4-triazol (0.290 g, 4.20 mmol) y carbonato de cesio (1.564 g, 4.80 mmol) en DMF (6 ml) se agitó a 50 °C. Después de 20 h, la reacción se enfrió hasta TA, se repartió entre agua y EtOAc y las capas se separaron. Las capas orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se suspendió en DCM (5 ml) y, a continuación, se filtró. El sólido se lavó con hexano, se secó al aire y se secó al vacío, dando 0.22 g (26.5 %) del intermediario 20A, en forma de un sólido amarillo. EM (ESI) m/z: 208.1 (M+H)+. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 8.2 Hz, 1 H), 7.72

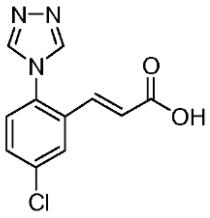
(dd, J = 2.2 Hz, 8.2 Hz, 1 H), 8.06 (d, J = 2.2 Hz, 1 H), 8.20 (s, 1 H), 8.48 (s, 1 H), 9,99 (s, 1 H).

Intermediario 20B. 3-(5-Cloro-2-(1H-1,2,4-triazol-1-il)fenil)acrilato de (E)-terc-butilo: A una suspensión de NaH (60 %, 0.100 g, 2.495 mmol) en THF (4 ml) se añadió gota a gota 2-(dimetoxifosforil)acetato de terc-butilo (0.530 ml, 2.67 mmol). La mezcla de reacción turbia se agitó a TA durante 45 min y, a continuación, se enfrió hasta 0 °C. A continuación, se añadió una solución de intermediario 20A (0.37 g, 1.78 mmol) en THF (14 ml). La mezcla de reacción se tornó naranja. Después de 30 min, la reacción se inactivó con NH_4Cl saturado y, a continuación, la reacción se diluyó con EtOAc y agua. Las capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación mediante cromatografía en fase normal proporcionó 0.178 g (26 %) del intermediario 20B, en forma de una goma amarilla. EM (ESI) m/z: 306.3 (M+H)+. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 6.38 (d, *J*=15.9 Hz, 1 H), 7.34 – 7.42 (m, 2 H), 7.48 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.73 (d, *J*=2.2 Hz, 1 H), 8.17 (s, 1 H), 8.29 (s, 1 H).

Intermediario 20. A una solución del intermediario 20B (0.178 g, 0.582 mmol) en DCM (1 ml) se añadió TFA (1 ml, 12.98 mmol). La mezcla de reacción se agitó a TA durante 1 h y después se concentró a sequedad. Se añadió MeOH (3 ml) dando una suspensión blanca. El sólido se recogió mediante

filtración y se lavó con una cantidad pequeña de metanol. El sólido se secó al aire y se secó al vacío, dando 0.076 g (52 %) del intermediario 20, en forma de un sólido blanco. EM (ESI) m/z: 250.1 (M+H)+. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.65 (d, 15.9 Hz, 1 H), 7.21 (d, 15.9 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.68 (dd, J = 2.2 Hz, 8.2 Hz, 1 H), 8.16 (d, J = 2.2 Hz, 1 H), 8.32 (s, 1 H), 8.93 (s, 1 H), 12.64 (s, 1 H).

Intermediario 21. Ácido (E)-3-(5-cloro-2-(4H-1,2,4-triazol-4-il)fenil)acrílico



Intermediario 21A 4-(4-Cloro-2-yodofenil)-4H-1,2,4-triazol: A una suspensión de 4-cloro-2-yodoanilina (0.760 g, 3 mmol) y N'-formilformohidrazida (0.793 g, 9 mmol) en piridina (12 ml) se añadió gota a gota clorotrimetilsilano (5.71 ml, 45 mmol) seguido de TEA (2.84 ml, 20.4 mmol). La mezcla de reacción se calentó a 100 °C. Después de 4 h, la reacción se enfrió hasta TA y la reacción se concentró, dando un sólido. El sólido se suspendió en agua y el sólido se recogió por filtración, lavándolo con agua. El sólido se secó al aire y se secó al vacío, dando 0.8 g de un sólido blancuzco. La purificación mediante cromatografía en fase normal proporcionó 0.59 g (64 %) del intermediario 21A, en

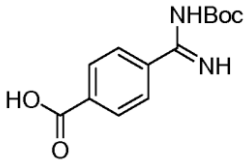
forma de un sólido blanco. EM (ESI) m/z: 306.1 (M+H)+. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.56 (d, J = 8.2 Hz, 1 H), 7.67 (dd, J = 2.2 Hz, 8.2 Hz, 1 H), 8.17 (d, J = 2.2 Hz, 1 H), 8.78 (s, 2 H).

Intermediario 21B. 3-(5-Cloro-2-(4H-1,2,4-triazol-4-il)fenil)acrilato de (E)-terc-butilo: A una solución desgasificada del intermediario 21A (0.48 g, 1.571 mmol), tributilamina (0.749 ml, 3.14 mmol) y acrilato de terc-butilo (1.151 ml, 7.86 mmol) en DMF (7.86 ml) se añadió paladio sobre carbono (10 %, 0.167 g, 0.157 mmol) y acetato de paladio (II) (0.035 g, 0.157 mmol). La reacción se calentó a 100 °C durante 18 h. Se añadió acrilato de terc-butilo (1.151 ml, 7.86 mmol) adicional y acetate de paladio (II) (0.035 g, 0.157 mmol) y la reacción se agitó a 100 °C durante otras 48 h. La reacción se enfrió hasta TA, se filtró a través de GMF de 0.45 µm y se lavó con EtOAc. El filtrado se diluyó con EtOAc, se lavó con agua, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en fase normal seguida de cromatografía en fase inversa proporcionó 0.122 g (25%) del intermediario 21B, en forma de un sólido blanco. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.47 (s, 9 H), 6.51 (d, *J*=16.0 Hz, 1 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.52 (d, *J*=8.5 Hz, 1 H), 7.62 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 8.86 (s, 2 H).

Intermediario 21. A una solución del intermediario

21B (0.122 g, 0.399 mmol) en DCM (0.5 ml) se añadió TFA (0.5 ml, 6.49 mmol). La reacción se agitó a TA durante 2 h y después se concentró, proporcionando 0.100 g (100 %) del intermediario 21, en forma de un sólido blanco. EM (ESI) m/z: 249.9 (M+H)+.

Intermediario 22. Ácido 4-(N-(terc-butoxicarbonil)carbamimidoil)benzoico, sal de 2NaOH



Intermediario 22A 4-(N-Hidroxicarbamimidoil)benzoato de metilo: A una solución de 4-cianobenzoato de metilo (1.003 g, 6.22 mmol) en MeOH (15 ml) se añadió clorhidrato de hidroxilamina (2.162 g, 31.1 mmol) y TEA (4.34 ml, 31.1 mmol). La reacción se agitó a TA durante 24 h y después la reacción se concentró, dando un sólido blanco. Se añadió agua y DCM, dando una suspensión. La suspensión se filtró y el sólido se lavó con agua y después se secó al aire, dando 1.14 g (94 %) del intermediario 22A en forma de un sólido blanco. EM (ESI) m/z: 195.0 (M+H)+. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 3.91 (s, 3 H), 7.74 – 7.77 (m, 2 H), 8.01 – 8.04 (m, 2 H). El material se llevó a la siguiente etapa sin purificación adicional.

Intermediario 22B 4-Carbamimidoilbenzoato de metilo, 1 sal de ácido acético: A una solución de

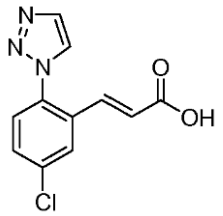
intermediario 22A (1.14 g, 5.87 mmol) en ácido acético (5 ml) se añadió anhídrido acético (2 ml, 21.20 mmol). La reacción se tornó en un gel blanco. Después de 10 min, se añadió MeOH (50 ml) seguido de paladio sobre carbono (10 % p/p, 0.625 g, 0.587 mmol). Se burbujeó hidrógeno gas a través de la mezcla de reacción durante unos pocos minutos y después se agitó la reacción bajo un globo de H_2. Después de 24 h, la reacción se filtró a través de GMF de 0.45 µm, lavándose con MeOH. El filtrado se concentró, dando 32 g (94 %) del intermediario 22B en forma de un sólido blanco. EM (ESI) m/z: 179.0 (M+H)+. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.90 (s, 3 H), 3.96 (s, 3 H), 7.89 (d, *J*=8.8 Hz, 2 H), 8.22 (d, *J*=8.8 Hz, 2 H).

Intermediario 22C. 4-(N-(terc-butoxicarbonil)carbamimidoil)benzoato de metilo: A una suspensión blanca del intermediario 22B (1.82 g, 7.64 mmol) en DCM (102 ml) se añadio dicarbonato de di-terc-butilo (2.452 g, 11.24 mmol) y TEA (4.27 ml, 30.6 mmol). La mezcla de reacción se agitó a TA. Con el tiempo, la reacción se tornó en una solución clara. Después de 72 h, se añadió dicarbonato de di-terc-butilo (0.4 eq, 0.879 g) adicional y la reacción se agitó a TA. Después de 24 horas adicionales, la reacción se concentró. La purificación mediante cromatografía en fase normal proporcionó 0.84 g (30 %) del intermediario 22C, en forma de un sólido blanco. EM (ESI) m/z: 277.3 (M-H)-. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.52 (s, 9

H), 3.93 (s, 3 H), 7.86 – 7.91 (m, 2 H), 8.07 – 8.10 (m, 2 H).

Intermediario 22. A una solución del intermediario 22C (0.84 g, 3.02 mmol) en MeOH (15.09 ml) se añadió NaOH 1 N (6.04 ml, 6.04 mmol), dando una mezcla blanca turbia. Se añadió MeOH (15.09 ml) adicional y la solución clara resultante se agitó a TA. Después de 24 h, el solvente se concentró, dando 0.895 g (86 %) del intermediario 22 en forma de un sólido blanco. EM (ESI) m/z: 265.3 (M+H)+. El material se usó en la siguiente etapa sin purificación adicional.

Intermediario 23. Ácido (E)-3-(5-cloro-2-triazol-1-il-fenil)acrílico



Intermediario 23A 5-Cloro-2-1,2,3-triazol-1-il-benzaldehído e intermediario 23B. 5-Cloro-2-1,2,3-triazol-2-il-benzaldehído: A una solución de 5-cloro-2-fluorobenzaldehído (1 g, 6.31 mmol) en DMF (12.6 ml) se añadió 1H-1,2,3-triazol (0.365 ml, 6.31 mmol) y Cs_2CO_3 (4.11 g, 12.61 mmol). La reacción se agitó a TA durante 18 h. Se añadió agua a la reacción, y la suspensión resultante se acidificó con HCl 1 N a pH<3, y después la reacción se filtró. El filtrado se extrajo con EtOAc (3x). Las fases

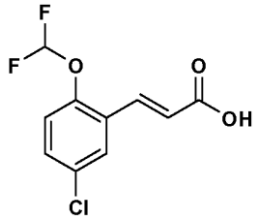
orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La trituración con DCM/hexano dio 0.35 g como una mezcla del intermediario 23A y el intermediario 23B en forma de un sólido amarillo. El material se usó en la siguiente etapa sin purificación adicional.

Intermediario 23C. Éster terc-butílico del ácido (E)-3-(5-cloro-2-1,2,3-triazol-1-il-fenil)acrílico e intermediario 23D. Éster terc-butílico del ácido (E)-3-(5-cloro-2-1,2,3-triazol-2-il-fenil)acrílico e intermediario 23D. El compuesto del título se preparó de acuerdo con el procedimiento descrito en el intermediario 20B, reemplazando el intermediario 20A por una mezcla de intermediario 23A e intermediario 23B. Los regioisómeros de triazol se separaron por cromatografía en fase normal, lo que dio 0.147 g (28.5 %) del intermediario 23C. EM (ESI) m/z: 306.1 (M+H)+. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.48 (s, 9 H), 6.36 (d, *J*=16.0 Hz, 1 H), 7.21 (d, *J*=16.0 Hz, 1 H), 7.44 (d, *J*=8.5 Hz, 1 H), 7.48 – 7.52 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.74 (d, *J*=2.2 Hz, 1 H), 7.79 (d, *J*=1.1 Hz, 1 H), 7.89 (d, *J*=1.1 Hz, 1 H).

Intermediario 23. El compuesto del título se preparó de acuerdo con el procedimiento descrito en el intermediario 20, reemplazando el intermediario 20B por el intermediario 23C. EM (ESI) m/z: 250.0 (M+H)+. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 6.51 (d, *J*=15.7 Hz, 1 H), 7.22 (d, *J*=16.0

Hz, 1 H), 7.53 (d, *J*=8.5 Hz, 1 H), 7.63 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.96 (d, *J*=0.83 Hz, 1 H), 8.00 (d, *J*=2.2 Hz, 1 H), 8.30 (d, *J*=0.83 Hz, 1 H).

Intermediario 24. Ácido (E)-3-(5-cloro-2-difluorometoxi-fenil)-acrílico

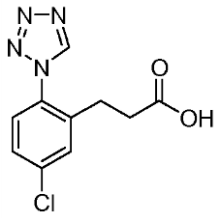


Intermediario 24A. Éster terc-butílico del ácido (E)-3-(5-cloro-2-difluorometoxi-fenil)-acrílico A una solución enfriada (0 °C) de terc-butóxido de potasio (0.407 g, 3.63 mmol) en THF (10 ml) se añadió 2-(dimetoxifosforil)acetato de terc-butilo (0.528 ml, 2.66 mmol) y 5-cloro-2-(difluorometoxi)benzaldehído (0.50 g, 2.420 mmol). La reacción se dejó calentar lentamente a TA. Después de 4h, la reacción se inactivó con la adición de cloruro de amonio sat. La reacción se diluyó con EtOAc, se lavó con cloruro de amonio sat., $NaHCO_3$ sat. y salmuera. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en fase normal proporcionó 550 mg (74 %) del intermediario 24A, en forma de un sólido blanco. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.77 (1 H, d, J=16.31 Hz), 7.58 (1 H, d, J=2.51 Hz), 7.31 (1 H, dd, J=8.66, 2.64 Hz), 7.12 (1 H, d, J=8.78 Hz),

6.52 (1 H, t, J=72.78 Hz) 6.40 (1 H, d, J=16.31 Hz), 1.53 (9 H, s). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm-81.11, EM (ESI) m/z: 327.0 (M+Na)+.

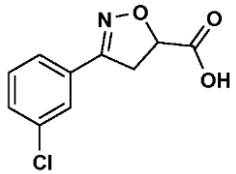
Intermediario 24. A una solución del intermediario 24A (458 mg, 1.503 mmol) en DCM (4.0 ml) se añadió TFA (2.0 ml, 26.0 mmol). La reacción se agitó en atmósfera de argón a TA durante 1 h. El solvente se retiró, dando el intermediario 24 en forma de un sólido blanco. EM (ESI) m/z: 249.0 (M+H)+.

Intermediario 25. Ácido 3-(5-cloro-2-tetrazol-1-il-fenil)-propiónico



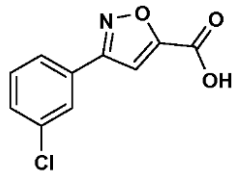
La síntesis se describe como ejemplo 63A en la solicitud internacional PCT N° WO 2007/070826, publicada el 21/06/07.

Intermediario 26: Ácido 3-(3-clorofenil)-4.5-dihidroisoxazol-5-carboxílico



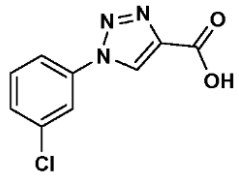
El intermediario 26 se obtuvo usando el procedimiento descrito en el documento de patente de Estados Unidos N° 4,889,551 A1 (1989).

Intermediario 27: Ácido 3-(3-clorofenil)isoxazol-5-carboxílico



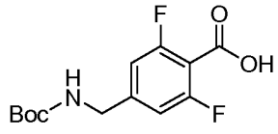
El intermediario 27 se obtuvo mediante el procedimiento descrito por Gruenanger, F., *Gazz. Chim. Ital.*, 89:598-609 (1959).

Intermediario 28: Ácido 1-(3-clorofenil)- 1H-1,2,3-triazol-4-carboxílico



El intermediario 28 mediante el procedimiento descrito por Sader Al, B.H. y col., *Tetrahedron Letters*, 4661-4664 (1985).

Intermediario 29. Ácido 4-(terc-butoxicarbonilamino-metil)-2,6-difluoro-benzoico



Intermediario 29A. Ácido 4-ciano-2,6-difluoro-benzoico: A una solución clara, incolora, enfriada (-78 °C) de 3.5-difluorobenzonitrilo (1 g, 7.19 mmol) en THF (28.8 ml) se añadió gota a gota n-butil-litio 1.6 M en hexano (4.49 ml,

7.19 mmol), dando una solución roja-naranja. Después de 45 min, se burbujeó dióxido de carbono (sublimación de hielo seco pasando a través de una torre de drierita) a través de la reacción, dando eventualmente una suspensión blancuzca. Después de 25 min, la reacción se inactivó con HCl (aq) 1 M y la reacción se dejó calentar hasta TA. La reacción se extrajo con EtOAc (2x). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron hasta un residuo blanco. El residuo bruto se fraccionó entre EtOAc y NaOH (aq) 1 M y las capas se separaron. La capa orgánica se extrajo con NaOH (aq) 1 N (2x). Las capas acuosas se combinaron y después se lavaron con EtOAc (2x). La capa acuosa se acidificó después a pH ~2, dando una suspensión blanca turbia. La capa acuosa se extrajo con EtOAc (2x). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron, dando 922.5 mg (65.3 %) del intermediario 29A en forma de un sólido blanco. EM (ESI) m/z: 184.0 (M+H)+.

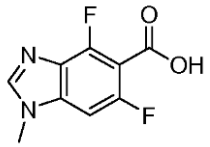
Intermediario 29B. Ácido 4-aminometil-2,6-difluoro-benzoico: Una suspensión negra del intermediario 29A (922.5mg, 5.04 mmol) y Pd/C (268 mg, 0.126 mmol) en EtOH (50.4 ml) se desgasificó con hidrógeno (globo) durante varios minutos. La reacción se agitó en atmósfera de hidrógeno durante 24 h. La reacción se filtró a través de CELITE® eluyendo con HCl (aq) 1 M y MeOH. El filtrado se concentró

hasta un sólido amarillo pálido. El sólido se disolvió en HCl 1 N y EtOAc (1:1) y las capas se separaron. La capa acuosa se neutralizó a pH 7 y se extrajo con isopropanol al 15%/cloroformo. La capa acuosa todavía contenía algo de producto, así que las capas orgánica y acuosa se concentraron y combinaron, dando el intermediario 29B en forma de un sólido blancuzco. EM (ESI) m/z: 188.0 (M+H)+. El producto se usó como tal, sin purificación adicional.

Intermediario 29. A una suspensión del intermediario 29B (943 mg, 4.22 mmol) en DCM (14.1 ml) se añadió trietilamina (2.351 ml, 16.87 mmol) seguida de BOC_2O (1.077 ml, 4.64 mmol). Se añadió DMF (5ml) para facilitar la mezcla. Después de agitar durante 1.5 h, la suspensión ligeramente violeta se diluyó con agua y DCM y las capas se separaron. La capa acuosa se neutralizó a pH~7 usando HCl (aq) 1 N y después se extrajo con EtOAc (2x). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron, dando un aceite viscoso rosa. La purificación por cromatografía en fase normal dio (0-10 % DCM:MeOH) dio 803.2 mg (55.0 %) del intermediario 29, en forma de un aceite claro. EM (ESI) m/z: 232.2 (M – C_4H_8 + H)+. ^{1}H NMR (500 MHz, CD_3OD) δ: 1.46 (s, 9 H), 4.24 (s, 2 H), 6.95 (d, *J*=9.3 Hz, 2 H).

Intermediario 30. 4,6-Difluoro-1-metil-1H-

benzo[d]imidazol-5-carboxílico



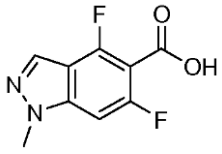
Intermediario 30A. 3,5-Difluoro-N-metil-2-nitroanilina: Una solución de 1,3,5-trifluoro-2-nitrobenceno (1.0 g, 5.65 mmol) y metanamina (8.47 ml, 16.94 mmol) en MeOH (10 ml) se agitó durante 4 h a 80 °C. La mezcla de reacción se concentró al vacío, proporcionando un aceite, que se sometió a la reacción siguiente sin purificación adicional. EM (ESI) m/z: 189.2 (M+H)+.

Intermediario 30B. 4,6-Difluoro-1-metil-1H-benzo[d]imidazol: Se calentó una solución del intermediario 30A (1.063 g, 5.65 mmol) en ácido fórmico (5 ml) a 80 °C durante 12 h. Después de la concentración, la mezcla de reacción se diluyó en EtOAc (100 ml) y se lavó con NaOH aq 1N. La solución orgánica se secó sobre Na_2SO_4 y se concentró al vacío, dando una mezcla oleosa. Se purificó mediante cromatografía de columna en fase normal, proporcionando el intermediario 30B (0.39 g, 41.1 %).

Intermediario 30. (Referencia: documento WO 2009/083526). A una solución del intermediario 30B (227 mg, 1.35 mmol) en THF (10 ml) se añadió BuLi (0.74 ml, 1.485 mmol) gota a gota, y la solución resultante se agitó durante 0.5 h a -78 °C. A la solución se añadió bromotrimetilsilano

(0.175 ml, 1.350 mmol) gota a gota, y la solución se agitó durante 15 min. A la solución se añadió gota a gota sec-butil-litio (1.298 ml, 1.688 mmol) y la solución se agitó durante 0.5 h. La solución se vertió entonces en solución en THF de hielo seco (2 trozos). La solución se agitó durante 1h a -78 °C. La reacción se inactivó después añadiendo HCl 1 N y la reacción se calentó hasta TA. La reacción se concentró y después se purificó mediante cromatografía de fase inversa, lo que dio el intermediario 30 (121 mg, 41.0 %). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.80 (s, 1 H), 7.51 (d, *J*=9.0 Hz, 1 H), 3.99 (s, 3 H). EM (ESI) m/z: 213.0 (M+H)+.

Intermediario 31. Ácido 4,6-difluoro-1-metil-1H-indazol-5-carboxílico



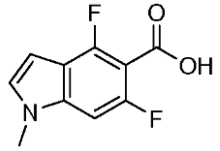
Intermediario 31A. (E)-1-Metil-2-(2.4,6-trifluorobencilideno)hidrazina: Una solución de monometil hidrazina (2.158 g, 46.8 mmol) y 2,4,6-trifluorobenzaldehído (2.5g, 15.6 mmol) en THF (20 ml) se agitó a TA durante 5 h. La mezcla de reacción se concentró al vacío, proporcionando un residuo oleoso, que se sometió a la reacción siguiente sin purificación adicional. EM (ESI) m/z: 189.4 (M+H)+.

Intermediario 31B. 4,6-Difluoro-1-metil-1H-indazol: Una solución de intermediario 31A (8.84 g, 47 mmol) en DMF (5

ml) y piridina (5.00 ml) se agitó a 90 °C durante 12 h. La mezcla de reacción se concentró al vacío, proporcionando una mezcla oleosa, que se purificó usando cromatografía en fase normal, proporcionando el intermediario 31B (2.3 g, 29.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (s, 1 H), 6.78 (d, *J*=8.5 Hz, 1 H), 6.55 (td, *J*=9.7, 1.8 Hz, 1 H), 3.95 (s, 3 H). EM (ESI) m/z: 169.0 (M+H)+.

Intermediario 31. A una solución de intermediario 31B (250 mg, 1.48 mmol) en THF (15 ml) se añadió LDA (0.89 µl, 1.78 mmol) en varias porciones y la solución oscura resultante se agitó durante 0.5 h a -78 °C. A la solución se añadieron unos pocos trozos de hielo seco. La solución resultante se agitó a -78 °C durante 0.5 h y a 25 °C durante 0.5 h. Se diluyó con EtOAc (40 ml) y se lavó con HCl 1 N. La solución orgánica se secó sobre $MgSO_4$ y se concentró al vacío, proporcionando un aceite, que se purificó mediante cromatografía de fase inversa, proporcionando el intermediario 31 (0.26 g, 82 %). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.15 (s, 1 H), 7.27 (d, *J*=10.0 Hz, 1 H), 4.04 (s, 3 H). EM (ESI) m/z: 212.9 (M+H)+.

Intermediario 32: Ácido 4,6-difluoro-1-metil-1H-indol-5-carboxílico

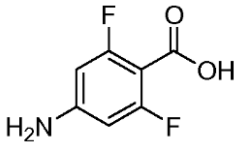


Intermediario 32A. 4,6-Difluoro-1-metil-1H-indol:

La síntesis se describe en el documento WO 2009/050235.

Intermediario 32. En un matraz de fondo redondo de 25 ml secado a la llama, se enfrió diisopropilamina (0.352 ml, 2.51 mmol) en 10 ml de THF seco hasta 0 °C con atmósfera de argón, se añadió butil-litio (1.6 M en hexano) (1.571 ml, 2.51 mmol) y se agitó a 0 °C durante 30 min, antes de enfriarlo hasta -78 °C. Se añadió gota a gota el intermediario 32A (382 mg, 2.285 mmol) en 2 ml de THF seco y se agitó a -78 °C durante 1 h, antes de añadir hielo seco a la reacción. La reacción se agitó a -78 °C durante 30 min y después se calentó hasta TA y se agitó a TA durante la noche. La reacción se concentró, se diluyó con EtOAc, se lavó con H_2O y se lavó de nuevo con EtOAc. La capa acuosa se acidificó con HCl 1 N, formándose un precipitado blanco inmediatamente. Se extrajo con EtOAc dos veces. Las capas de EtOAc se lavaron con salmuera, se secaron sobre $MgSO_4$, se retiró el sólido por filtración y se concentraron, dando el intermediario 32 en forma de un sólido amarillo pálido (177 mg, 38 %). EM (ESI) m/z: 212.1 (M+H)+.

Intermediario 33: Ácido 4-amino-2,6-difluoro-benzoico:



Intermediario 33A. Éster metílico del ácido 4-

bromo-2,6-difluorobenzoico: A una solución de ácido 4-bromo-2,6-difluorobenzoico (1.00 g, 4.22 mmol) en 30 ml de metanol se añadió TMS-Cl (1.1 ml, 8.61 mmol), y la mezcla se calentó a 60 °C en atmósfera de N_2 durante la noche. Se añadió 1 ml adicional de TMS-Cl y se continuó calentando a 60 °C durante 4 h adicionales. La mezcla de reacción se enfrió a TA y se diluyó con NaOH aq. y después se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con NaOH aq. diluido para eliminar el material de partida sin reaccionar, después se secaron sobre Na_2SO_4, se filtraron y se evaporaron, obteniéndose el intermediario 33A en forma de un sólido rosa pálido (0.86g, 81 %) EM (ESI) *m/z*: 251.05 (M+H)+.

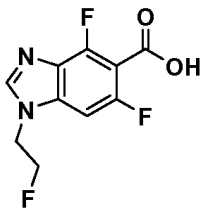
Intermediario 33B. Éster metílico del ácido 4-(benzhidrilideno-amino)-2,6-difluoro-benzoico: Intermediario 33A (0.600 g, 2.390 mmol) y carbonato de cesio (1.324 g, 4.06 mmol) se pesaron en un matraz de fondo redondo de 3 bocas de 50 ml y se purgó con N_2. Se añadió acetato de paladio (II) (10.73 mg, 0.048 mmol) y rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (0.045 g, 0.072 mmol) y a continuación 7.5 ml de tolueno. Se añadió a continuación benzofenona imina (0.521 ml, 3.11 mmol) a la mezcla de reacción, y la reacción se calentó con agitación a 100 °C durante la noche. La mezcla de reacción se diluyó con ~50 ml de Et_2O y se filtró. El filtrado se evaporó y el residuo se purificó mediante

cromatografía ultrarrápida, proporcionando el intermediario 33B en forma de un aceite amarillo, que se usó sin purificación adicional en la etapa siguiente. EM (ESI) m/z: 352.2 (M+H)+.

Intermediario 33. Se disolvió el intermediario 33B (0.840 g, 2.39 mmol) en MeOH (16 ml) y se añadió clorhidrato de hidroxilamina (0.332 g, 4.78 mmol) y acetato de sodio (0.490 g, 5.98 mmol). La mezcla se agitó durante ~1h y después se diluyó con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre Na_2SO_4, se filtraron y se evaporaron. El producto bruto se disolvió en EtOH (~12 ml) y se añadió NaOH 1 M (6 ml, 6.0 mmol). La mezcla se agitó durante 3 días a temperatura ambiente. La mezcla de reacción se neutralizó con HCl 1 M y después se evaporó para eliminar el etanol. El residuo se volvió a disolver en MeOH, se filtró y se evaporó (2X) para eliminar las cantidades de sales inorgánicas. El filtrado se evaporó y el residuo se purificó mediante HPLC en fase inversa, proporcionando el intermediario 33 (0.36g, 88 %) en forma de un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.99 (s, 2 H) 6.10 (d, *J*=10.99 Hz, 2 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -111.82 (s, 2 F).

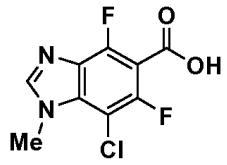
Intermediario 34. Ácido 4,6-difluoro-1-(2-fluoro-etil)-1*H*-

benzoimidazol-5-carboxílico



El intermediario 34 se preparó siguiendo los procedimientos descritos en el intermediario 30, reemplazando la metilamina por 2-fluroetanamina, HCl. EM (ESI) m/z: 245.1 (M+H)+.

Intermediario 35. Ácido 7-cloro-4,6-difluoro-1-metil-1H-benzo[d]imidazol-5-carboxílico

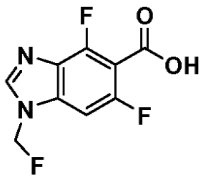


Intermediario 35A. 2-Cloro-3,5-difluoro-N-metil-6-nitroanilina: Se agitaron una solución del intermediario 30A (1.1 g, 5.85 mmol) y NCS (0.781 g, 5.85 mmol) en acetonitrilo (25 ml) durante 12 h a 70 °C. La mezcla de reacción se concentró al vacío, proporcionando un sólido amarillo, que se volvió a disolver en EtOAc y se lavó con $NaHCO_3$ aq. y salmuera. La concentración de la solución orgánica proporcionó un residuo oleoso, que se purificó mediante cromatografía en fase normal, proporcionando el intermediario 35A (0.78 g, 60 %). EM (ESI) m/z: 222.9/224.8 (M+H)+.

Intermediario 35. El intermediario 35 se preparó

siguiendo los procedimientos descritos en el intermediario 30, reemplazando el intermediario 30A por el intermediario 35A. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.18 (s, 1 H), 4.16 (s, 3 H). EM (ESI) m/z: 246.9/248.8 (M+H)+.

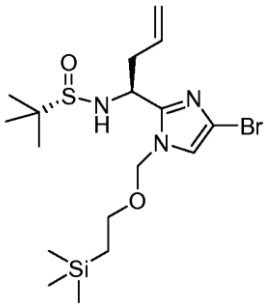
Intermediario 36. Ácido 4,6-difluoro-1-fluorometil-1H-benzoimidazol-5-carboxílico



Intermediario 36A. 4,6-Difluoro-1-(fluorometil)-1H-benzo[d]imidazol: (Referencia: *Tetrahedron*, 63:10569-10575 (2007)). A una solución de 4,6-difluoro-1H-benzo[d]imidazol (100 mg, 0.649 mmol) en DMF (5 ml) se añadió NaH (57.1 mg, 1.43 mmol) y la solución resultante se agitó durante 0.5 h a TA. La solución se enfrió hasta -78 °C y se burbujeó FCH_2Cl durante 10 min. Después, la mezcla de reacción se selló en un vial de microondas y se agitó a 80 °C durante 2h. La mezcla de reacción se diluyó con EtOAc (30 ml) y se lavó con HCl 1 N (20 ml) y después con NH_4Cl aq. La solución orgánica se concentró y se purificó usando cromatografía en fase inversa, proporcionando el intermediario 36A (52 mg, 43 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.02 (d, 2 H), 7.29 – 7.40 (m, 1 H), 7.00 – 7.13 (m, 1 H), 6.82 – 6.98 (m, 2 H), 6.29 (s, 1 H), 6.18 (d, *J*=5,5 Hz, 2 H), 6.07 (s, 1 H), 1.59 (s, 2 H). EM (ESI) m/z: 187.0 (M+H)+.

Intermediario 36. El intermediario 36 se preparó siguiendo el procedimiento descrito en el intermediario 30, reemplazando el intermediario 30B por el intermediario 36A. EM (ESI) m/z: 231.1 (M+H)+.

Intermediario 37. Ácido 2-metil-propano-2-sulfínico {(S)-1-[4-bromo-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-but-3-enil}-amida



Intermediario 37A. 2,4,5-Tribromo-1-(2-trimetilsilanil-etoximetil)-1H-imidazol: A una suspensión enfriada (0 °C) de hidruro de sodio (0.9 g, 0.03 mol) en THF (50 ml) se añadió gota a gota una solución de 2,4,5-tribromo imidazol (5 g, 0.016 mol) en THF (50 ml). Después de 1 h, se añadió gota a gota una cloruro de trimetilsililetoximetilo (SEMCl) (3 ml, 0.017 mol) en THF (30 ml). La mezcla de reacción se inactivó con solución saturada de cloruro de amonio y después la reacción se extrajo con acetato de etilo [3 x 100 ml]. Las capas orgánicas se combinaron y se lavaron con solución de bicarbonato de sodio al 10 %, agua, salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron, proporcionando 7.2 g del intermediario 37A en

forma de un aceite amarillo pálido que solidificó en reposo. El material se usó en la siguiente etapa sin purificación adicional. EM (ESI) m/z: 435 (M+2+H)+.

Intermediario 37B. 4,5-Dibromo-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-carbaldehído: A una solución enfriada (-78 °C) del intermediario 37A (16 g, 0.03 mol) en THF (160 ml) se añadió una solución de n-BuLi (13.5 ml, 3 M en hexano; 0.04 mol) gota a gota. Después de 1 h, se añadió gota a gota DMF (14 ml, 0.2 mol). Después de 1h, la reacción se inactivó con solución saturada de cloruro de amonio y, a continuación, la reacción de dejó calentar hasta TA. La reacción se extrajo con acetato de etilo (2 x 100 ml). Las capas orgánicas se combinaron y se lavaron con solución de bicarbonato de sodio al 10 %, agua, salmuera y después se concentraron. La purificación mediante cromatografía en fase normal (gradiente de elusión éter de petróleo: acetato de etilo) dio 11.5 g (40 %) del intermediario 37B. EM (ESI) m/z: 384.1 (M)+.

Intermediario 37C. (S,E)-N-((4,5-Dibromo-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)metileno)-2-metilpropano-2-sulfinamida: A una solución de intermediario 37B (35 g, 0.09 mol) en cloruro de metileno (350 ml) se añadió (*S*)-(-)-2-metil-2-propanosulfinamida (22 g, 0.18 mol) y sulfato de cobre anhidro (72 g, 0.45 mol). La suspensión resultante se agitó a TA. Después de 20 h, la reacción se

filtró a través de CELITE®. El filtrado se concentró y la purificación mediante cromatografía en fase normal (gradiente de elusión éter de petróleo:acetato de etilo) dio 42 g (94 %) del intermediario 37C en forma de un aceite amarillo que solidificó en reposo. EM (ESI) m/z: 487.3 (M+H)+.

Intermediario 37D. Ácido 2-metil-propano-2-sulfínico {(S)-1-[4,5-dibromo-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-but-3-enil}-amida A una solución enfriada (-78 °C) del intermediario 37C (17 g, 0.03 mol) en THF (170 ml) se añadió gota a gota bromuro de alilmagnesio (1 M en dietil éter, 52.3 ml, 0.05 mol). Después de 1 h, la reacción se inactivó con solución saturada de cloruro de amonio y, a continuación, la reacción de dejó calentar hasta TA. La reacción se extrajo con acetato de etilo (2 x 250 ml). Las capas orgánicas se combinaron, se lavaron con solución de bicarbonato de sodio, salmuera, agua, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron. La purificación mediante cromatografía en fase normal (gradiente de elución; hexano:acetato de etilo) dio 25 g (67 %) del intermediario 37D, en forma de un aceite amarillo pálido. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.71 (m, 1H), 5.60 (d, 1H, J = 11.6 Hz), 5.28 (m, 1H), 5.06 (m, 2H), 4.57 (c, 1H, J = 7.2 Hz), 3.98 (d, 1H, J = 8.4Hz), 3.55 (m, 2H), 2.70 (t, 2H, 7.2 Hz), 1.2 (s, 9H), 0.92 (m, 2H), -0.01 (s, 9H). EM (ESI) m/z: 529.4 (M+H)+.

Intermediario 37. Una solución del intermediario 37D (5.25 g, 9.92 mmol) en THF (33.1 ml) se desgasificó con argón durante 15 min. La solución se enfrió hasta -3°C (hielo/salmuera) y se añadió gota a gota complejo de cloruro de isopropilmagnesio y cloruro de litio en THF (8.00 ml, 10.4 mmol) durante 20 min, manteniendo la temperatura por debajo de 0 °C durante la adición. Después de 30 min, se añadió gota a gota un segundo equivalente de complejo de cloruro de isopropilmagnesio y cloruro de litio en THF (8.00 ml, 10.4 mmol) durante 20 min, manteniendo la temperatura por debajo de 0 °C durante la adición. Después de 30 min, la reacción se inactivó con cloruro de aminio sat. (30 ml) y la reacción se dejó calentar hasta TA. La reacción se fraccionó entre EtOAc y cloruro de amonio sat. y las capas se separaron. La capa acuosa se extrajo con EtOAc (1x). Las capas orgánicas se combinaron y se lavaron con $NaHCO_3$ sat., salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron, dando un aceite viscoso amarillo, claro, que pesó 4.67 g. La purificación mediante cromatografía en fase normal dio 3.98 g (89 %) del intermediario 37, en forma de un sólido blanco. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.20 (s, 1 H), 5.69 – 5.82 (m, 1 H), 5.49 (d, J=11.3 Hz, 1 H), 5.30 (d, J=11.3 Hz, 1 H), 5.09 (dd, J=17.1, 1.7 Hz, 1 H), 5.04 (d, J=10.5 Hz, 1 H), 4.62 (t, J=7.3 Hz, 1 H), 3.51 – 3.67 (m, 2 H), 2.69 (t, J=7.3 Hz, 2 H), 1.20 (s, 9 H), 0.85 – 1.04 (m, 2 H), 0.00 (s, 9 H). EM

(ESI) m/z: 450.1 (M+H)+. $[\alpha]_D^{23.6}$ = + 70.13 (c = 1.70; cloroformo).

Alternativamente, el intermediario 37 puede prepararse mediante la secuencia siguiente:

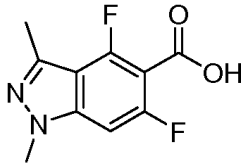
Intermediario 37E. 2,4-Dibromo-1-(2-trimetilsilanil-etoximetil)-1H-imidazol: A una suspensión enfriada (0 °C) de NaH (1.062 g, 26.6 mmol) en THF (44.3 ml) se añadió gota a gota durante 20 min una solución amarilla pálida, clara, de 2,4-dibromo-1H-imidazol (5.00 g, 22.14 mmol) en THF (20 ml). La suspensión violeta-gris resultante se agitó a 0 °C durante 1 h. A continuación, se añadió SEMCl (4.71 ml, 26.6 mmol) gota a gota. La reacción se mantuvo a 0°C durante 1 h y después se inactivó añadiendo lentamente cloruro de amonio sat. La mezcla se diluyó con EtOAc y las capas se separaron. La capa acuosa se extrajo con EtOAc (2x). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ sat., salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron, dando un líquido claro que pesó 9.06 g. La purificación mediante cromatografía en fase normal dio 5.97 g (76 %) del intermediario 37E, en forma de un líquido incoloro claro. La relación de regioisómeros por HPLC fue de 14.7:1. EM (ESI) *m/z*: 357.0 (M+2+H)+.

Intermediario 37F. 4-Bromo-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-carbaldehído: A una solución incolora, clara, enfriada (-78 °C) del intermediario 37E (1.0

g, 2.81 mmol) en THF (9.36 ml) se añadió gota a gota durante 10 min n-BuLi (1.930 ml, 3.09 mmol). La solución amarilla oro, clara, se agitó a-78 °C durante 1 h y después se añadió DMF (1.087 ml, 14.04 mmol). La reacción se agitó a -78 °C durante 1 h y después la reacción se inactivó con cloruro de amonio sat. y la reacción se dejó calentar hasta TA. La reacción se fraccionó entre EtOAc y agua y las capas se separaron. La capa orgánica se lavó con $NaHCO_3$ sat., salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en fase normal proporcionó 0.130 g (16 %) del intermediario 37F, en forma de un sólido blanco. EM (ESI) m/z: 339.1 $(M+CH_4O+2+H)+$, consecuente con el hemiacetal de la adición de metano al aldehído.

Intermediario 37. El intermediario 37 se preparó siguiendo los procedimientos descritos en el intermediario 37C, reemplazando el intermediario 37B por el intermediario 37F; seguido del procedimiento descrito en el intermediario 37D, lo que dio una mezcla 9:1 de diestereómeros.

Intermediario 38. Ácido 4,6-difluoro-1,3-dimetil-1H-indazol-5-carboxílico



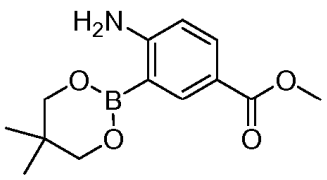
Intermediario 38A. 4,6-Difluoro-1,3-dimetil-1H-

indazol: Se pesaron en un tubo de microondas K_2CO_3 (1.191 g, 8.61 mmol) y óxido de cobre (II) (0.023 g, 0.287 mmol). Vacío y llenado con argón varias veces. Se añadió metilhidrazina (0.363 ml, 6.89 mmol). La reacción se enfrió hasta 0 °C. Se añadió gota a gota 1-(2,4,6-trifluorofenil)etanona (0.767 ml, 5.74 mmol). El tubo se colocó en una baño de aceite y se calentó a 100 °C durante 4 h, después se enfrió hasta TA durante la noche. La mezcla de reacción se diluyó con EtOAc, se lavó con H_2O, salmuera y se secó sobre $MgSO_4$. La purificación mediante cromatografía en fase normal proporcionó 877 mg (84 %) del intermediario 38A, en forma de un sólido blanco. EM (ESI) m/z: 183.0 (M+H)+.

Intermediario 38. En un matraz de fondo redondo de 25 ml secado a la llama se enfrió diisopropilamina (0.494 ml, 3.52 mmol) en THF (14.68 ml) hasta 0 °C en atmósfera de Ar. Se añadió butil-litio (1.6 M en hexano) (1.571 ml, 2.51 mmol). La reacción se agitó a 0 °C durante 1 h, antes de enfriarla hasta -78 °C. Se añadió gota a gota 4,6-difluoro-1,3-dimetil-1H-indazol (535 mg, 2.94 mmol) en 4 ml de THF seco. La reacción se agitó a -78 °C durante 1 h, antes de añadir a la reacción hielo seco. La reacción se agitó a -78°C durante 30 min y después se calentó hasta TA y se agitó a TA durante la noche. La reacción se concentró, se diluyó con EtOAc y se lavó con H_2O. La capa acuosa se acidificó con HCl 1 N. Se filtró y el sólido blanco se secó en un horno de

vacío dando160 mg (24 %) del intermediario 38 en forma de un sólido blanco. EM (ESI) m/z: 227.0 (M+H)+.

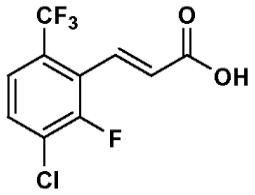
Intermediario 39. Éster metílico del ácido 4-amino-3-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-benzoico



A un recipiente secado con llama, equipado con un condensador de reflujo, que contenía 4-amino-3-bromobenzoato de metilo (2.5 g, 10.87 mmol), bis(neopentil glicolato)diboro (3.07 g, 13.58 mmol), acetato de potasio (3.20 g, 32.6 mmol) y aducto $PdCl_2$(dppf)-CH_2Cl_2 (0.222 g, 0.272 mmol) se añadió DMSO desgasificado (31.0 ml). La suspension roja-marrón oscura resultante se calentó hasta 85 °C. Después de 2.5 h, la reacción negra oscura resultante se enfrío hasta TA y se vertió en agua fría (100 ml), dando una suspensión. La suspensión se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ sat., salmuera, se secaron sobre sulfato de sodio, se filtraron y se concentraron, dando un sólido marrón que pesó 3.1 g. La purificación mediante cromatografía en fase normal dio 1.64 g (55 %) del intermediario 39, en forma de un sólido amarillo pálido. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.35 (d, J=2.20 Hz, 1 H), 7.84 (dd, J=8.53, 2.20 Hz, 1 H), 6.52 (d, J=8.53 Hz, 1 H), 5.25 (s ancho, 2 H), 3.84 (s, 3 H), 3.79 (s, 4 H), 1.03 (s, 6 H). EM

(ESI) m/z: 196.0 (M-C_5H_8+H)+.

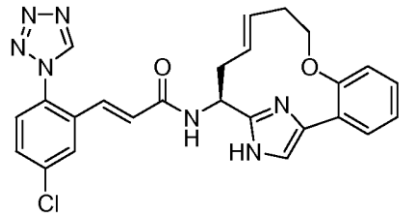
Intermediario 40. Ácido (E)-3-(3-cloro-2-fluoro-6-(trifluorometil)fenil)acrílico



El intermediario 40 se preparó siguiendo los procedimiento descritos en el intermediario 24, reemplazando 5-cloro-2-(difluorometoxi) benzaldehído por 3-cloro-2-fluoro-6-(trifluorometil)benzaldehído. EM (ESI) m/z: 292 (M+Na)+. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 (1 H, dd, *J*=16.17, 2.02 Hz), 7.49 – 7.62 (2 H, m), 6.67 (1 H, dd, *J*=16.30, 1.39 Hz).

Ejemplo 1.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-(E)-(S)-8-oxa-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il-acrilamida, sal 1 TFA



1A. Éster 2-(2-but-3-eniloxi-fenil)-2-oxo-etílico del ácido (S)-2-*terc*-butoxicarbonilamino-pent-4-enoico: Se agitó a ta durante una suspensión de ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico (515 mg, 2.394 mmol) y hidrógeno carbonato potásico (0.288 g, 2.87 mmol) en DMF (12.00 ml) 20 min. La reacción se enfrió entonces hasta 0°C

y se añadió Intermediario 6 (0.773 g, 2.87 mmol). La solución amarilla resultante se dejó calentar hasta ta. Después de agitar durante la noche, la reacción se enfrió hasta 0°C y luego se vertió en agua fría dando una suspensión blanca. La suspensión blanca se extrajo seguidamente con EtOAc (3 x 75 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron dando 1.072 g de 1A como un aceite amarillo. Este se usó sin purificación posterior. EM (IEP) m/z: 304.3 $(M-C_5H_8O_2+H)+$.

1B. Éster *terc*-butílico del ácido {(S)-1-[4-(2-but-3-eniloxi-fenil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico: El compuesto 1A (1.07 g, 2.66 mmol) se disolvió en xileno (26.6 ml) y se dividió a partes iguales entre dos viales de microondas de 20 ml. A continuación, se añadió acetato amónico (2.047 g, 26.6 mmol) a cada vial. Los viales se trataron en microondas a 140°C durante 30 min. Las soluciones naranja brillante resultantes se reunieron, se repartieron entre EtOAc y $NaHCO_3$ saturado y se separaron las fases. La fase acuosa se extrajo con EtOAc (2 x 100 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron dando un residuo color durazno. La purificación por cromatografía en fase normal dio 0.626 g (62 %) de 1B como un sólido amarillo pegajoso. EM (IEP) m/z: 384.4(M+H)+.

1C. Éster *terc*-butílico del ácido {(S)-1-[4-(2-but-3-eniloxi-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico: A una suspensión enfriada (0°C) de NaH (58.7 mg, 1.468 mmol) en DMF (2.06 ml) se añadió gota a gota una solución de 1B (536.2 mg, 1.40 mmol) en DMF (1.3 ml). La solución naranja resultante se dejó calentar hasta ta. Después de 1 h, la reacción se enfrió hasta 0°C y se añadió gota a gota SEMCl (0.27 ml, 1.52 mmol). La solución durazno resultante se dejó calentar hasta ta. Después de 1h y 45min, la mezcla amarilla turbia se enfrió hasta 0°C y inactivó con agua (20 ml). La reacción se extrajo con EtOAc (3 x 20 ml). Las fases orgánicas combinadas se lavaron con agua (3 x 6 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por cromatografía en fase normal dio 462.5 mg (64 %) de 1C como un aceite amarillo pálido. EM (IEP) m/z: 514.3(M+H)+.

1D. Éster *terc*-butílico del ácido [(E)-(S)-16-(2-trimetilsilanil-etoximetil)-8-oxa-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il]-carbámico, sal 1 TFA; y 1E. éster *terc*-butílico del ácido [(Z)-(S)-16-(2-trimetilsilanil-etoximetil)-8-oxa-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il]-carbámico, sal 1 TFA: (Matraz 1): A un matraz de fondo redondo secado a la llama se añadió Grubbs (II) (681 mg, 0.802 mmol). El matraz se desgasificó con argón durante varios minutos y luego se

añadió DCM desgasificado (10 ml) dando una solución transparente color borgoña. (Matraz 2): A un matraz de fondo redondo secado a la llama, separado se añadió 1C (412 mg, 0.802 mmol), pTsOH monohidratado (168 mg, 0.882 mmol) y DCM (779 ml). El matraz estaba equipado con un condensador de reflujo y la solución se desgasificó con argón durante 30 min. A continuación, la reacción se calentó hasta 40°C. Después de 1h, se añadió gota a gota la solución de Grubbs (II). Después de 1 h, la reacción se enfrió hasta ta y se lavó con $NaHCO_3$, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por cromatografía en fase normal dio un aceite marrón pálido. La purificación posterior por cromatografía en fase inversa dio 78.6mg (20 %) de 1D (E-alqueno) como un aceite marrón pálido y 33.2 mg (9 %) de 1E (Z-alqueno) como un aceite marrón pálido. Para 1D: EM (IEP) m/z: 486.5 (M+H)+. Para 1E: EM (IEP) m/z: 486.5 (M+H)+.

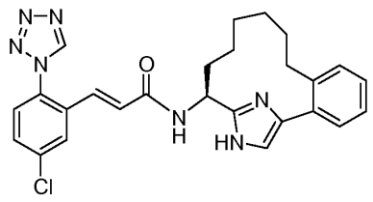
1F. (E)-(S)-(8-Pxa-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il)amina, 2 TFA: Una solución de 1D (59.2 mg, 0.122 mmol) en HCl 5M (2.50 ml, 82 mmol) y EtOH (2.44 ml) se calentó hasta 50°C. Después de agitar durante la noche, la reacción se concentró para eliminar el EtOH y la fase acuosa restante se ajustó a pH > 10 con K_2CO_3 saturado. La reacción se extrajo con EtOAc (3x). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron dando un residuo marrón. La purificación por cromatografía en fase inversa dio

0.0246 g (42 %) de 1F como un aceite incoloro transparente. EM (IEP) m/z: 256.3 (M+H)+.

1G. Ejemplo 1: A una solución de Intermediario 1 (33.5 mg, 0.096 mmol) y 1F (24.6 mg, 0.096 mmol) en DMF (0.321 ml) se añadió base de Hunig (0.084 ml, 0.482 mmol). Después de 45 min, se añadió agua dando una suspensión. El sólido se recogió por filtración. La purificación por cromatografía en fase inversa dio después de concentración y liofilización 0.0195 g (33 %) del Ejemplo 1 como un sólido blanco. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.40 - 2.71 (m, 3 H), 2.76 - 2.88 (m, 1 H), 3.68 - 3.84 (m, 1 H), 4.21 - 4.42 (m, 1 H), 5.13 - 5.28 (m, 2 H), 5.77 - 5.91 (m, 1 H), 6.81 (d, *J*=15.9 Hz, 1 H), 7.14 - 7.23 (m, 2 H), 7.29 (dd, *J*=8.2, 1.1 Hz, 1 H), 7.47 (td, *J*=7.7, 1.6 Hz, 1 H), 7.55 (s, 1 H), 7.57 - 7.62 (m, 2 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 8.00 (d, *J*=2.2 Hz, 1 H), 9.54 (s, 1 H). EM (IEP) m/z: 488.3 (M+H)+. HPLC analítica: TR= 5.35 min.

Ejemplo 2.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-(S)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il-acrilamida, sal 1 TFA



2A. 2-(*terc*-Butoxicarbonilamino)pent-4enoato de

(S)-2-(2-bromofenil)-2-oxoetilo: A una solución incolora transparente de ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico (3,33 g, 15.47 mmol) en DMF (38.7 ml) se añadió hidrógeno carbonato potásico (1.859 g, 18.57 mmol). La reacción se agitó durante 20 min a ta y luego se enfrió hasta 0°C. A continuación, se añadió gota a gota una solución de 2-bromo-1-(2-bromofenil)etanona (4.3 g, 15.47 mmol) en DMF (38.7 ml) y la reacción se dejó calentar hasta ta. Después de 3 h, la reacción se enfrió hasta 0°C, se vertió en agua enfriada con hielo y luego se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con agua (1x), salmuera (1x), se secaron sobre sulfato sódico, se filtraron y se concentraron dando 2A (6.37 g) como un aceite amarillo que solidificó al almacenar en el congelador. EM (IEP) m/z: 410.2 (M-H)-, 412.2 (M+2-H)-. El material se usó en la etapa siguiente sin purificación posterior.

2B. 1-(5-(2-Bromofenil)-1H-imidazol-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: A una solución amarilla transparente de 2A (6.37 g, 15.45 mmol) en xileno (155 ml) se añadió acetato amónico (11.91 g, 155 mmol). La mezcla de reacción se calentó hasta reflujo con una trampa de Dean-Stark para eliminar el agua azeotrópicamente. Después de 4 h, la reacción se enfrió hasta ta, se diluyó con EtOAc (500 ml) y luego se lavó con bicarbonato sódico saturado, salmuera, se secó sobre sulfato sódico, se filtró y se concentró dando un

residuo marrón. La purificación por cromatografía en fase normal proporcionó 2B (2.768 g, 45.7 %) como un sólido amarillo. EM (IEP) m/z: 392.3 (M+H)+, 394.3 (M+2+H)+.

2C. 1-(4-(2-bromofenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: A una suspensión enfriada (0°C) de NaH (dispersión al 60 % en aceite mineral, 0.299 g, 7.48 mmol) en THF (10.0 ml) se añadió gota a gota una solución de 2B (2.668 g, 6.80 mmol) en THF (15.0 ml). Se observó generación de gas. Se aclaró el matraz que contenía 2B con THF (2.2 ml) y luego esta solución se añadió a la mezcla de reacción. La solución naranja transparente resultante se agitó a 0°C durante 30 min, luego se añadió gota a gota SEM-Cl (1.206 ml, 6.80 mmol). La solución naranja resultante se mantuvo a 0°C. Después de 3 h, la reacción se inactivó con cloruro amónico saturado y se diluyó con EtOAc (200 ml) y agua. Se separaron las fases y la fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron dando aceite naranja transparente. La purificación por cromatografía en fase normal dio 2C (2.76 g, 78 %) como un aceite amarillo. EM (IEP) m/z: 522.5 (M+H)+, 524.5 (M+2+H)+.

2D. 1-(4-(2-(pent-4-enil)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)but-3-

enilcarbamato de (S)-*terc*-butilo: A un vial de pared gruesa secado a la llama se añadió 2C (1.085 g, 2.076 mmol), ácido pent-4-enilborónico (0.757 g, 6.64 mmol), óxido de plata (1.203 g, 5.19 mmol), carbonato potásico (1.722 g, 12.46 mmol), y aducto de $PdCl_2$(dppf)-CH_2Cl_2 (0.170 g, 0.208 mmol). El vial se purgó con argón durante varios minutos y luego se añadió THF desgasificado (8.3 ml). El vial se selló con una tapa a rosca revestida de teflón y la suspensión negra se calentó hasta 80°C. Después de 16 h la reacción se enfrió hasta ta. La mezcla de reacción se diluyó con EtOAc, se lavó con agua, bicarbonato sódico saturado, salmuera, se secó sobre sulfato sódico, se filtró y se concentró dando un residuo naranja-marrón. La purificación por cromatografía en fase normal proporcionó un aceite incoloro transparente que era una mezcla de 2D y material de partida. El material se purificó de nuevo por cromatografía de fase inversa. Las fracciones puras se neutralizaron con bicarbonato sódico saturado y luego se concentraron para eliminar el solvente orgánico. El residuo que quedó se extrajo con EtOAc (2x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron proporcionando 2D (0.21 g, 20 %) como un aceite incoloro transparente. EM (IEP) m/z: 512.6 (M+H)+.

2E. Éster *terc*-butílico del ácido [(E)-(S)-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-

triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il]-carbámico y 2F. Éster *terc*-butílico del ácido [(Z)-(S)-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il]-carbámico ácido: (Matraz 1): A un matraz secado a la llama se añadió Grubbs (II) (0.139 g, 0.164 mmol). El matraz se desgasificó con argón durante varios minutos y luego se añadió DCM desgasificado (2 ml) dando una solución borgoña transparente. (Matraz 2): A un matraz de fondo redondo secado a la llama separado se añadió 2D (0.21 g, 0.410 mmol), ácido p-toluenosulfónico monohidratado (0.086 g, 0.451 mmol) y DCM (420 ml). El matraz estaba equipado con un condensador de reflujo y la solución se desgasificó con argón durante 30 min. La reacción se calentó hasta 40°C. Después de 1 h, se añadió gota a gota la solución de Grubbs (II). Después de 1 h, la reacción se enfrió hasta ta, se lavó con bicarbonato sódico saturado, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró dando una espuma marrón. La purificación por cromatografía en fase inversa dio, después de neutralización y tratamiento de extracción como se describe en 2D, 2E (0.09 g, 45.3 %, E-alqueno) como un sólido amarillo y 2F (0.035 g, 17.6 %, Z-alqueno) como un sólido amarillo. Para 2E: EM (IEP) m/z: 484.6 (M+H)+. Para 2F: EM (IEP) m/z: 484.6 (M+H)+.

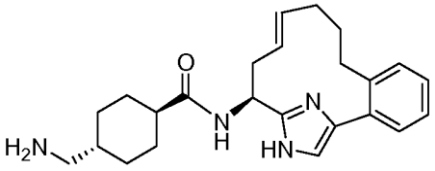
2G. Éster *terc*-butílico del ácido [(S)-16-(2-

trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A la solución de 2E y 2F (mezcla de isómeros E/Z) (0.049 g, 0.101 mmol) en MeOH (3 ml) se añadió paladio al 10 % sobre carbón (10.78 mg, 10.13 µmol). La mezcla de reacción se agitó bajo un globo de hidrógeno. Después de 2 h, la reacción se filtró a través de un filtro de microfibra de vidrio de 0.45 µm (GMF) y se aclaró el Pd/C con MeOH. El filtrado se concentró dando 2G (0.046 g, 93 %) como un residuo incoloro transparente. EM (IEP) m/z: 486.7 (M+H)+. El material se usó en la etapa siguiente sin purificación posterior.

2H. El Ejemplo 2 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 2G; seguido por la etapa 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.47 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.57 (d, *J*=8.8 Hz, 1 H), 7.43 - 7.49 (m, 3 H), 7.32 - 7.39 (m, 2 H), 7.18 (d, *J*=16.0 Hz, 1 H), 6.76 (dd, *J*=15.7, 3.6 Hz, 1 H), 4.99 - 5.04 (m, 1 H), 2.52 - 2.60 (m, 1 H), 2.40 - 2.48 (m, 1 H), 2.18 - 2.26 (m, 1 H), 1.84-1.90 (m, 1 H), 1.31 - 1.58 (m, 4 H), 1.21 - 1.29 (m, 2 H), 0.87-1.01 (m, 1 H), 0.40-0.54 (m, 1 H). EM (IEP) m/z: 488.0 (M+H)+. HPLC analítica: TR= 5.78 min.

Ejemplo 3.

Sal 2 TFA



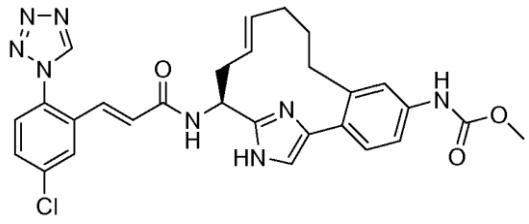
3A. (E)-(S)-(16.18-Diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il)amina, sal 2 TFA: Este compuesto se preparó siguiendo los procedimientos descritos en 1F, sustituyendo 1D por 2E. EM (IEP) m/z: 254.5 (M+H)+.

3B. Éster *terc*-butílico del ácido {4-[(E)-(S)-(16,18-Diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il)carbamoil]-ciclohexilmetil}-carbámico: A una solución de 3A (0.014 g, 0.029 mmol) en DMF (0.5 ml) se añadió ácido (1r,4r)-4-((*terc*-butoxicarbonilamino)metil)ciclohexanocarboxílico (8.23 mg, 0.032 mmol), EDC (0.011 g, 0.058 mmol), HOBt (8.91 mg, 0.058 mmol) y base de Hunig (0.015 g, 0.116 mmol). La reacción se agitó a ta durante 16 h y luego se inactivó con agua dando una suspensión. El sólido se recogió por filtración y luego se aclaró el sólido con agua, se secó al aire y luego se secó en un horno de vació (50°C) durante 2 h proporcionando 3B (0.010 g, 69.8 %) como sólido blanco. EM (IEP) m/z: 293.7 (M+H)+. El material se usó en la etapa siguiente sin purificación posterior.

3C. Ejemplo 3: A una solución de 3B (0.01 g, 0.020 mmol) en DCM (0.3 ml) se añadió TFA (0.3 ml, 3.89 mmol). La reacción se agitó a ta durante 1 h y luego se concentró. La purificación por cromatografía de fase inversa proporcionó el Ejemplo 3 (0.0095 g, 73.7 %) como un sólido blanco. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 7.40 - 7.45 (m, 2 H), 7.38 (s, 1 H), 7.29 - 7.37 (m, 2 H), 5.48 - 5.56 (m, 1 H), 5.07 - 5.15 (m, 1 H), 5.01 (dd, *J*=10.4, 4.9 Hz, 1 H), 2.75 - 2.84 (m, 3 H), 2.58 - 2.66 (m, 1 H), 2.43 - 2.51 (m, 2 H), 2.35-2.45 (m, 1 H), 1.82 - 2.03 (m, 6 H), 1.44 - 1.69 (m, 4 H), 1.20 - 1.30 (m, 1 H), 1.06 - 1.18 (m, 2 H). EM (IEP) m/z: 393.6 (M+H)+. HPLC analítica: TR= 3.70 min.

Ejemplo 4.

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-il}-carbámico, sal 1 TFA

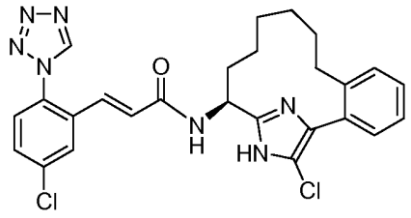


El Ejemplo 4 se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 8; seguido por las etapas 2B-2E; 1F; y 1G. ^{1}H NMR (50°C, 500 MHz, CD_3OD)

δ ppm 9.47 (s, 1 H), 7.96 (d, *J*=1.6 Hz, 1 H), 7.67 (d, *J*=8.8 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.46 (s, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.29 - 7.37 (m, 2 H), 7.19 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.50 - 5.60 (m, 1 H), 5.09 - 5.19 (m, 1 H), 5.02 - 5.09 (m, 1 H), 3.75 (s, 3 H), 2.77 - 2.86 (m, 1 H), 2.40 - 2.60 (m, 3 H), 1.95 - 2.05 (m, 1 H), 1.85 - 1.95 (m, 1 H), 1.49 - 1.62 (m, 1 H), 1.25 - 1.38 (m, 1 H). EM (IEP) m/z: 559.1 (M+H)+ y 561.1 $(M+2+H)^+$. HPLC analítica (Método D): TR= 5.42 min.

Ejemplo 5.

(E)-*N*-((S)-17-Cloro-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA



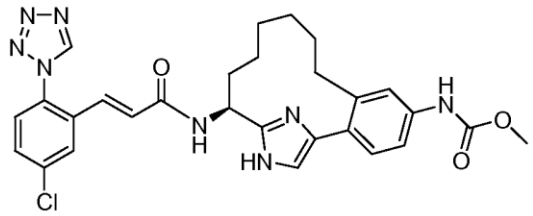
5A. Éster *terc*-butílico del ácido [(S)-17-Cloro-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A una solución de 2G (0.068 g, 0.140 mmol) en acetonitrilo (0.5 ml)/$CHCl_3$ (0.5 ml) se añadió NCS (0.022 g, 0.168 mmol). El vial se selló con un tapón a rosca revestido de teflón y la reacción se calentó hasta 65°C. Después de 3 h, la reacción se enfrió hasta ta. La reacción se diluyó con EtOAc, se lavó con salmuera, se secó sobre sulfato sódico, se filtró y se

concentró. La purificación por cromatografía en fase inversa dio, después de neutralización de las fracciones puras y tratamiento como se describe en la etapa 2D, 0.020 g (27.5 %) de 5A como un sólido blanco. EM (IEP) m/z: 520.7 (M+H)+.

5B. El Ejemplo 5 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 5A; seguido por la etapa 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.65 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.56 (d, *J*=8.8 Hz, 1 H), 7.35 - 7.39 (m, 2 H), 7.32 (s, 1 H), 7.26 - 7.31 (m, 2 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 4.86 (dd, *J*=10.4, 5.5 Hz, 1 H), 2.48 - 2.56 (m, 1 H), 2.36 - 2.43 (m, 1 H), 2.08 - 2.16 (m, 1 H), 1.60 - 1.70 (m, 1 H), 1.33 - 1.55 (m, 3 H), 1.11 - 1.31 (m, 3 H), 0.97 - 1.08 (m, 1 H), 0.28-0.41 (m, 1 H). EM (IEP) m/z: 522.4 (M+H)+. HPLC analítica: TR= 8.48 min.

Ejemplo 6.

Éster metílico del ácido {(S)-14-[(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-acriloilamino]-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA

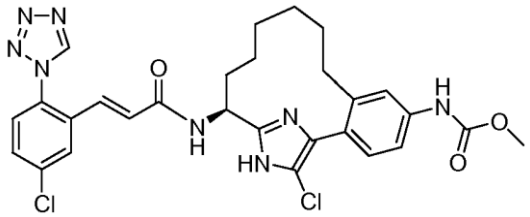


El Ejemplo 6 se preparó siguiendo los

procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 8; seguido por las etapas 2B-2G; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.47 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.46 (d, *J*=2.2 Hz, 1 H), 7.41 - 7.44 (m, 2 H), 7.37 (d, *J*=8.3 Hz, 1 H), 7.17 (d, *J*=15.9 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 5.01 (dd, *J*=9.1, 5.8 Hz, 1 H), 3.75 (s, 3 H), 2.47 - 2.56 (m, 1 H), 2.36 - 2.44 (m, 1 H), 2.17 - 2.25 (m, 1 H), 1.82 - 1.91 (m, 1 H), 1.31 - 1.56 (m, 4 H), 1.23-1.26 (m, 2 H), 0.87 - 0.98 (m, 1 H), 0.38-0.53 (m, 1 H). EM (IEP) m/z: 561.1 (M+H)+. HPLC analítica: TR= 5.45 min.

Ejemplo 7.

Éster metílico del ácido {(S)-17-Cloro-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA

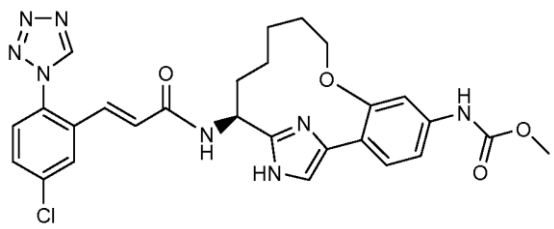


A la solución del Ejemplo 6 (0.012 g, 0.018 mmol) en acetonitrilo (0.3 ml)/cloroformo (0.300 ml) se añadió NCS (2.85 mg, 0.021 mmol). El vial se selló con un tapón a

rosca revestido de teflón y la reacción se calentó hasta 65°C. Después de 4 h, se añadió más NCS (2.85 mg, 0.021 mmol). Después de otra 1 h, la reacción se enfrió hasta ta y luego se concentró. La purificación por cromatografía de fase inversa proporcionó 0.0040 g (30.9 %) del Ejemplo 7 como un sólido amarillo. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.65 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 7.40 (d, *J*=2.2 Hz, 1 H), 7.36 (dd, *J*=8.3, 1.6 Hz, 1 H), 7.27 (d, *J*=8.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 4.85 (dd, *J*=10.4, 5.5 Hz, 1 H), 3.75 (s, 3 H), 2.43 - 2.52 (m, 1 H), 2.31 - 2.40 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.57 - 1.68 (m, 1 H), 1.10 - 1.53 (m, 6 H), 0.95 - 1.07 (m, 1 H), 0.26-0.38 (m, 1 H). EM (IEP) m/z: 561.1 (M+H)+. HPLC analítica: TR= 7.48 min.

Ejemplo 8.

Éster metílico del ácido {(S)-14-[(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA

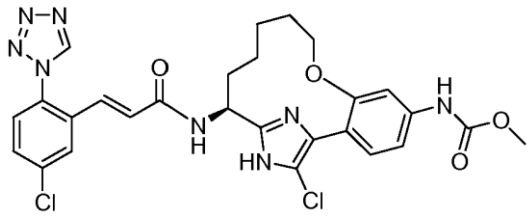


El Ejemplo 8 se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-

bromo-1-(2-bromofenil)etanona por el Intermediario 7; seguido por las etapas 2B-2C; 2E/2F-2G; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.48 - 7.52 (m, 2 H), 7.46 (d, *J*=8.2 Hz, 1 H), 7.21 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.16 (d, *J*=15.9 Hz, 1 H), 6.78 (d, *J*=15.9 Hz, 1 H), 5.14 (dd, *J*=10.4, 6.0 Hz, 1 H), 3.82 - 3.88 (m, 1 H), 3.75 (s, 3 H), 3.67 - 3.72 (m, 1 H), 2.19 - 2.28 (m, 1 H), 1.84 - 1.99 (m, 2 H), 1.46 - 1.62 (m, 2 H), 1.35 - 1.45 (m, 1 H), 1.11 - 1.21 (m, 1 H), 0.88 - 0.99 (m, 1 H). EM (IEP) m/z: 562.9 (M+H)+. HPLC analítica: TR= 5.65 min.

Ejemplo 9.

Éster metílico del ácido {(S)-17-Cloro-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA

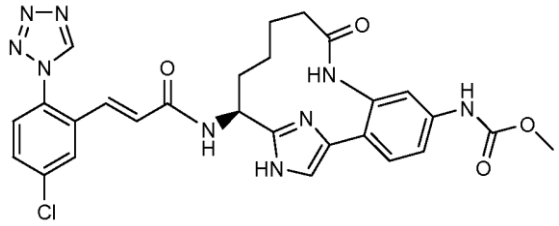


A una solución del Ejemplo 8 (0.013 g, 0.019 mmol) en acetonitrilo (0.5 ml)/cloroformo (0.500 ml) se añadió base de Hunig (6.69 µl, 0.038 mmol). La reacción se agitó a ta durante 10 min, luego se añadió NCS (3.08 mg, 0.023

mmol). El vial se selló con un tapón a rosca revestido de teflón y la reacción se calentó hasta 65°C. Después de 4 h, se añadió más NCS (3.08 mg, 0.023 mmol). Después de otras 2 h, la reacción se enfrió hasta ta y luego se concentró. La purificación por cromatografía de fase inversa proporcionó 0.0050 g (35.5 %) del Ejemplo 9 como un sólido amarillo. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.3 Hz, 1 H), 7.47 - 7.51 (m, 2 H), 7.20 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.05 (dd, *J*=10.4, 6.0 Hz, 1 H), 3.80 - 3.85 (m, 1 H), 3.75 (s, 3 H), 3.64 - 3.70 (m, 1 H), 2.13 - 2.22 (m, 1 H), 1.81 - 1.92 (m, 2 H), 1.49 - 1.61 (m, 2 H), 1.30 - 1.41 (m, 1 H), 1.10 - 1.20 (m, 1 H), 0.89 - 1.01 (m, 1 H). EM (IEP) m/z: 597.0 (M+H)+. HPLC analítica: TR= 8.09 min.

Ejemplo 10.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8.16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA



10A. Éster metílico del ácido {3-bromo-4-[2-((S)-1-

terc-butoxicarbonilamino-but-3-enil)-3*H*-imidazol-4-il]-fenil}-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 8; seguido por la etapa 2B. EM (IEP) m/z: 467.1 (M+2+H)+.

10B. Éster metílico del ácido {3-bromo-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: (El siguiente es un procedimiento alternativo al procedimiento 2C). A una solución enfriada (0°C) de 10A (15 g, 32.2 mmol) en THF (77 ml) se añadió N,N-diciclohexilmetilamina (7.52 ml, 35.5 mmol) seguido por la adición gota a gota de SEM-Cl (6.29 ml, 35.5 mmol). La reacción se agitó a 0°C durante 2h y luego se dejó calentar lentamente hasta ta. Después de 18 h, la suspensión amarilla se diluyó con EtOAc, se lavó con bicarbonato sódico saturado, salmuera, se secó sobre MgSO4, se filtró y se concentró. La purificación por cromatografía en fase normal dio 12.24 g (63.8 %) de 10B como un sólido blanquecino. EM (IEP) m/z: 595.1 (M+H)+ y 597.2 (M+2+H)+.

10C. Éster metílico del ácido {3-amino-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: Se llevó a vacío y se volvió a llenar con argón tres veces un vial de pared gruesa que contenía 10B (2 g, 3.36 mmol), yoduro de cobre(I) (0.128 g, 0.672 mmol), L-prolina (0.155 g, 1.343

mmol) y carbonato potásico (1.392 g, 10.07 mmol) en DMSO (6.72 ml). A continuación, se añadió hidróxido amónico acuoso al 28 % (0.607 ml, 4.37 mmol). El vial se selló con un tapón a rosca revestido de teflón y la reacción se calentó hasta 85°C. Después de 20 h, la reacción se enfrió hasta ta, se diluyó con EtOAc, se lavó con agua, salmuera, se secó sobre sulfato sódico, se filtró y se concentró. La purificación por cromatografía en fase normal proporcionó 1.05 g (58.8 %) de 10C como un sólido amarillo. EM (IEP) m/z: 532.5 (M+H)+.

10C. (Ruta alternativa). El compuesto 10B (1.0 g, 1.679 mmol), yoduro de cobre(I) (0.032 g, 0.168 mmol), L-prolina (0.058 g, 0.504 mmol) y azida de sodio (0.131 g, 2.015 mmol) se añadieron a un tubo de presión de 35 ml. A continuación, se añadieron EtOH (2.52 ml), agua (0.839 ml), y NaOH 1N (0.504 ml, 0.504 mmol). El recipiente de reacción se llevó a vacío y se volvió a llenar tres veces con argón. El tubo de presión se selló con un tapón de rosca con teflón que contenía una junta tórica viton, y luego se calentó la reacción hasta 95°C. Después de 20 h, la reacción se enfrió hasta ta, y se añadieron más azida de sodio (0.131 g, 2.015 mmol), L-prolina (0.058 g, 0.504 mmol), yoduro de cobre(I) (0.032 g, 0.168 mmol), NaOH (0.504 ml, 0.504 mmol) y EtOH (2.52 ml). El recipiente se selló y la reacción se calentó hasta 95°C. Después de otras 24 h, la reacción se enfrió

hasta ta, se diluyó con EtOAc, se lavó con agua, salmuera, se secó sobre sulfato sódico, se filtró y se concentró. La purificación por cromatografía en fase normal dio 0.475 g (53.2 %) de 10C como un sólido naranja. EM (IEP) m/z: 532.4 (M+H)+.

10D. Éster metílico del ácido {3-but-3-enoilamino-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: A una solución enfriada (-10°C) de base de Hunig (0.300 ml, 1.715 mmol), ácido but-3-enoico (0.049 g, 0.572 mmol) y 10C (0.304 g, 0.572 mmol) en acetato de etilo (16.34 ml) se añadió anhídrido cíclico del ácido 1-propanofosfónico (T3P) (50 % en EtOAc, 0.674 ml, 1.143 mmol). Después de 5 min, la reacción se dejó calentar hasta ta. Después de 1 h a ta, la reacción se concentró. La purificación por cromatografía en fase normal dio 0.30 g (87 %) de 10D como un sólido amarillo. EM (IEP) m/z: 600.3 (M+H)+.

10E. Éster metílico del ácido [(E)-(S)-14-*terc*-butoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8.16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-il]-carbámico; y 10F. Éster metílico del ácido [(Z)-(S)-14-*terc*-butoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-il]-carbámico: El compuesto 10E, el E-alqueno, y el compuesto

10F, el Z-alqueno, se prepararon siguiendo el procedimiento descrito en 2E/2F, sustituyendo 2D por 10D. EM (IEP) m/z: 572.2 (M+H)+.

10G. Éster metílico del ácido [(S)-14-*terc*-butoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il]-carbámico: A una suspensión de 10E (0.25 g, 0.437 mmol) en MeOH (10 ml)/EtOAc (5 ml) se añadió paladio al 10 % sobre carbón (0.047 g, 0.044 mmol). Se burbujeó hidrógeno a través de la mezcla de reacción durante 5 min y luego se agitó la reacción intensamente bajo una atmósfera de hidrógeno (globo). Después de 24 h, la reacción se filtró a través de un GMF de 0.45 µm, se aclaró con MeOH, DCM y EtOAc. El filtrado se concentró y la purificación por cromatografía de fase inversa proporcionó 0.220 g (88 %) de 10G, como un sólido blanquecino. EM (IEP) m/z: 574.4 (M+H)+.

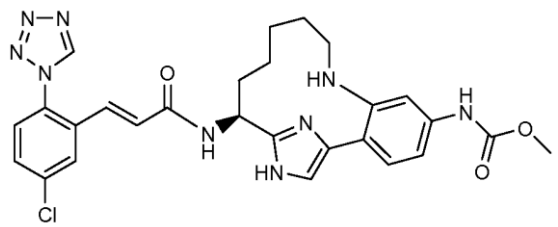
10H. Éster metílico del ácido ((S)-14-amino-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico, sal 2 HCl: Una mezcla de 10G (0.099 g, 0.173 mmol) y HCl 4M en dioxano (2 ml, 8.00 mmol) en un tubo sellado se calentó a 50°C. Después de 2 h, la suspensión amarilla se enfrió hasta ta y luego se concentró. El residuo se suspendió en MeOH (0.2 ml) y Et_2O. El sólido se recogió por filtración. El sólido se aclaró con

Et_2O, se secó al aire (muy higroscópico) proporcionando 0.053 g (73.8 %) de 10H como un sólido amarillo. EM (IEP) m/z: 344.2 (M+H)+.

10I. El Ejemplo 10 se preparó siguiendo el procedimiento descrito en 1G, sustituyendo 1F por 10H. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.50 (d, *J*=8.2 Hz, 1 H), 7.44 (s, 1 H), 7.42 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.9 Hz, 1 H), 5.13 (dd, *J*=10.2, 6.3 Hz, 1 H), 3.75 (s, 3 H), 2.42 - 2.52 (m, 1 H), 2.17 - 2.29 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.96 (m, 1 H), 1.51 - 1.71 (m, 2 H), 1.36 - 1.49 (m, 1 H), 0.92 - 1.07 (m, 1 H). EM (IEP) m/z: 576.3 (M+H)+. HPLC analítica: TR= 4.60 min.

Ejemplo 11.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA

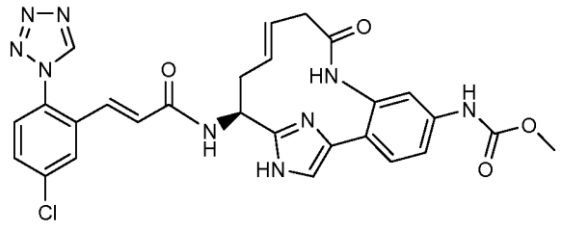


El Ejemplo 11 se preparó siguiendo los procedimientos descritos en la etapa 10C, sustituyendo

hidróxido amónico por but-3-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 10E/F; 10G, sustituyendo la mezcla de metanol/EtOAc por EtOAc; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 8.01 (d, *J*=2.2 Hz, 1 H), 7.82 (s, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.61 (d, *J*=8.8 Hz, 1 H), 7.55 (d, *J*=8.2 Hz, 1 H), 7.40 (s, 1 H), 7.28 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.24 (d, *J*=15.9 Hz, 1 H), 6.81 (d, *J*=15.4 Hz, 1 H), 5.29 (dd, *J*=10.7, 6.3 Hz, 1 H), 3.72 (s, 3 H), 3.16 - 3.24 (m, 1 H), 2.93 (t, *J*=11.5 Hz, 1 H), 2.00 - 2.20 (m, 3 H), 1.82 - 1.92 (m, 1 H), 1.62 - 1.76 (m, 2 H), 1.27 - 1.41 (m, 1 H), 0.78-0.87 (m, 1 H). EM (IEP) m/z: 562.2 (M+H)+. HPLC analítica: TR= 5.59 min.

Ejemplo 12.

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-il}-carbámico, sal 1 TFA

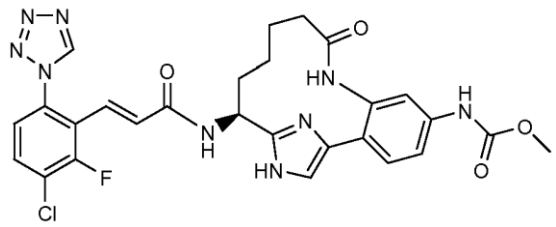


El Ejemplo 12 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G por 10E; seguido por la etapa 1G. ^{1}H NMR (500 MHz, CD_3OD) δ

ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.66 - 7.72 (m, 2 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.45 (s, 2 H), 7.35 (s, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.73 - 5.82 (m, 1 H), 5.21 - 5.29 (m, 1 H), 5.10 (dd, *J*=9.1, 5.2 Hz, 1 H), 3.75 (s, 3 H), 2.91 - 3.03 (m, 2 H), 2.81 - 2.89 (m, 1 H), 2.48-2.59 (m, 1 H). EM (IEP) m/z: 574.1 (M+H)+. HPLC analítica: TR= 4.78 min.

Ejemplo 13.

Éster metílico del ácido {(S)-14-[(E)-3-(3-cloro-2-fluoro-6-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA

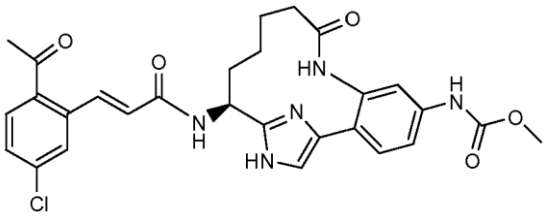


El Ejemplo 13 se preparó siguiendo el procedimiento descrito en 1G, sustituyendo 1F por 10H y sustituyendo el Intermediario 1 por el Intermediario 3. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.78 (t, *J*=8.2 Hz, 1 H), 7.56 (s, 1 H), 7.40 - 7.52 (m, 4 H), 7.00 (d, *J*=15.9 Hz, 1 H), 6.81 (d, *J*=15.9 Hz, 1 H), 5.12 (dd, *J*=9.9, 6.6 Hz, 1 H), 3.75 (s, 3 H), 2.42 - 2.51 (m, 1 H), 2.16 - 2.26 (m, 1 H), 2.04 - 2.13 (m, 1 H), 1.89 - 2.00 (m, 1 H), 1.51 - 1.69 (m, 2 H), 1.36 - 1.48 (m, 1

H), 0.90 - 1.03 (m, 1 H). EM (IEP) m/z: 594.3 (M+H)+. HPLC analítica: TR= 4.79 min.

Ejemplo 14.

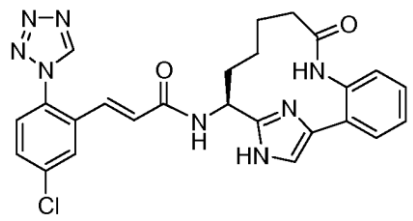
Éster metílico del ácido {(S)-14-[(E)-3-(2-acetil-5-cloro-fenil)-acriloilamino]-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA



El Ejemplo 14 se preparó siguiendo el procedimiento descrito en la etapa 1G, sustituyendo 1F por 10H, sustituyendo el Intermediario 1 por el Intermediario 4, y usando EDC, HOBt y trietilamina. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.97 (d, *J*=15.4 Hz, 1 H), 7.91 (d, *J*=8.2 Hz, 1 H), 7.65 (d, *J*=1.6 Hz, 1 H), 7.58 (d, *J*=2.2 Hz, 1 H), 7.50 - 7.55 (m, 2 H), 7.47 (s, 1 H), 7.43 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.54 (d, *J*=15.9 Hz, 1 H), 5.17 (dd, *J*=10.2, 6.3 Hz, 1 H), 3.76 (s, 3 H), 2.59 (s, 3 H), 2.45 - 2.53 (m, 1 H), 2.20 - 2.31 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.92 - 2.02 (m, 1 H), 1.55 - 1.72 (m, 2 H), 1.40 - 1.52 (m, 1 H), 0.94 - 1.07 (m, 1 H). EM (IEP) m/z: 550.2 (M+H)+. HPLC analítica: TR= 5.01 min.

Ejemplo 15.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il)-acrilamida, sal 1 TFA



15A. Éster *terc*-butílico del ácido {(S)-1-[4-(2-nitro-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por 2-bromo-1-(2-nitrofenil)etanona; seguido por las etapas 2B, sustituyendo xileno por tolueno; y 2C. EM (IEP) m/z: 489.4(M+H)+.

15B. Éster *terc*-butílico del ácido {(S)-1-[4-(2-amino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico : A una solución de 15A (1.0441 g, 2.137 mmol) en MeOH (14.15 ml) se añadió polvo de zinc (1.397 g, 21.37 mmol) y cloruro amónico (1.143 g, 21.37 mmol). La suspensión gris se agitó vigorosamente a ta. Después de 1h, el matraz se equipó con un condensador de reflujo y la reacción se calentó hasta 60°C. Después de 1h, la reacción se enfrió hasta ta y se dejó agitar durante la

noche. La reacción se filtró a través de un filtro GMF de 0.45 µm, eluyendo con metanol. El filtrado se concentró dando un sólido amarillo. El sólido se repartió entre EtOAc y HCl 0.5M (ac). Se separaron las fases y la fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con NaHCO3 saturado, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron dando un aceite naranja. La purificación por cromatografía en fase normal dio 0.818g (83 %) de 15B como una espuma amarilla. EM (IEP) m/z: 459.4(M+H)+.

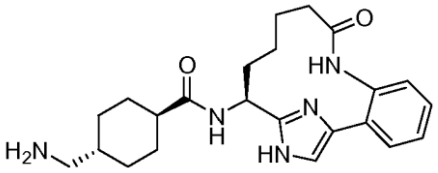
15C. (S)-14-Amino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-9-ona, 2HCl: Este compuesto se preparó siguiendo los procedimientos de la etapa 10D, sustituyendo 10C por 15B; seguido por las etapas 2E/2F; 2G, sustituyendo el globo de hidrógeno por hidrógeno (3.446-3.791 x 105 Pa); y 10H. EM (IEP) m/z: 489.4(M+H)+.

15D. Ejemplo 15: Una suspensión de Intermediario 2 (0.074g, 0.296 mmol), 15C (0.113g, 0.329 mmol), EDC (0.095g, 0.494 mmol), y HOBT (0.076g, 0.494 mmol) en DMF (1.65 ml) y base de Hunig (0.172 ml, 0.988 mmol) se agitó a ta durante la noche. Se añadió agua a la solución marrón dando una suspensión. La mezcla se extrajo con EtOAc (2x). Las fases orgánicas se reunieron y se lavaron con $NaHCO_3$ saturado, salmuera, se secaron sobre Na_2SO_4, se filtraron y se

concentraron. La purificación por cromatografía en fase inversa dio 0.0964g (47 %) del Ejemplo 15 como un sólido blanco. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.96 - 1.13 (m, 1 H), 1.37 - 1.50 (m, 1 H), 1.51 - 1.72 (m, 2 H), 1.90 - 2.01 (m, 1 H), 2.05 - 2.15 (m, 1 H), 2.18 - 2.28 (m, 1 H), 2.44 - 2.50 (m, 1 H), 5.13 (dd, *J*=10.2, 6.3 Hz, 1 H), 6.75 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.31 (dd, *J*=7.8, 0.7 Hz, 1 H), 7.44 (td, *J*=7.6, 1.1 Hz, 1 H), 7.49 (s, 1 H), 7.53 (td, *J*=7.7, 1.4 Hz, 1 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.61 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). EM (IEP) m/z: 503.3(M+H)+. HPLC analítica: TR= 4.72 min.

Ejemplo 16.

((S)-9-Oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il)-amida del ácido 4-aminometil-ciclohexanocarboxílico, sal 2 TFA

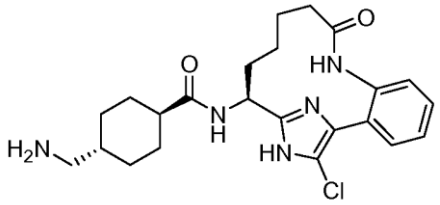


16A. Éster *terc*-butílico del ácido [4-((S)-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-ilcarbamoil)-ciclohexilmetil]-carbámico: Este compuesto se preparó siguiendo el procedimiento descrito en 3B, sustituyendo 3A por 15C. EM (IEP) m/z: 510.4(M+H)+.

16B. El Ejemplo 16 se preparó siguiendo el procedimiento descrito en 3C, sustituyendo 3B por 16A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.91 - 1.18 (m, 3 H), 1.28 - 1.75 (m, 6 H), 1.84 - 1.98 (m, 5 H), 2.07 - 2.23 (m, 2 H), 2.33 (tt, *J*=12.1, 3.3 Hz, 1 H), 2.43 - 2.53 (m, 1 H), 2.79 (d, *J*=6.9 Hz, 2 H), 5.05 (dd, *J*=10.7, 6.3 Hz, 1 H), 7.32 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.44 (td, *J*=7.7, 1.3 Hz, 1 H), 7.49 (s, 1 H), 7.53 (td, *J*=7.7, 1.5 Hz, 1 H), 7.60 (dd, *J*=7.7, 1.4 Hz, 1 H). EM (IEP) m/z: 410.4(M+H)+. HPLC analítica: TR= 1.56, 2.10 min.

Ejemplo 17.

((S)-17-Cloro-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il)-amida del ácido 4-aminometil-ciclohexanocarboxílico, sal 2 TFA



17A. Éster *terc*-butílico del ácido [4-((S)-17-cloro-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-ilcarbamoil)-ciclohexilmetil]-carbámico: El compuesto 16A se disolvió en EtOAc y se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró dando la base libre de 16A. A una suspensión de la base libre de 16A (0.067g,

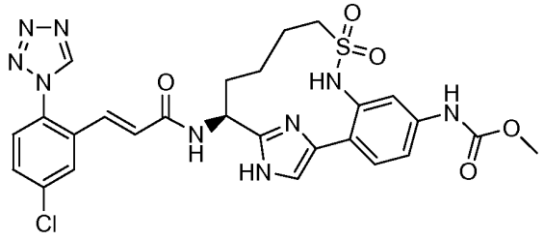
0.131 mmol) en acetonitrilo (1.32 ml) y cloroformo (1.32 ml) se añadió NCS (0.018 mg, 0.131 mmol). El vial de pared gruesa se selló con un tapón a rosca revestido con teflón y la reacción se calentó hasta 65°C. Después de 1h y 35min, la reacción se enfrió hasta ta y se repartió entre EtOAc y agua. Se separaron las fases y la fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas se reunieron, se lavaron con $NaHCO_3$ saturado, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por cromatografía en fase inversa dio 0.018 g (17 %) de 17A como un sólido blanco. EM (IEP) m/z: 544.3(M+H)+.

17B. El Ejemplo 17 se preparó siguiendo el procedimiento descrito en 3C, sustituyendo 3B por 17A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.93 - 1.17 (m, 3 H), 1.34 - 1.80 (m, 7 H), 1.86 - 2.10 (m, 6 H), 2.25 - 2.34 (m, 1 H), 2.36 - 2.43 (m, 1 H), 2.80 (d, *J*=7.2 Hz, 2 H), 4.93 (dd, *J*=10.7, 6.1 Hz, 1 H), 7.27 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.41 (td, *J*=7.6, 1.3 Hz, 1 H), 7.46 (td, *J*=7.6, 1.6 Hz, 1 H), 7.60 (dd, *J*=7.4, 1.4 Hz, 1 H). EM (IEP) m/z: 444.2(M+H)+. HPLC analítica: TR= 3.36 min.

Ejemplo 18.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9,9-dioxo-9λ^6-tia-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-

il}-carbámico, sal 1 TFA



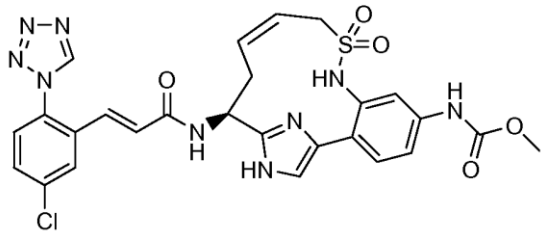
18A. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(prop-2-en-1-sulfonilamino)-fenil]-carbámico: A una solución de 10C (178 mg, 0.335 mmol) en CH_2Cl_2 (2 ml) se añadió DIEA (0.117 ml, 0.670 mmol). La reacción se enfrió hasta 0°C. A continuación, se añadió gota a gota una solución de cloruro de prop-2-en-1-sulfonilo (54.5 mg, 0.368 mmol) en DCM (1 ml). La mezcla resultante se agitó a 0°C durante 2 h. La reacción se concentró y la purificación por cromatografía en fase normal dio 18A como sólido amarillo pálido (124 mg, 58 %). EM (IEP) m/z: 636.4 (M+H)+.

18B. El Ejemplo 18 se preparó siguiendo los procedimientos descritos en la etapa 2E/2F, sustituyendo 2D por 18A; seguido por las etapas 2G; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.64 - 7.75 (m, 2 H), 7.54 - 7.64 (m, 2 H), 7.43 - 7.54 (m, 2 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.78 (d, *J*=15.4 Hz, 1 H), 5.04 (dd, *J*=9.3, 4.9 Hz, 1 H), 3.75 (s, 3 H), 2.92 - 3.01 (m, 2 H), 2.16 - 2.27 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.69 - 1.81

(m, 1 H), 1.52 - 1.66 (m, 1 H), 1.08 - 1.25 (m, 1 H), 0.72 - 0.93 (m, 1 H). EM (IEP) m/z: 612.3 (M+H)+. HPLC analítica: TR= 3.92 min (Método B).

Ejemplo 19.

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9,9-dioxo-9λ^6-tia-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-il}-carbámico, sal 1 TFA

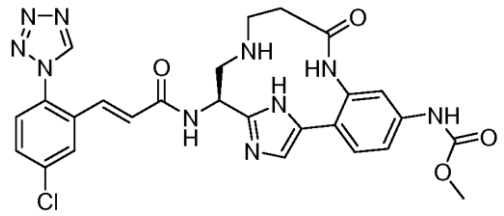


El Ejemplo 19 se preparó siguiendo los procedimientos descritos en la etapa 2E, sustituyendo 2D por 18A; seguido por las etapas 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.98 (d, *J*=2.3 Hz, 1 H), 7.74 (s, 1 H), 7.68 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.54 - 7.62 (m, 1 H), 7.46 - 7.54 (m, 2 H), 7.43 (s, 1 H), 7.17 (d, *J*=15.7 Hz, 1 H), 6.78 (d, *J*=15.7 Hz, 1 H), 5.88 - 6.06 (m, 1 H), 5.07 - 5.22 (m, 2 H), 3.85 - 4.08 (m, 2 H), 3.76 (s, 3 H), 2.81 - 2.95 (m, 1 H), 2.47 - 2.64 (m, 1 H). EM (IEP) m/z: 610.3 (M+H)+. HPLC analítica: TR= 3.49 min (Método B).

Ejemplo 20.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,12,16,18-tetraaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15-pentaen-5-il}-

carbámico, sal 2 TFA



20A. Éster *terc*-butílico del ácido {(S)-2-benciloxicarbonilamino-2-[4-(2-bromo-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-etil}-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico por ácido (S)-2-benciloxicarbonilamino-3-*terc*-butoxicarbonilamino-propiónico y sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 8; seguido por las etapas 2B; y 10B. EM (IEP) m/z: 720.5(M+H)+.

20B. Éster metílico del ácido {4-[2-((S)-2-amino-1-benciloxicarbonilamino-etil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-bromo-fenil}-carbámico: Este compuesto se preparó siguiendo el procedimiento descrito en 3C, sustituyendo 3B por 20A. EM (IEP) m/z: 620.3(M+H)+.

20C. Éster metílico del ácido 3-{(S)-2-benciloxicarbonilamino-2-[4-(2-bromo-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-etilamino}-propiónico: A una mezcla de 20B (204 mg, 0.330 mmol), acrilato de metilo (0.089 ml, 0.989 mmol) y

trietilamina (0.230 ml, 1.649 mmol) se añadió alcohol isopropílico (3 ml) en un tubo de microondas sellado. La reacción se agitó a 80°C durante la noche. La mezcla de reacción se concentró dando 20C (208 mg, 90 % de rendimiento) como un sólido beige. EM (IEP) m/z: 706.4(M+H)+.

20D. Éster metílico del ácido 3-({(S)-2-benciloxicarbonilamino-2-[4-(2-bromo-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-etil}-*terc*-butoxicarbonil-amino)-propiónico: A una solución de 20C (208 mg, 0.295 mmol) en CH_2Cl_2 (2952 µl) a 0°C se añadió dicarbonato de di-*terc*-butilo (64.4 mg, 0.295 mmol) y DMAP (3.61 mg, 0.030 mmol). La mezcla de reacción se agitó a 0°C y se dejó calentar lentamente hasta ta. Después de 4 h, la mezcla de reacción se concentró y se purificó por cromatografía en fase normal dando 20D (180 mg, 0.224 mmol, 76 % de rendimiento) como un sólido amarillo pálido. EM (IEP) m/z: 806.2(M+H)+.

20E. Ácido 3-({(S)-2-[4-(2-amino-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-2-benciloxicarbonilamino-etil}-*terc*-butoxicarbonil-amino)-propiónico: Este compuesto se preparó siguiendo el procedimiento descrito en 10C (ruta alternativa), sustituyendo 10B por 20D. EM (IEP) m/z: 727.6(M+H)+.

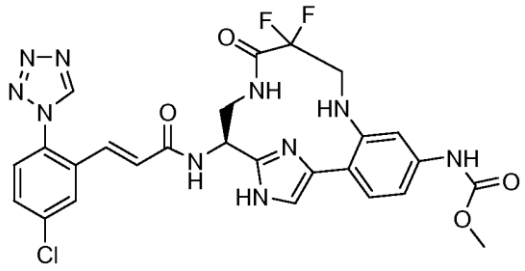
20F. Éster *terc*-butílico del ácido (S)-14-

benciloxicarbonilamino-5-metoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,12,16,18-tetraaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-12-carboxílico: A una solución de BOP (50.2 mg, 0.113 mmol) en DCM (44.900 ml) y DMF (0.449 ml) a ta se añadió una solución de 20E (33 mg, 0.045 mmol) y DIEA (0.079 ml, 0.454 mmol) en DMF (3 ml) mediante una bomba de jeringa durante 5h. La mezcla de reacción se concentró para eliminar DCM, luego se diluyó con acetato de etilo y se lavó con bicarbonato sódico saturado. La fase acuosa se extrajo con acetato de etilo y las fases orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. La cromatografía en fase normal dio 20F (28 mg, 87 % de rendimiento) como un sólido blanquecino. EM (IEP) m/z: 709.3(M+H)+.

20G. El Ejemplo 20 se preparó siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E/2F por 20F; seguido por las etapas 1G; y 3C. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 9.49 (s, 1 H) 7.93 (d, *J*=2.2 Hz, 1 H) 7.66 (dd, *J*=8.79, 2.2 Hz, 1 H) 7.57 (d, *J*=8.24 Hz, 2 H) 7.42 (m, 3 H) 7.22 (d, *J*=15.94 Hz, 1 H) 6.62 (d, *J*=15.39 Hz, 1 H) 5.40 (dd, *J*=6.05, 2.75 Hz, 1 H) 3.74 (s, 3 H) 3.51-3.69 (m, 2 H) 3.25-3.39 (m, 2 H) 2.89-2.98 (m, 2 H). EM (IEP) m/z: 577.3(M+H)+. HPLC analítica: TR= 4.72min.

Ejemplo 21.

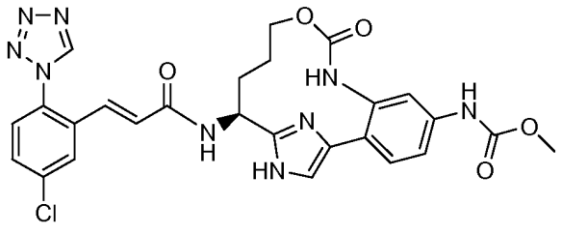
Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10,10-difluoro-11-oxo-8,12,16,18-tetraaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA



El Ejemplo 21 se preparó siguiendo los procedimientos descritos en la etapa 10C (ruta alternativa), sustituyendo azida de sodio por ácido 3-amino-2,2-difluoropropanoico y sustituyendo 10B por 20A; seguido por las etapas 3C; 20F; 2G; 1G; y 3C. EM (IEP) m/z: 613.3(M+H)+. HPLC analítica: TR= 5.24 min.

Ejemplo 22.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-10-oxa-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA



22A. 5-(Benciloxi)-2-(*terc*-

butoxicarbonilamino)pentanoato de (S)-2-(2-bromo-4-nitrofenil)-2-oxoetilo: Este compuesto se preparó siguiendo el procedimiento descrito en 2A, sustituyendo ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico por ácido (S)-5-(benciloxi)-2-(*terc*-butoxicarbonilamino)pentenoico y sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 10. EM (IEP) m/z: 565.4 (M+2-H)-.

22B. 5-(Benciloxi)-2-(*terc*-butoxicarbonilamino)pentanoato de (S)-2-(4-amino-2-bromofenil)-2-oxoetilo: A una solución de 22A (2.6 g, 4.60 mmol) en etanol (30 ml) se añadió hierro en polvo (2.57 g, 46.0 mmol). La suspensión se mezcló rápidamente y luego se añadió ácido clorhídrico acuoso 1.0 M (2.299 ml, 2.299 mmol). La mezcla de reacción se calentó hasta 50°C. Después de 2 h, la reacción se enfrió hasta ta, se diluyó con acetato de etilo y se filtró a través de una almohadilla de CELITE®, eluyendo con acetato de etilo. El filtrado se concentró, se volvió a disolver en acetato de etilo, se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre sulfato sódico y se concentró dando 22B (1.954 g, 79 % de rendimiento) como un sólido amarillo. El material se usó en la etapa siguiente sin purificación posterior. EM (IEP) m/z: 537.4 (M+2+H)+.

22C. Éster metílico del ácido {3-amino-4-[2-((S)-4-benciloxi-1-*terc*-butoxicarbonilamino-butil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-

carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa Intermediario 7B, sustituyendo el Intermediario 7A por 22B; seguido por las etapas 1B; 10B; y 10C (alternativa). EM (IEP) m/z: 640.5 (M+H)+.

22D. Éster metílico del ácido {3-amino-4-[2-((S)-1-*terc*-butoxicarbonilamino-4-hidroxi-butil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: A una solución de 22C (0.446 g, 0.697 mmol) en EtOAc (10 ml) se añadió TFA (0.081 ml, 1.046 mmol). La reacción se agitó a ta durante 5 min, luego se añadió paladio al 10 % sobre carbón (0.074 g, 0.070 mmol). Se burbujeó hidrógeno a través de la reacción durante unos pocos minutos, luego se agitó la reacción intensamente bajo una atmósfera de hidrógeno (globo). Después de 17 h, la reacción se filtró a través de un filtro GMF de 0.45 micrómetros, se aclaró con EtOAc y MeOH. El filtrado se concentró, se volvió a disolver en EtOAc, se lavó con bicarbonato sódico saturado, salmuera, se secó sobre sulfato sódico, se filtró y se concentró proporcionando 22D (0.35 g, 91 %) como un sólido amarillo. EM (IEP) m/z: 550.4 (M+H)+. El material se usó en la etapa siguiente sin purificación posterior.

22E. Éster *terc*-butílico del ácido [(S)-5-metoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-10-oxa-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-

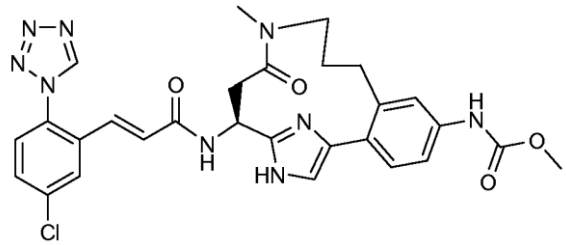
1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A una solución de 22D (0.19 g, 0.346 mmol) en DCM (15.03 ml) a 0°C se añadió TEA (0.096 ml, 0.691 mmol) seguido por carbonocloridato de 4-nitrofenilo (0.077 g, 0.380 mmol). Después de 1 h, la reacción se calentó hasta ta. Después de 18 h, la reacción se concentró. La purificación por cromatografía de fase inversa proporcionó 22E (0.049 g, 24.63 %), como un sólido amarillo. EM (IEP) m/z: 576.5 (M+H)+.

22F. El Ejemplo 22 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1E por 22E, sustituyendo etanol por metanol, y llevando a cabo la reacción a 75°C; seguido por la etapa 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.42 (s, 1 H), 7.76 (d, *J*=2.2 Hz, 1 H), 7.59 - 7.68 (m, 2 H), 7.46 - 7.55 (m, 2 H), 7.22 (d, *J*=8.3 Hz, 1 H), 7.16 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.88 (d, *J*=15.4 Hz, 1 H), 6.65 (d, *J*=15.4 Hz, 1 H), 5.26 (t, *J*=7.7 Hz, 1 H), 3.71 (s, 3 H), 3.61 (t, *J*=6.0 Hz, 2 H), 2.08 - 2.22 (m, 2 H), 1.54 - 1.74 (m, 2 H). EM (IEP) m/z: 578.3 (M+H)+. HPLC analítica: TR= 4.70 min.

Ejemplo 23.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-metil-12-oxo-11,16,18-triaza-triciclo[13.2.1.2.7]octadeca-

1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA



23A. Éster bencílico del ácido (S)-3-[4-(2-bromo-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-3-*terc*-butoxicarbonilamino-propiónico: Este compuesto se preparó siguiendo los procedimientos descritos en 2A, sustituyendo ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico por éster 4-bencílico del ácido (S)-2-*terc*-butoxicarbonilamino-succínico, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 8 y sustituyendo hidrógeno carbonato potásico por carbonato potásico; seguido por las etapas 2B, sustituyendo xileno por tolueno; y 10B. EM (IEP) m/z: 703.3, 705.3 (M+H)+.

23B. Éster bencílico del ácido metil-prop-2-inil-carbámico: A una solución de N-metilprop-2-in-1-amina (3.50 g, 50.6 mmol) en DCM (50 ml) se añadieron TEA (8.47 ml, 60.8 mmol) y Cbz-Cl (7.95 ml, 55.7 mmol) gota a gota a 0°C. La reacción se agitó bajo argón a 0°C durante 1 h. La mezcla de reacción se diluyó con CH_2Cl_2, se lavó con HCl 1M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró dando 23B (10.02 g, 97 % de rendimiento) como un aceite

transparente. EM (IEP) m/z: 204.1 (M+H)+.

23C. Éster bencílico del ácido (S)-3-[4-{2-[3-(benciloxicarbonil-metil-amino)-prop-1-inil]-4-metoxicarbonilamino-fenil}-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-3-*terc*-butoxicarbonilamino-propiónico: A una solución de 23A (200 mg, 0.284 mmol) en DMF (5 ml) se añadió 23B (69.3 mg, 0.341 mmol), CuI (10.83 mg, 0.057 mmol), TEA (0.119 ml, 0.853 mmol) y $Pd(Ph_3P)_4$ (32.8 mg, 0.028 mmol). La reacción se purgó con argón durante 3 min y luego se agitó bajo argón a 90°C durante 6 h. La reacción se enfrió hasta ta y se diluyó con EtOAc. La fase orgánica se lavó con $NaHCO_3$ saturado y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal dando 23C (205 mg, 87 % de rendimiento) como un sólido. CL-EM (IEP) m/z: 826.5 (M+H)+.

23D. Ácido (S)-3-(*terc*-butoxicarbonilamino)-3-(4-(4-(metoxicarbonilamino)-2-(3-(metilamino)propil)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)propanoico, sal TFA: Este compuesto se preparó siguiendo el procedimiento descrito en 2G, sustituyendo 2E por 23C. EM (IEP) m/z: 606.4 (M+H)+.

23E. Éster *terc*-butílico del ácido [(S)-5-metoxicarbonilamino-11-metil-12-oxo-16-(2-trimetilsilanil-etoximetil)-11,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A una solución

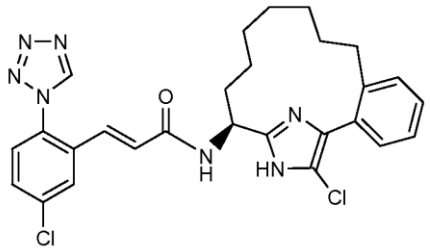
de DMAP (23.19 mg, 0.190 mmol), DIEA (0.166 ml, 0.949 mmol) y BOP (168 mg, 0.380 mmol) en DCM (20 ml) se añadió una solución de 23D (115 mg, 0.190 mmol) en DMF (2 ml) a ta a través de una bomba de jeringa durante 1.5 h. Tras la adición, la reacción se agitó durante otros 30 min y se eliminó el solvente. El producto puro se purificó por cromatografía de fase inversa dando 23E (44 mg, 39.4 % de rendimiento) como un sólido. EM (IEP) m/z: 588.4 (M+H)+.

23F. El Ejemplo 23 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 23E y sustituyendo etanol por metanol; seguido por la etapa 1G. ^{1}H NMR (400 MHz, CD_3OD, rotámeros) δ ppm 9.52 (dos singletes, 1H), 9.36 (s, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.68 (ddd, *J* = 8.6, 6.3, 2.3 Hz, 1H), 7.59 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.49 - 7.43 (m, 1H), 7.41 - 7.33 (m, 3H), 7.19 (dos dobletes, *J* = 16.0 Hz, 1H), 6.81 (dos dobletes, *J* = 15.6 Hz, 1H), 5.49 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.12 (ddd, *J* = 7.3, 6.0, 3.7 Hz, 1H), 3.75 (dos singletes, 3H), 3.55 - 3.43 (m, *J* = 9.2, 7.6, 5.9 Hz, 1H), 3.00 (dos singletes, 3H), 2.81 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.69 - 2.57 (m, 2H), 2.48 - 2.28 (m, 1H), 1.91 - 1.76 (m, 1H), 1.64 - 1.44 (m, 1H). CL-EM (IEP) m/z: 590.2 (M+H)+. HPLC analítica: TR= 5.328 min.

Ejemplo 24.

(E)-*N*-((S)-18-Cloro-17.19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-3-(5-cloro-2-tetrazol-1-il-

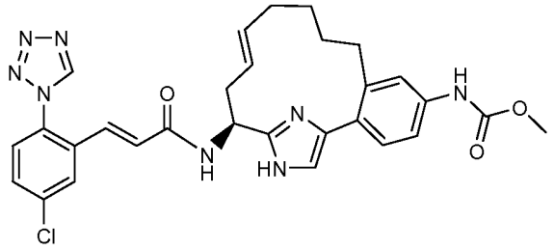
fenil)-acrilamida, sal 1 TFA



El Ejemplo 24 se preparó siguiendo los procedimientos descritos en la etapa 2D, sustituyendo ácido pent-4-enilborónico por ácido hex-5-enilborónico; seguido por las etapas 2E/2F; 2G; 1F; 1G; y 7. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.45 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.64 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 7.24 - 7.35 (m, 4 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.9 Hz, 1 H), 4.91 (dd, *J*=9.6, 4.1 Hz, 1 H), 2.68 - 2.76 (m, 1 H), 2.39 - 2.48 (m, 1 H), 2.06 - 2.14 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.56 - 1.65 (m, 1 H), 1.23 - 1.45 (m, 7 H), 0.76 - 0.86 (m, 1 H), 0.49 - 0.59 (m, 1 H). EM (IEP) m/z: 536.4 (M+H)+. HPLC analítica: TR= 8.84 min.

Ejemplo 25.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

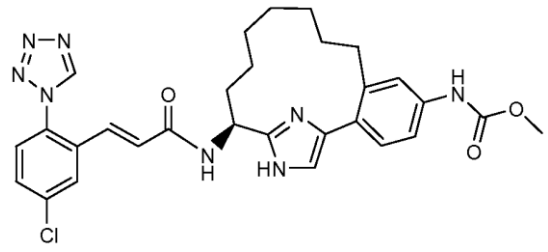


El Ejemplo 25 se preparó siguiendo los

procedimientos descritos en la etapa 2D, sustituyendo 2C por 10B y sustituyendo ácido pent-4-enilborónico por ácido hex-5-enilborónico; seguido por las etapas 2E; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 50-75°C; y 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.96 (d, *J*=2.7 Hz, 1 H), 7.64 - 7.70 (m, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.37 - 7.46 (m, 2 H), 7.32 - 7.35 (m, 1 H), 7.28 (d, *J*=8.2 Hz, 1 H), 7.19 (d, *J*=15.9 Hz, 1 H), 6.74 (d, *J*=15.9 Hz, 1 H), 5.48 - 5.58 (m, 1 H), 5.22 - 5.31 (m, 1 H), 5.09 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.81 - 2.89 (m, 1 H), 2.69 - 2.78 (m, 1 H), 2.52 - 2.62 (m, 1 H), 2.38 - 2.48 (m, 1 H), 2.06 - 2.23 (m, 2 H), 1.38 - 1.59 (m, 2 H), 1.09 - 1.19 (m, 2 H). EM (IEP) m/z: 573.4 (M+H)+. HPLC analítica: TR= 5.63 min.

Ejemplo 26.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

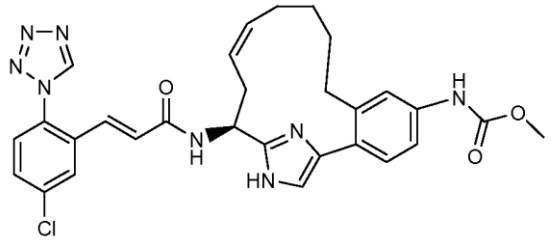


El Ejemplo 26 se preparó siguiendo los procedimientos descritos en la etapa 2D, sustituyendo 2C por

10B y sustituyendo ácido pent-4-enilborónico por ácido hex-5-enilborónico; seguido por las etapas 2E/2F; 2G; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 50-75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.43 - 7.46 (m, 2 H), 7.41 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.31 (d, *J*=8.2 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.00 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.56 - 2.67 (m, 2 H), 2.21 - 2.30 (m, 1 H), 2.03 - 2.13 (m, 1 H), 1.66 - 1.76 (m, 1 H), 1.25 - 1.57 (m, 7 H), 0.47-0.60 (m, 2 H). EM (IEP) m/z: 575.5 (M+H)+. HPLC analítica: TR= 5.73 min.

Ejemplo 27.

Éster metílico del ácido {(Z)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

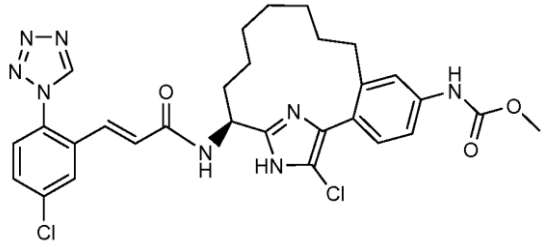


El Ejemplo 27 se preparó siguiendo los procedimientos descritos en la etapa 2D, sustituyendo 2C por 10B y sustituyendo ácido pent-4-enilborónico por ácido hex-5-enilborónico; seguido por las etapas 2F; 1F, sustituyendo

etanol por metanol y llevando a cabo la reacción a 50-75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.44 (s, 1 H), 7.41 (dd, *J*=8.3, 4.7 Hz, 1 H), 7.32 (s, 1 H), 7.30 (d, *J*=8.2 Hz, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.78 (d, *J*=15.4 Hz, 1 H), 5.33 - 5.48 (m, 2 H), 5.10 - 5.17 (m, 1 H), 3.74 (s, 3 H), 2.71 - 2.97 (m, 3 H), 2.44 - 2.61 (m, 1 H), 1.99 - 2.23 (m, 2 H), 1.48 - 1.58 (m, 2 H), 0.99 - 1.25 (m, 2 H). EM (IEP) m/z: 573.5 (M+H)+. HPLC analítica: TR= 5.67 min.

Ejemplo 28.

Éster metílico del ácido {(S)-18-cloro-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

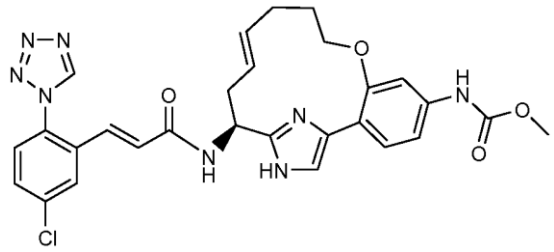


El Ejemplo 28 se preparó siguiendo el procedimiento descrito en 7, sustituyendo el Ejemplo 6 por el Ejemplo 26. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.45 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.64 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 (d, *J*=8.2 Hz, 1 H), 7.40 (d, *J*=2.2 Hz, 1 H), 7.35 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.25 (d, *J*=8.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.75

(d, *J*=15.9 Hz, 1 H), 4.90 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.62 - 2.73 (m, 1 H), 2.35 - 2.45 (m, 1 H), 2.07 - 2.16 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.56 - 1.67 (m, 1 H), 1.22 - 1.45 (m, 7 H), 0.72 - 0.86 (m, 1 H), 0.47-0.58 (d, 1 H). EM (IEP) m/z: 609.1 (M+H)+. HPLC analítica: TR= 7.81 min.

Ejemplo 29.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

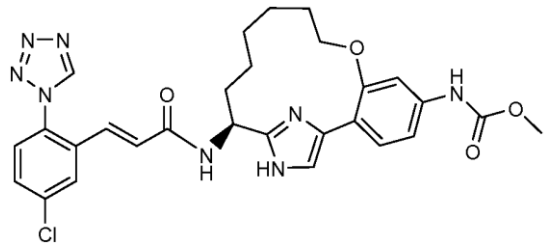


El Ejemplo 29 se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 11; seguido por las etapas 2B; 2C; 2E; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.46 (s, 1 H), 7.42 (s, 1 H), 7.37 (d, *J*=8.2 Hz, 1 H), 7.17 (d, *J*=15.4 Hz, 1 H), 7.05 (dd, *J*=8.3, 1.6 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.66 - 5.74 (m, 1 H), 5.48 - 5.56 (m, 1 H), 5.11 (dd, *J*=10.2, 3.6 Hz, 1 H), 4.09 - 4.16 (m, 2 H), 3.75

(s, 3 H), 2.69 - 2.77 (m, 1 H), 2.52 - 2.61 (m, 1 H), 2.33 - 2.47 (m, 2 H), 2.01 - 2.09 (m, 1 H), 1.91 - 2.00 (m, 1 H). EM (IEP) m/z: 575.0 (M+H)+. HPLC analítica: TR= 6.15 min.

Ejemplo 30.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

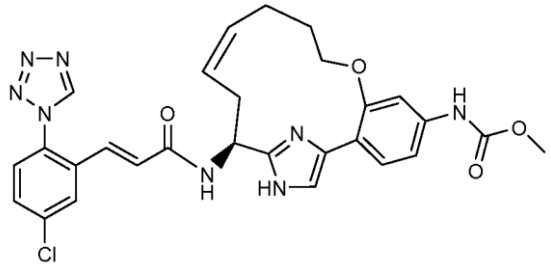


El Ejemplo 30 se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 11; seguido por las etapas 2B; 2C; 2E/2F; 2G; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.40 (s, 1 H), 7.33 - 7.38 (m, 2 H), 7.14 (d, *J*=15.4 Hz, 1 H), 7.06 (d, *J*=8.2 Hz, 1 H), 6.78 (d, *J*=15.9 Hz, 1 H), 5.04 (dd, *J*=9.9, 4.4 Hz, 1 H), 4.05 - 4.10 (m, 1 H), 3.93 (td, *J*=8.2, 2.7 Hz, 1 H), 3.75 (s, 3 H), 2.19 - 2.27 (m, 1 H), 1.94 - 2.03 (m, 1 H), 1.69 - 1.83 (m, 2 H), 1.49 - 1.63 (m, 4 H), 0.91 - 1.09 (m, 2 H). EM (IEP) m/z: 577.1 (M+H)+.

HPLC analítica: TR= 6.16 min.

Ejemplo 31.

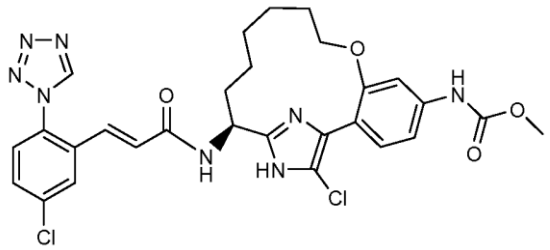
Éster metílico del ácido {(Z)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA



El Ejemplo 31 se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 11; seguido por las etapas 2B; 2C; 2F; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.59 (d, *J*=8.2 Hz, 1 H), 7.50 (d, *J*=1.6 Hz, 1 H), 7.44 (s, 1 H), 7.38 (d, *J*=8.2 Hz, 1 H), 7.15 - 7.21 (m, 2 H), 6.74 (d, *J*=15.9 Hz, 1 H), 5.41 - 5.51 (m, 2 H), 5.20 - 5.25 (m, 1 H), 3.74 - 3.82 (m, 4 H), 3.66 - 3.72 (m, 1 H), 2.95 - 3.06 (m, 1 H), 2.79 - 2.89 (m, 1 H), 2.47 - 2.58 (m, 1 H), 2.23 - 2.34 (m, 1 H), 1.89 - 2.03 (m, 1 H), 1.65-1.77 (m, 1 H). EM (IEP) m/z: 575.1 (M+H)+. HPLC analítica: TR= 5.94 min.

Ejemplo 32.

Éster metílico del ácido {(S)-18-cloro-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

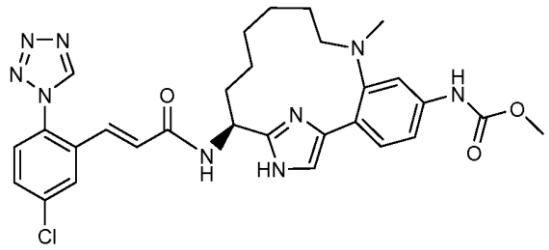


El Ejemplo 32 se preparó siguiendo el procedimiento descrito en 9, sustituyendo el Ejemplo 8 por el Ejemplo 30. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.46 (s, 1 H), 7.94 (d, *J*=2.2 Hz, 1 H), 7.64 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.55 (d, *J*=8.8 Hz, 1 H), 7.32 - 7.37 (m, 2 H), 7.15 (d, *J*=15.9 Hz, 1 H), 7.05 (d, *J*=8.2 Hz, 1 H), 6.74 (d, *J*=15.4 Hz, 1 H), 4.94 (dd, *J*=9.6, 3.6 Hz, 1 H), 4.00 - 4.06 (m, 1 H), 3.88 - 3.94 (m, 1 H), 3.76 (s, 3 H), 2.12 - 2.20 (m, 1 H), 1.75 - 1.93 (m, 2 H), 1.65 - 1.74 (m, 1 H), 1.46 - 1.60 (m, 4 H), 1.0 -1,12 (m, 1 H), 0.92 - 1.02 (m, 1 H). EM (IEP) m/z: 610.9 (M+H)+. HPLC analítica: TR= 7.74 min.

Ejemplo 33.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-metil-8.17.19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-

il}-carbámico, sal 2 TFA

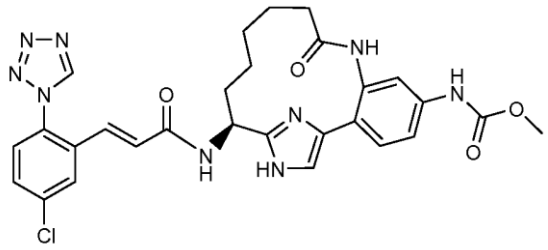


El Ejemplo 33 se preparó siguiendo los procedimientos descritos en la etapa 10C, sustituyendo hidróxido de amonio por pent-4-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 2E/2F; 2G (se produjo N-metilación durante la etapa de hidrogenación en presencia de metanol); 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.52 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.63 - 7.71 (m, 2 H), 7.55 - 7.60 (m, 2 H), 7.46 (d, *J*=8.2 Hz, 1 H), 7.28 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.73 (d, *J*=15.4 Hz, 1 H), 5.08 (t, *J*=6.9 Hz, 1 H), 3.76 (s, 3 H), 2.94 (s, 3 H), 2.87 - 2.92 (m, 2 H), 2.15 - 2.22 (m, 2 H), 1.66 - 1.85 (m, 2 H), 1.39 - 1.65 (m, 4 H), 0.75 - 0.87 (m, 2 H). EM (IEP) m/z: 590.3 (M+H)+. HPLC analítica: TR= 6.26 min.

Ejemplo 34.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8.17.19-triaza-

triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

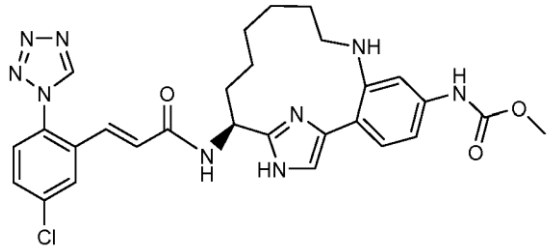


El Ejemplo 34 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por las etapas 2E/2F; 2G; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.61 (s, 1 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.38 - 7.45 (m, 3 H), 7.12 (d, *J*=15.9 Hz, 1 H), 6.74 (d, *J*=15.9 Hz, 1 H), 5.01 (dd, *J*=10.2, 4.7 Hz, 1 H), 3.75 (s, 3 H), 2.28 - 2.41 (m, 2 H), 2.15 - 2.25 (m, 1 H), 1.95 - 2.07 (m, 1 H), 1.41 - 1.76 (m, 4 H), 0.71 - 0.98 (m, 2 H). EM (IEP) m/z: 590.1 (M+H)+. HPLC analítica: TR= 4.96 min.

Ejemplo 35.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-

il}-carbámico, sal 2 TFA

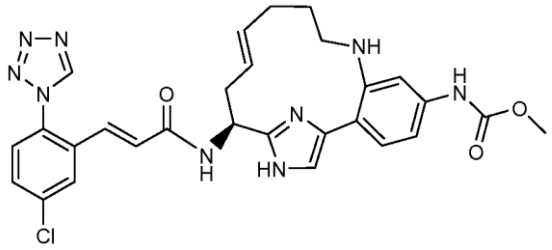


El Ejemplo 35 se preparó siguiendo los procedimientos descritos en la etapa 10C, sustituyendo hidróxido de amonio por pent-4-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 2E/2F; 2G sustituyendo MeOH por EtOAc; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.82 (s, 1 H), 7.66 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.60 (d, *J*=8.8 Hz, 1 H), 7.56 - 7.59 (m, 2 H), 7.26 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 6.68 (d, *J*=15.9 Hz, 1 H), 5.12 (dd, *J*=9.9, 3.3 Hz, 1 H), 3.76 (s, 3 H), 3.09 - 3.24 (m, 2 H), 2.31 - 2.43 (m, 1 H), 1.89 - 2.10 (m, 2 H), 1.53 - 1.85 (m, 5 H), 1.07 - 1.27 (m, 2 H). EM (IEP) m/z: 576.3 (M+H)+. HPLC analítica: TR= 5.91 min.

Ejemplo 36.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-

il}-carbámico, sal 2 TFA

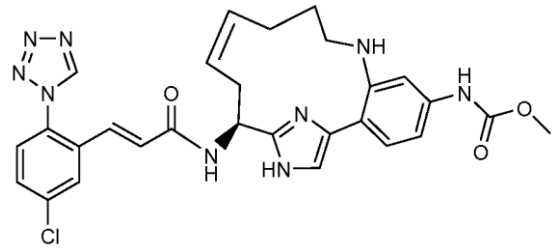


El Ejemplo 36 se preparó siguiendo los procedimientos descritos en la etapa 10C, sustituyendo hidróxido de amonio por pent-4-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 2E; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.59 (d, *J*=8.8 Hz, 1 H), 7.43 (s, 1 H), 7.28 - 7.32 (m, 2 H), 7.18 (d, *J*=15.4 Hz, 1 H), 6.98 (dd, *J*=8.8, 2.2 Hz, 1 H), 6.76 (d, *J*=15.9 Hz, 1 H), 5.69 - 5.79 (m, 1 H), 5.45 - 5.54 (m, 1 H), 5.15 (dd, *J*=9.3, 4.4 Hz, 1 H), 3.74 (s, 3 H), 3.03 - 3.20 (m, 2 H), 2.72 - 2.82 (m, 1 H), 2.56 - 2.68 (m, 1 H), 2.28 - 2.48 (m, 2 H), 1.82 - 2.03 (m, 2 H). EM (IEP) m/z: 574.2 (M+H)+. HPLC analítica: TR= 5.85 min.

Ejemplo 37.

Éster metílico del ácido {(Z)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-

il}-carbámico, sal 2 TFA

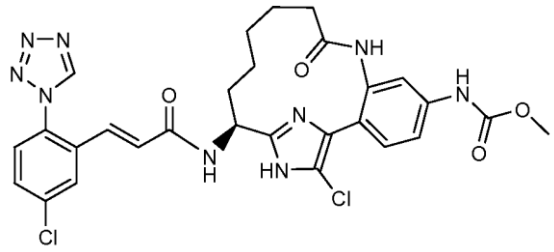


El Ejemplo 37 se preparó siguiendo los procedimientos descritos en la etapa 10C, sustituyendo hidróxido de amonio por pent-4-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 2F; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.48 (s, 1 H), 7.86 - 7.95 (m, 2 H), 7.69 (d, *J*=8.2 Hz, 1 H), 7.65 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.54 - 7.58 (m, 2 H), 7.33 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.21 (d, *J*=15.9 Hz, 1 H), 6.65 (d, *J*=15.9 Hz, 1 H), 5.52 - 5.60 (m, 1 H), 5.36 - 5.44 (m, 1 H), 5.30 (dd, *J*=9.9, 3.3 Hz, 1 H), 3.78 (s, 3 H), 3.10 - 3.28 (m, 3 H), 2.60 - 2.76 (m, 2 H), 2.36 - 2.47 (m, 1 H), 2.15 - 2.25 (m, 1 H), 1.96 - 2.07 (m, 1 H). EM (IEP) m/z: 574.2 (M+H)+. HPLC analítica: TR= 5.88 min.

Ejemplo 38.

Éster metílico del ácido {(S)-18-Cloro-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-

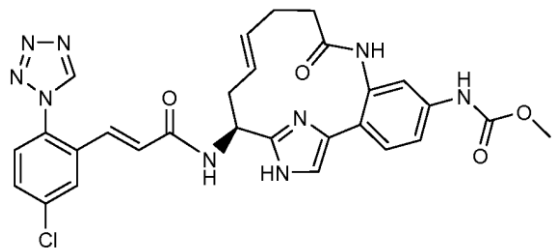
1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA



El Ejemplo 38 se preparó siguiendo el procedimiento descrito en 7, sustituyendo el Ejemplo 6 por el Ejemplo 34. ^{1}H NMR (500 MHz, DMSO-d_6+2 gotas de D_2O) δ ppm 9.76 (s, 1 H), 7.90 (d, *J*=1.6 Hz, 1 H), 7.67 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.63 (d, *J*=8.3 Hz, 1 H), 7.38 (s, 1 H), 7.30 - 7.36 (m, 2 H), 6.77 - 6.84 (m, 2 H), 4.76 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.62 (s, 3 H), 2.07 - 2.21 (m, 2 H), 1.83 - 1.91 (m, 1 H), 1.56 - 1.66 (m, 1 H), 1.44 - 1.54 (m, 1 H), 1.34 - 1.44 (m, 1 H), 1.19 - 1.31 (m, 2 H), 0.85 - 0.96 (m, 1 H), 0.38 - 0.49 (m, 1 H). EM (IEP) m/z: 624.3 (M+H)+. HPLC analítica: TR= 6.32 min.

Ejemplo 39.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA



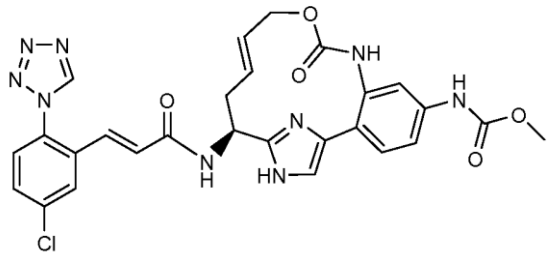
39A. Éster metílico del ácido ((E)-(S)-15-*terc*-

butoxicarbonilamino-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il)-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por la etapa 2E. EM (IEP) m/z: 586.4 (M+H)+.

39B. El Ejemplo 39 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G por 39A; seguido por la etapa 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 2 H), 7.37 - 7.41 (m, 3 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.50 - 5.59 (m, 1 H), 5.37 - 5.45 (m, 1 H), 5.08 (dd, *J*=10.2, 4.7 Hz, 1 H), 3.75 (s, 3 H), 2.76 - 2.84 (m, 1 H), 2.32 - 2.60 (m, 5 H). EM (IEP) m/z: 588.1 (M+H)+. HPLC analítica: TR= 4.79 min

Ejemplo 40.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-10-oxa-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

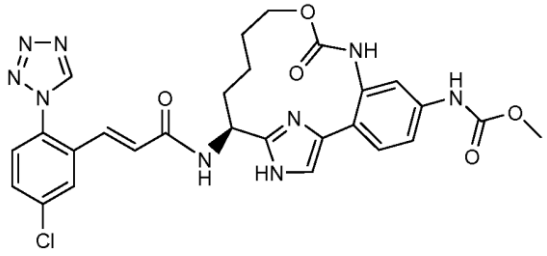


El Ejemplo 40 se preparó siguiendo los

procedimientos descritos en el Intermediario 7B, sustituyendo el Intermediario 7A por 10C y sustituyendo cloroformiato de metilo por cloroformiato de alilo; seguido por las etapas 2E; 10H; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.50 (s ancho, 1 H), 7.34 - 7.43 (m, 3 H), 7.14 (d, *J*=15.7 Hz, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 5.83 - 5.93 (m, 1 H), 5.68 - 5.76 (m, 1 H), 5.13 (dd, *J*=10.2, 5.2 Hz, 1 H), 4.28 - 4.43 (m, 2 H), 3.75 (s, 3 H), 2.88 - 2.97 (m, 1 H), 2.53 - 2.65 (m, 1 H). EM (IEP) m/z: 590.2 (M+H)+. HPLC analítica: TR= 4.90 min.

Ejemplo 41.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-10-oxa-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

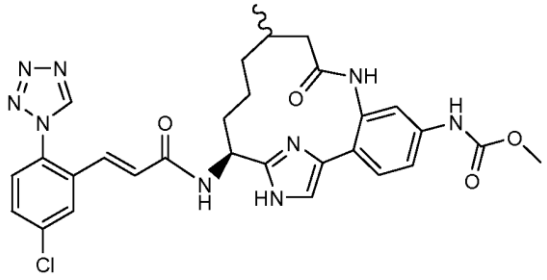


El Ejemplo 41 se preparó siguiendo los procedimientos descritos en el Intermediario 7B, sustituyendo el Intermediario 7A por 10C y sustituyendo cloroformiato de metilo por cloroformiato de alilo; seguido por las etapas 2E/2F; 2G, sustituyendo metanol por EtOAc; 1F,

sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C durante 2 h; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.55 (d, *J*=1.6 Hz, 1 H), 7.43 - 7.47 (m, 2 H), 7.39 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.12 (d, *J*=15.4 Hz, 1 H), 6.74 (d, *J*=15.4 Hz, 1 H), 4.98 (dd, *J*=10.4, 4.9 Hz, 1 H), 4.13 - 4.26 (m, 1 H), 3.89 - 4.03 (m, 1 H), 3.75 (s, 3 H), 2.18 - 2.31 (m, 1 H), 1.84 - 1.98 (m, 1 H), 1.42 - 1.65 (m, 3 H), 1.19 - 1.35 (m, 1 H). EM (IEP) m/z: 592.2 (M+H)+. HPLC analítica: TR= 5.11 min.

Ejemplo 42.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA. Mezcla de diastereómeros



El Ejemplo 42 (mezcla de diastereómeros) se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 3-metilpent-4-enoico; seguido por las etapas 2E/2F; 2G; 10H; y 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50, 9.51 (s, 1 H), 7.94 - 7.98 (m, 1

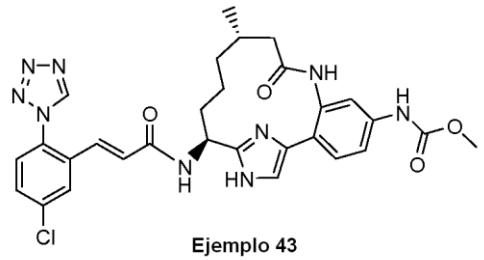
H), 7.64 - 7.69 (m, 1 H), 7.55 - 7.60 (m, 2 H), 7.37 - 7.44 (m, 3 H), 7.08 - 7.15 (m, 1 H), 6.70 - 6.82 (m, 1 H), 4.96 - 5.02 (m, 1 H), 3.75 (s, 3 H), 2.38 - 2.47 (m, 1 H), 2.19 - 2.26 (m, 0.5 H), 2.10 - 2.18 (m, 0.5 H), 1.87 - 2.07 (m, 3 H), 1.54 - 1.70 (m, 1 H), 1.36 - 1.52 (m, 1 H), 0.95 - 1.02 (m, 3.5 H), 0.80 - 0.89 (m, 0.5 H), 0.67 - 0.77 (m, 0.5 H), 0.46 - 0.55 (m, 0.5 H). EM (IEP) m/z: 604.3 (M+H)+. HPLC analítica: TR= 5.11 min.

Ejemplo 43.

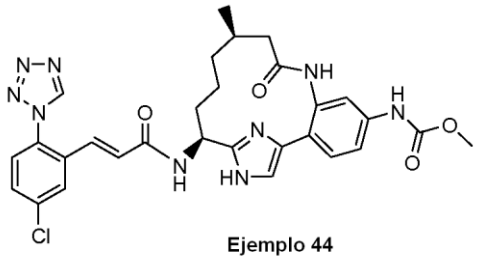
Éster metílico del ácido {(11S,15S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA; y

Ejemplo 44.

Éster metílico del ácido {(11R,15S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA



Ejemplo 43



Ejemplo 44

Los diastereómeros del Ejemplo 42 se separaron en una columna CHIRALCEL® OD-H (isocrática; MeOH:EtOH/heptano

1:1 30 %; 20 ml/min; detección a 254 nm). Las fracciones puras se concentraron, se disolvieron en metanol que contenía dos gotas de TFA, se concentraron y luego se liofilizaron dando 0.0047 g del Ejemplo 43, como un sólido blanco y 0.0042 g del Ejemplo 44, como un sólido blanco.

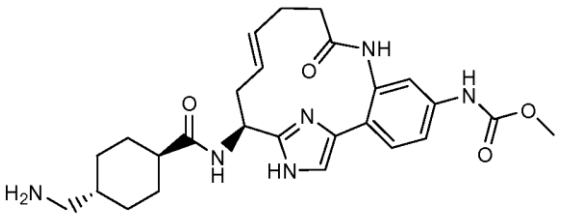
Ejemplo 43: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.37 - 7.44 (m, 3 H), 7.14 (d, *J*=15.9 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 5.00 (dd, *J*=9.3, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.43 (d, *J*=10.4 Hz, 1 H), 2.18 - 2.30 (m, 1 H), 1.84 - 1.98 (m, 3 H), 1.61 - 1.74 (m, 1 H), 1.34 - 1.49 (m, 1 H), 0.93 - 1.05 (m, 4 H), 0.46 - 0.58 (m, 1 H). EM (IEP) m/z: 604.3 $(M+H)^+$ y 606.2 $(M+2+H)^+$. HPLC analítica (Método D): TR= 4.63 min. CHIRALCEL® OD (MeOH:EtOH/heptano 1:1 40 %; 4.6 x 250 mm; 1 ml/min.; 220 nm): 10.08 min. (>99 % ed).

Ejemplo 44: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.60 (s, 1 H, intercambiable), 9.50 (s, 1 H), 7.95 (d, *J*=1.6 Hz, 1 H), 7.66 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.59 (s ancho, 1 H), 7.57 (d, *J*=8.8 Hz, 1 H), 7.36 - 7.45 (m, 3 H), 7.11 (d, *J*=15.9 Hz, 1 H), 6.71 (d, *J*=15.9 Hz, 1 H), 4.98 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.42 (d, *J*=11.0 Hz, 1 H), 2.08 - 2.19 (m, 1 H), 1.91 - 2.08 (m, 3 H), 1.56 - 1.65 (m, 1 H), 1.41 - 1.52 (m, 1 H), 0.99 (d, *J*=6.6 Hz, 3 H), 0.81 - 0.94 (m, 1 H), 0.69 - 0.79 (m, 1 H). EM (IEP) m/z: 604.3 $(M+H)^+$ y 606.2 $(M+2+H)^+$.

HPLC analítica (Método D): TR= 4.69 min. CHIRALCEL® OD (MeOH:EtOH/heptano 1:1 40 %; 4.6 x 250 mm; 1 ml/min.; 220 nm): 13.74 min. (>99 % ed).

Ejemplo 45.

Éster metílico del ácido {(E)-(S)-15-[(4-aminometil-ciclohexanocarbonil)-amino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 2 TFA

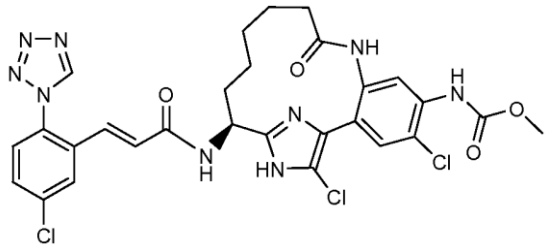


El Ejemplo 45 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G por 39A; seguido por las etapas 3B, sustituyendo base de Hunig por trietilamina y llevando a cabo la reacción a 50°C; y 3C. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.55 (d, *J*=1.6 Hz, 1 H), 7.43 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.37 - 7.40 (m, 2 H), 5.46 - 5.56 (m, 1 H), 5.34 - 5.43 (m, 1 H), 4.98 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.71 - 2.82 (m, 3 H), 2.27 - 2.55 (m, 6 H), 1.83 - 1.99 (m, 4 H), 1.56 - 1.67 (m, 1 H), 1.39 - 1.53 (m, 2 H), 1.01 - 1.17 (m, 2 H). EM (IEP) m/z: 495.3 (M+H)+. HPLC analítica: TR= 1.8, 2.4 min.

Ejemplo 46.

Éster metílico del ácido {(S)-4.18-dicloro-15-[(E)-

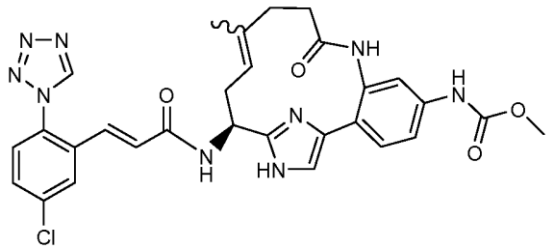
3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA



A una solución del Ejemplo 34 (0.023 g, 0.033 mmol) en acetonitrilo (1 ml)/cloroformo (1.000 ml) se añadió NCS (5.23 mg, 0.039 mmol). El vial de pared gruesa se selló con un tapón a rosca revestido con teflón y la reacción se calentó hasta 65°C. Después de 6 h, se añadió más NCS (5.23 mg, 0.039 mmol). Después de otras 4 h, la reacción se enfrió hasta ta y se concentró. La purificación por cromatografía de fase inversa proporcionó el Ejemplo 46 (0.006 g, 23.2 %) como un sólido amarillo. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.93 - 8.02 (m, 2 H), 7.62 - 7.68 (m, 1 H), 7.53 - 7.59 (m, 2 H), 7.10 (d, *J*=15.4 Hz, 1 H), 6.75 (d, *J*=15.4 Hz, 1 H), 4.79 - 4.98 (m, 1 H), 3.78 (s, 3 H), 2.26 - 2.37 (m, 2 H), 2.01 - 2.12 (m, 1 H), 1.84 - 1.95 (m, 1 H), 1.59 - 1.72 (m, 2 H), 1.32 - 1.50 (m, 2 H), 1.05 - 1.19 (m, 1 H), 0.73 - 0.86 (m, 1 H). EM (IEP) m/z: 656.4 (M-H)-. HPLC analítica: TR= 7.49 min.

Ejemplo 47.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

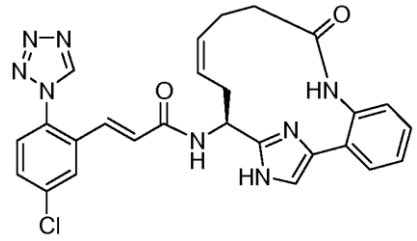


El Ejemplo 47 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 4-metilpent-4-enoico; seguido por las etapas 2E/2F; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 - 7.62 (m, 2 H), 7.33 - 7.44 (m, 3 H), 7.15 (d, *J*=15.9 Hz, 1 H), 6.78 (d, *J*=15.9 Hz, 1 H), 5.14 - 5.21 (m, 1 H), 5.06 (dd, *J*=10.2, 5.2 Hz, 1 H), 3.76 (s, 3 H), 2.75 - 2.83 (m, 1 H), 2.48 - 2.69 (m, 3 H), 2.34 - 2.42 (m, 2 H), 1.56 (s, 3 H). EM (IEP) m/z: 602.3 (M+H)+. HPLC analítica: TR= 5.09 min.

Ejemplo 48.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((Z)-(S)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-

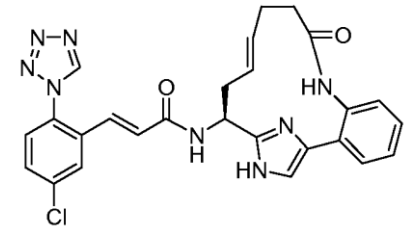
1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA



El Ejemplo 48 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo 10C por 15B y sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por 2F; 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.25 - 3.00 (m, 6 H), 5.14 - 5.24 (m, 1 H), 5.41 - 5.54 (m, 1 H), 5.57 - 5.70 (m, 1 H), 6.75 (d, *J*=15.7 Hz, 1 H), 7.17 (d, *J*=15.7 Hz, 1 H), 7.33 - 7.40 (m, 3 H), 7.48 - 7.54 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 515.3(M+H)+. HPLC analítica: TR= 5.06 min.

Ejemplo 49.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA

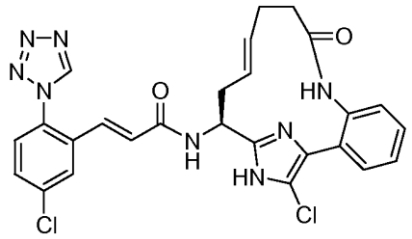


El Ejemplo 49 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo 10C

por 15B y sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por las etapas 2E; 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.32 - 2.62 (m, 5 H), 2.77 - 2.86 (m, 1 H), 5.09 (dd, *J*=10.2, 4.7 Hz, 1 H), 5.38 - 5.47 (m, 1 H), 5.52 - 5.61 (m, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 7.34 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.41 (td, *J*=7.6, 1.2 Hz, 1 H), 7.44 (s, 1 H), 7.52 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.55 (td, *J*=7.7, 1.6 Hz, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 515.3(M+H)+. HPLC analítica: TR= 5.00min.

Ejemplo 50.

(E)-*N*-((E)-(S)-18-Cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

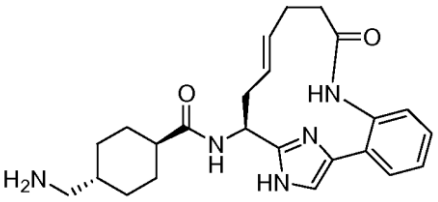


El Ejemplo 50 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 49. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.30 - 2.53 (m, 5 H), 2.66 - 2.76 (m, 1 H), 4.97 (dd, *J*=10.3, 4.3 Hz, 1 H), 5.32 - 5.42 (m, 1 H), 5.49 - 5.59 (m, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.32 (dd, *J*=7.7, 1.2 Hz, 1 H), 7.40 (td, *J*=7.6, 1.3 Hz, 1 H), 7.48 - 7.53 (m, 2 H), 7.58 (d, *J*=8.3 Hz,

1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 549.2(M+H)+. HPLC analítica: TR= 6.87min.

Ejemplo 51.

((E)-(S)-9-Oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-amida del ácido 4-aminometil-ciclohexanocarboxílico, sal 2 TFA

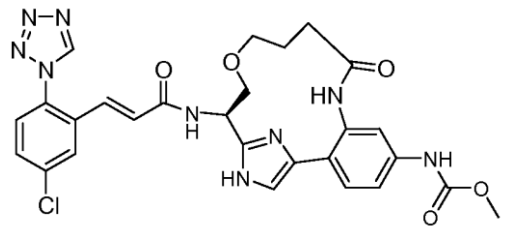


El Ejemplo 51 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo 10C por 15B y sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por las etapas 2E; 10H; 3B; y 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.03 - 1.17 (m, 2 H), 1.40 - 1.53 (m, 2 H), 1.56 - 1.67 (m, 1 H), 1.83 - 2.00 (m, 4 H), 2.29 - 2.45 (m, 4 H), 2.45 - 2.55 (m, 2 H), 2.72 - 2.81 (m, 3 H), 5.00 (dd, *J*=10.6, 4.8 Hz, 1 H), 5.35 - 5.44 (m, 1 H), 5.47 - 5.56 (m, 1 H), 7.33 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.42 (td, *J*=7.6, 1.3 Hz, 1 H), 7.44 (s, 1 H), 7.50 (dd, *J*=7.7, 1.7 Hz, 1 H), 7.55 (td, *J*=7.7, 1.7 Hz, 1 H). EM (IEP) m/z: 422.3(M+H)+. HPLC analítica: TR= 1.62min.

Ejemplo 52.

Éster metílico del ácido {(R)-15-[(E)-3-(5-cloro-2-tetrazol-

1-il-fenil)-acriloilamino]-9-oxo-13-oxa-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA



52A. Éster metílico del ácido (S)-3-aliloxi-2-*terc*-butoxicarbonilamino-propiónico: Este compuesto se preparó siguiendo un procedimiento descrito en *Organic Letters*, 10(17):3883 (2008). A una solución de éster metílico de N-(*terc*-butoxicarbonil)-L-serina (0.781 ml, 3.85 mmol) en THF (15 ml) se añadió metil carbonato de alilo (0.524 ml, 4.61 mmol). La solución se purgó con N_2, seguido por la adición de de *tetraquis*(trifenilfosfina)paladio(0) (444 mg, 0.385 mmol). El recipiente se selló y se calentó a 60°C durante la noche. La mezcla de reacción se diluyó con acetato de etilo, se lavó con $NaHCO_3$ saturado y salmuera. La fase orgánica se concentró. La purificación por cromatografía en fase normal proporcionó 52A (550 mg, 55.2 % de rendimiento) como un aceite amarillo. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.75 - 5.94 (m, 1 H) 5.32 - 5.47 (m, 1 H) 5.11 - 5.29 (m, 2 H) 4.35 - 4.53 (m, 1 H) 3.92 - 4.03 (m, 2 H) 3.80 - 3.89 (m, 1 H) 3.76 (m, 3 H) 3.61 - 3.70 (m, 1 H) 1.46 (m, 9 H).

52B. Ácido (S)-3-aliloxi-2-*terc*-

butoxicarbonilamino-propiónico: Una solución de 52A (1000 mg, 3.86 mmol) e hidróxido de litio (486 mg, 11.57 mmol) en THF, agua y MeOH se agitó a ta durante 4 h. La solución se acidificó usando HCl 5M en agua (pH ~3). La mezcla se extrajo con EtOAc. Las fases orgánicas combinadas se concentraron dando 52B (0.96 g, 100 % de rendimiento) como un aceite amarillo. EM (IEP) m/z: 146.0 (M+H-boc)+.

52C. Éster 2-(2-bromo-4-nitro-fenil)-2-oxo-etílico del ácido (S)-3-aliloxi-2-*terc*-butoxicarbonilamino-propiónico: A una solución de 52B (0.95 g, 3.87 mmol) e Intermediario 10 (1.376 g, 4.26 mmol) en DMF (20 ml) se añadió bicarbonato potásico (0.465 g, 4.65 mmol). Después de 1.5 h a ta, la reacción se diluyó con EtOAc, se lavó con agua, solución saturada de bicarbonato sódico, luego salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró dando 52C (1.82 g, 96 % de rendimiento) como un aceite naranja espeso. EM (IEP) m/z: 389.0(M+H-boc)+.

52D. Éster 2-(4-amino-2-bromo-fenil)-2-oxo-etílico del ácido (S)-3-aliloxi-2-*terc*-butoxicarbonilamino-propiónico: A una mezcla de 52C (1700 mg, 3.49 mmol) y hierro (3896 mg, 69.8 mmol) en etanol (15 ml) y agua (15.00 ml) se añadió HCl 12M conc. (0.204 ml, 2.442 mmol). La suspensión se calentó a 50°C durante 2 horas. La suspensión oscura se filtró, se lavó con metanol y se concentró dando 52D (1.7 g, 100 %). EM (IEP)

m/z: 359.0(M+H-boc)+.

52E. Éster 2-(2-bromo-4-metoxicarbonilamino-fenil)-2-oxo-etílico del ácido (S)-3-aliloxi-2-*terc*-butoxicarbonilamino-propiónico: A una solución enfriada (baño de hielo) de 52D (1670 mg, 3.65 mmol) y piridina (0.325 ml, 4.02 mmol) en diclorometano (50 ml) se añadió cloroformiato de metilo (0.297 ml, 3.83 mmol). La mezcla de reacción se agitó durante 10 min, se lavó con salmuera, se secó ($MgSO_4$) y se concentró dando 52E (1.8 g, 96 % de rendimiento) como una espuma amarilla. EM (IEP) m/z: 417.1(M+H-boc)+.

52F. Éster metílico del ácido {4-[2-((R)-2-aliloxi-1-*terc*-butoxicarbonilamino-etil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-amino-fenil}-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 1B, sustituyendo 1A por 52E; seguido por las etapas 10B; y 10C (alternativa). EM (IEP) m/z: 562.3(M+H)+.

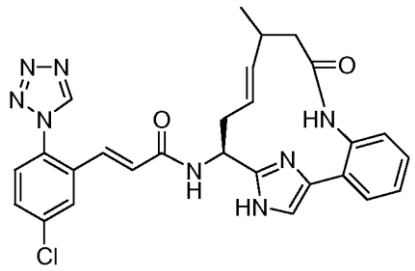
52G. Éster metílico del ácido {3-acriloilamino-4-[2-((R)-2-aliloxi-1-*terc*-butoxicarbonilamino-etil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: Una solución de 52F (50 mg, 0.089 mmol) y DIEA (50 µl, 0.286 mmol) en THF (2 ml) se enfrió en un baño de hielo. Se añadió a la solución en una porción cloruro de acriloilo (10µl, 0.123 mmol). A continuación, se retiró el baño de hielo y la mezcla de reacción se agitó durante 1 hora a ta. A la mezcla de reacción se añadió NaHCO3 saturado y la mezcla se extrajo con EtOAc. Las

fases orgánicas combinadas se lavaron con salmuera y se concentraron proporcionando un residuo oleoso que era como un material insoluble en CH_2Cl_2. La porción soluble del residuo se purificó por cromatografía en fase normal dando 52G (43 mg, 78 % de rendimiento). EM (IEP) m/z: 616.4 (M+H)+.

52H. El Ejemplo 52 se preparó siguiendo los procedimientos descritos en la etapa 2E/2F, sustituyendo 2D por 52G; seguido por las etapas 2G; 10H; y 1G. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 (s, 1 H) 7.79 (s, 1 H) 7.50 - 7.62 (m, 1 H) 7.42 (t, *J*=7.91 Hz, 2 H) 7.10 (s ancho, 1 H) 6.60 (d, *J*=15.31 Hz, 1 H) 5.22 (s ancho, 1 H) 4.04 - 4.18 (m, 1 H) 3.92 - 4.02 (m, 1 H) 3.78 (s, 4 H) 3.60 (d, *J*=6.27 Hz, 2 H) 3.28 - 3.49 (m, 1 H) 2.81 (t, *J*=7.28 Hz, 1 H) 2.34 (s, 1 H) 2.05 (d, *J*=5.02 Hz, 2 H) 1.63 (s ancho, 1 H) 0.88 (t, *J*=6.90 Hz, 2 H). EM (IEP) m/z: 592.3(M+H)+. HPLC analítica: TR= 5.16 min.

Ejemplo 53.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA



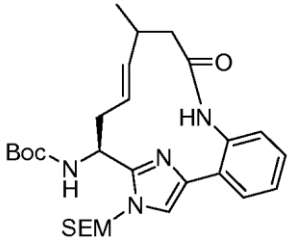
53A. Éster *terc*-butílico del ácido {(S)-1-[4-[2-(3-

metil-pent-4-enoilamino)-fenil]-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico: Este compuesto se preparó siguiendo el procedimiento descrito en 10D, sustituyendo 10C por 15B y sustituyendo ácido but-3-enoico por ácido 3-metil-4-pentenoico. EM (IEP) m/z: 555.5(M+H)+.

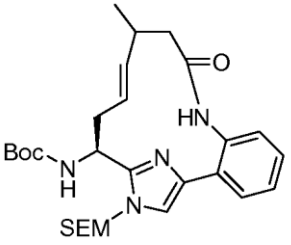
53B. Éster *terc*-butílico del ácido [(E)-(S)-11-metil-9-oxo-17-(2-trimetilsilanil-etoximetil)-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il]-carbámico, sal 1 TFA, diastereómero A;

53C. Éster *terc*-butílico del ácido [(E)-(S)-11-metil-9-oxo-17-(2-trimetilsilanil-etoximetil)-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il]-carbámico, sal 1 TFA, diastereómero B; y

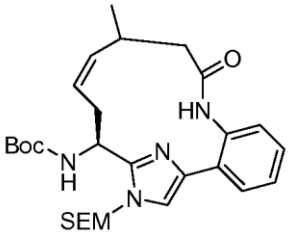
53D. Éster *terc*-butílico del ácido [(Z)-(S)-11-metil-9-oxo-17-(2-trimetilsilanil-etoximetil)-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il]-carbámico, sal 1 TFA



53B, diastereómero A



53C, diastereómero B



53D

Estos compuestos se prepararon siguiendo el

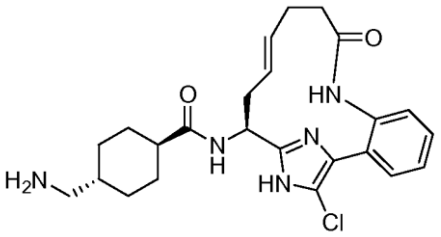
procedimiento descrito en 2E/2F sustituyendo 2D por 53A. La purificación por cromatografía en fase inversa dio 53B, diastereómero A (16.3 mg, 2.291 % de rendimiento) como una espuma color púrpura pálido; 53C, diastereómero B (180.6 mg, 25.4 % de rendimiento) como una espuma color púrpura pálido; y 53D (90.5 mg, 12.72 % de rendimiento) como una espuma color púrpura pálido.

53E. El Ejemplo 53 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G por 53C; seguido por la etapa 15D. 1H NMR (500 MHz, CD3OD) δ ppm 1.06 (d, *J*=6.9 Hz, 3 H), 2.13 (dd, *J*=13.9, 11.7 Hz, 1 H), 2.43 - 2.53 (m, 2 H), 2.65 - 2.77 (m, 1 H), 2.83 - 2.91 (m, 1 H), 5.05 (dd, *J*=11.8, 4.7 Hz, 1 H), 5.28 (ddd, *J*=15.1, 9.4, 1.1 Hz, 1 H), 5.53 (ddd, *J*=15.1, 10.5, 4.1 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.17 (d, *J*=15.7 Hz, 1 H), 7.34 (d, *J*=8.0 Hz, 1 H), 7.39 - 7.44 (m, 2 H), 7.51 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.56 (td, *J*=7.7, 1.4 Hz, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.69 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 9.52 (s, 1 H). EM (IEP) m/z: 529.3(M+H)+. HPLC analítica: TR= 5.39 min.

Ejemplo 54.

((E)-(S)-18-Cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-

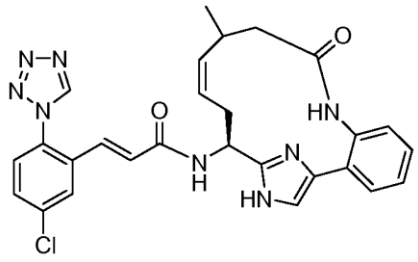
amida del ácido 4-aminometil-ciclohexanocarboxílico , sal 2 TFA



El Ejemplo 54 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo 10C por 15B y sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por las etapas 2E; 10H; 3B; 17A; y 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.02 - 1.18 (m, 2 H), 1.40 - 1.55 (m, 2 H), 1.56 - 1.68 (m, 1 H), 1.84 - 1.98 (m, 4 H), 2.26 - 2.53 (m, 6 H), 2.68 - 2.76 (m, 1 H), 2.79 (d, *J*=7.2 Hz, 2 H), 4.88 - 4.92 (m, 1 H), 5.33 - 5.43 (m, 1 H), 5.46 - 5.55 (m, 1 H), 7.33 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.43 (td, *J*=7.6, 1.1 Hz, 1 H), 7.51 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.55 (td, *J*=7.7, 1.6 Hz, 1 H). EM (IEP) m/z: 456.2(M+H)+. HPLC analítica: TR= 3.36min.

Ejemplo 55.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((Z)-(S)-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA

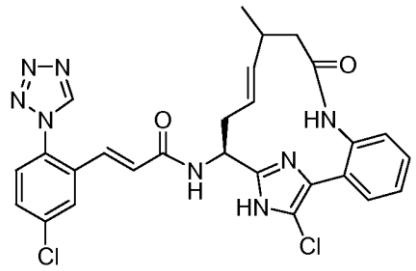


El Ejemplo 55 se preparó siguiendo los

procedimientos descritos en la etapa 10H, sustituyendo 10G por 53D; seguido por la etapa 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.06 (d, *J*=6.6 Hz, 3 H), 2.08 (t, *J*=12.0 Hz, 1 H), 2.47 (dd, *J*=12,4, 2.5 Hz, 1 H), 2.58 - 2.67 (m, 1 H), 2.83 - 2.96 (m, 1 H), 2.99 - 3.08 (m, 1 H), 5.14 (dd, *J*=12,4, 4.4 Hz, 1 H), 5.33 (td, *J*=11.5, 3.4 Hz, 1 H), 5.46 - 5.54 (m, 1 H), 6.74 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 7.27 (d, *J*=8.0 Hz, 1 H), 7.36 - 7.42 (m, 2 H), 7.47 - 7.53 (m, 2 H), 7.56 (d, *J*=8.5 Hz, 1 H), 7.65 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). EM (IEP) m/z: 529.3(M+H)+. HPLC analítica: TR= 5.35 min.

Ejemplo 56.

(E)-N-((E)-(S)-18-Cloro-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

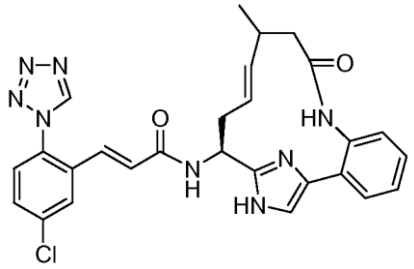


El Ejemplo 56 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 53. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.05 (d, *J*=6.9 Hz, 3 H), 2.16 (dd, *J*=13.9, 11.7 Hz, 1 H), 2.30 - 2.39 (m, 1 H), 2.42 (dd, *J*=13.9, 3.2 Hz, 1 H), 2.64 - 2.79 (m, 2 H), 4.92 (dd, *J*=11.8,

4.1 Hz, 1 H), 5.19 (ddd, *J*=15.1, 9.4, 1.1 Hz, 1 H), 5.52 (ddd, *J*=14.9, 10.7, 4.1 Hz, 1 H), 6.79 (d, *J*=15.7 Hz, 1 H), 7.15 (d, *J*=15.7 Hz, 1 H), 7.32 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.40 (td, *J*=7.6, 1.2 Hz, 1 H), 7.47 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.51 (td, *J*=7.7, 1.5 Hz, 1 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 8.01 (d, *J*=2.5 Hz, 1 H), 9.52 (s, 1 H). EM (IEP) m/z: 563.3(M+H)+. HPLC analítica: TR= 7.22 min.

Ejemplo 57.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA

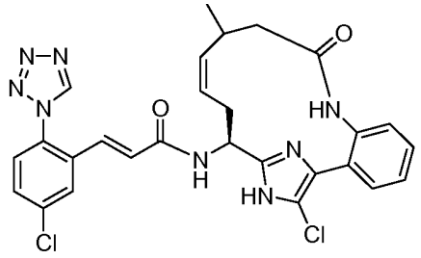


El Ejemplo 57 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G por 53B; seguido por la etapa 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.08 (d, *J*=6.9 Hz, 3 H), 2.26 (dd, *J*=14.3, 11.6 Hz, 1 H), 2.49 (dd, *J*=14.4, 3.7 Hz, 1 H), 2.63 - 2.75 (m, 3 H), 5.18 (dd, *J*=6.7, 5.4 Hz, 1 H), 5.44 (dd, *J*=15.5, 8.7 Hz, 1 H), 5.55 - 5.64 (m, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.31 (d, *J*=8.0 Hz, 1 H), 7.40 (td, *J*=7.6, 1.1 Hz, 1 H), 7.48 (s, 1 H), 7.50 - 7.56 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.96 (d, *J*=2.2

Hz, 1 H), 9.50 (s, 1 H). EM (IEP) m/z: 529.3(M+H)+. HPLC analítica: TR= 6.03 min.

Ejemplo 58.

(E)-*N*-((Z)-(S)-18-Cloro-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

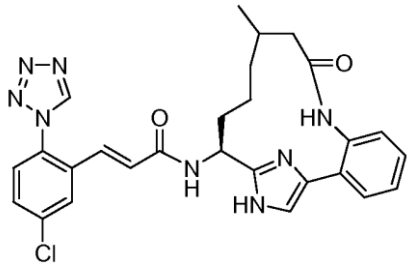


El Ejemplo 58 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 55. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.06 (d, *J*=6.9 Hz, 3 H), 2.16 (t, *J*=12.1 Hz, 1 H), 2.40 (dd, *J*=12.8, 2.3 Hz, 1 H), 2.54 - 2.63 (m, 1 H), 2.81 - 2.96 (m, 2 H), 4.97 (dd, *J*=12.0, 4.3 Hz, 1 H), 5.35 (td, *J*=11.5, 3.4 Hz, 1 H), 5.50 (td, *J*=10.6, 1.7 Hz, 1 H), 6.71 (d, *J*=15.7 Hz, 1 H), 7.16 (d, *J*=15.7 Hz, 1 H), 7.30 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.39 (td, *J*=7.6, 1.3 Hz, 1 H), 7.50 (td, *J*=7.8, 1.5 Hz, 1 H), 7.54 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 563.3(M+H)+. HPLC analítica: TR= 6.93 min.

Ejemplo 59.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-

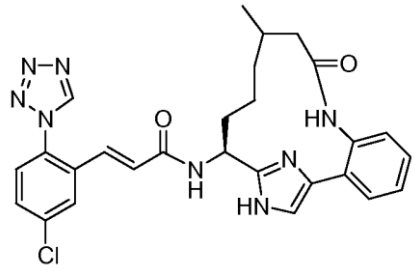
1(18),2,4,6,16(19)-pentaen-15-il)-acrilamida, sal 1 TFA



El Ejemplo 59 se preparó siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E/2F por una mezcla de 53B y 53C y sustituyendo el globo de hidrógeno por hidrógeno (3.446 x 105 Pa); seguido por las etapas 10H; y 15D. EM (IEP) m/z: 531.3(M+H)+. HPLC analítica: TR= 5.79 min.

Ejemplo 60.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-acrilamida, sal 1 TFA



El Ejemplo 60 se preparó siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E/2F por 53C y sustituyendo el globo de hidrógeno por hidrógeno (3.446 x 105 Pa); seguido por las etapas 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.48 - 0.60 (m, 1 H), 0.98 - 1.02 (m, 4 H), 1.34 - 1.49 (m, 1 H), 1.58 - 1.74 (m, 1 H), 1.86 - 2.02

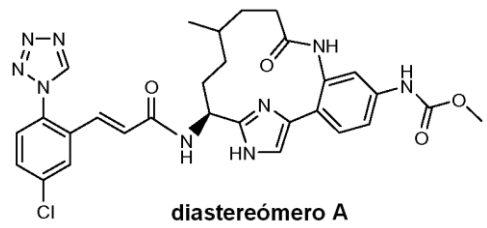
(m, 3 H), 2.22 - 2.29 (m, 1 H), 2.40 - 2.47 (m, 1 H), 5.00 (dd, *J*=9.6, 4.4 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.33 (dd, *J*=8.0, 0.8 Hz, 1 H), 7.41 - 7.47 (m, 2 H), 7.51 - 7.60 (m, 3 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). EM (IEP) m/z: 531.3(M+H)+. HPLC analítica: TR= 5.01min.

Ejemplo 61.

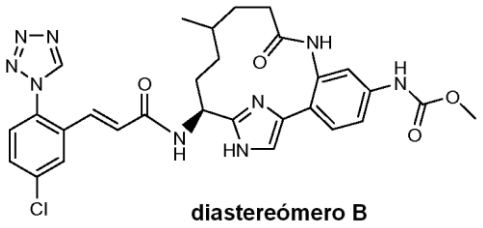
Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA, diastereómero A; y

Ejemplo 62.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA, diastereómero B



diastereómero A



diastereómero B

61A. N-4-(2-(1-(*terc*-Butoxicarbonilamino)but-3-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-4-il)-3-(4-metilpent-4-enamido)fenilmetanimidoperoxoato de (S)-metilo: Este compuesto se preparó siguiendo el procedimiento

descrito en 10D, sustituyendo ácido but-3-enoico por ácido 4-metilpent-4-enoico. EM (IEP) m/z: 628.2 (M+H)+.

61B. A una solución de 61A (0.066 g, 0.105 mmol) en DCE (1 ml) se añadió Grubbs (II) (0.018 g, 0.021 mmol). La mezcla de reacción llevó a vacío y se volvió a llenar tres veces con argón y luego se tapón el vial de microondas. La reacción se trató en un microondas a 120°C durante 20 min, se enfrió hasta ta y se concentró. La purificación por cromatografía de fase inversa proporcionó 61B (mezcla de isómeros E/Z) (0.026 g, 34.6 %) como un sólido marrón. EM (IEP) m/z: 600.5 (M+H)+ para ambos picos.

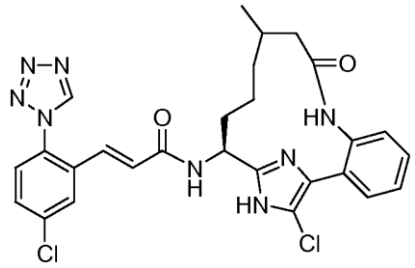
61C. El Ejemplo 61 y Ejemplo 62 se prepararon siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E/2F por 61B (mezcla de isómeros E/Z); seguido por las etapas 10H; y 1G. Los diastereómeros se separaron entonces por cromatografía de fase inversa dando el Ejemplo 61 (diastereómero A) y el Ejemplo 62 (diastereómero B).

Ejemplo 61: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.57 - 7.60 (m, 2 H), 7.38 - 7.44 (m, 3 H), 7.14 (d, *J*=15.7 Hz, 1 H), 6.75 (d, *J*=15.7 Hz, 1 H), 4.95 (dd, *J*=10.6, 4.5 Hz, 1 H), 3.76 (s, 3 H), 2.47 - 2.54 (m, 1 H), 2.23 - 2.33 (m, 2 H), 1.91 - 2.00 (m, 1 H), 1.53 - 1.61 (m, 1 H), 1.37 - 1.51 (m, 3 H), 0.86 (d, *J*=6.3 Hz, 3 H), 0.27 - 0.36 (m, 1 H). EM (IEP) m/z: 604.3 (M+H)+. HPLC analítica: TR= 5.28 min.

Ejemplo 62: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.49 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.40 - 7.45 (m, 3 H), 7.12 (d, *J*=15.7 Hz, 1 H), 6.71 (d, *J*=15.4 Hz, 1 H), 5.00 (dd, *J*=9.5, 5.4 Hz, 1 H), 3.75 (s, 3 H), 2.41 - 2.48 (m, 1 H), 2.24 - 2.32 (m, 1 H), 2.11 - 2.21 (m, 2 H), 1.60 - 1.69 (m, 1 H), 1.44 - 1.53 (m, 1 H), 1.27 - 1.42 (m, 2 H), 0.90 (d, *J*=6.3 Hz, 3 H), 0.68 - 0.78 (m, 1 H). EM (IEP) m/z: 604.3 (M+H)+. HPLC analítica: TR= 5.36 min.

Ejemplo 63.

(E)-*N*-((S)-18-Cloro-11-metil-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

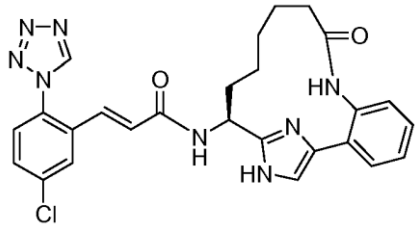


El Ejemplo 63 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 60. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.65 - 0.76 (m, 1 H), 0.99 (d, *J*=6.3 Hz, 3 H), 1.08 - 1.18 (m, 1 H), 1.31 - 1.45 (m, 1 H), 1.47 - 1.61 (m, 1 H), 1.80 - 1.91 (m, 1 H), 1.93 - 2.01 (m, 2 H), 2.06 - 2.15 (m, 1 H), 2.35 - 2.38 (m, 1 H), 4.90 (dd, *J*=10.2, 4.4 Hz, 1 H), 6.79 (d, *J*=15.7 Hz, 1 H), 7.12 (d, *J*=15.7 Hz, 1

H), 7.33 (d, *J*=8.0 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.48 - 7.53 (m, 2 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.66 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.99 (d, *J*=2.5 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 565.3(M+H)+. HPLC analítica: TR= 7.41 min.

Ejemplo 64.

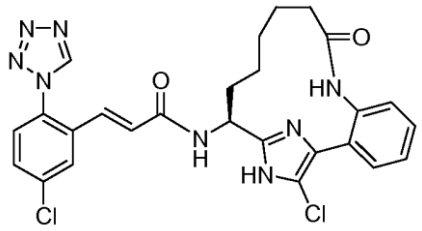
(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-acrilamida, sal 1 TFA



El Ejemplo 64 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo 10C por 15B y sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por las etapas 2F; 2G, sustituyendo el globo de hidrógeno por hidrógeno (3.446 x 105 Pa); 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.72 - 0.82 (m, 1 H), 0.83 - 0.94 (m, 1 H), 1.42 - 1.59 (m, 2 H), 1.59 - 1.77 (m, 2 H), 1.98 - 2.10 (m, 1 H), 2.16 - 2.25 (m, 1 H), 2.29 - 2.44 (m, 2 H), 5.05 (dd, *J*=10.0, 4.8 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.11 (d, *J*=15.7 Hz, 1 H), 7.33 (d, *J*=8.0 Hz, 1 H), 7.40 - 7.45 (m, 1 H), 7.49 (s, 1 H), 7.52 - 7.58 (m, 3 H), 7.65 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 9.49 (s, 1 H). EM (IEP) m/z: 517.3(M+H)+. HPLC analítica: TR= 5.02 min.

Ejemplo 65.

(E)-*N*-((S)-18-Cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

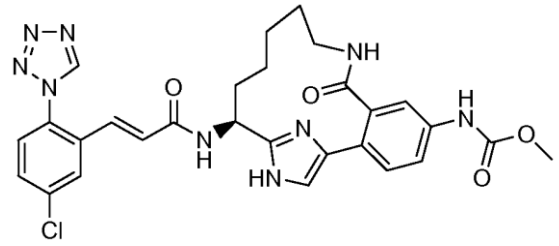


El Ejemplo 65 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 64. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.75 - 0.94 (m, 1 H), 1.07 - 1.21 (m, 1 H), 1.33 - 1.54 (m, 2 H), 1.62 - 1.72 (m, 2 H), 1.86 - 1.99 (m, 1 H), 2.05 - 2.16 (m, 1 H), 2.30 - 2.36 (m, 2 H), 4.90 (dd, *J*=10.6, 4.5 Hz, 1 H), 6.75 (d, *J*=15.4 Hz, 1 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.34 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.41 (td, *J*=7.7, 1.4 Hz, 1 H), 7.50 (td, *J*=7.7, 1.6 Hz, 1 H), 7.54 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.50 (s, 1 H). EM (IEP) m/z: 551.3(M+H)+. HPLC analítica: TR= 6.98 min.

Ejemplo 66.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxo-9.17.19-

triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA



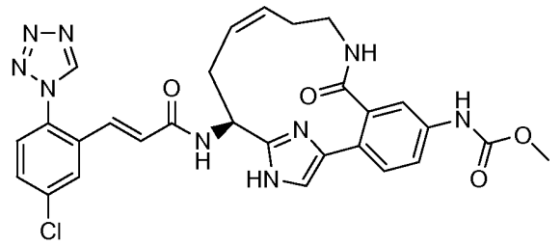
66A. Ácido 2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-5-metoxicarbonilamino-benzoico: A una solución de 10B (230 mg, 0.386 mmol) en THF seco (2 ml) a -78°C bajo Ar se añadió metil litio en THF (0.515 ml, 0.772 mmol). La reacción se agitó a -78°C durante 30 min, después de lo cual se añadió gota a gota butil litio en THF (0.232 ml, 0.579 mmol). Después de 30 min, se añadió hielo seco sólido a la mezcla de reacción y la mezcla se agitó a -78°C durante 30 min. La mezcla de reacción se inactivó con NH_4Cl concentrado (ac). Se extrajo con éter y la fase de éter se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró proporcionando 66A como un sólido blanco. Este era una mezcla del producto y material de partida. La mezcla se usó en la etapa siguiente sin purificación posterior. EM (IEP) m/z: 561.2 (M+H)+.

66B. El Ejemplo 66 se preparó siguiendo los procedimientos descritos en la etapa 3B, sustituyendo ácido (1R,4R)-4-((*terc*-butoxicarbonilamino)metil)

ciclohexanocarboxílico por 66A y sustituyendo 3A por but-3-en-1-amina; seguido por las etapas 2E/2F; 2G; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.96 (d, *J*=2.2 Hz, 1 H), 7.63 - 7.70 (m, 2 H), 7.54 - 7.63 (m, 2 H), 7.51 (s, 1 H), 7.30 (d, *J*=8.2 Hz, 1 H), 7.14 - 7.24 (d, *J*=15.7 Hz, 1 H), 6.70 - 6.81 (d, J=15.7 Hz, 1 H) 4.99 - 5.13 (m, 1 H), 3.68 (s, 3 H), 3.25 – 3.35 (m, 2 H), 2.24 - 2.44 (m, 1 H), 1.87 - 2.09 (m, 1 H), 1.42 - 1.82 (m, 4 H), 0.60 - 0.89 (m, 1 H), 0.30 - 0.60 (m, 1 H) EM (IEP) m/z: 590.3 (M+H)+. HPLC analítica: TR= 4.28 min (Método B).

Ejemplo 67.

Éster metílico del ácido {(Z)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxo-9.17.19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

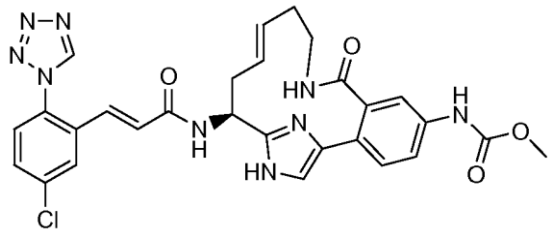


El Ejemplo 67 se preparó siguiendo los procedimientos descritos en la etapa 3B, sustituyendo ácido (1r,4r)-4-((*terc*-butoxicarbonilamino)metil)ciclohexanocarboxílico por 66A y sustituyendo 3A por but-3-en-1-amina; seguido por las etapas 2F;10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H),

7.98 (d, *J*=2.2 Hz, 1 H), 7.53 - 7.71 (m, 4 H), 7.41 (s, 1 H), 7.35 (d, *J*=8.8 Hz, 1 H), 7.17 (d, *J*=15.4 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.59 - 5.73 (m, 1 H), 5.29 - 5.41 (m, 1 H), 5.05 - 5.14 (m, 1 H), 3.73 (s, 3 H), 3.33 - 3.46 (m, 2 H), 2.72 - 2.87 (m, 1 H), 2.51 - 2.65 (m, 1 H), 2.41 - 2.51 (m, 1 H), 2.34 (ninguno, 1 H) EM (IEP) m/z: 588.3 (M+H)+. HPLC analítica: TR= 3.60 min (Método B).

Ejemplo 68.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxo-9.17.19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

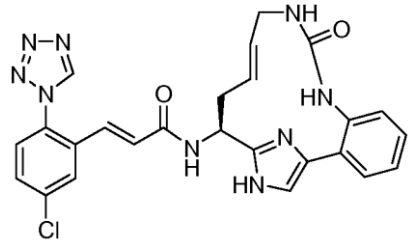


El Ejemplo 68 se preparó siguiendo los procedimientos descritos en la etapa 3B, sustituyendo ácido (1r,4r)-4-((*terc*-butoxicarbonilamino)metil)ciclohexanocarboxílico por 66A y sustituyendo 3A por but-3-en-1-amina; seguido por las etapas 2E;10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.95 (d, J=2.2 Hz, 1 H), 7.65 – 7.70 (m, 1 H), 7.57 (d, J=8.8 Hz, 2 H), 7.46 - 7.54 (m, 1 H), 7.41 (s, 1 H), 7.24 - 7.36 (m, 1 H), 7.13 – 7.17 (m, 1 H), 6.71 - 6.85 (m, 1 H), 5.50 -

5.62 (m, 1 H), 5.10 - 5.29 (m, 1 H), 3.69 (s, 3 H), 2.95 - 3.21 (m, 1 H), 2.63 - 2.87 (m, 1 H), 2.29 - 2.51 (m, 1 H), 2.06 - 2.29 (m, 1 H). EM (IEP) m/z: 588.3 (M+H)+. HPLC analítica: TR= 3.62 min. (Método B).

Ejemplo 69.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-9-oxo-8.10.17.19-tetraaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA



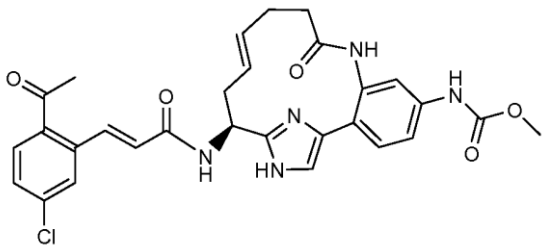
69A. Éster *terc*-butílico del ácido {(S)-1-[4-[2-(3-alil-ureido)-fenil]-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico: A una solución naranja enfriada (0°C) de 15B (150 mg, 0.327 mmol) y piridina (26.5 µl, 0.327 mmol) en DCM (1308 µl) se añadió gota a gota isocianato de alilo (28.9 µl, 0.327 mmol). Después de 35 min, se añadió más isocianato de alilo (28.9 µl, 0.327 mmol). Después de otros 30 min, se añadió NaHCO3 saturado (ac) (1.31 ml) y la reacción se agitó vigorosamente. La reacción se dejó calentar hasta ta y se agitó durante la noche. La reacción se repartió entre mezcla 1:1 de DCM y NaHCO3 saturado (ac.) y se separaron las fases. La fase acuosa se extrajo con DCM (2x). Las fases orgánicas se

reunieron, se lavaron con salmuera, se secaron sobre MgSO4, se filtraron y se concentraron dando un residuo naranja. La purificación por cromatografía en fase normal dio 69A (109.8 mg, 59.5 % de rendimiento) como una espuma amarilla. EM (IEP) m/z: 542.5(M+H)+.

69B. El Ejemplo 69 se preparó siguiendo los procedimientos descritos en la etapa 2E, sustituyendo 2D por 69A; seguido por las etapas 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.52 - 2.70 (m, 1 H), 2.81 - 2.93 (m, 1 H), 3.48 - 3.59 (m, 2 H), 5.15 (dd, *J*=10.0, 5.4 Hz, 1 H), 5.56 - 5.73 (m, 2 H), 6.77 (d, *J*=15.4 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 7.28 (d, *J*=8.0 Hz, 1 H), 7.33 (td, *J*=7.6, 1.1 Hz, 1 H), 7.39 (s, 1 H), 7.46 - 7.50 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 516.2(M+H)+. HPLC analítica: TR= 4.77min.

Ejemplo 70.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(2-acetil-5-cloro-fenil)-acriloilamino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

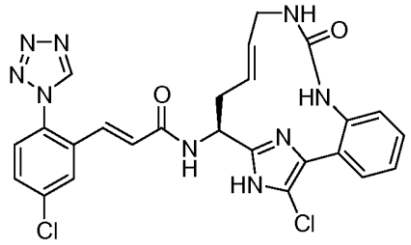


El Ejemplo 70 se preparó siguiendo los

procedimientos descritos en la etapa 10H, sustituyendo 10G por 39A; seguido por la etapa 15D, sustituyendo el Intermediario 2 por el Intermediario 4 y sustituyendo la base de Hunig por trietilamina. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.98 (d, *J*=15.9 Hz, 1 H), 7.91 (d, *J*=8.2 Hz, 1 H), 7.66 (d, *J*=2.2 Hz, 1 H), 7.59 (s, 1 H), 7.54 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.41 - 7.43 (m, 3 H), 6.55 (d, *J*=15.9 Hz, 1 H), 5.54 - 5.62 (m, 1 H), 5.38 - 5.46 (m, 1 H), 5.13 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.79 - 2.87 (m, 1 H), 2.34 - 2.63 (m, 8 H). EM (IEP) m/z: 562.5 (M+H)+. HPLC analítica: TR= 5.36 min.

Ejemplo 71.

(E)-*N*-((E)-(S)-18-Cloro-9-oxo-8.10.17.19-tetraaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

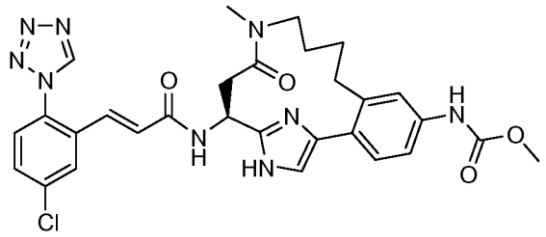


El Ejemplo 71 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 69. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.40 - 2.57 (m, 1 H), 2.72 - 2.84 (m, 1 H), 3.45 - 3.68 (m, 2 H), 5.03 (dd, *J*=9.9, 4.9 Hz, 1 H), 5.37 - 5.53 (m, 1 H), 5.54 - 5.67 (m, 1 H), 6.78 (d, *J*=15.4 Hz, 1 H), 7.15 (d, *J*=15.4 Hz, 1 H), 7.28 - 7.34 (m, 2 H), 7.43 - 7.48 (m, 2 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.67 (dd,

J=8.8, 2.2 Hz, 1 H), 7.97 - 8.00 (m, 1 H), 9.52 (s, 1 H). EM (IEP) m/z: 550.2 (M+H)+. HPLC analítica: TR= 6.48 min.

Ejemplo 72.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-metil-13-oxo-12,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA



72A. Éster bencílico del ácido (S)-3-[4-(2-alil-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-3-*terc*-butoxicarbonilamino-propiónico: Se añadieron 23A (0.30 g, 0.426 mmol), aliltributilestanano (0.282 g, 0.853 mmol), CsF (0.162 g, 1.065 mmol), Pd_2dba_3 (0.020 g, 0.021 mmol) y tri-(*terc*-butil)fosfina (0.173 g, 0.085 mmol) junto con dioxano (10 ml). La mezcla se calentó hasta 90°C bajo argón. Después de 2.5 h, se añadieron dos equivalentes de aliltributilestanano y CsF y una cantidad catalítica de Pd_2dba_3 y tri-(*terc*-butil)fosfina. La mezcla se agitó a 90°C bajo argón durante 3 h. El solvente se eliminó y el residuo se repartió entre EtOAc y agua. La solución de EtOAc se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía en

fase normal dando 72A (0.26 g, 92 % de rendimiento). EM (IEP) m/z: 665.3 (M+H)+.

72B. Ácido (S)-3-(4-(2-alil-4-(metoxicarbonilamino)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)-3-(*terc*-butoxicarbonilamino)propanoico: Se disolvió 72A (0.26 g, 0.39 mmol) en THF (6 ml) y se añadió LiOH 2N (2 ml). La mezcla se agitó a ta bajo argón durante 20 h. El solvente se eliminó y el residuo se diluyó con agua y se acidificó hasta pH aproximadamente 5 con HCl 1N. La mezcla se extrajo con EtOAc. La solución de EtOAc reunida se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró dando 72B (0.24 g, 100 % de rendimiento). EM (IEP) m/z: 575.3 (M+H)+.

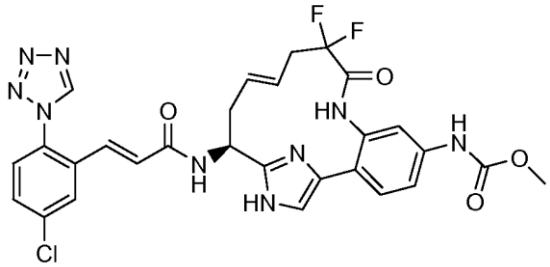
72C. Éster metílico del ácido {3-alil-4-[2-[(S)-2-(alil-metil-carbamoil)-1-*terc*-butoxicarbonilamino-etil]-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico : A una solución de 72B en DMF (4 ml) se añadieron PyBOP (0.26 g, 0.47 mmol), Et_3N (0.22 ml, 1.56 mmol), y metilalilamina (0.71 g, 0.998 mmol). La mezcla se agitó a ta bajo argón durante 1.5 h. Se añadió agua y la mezcla se extrajo con EtOAc. La solución de EtOAc reunida se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía en fase normal dando 72C (0.16 g, 64 % de rendimiento). EM (IEP) m/z: 628.4 (M+H)+.

72D. El Ejemplo 72 se preparó siguiendo los

procedimientos descritos en la etapa 2E/2F, sustituyendo 2D por 72C; seguido por las etapas 2G; 1F, sustituyendo etanol por metanol; y 1G. ^{1}H NMR (400 MHz, CD_3OD, rotámeros) δ ppm 9.52 (s, 1H), 9.30 (s, 1H), 8.00 (dd, *J* = 14.56 y 2.26 Hz, 1H), 7.64 - 7.77 (m, 1 H), 7.55 - 7.63 (m, 1 H), 7.46 (dd, *J* = 10.42 y 2.13 Hz, 1H), 7.36 - 7.43 (m, 1 H), 7.35 (d, *J* = 1.25 Hz, 1H), 7.30 (d, *J* = 8.03 Hz, 1H), 7.21 (dd, *J* = 15.69 y 5.14 Hz, 1H), 5.67 (m, 1H), 5.53 (m, 1H), 4.46 (m, 1H), 3.75 (dos singletes, 3H), 3.47 (m, 1H), 3.28 (m, 2H), 3.25(m, 1H), 2.92 (dos singletes, 3H), 2.68 (m, 2H), 2.29 (m, 1H), 1.29 (m, 1H). CL-EM (IEP) m/z: 604.3 (M+H)+. HPLC analítica: TR= 6.22/6.49 min (dos isómeros rotacionales).

Ejemplo 73.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10,10-difluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

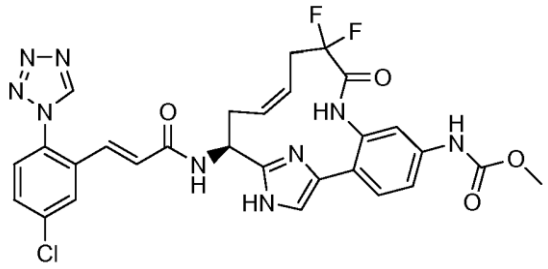


El Ejemplo 73 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2,2-difluoropent-4-enoico; seguido por las etapas 2E; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52

(s, 1 H), 7.97 (s, 1 H), 7.67 (s, 1 H), 7.54 - 7.62 (m, 2 H), 7.49 (s, 1 H), 7.38 - 7.47 (m, 2 H), 7.12 – 7.16 (d, *J*=15.4 Hz, 1 H), 6.74 - 6.78 (d, *J*=15.4 Hz, 1 H), 5.69 - 5.81 (m, 1 H), 5.23 - 5.35 (m, 1 H), 5.06 - 5.14 (m, 1 H), 3.76 (s, 3 H), 2.75 - 3.00 (m, 3 H), 2.53 - 2.68 (m, 1 H) EM (IEP) m/z: 624.3 (M+H)+. HPLC analítica: TR= 4.31 min. (Método B).

Ejemplo 74.

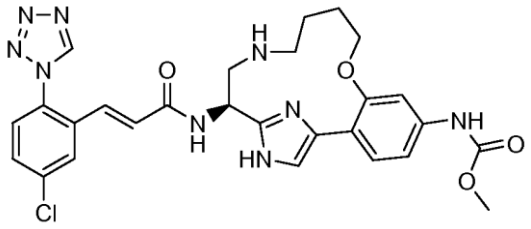
Éster metílico del ácido {(Z)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10,10-difluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA



El Ejemplo 74 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2,2-difluoropent-4-enoico; seguido por las etapas 2F; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (s, 1 H), 7.52 - 7.76 (m, 3 H), 7.27 - 7.52 (m, 3 H), 7.04 - 7.27 (m, 1 H), 6.66 - 6.87 (m, 1 H), 5.50 - 5.75 (m, 2 H), 5.09 - 5.29 (m, 1 H), 3.76 (s, 3 H), 2.52 - 3.18 (m, 4 H). EM (IEP) m/z: 624.2 (M+H)+. HPLC analítica: TR= 4.24 min. (Método B).

Ejemplo 75.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8-oxa-13.17.19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 2 TFA



75A. Éster 2-(2-hidroxi-4-metoxicarbonilamino-fenil)-2-oxo-etílico del ácido (S)-2-benciloxicarbonilamino-3-*terc*-butoxicarbonilamino-propiónico: Este compuesto se preparó siguiendo los procedimientos descritos en 2A, sustituyendo ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico por ácido (S)-2-benciloxicarbonilamino-3-*terc*-butoxicarbonilamino-propiónico y sustituyendo 2-bromo-1-(2-bromofenil)etanona por 4-(2-bromoacetil)-3-hidroxifenilcarbamato de metilo. EM (IEP) m/z: 546.3 (M+H)+.

75B. Éster 2-(2-aliloxi-4-metoxicarbonilamino-fenil)-2-oxo-etílico del ácido (S)-2-benciloxicarbonilamino-3-*terc*-butoxicarbonilamino-propiónico: A una solución 75A: (3.3 g, 6.05 mmol) en DMF (8.5 ml) se añadió carbonato potásico (1.254 g, 9.07 mmol), seguido por la adición de 3-bromoprop-1-eno (0.580 ml, 6.65 mmol). La reacción se calentó a 70°C durante 2 horas. La mezcla de reacción viró a

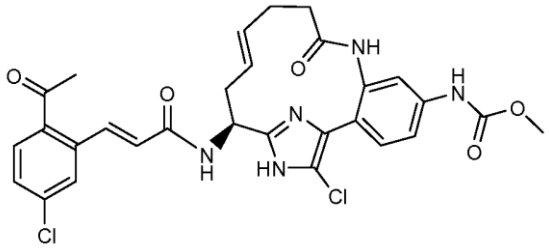
color rojo oscuro. Esta se enfrió, se repartió entre agua y EtOAc. La fase orgánica se lavó con agua, salmuera, se secó sobre $MgSO_4$, se separó el sólido por filtración y se concentró. La purificación por cromatografía en fase normal dio 75B como una espuma amarillo pálido (2.05 g, 58 %). EM (IEP) m/z: 586.4 (M+H)+.

75C. Éster metílico del ácido {4-[2-((S)-2-alilamino-1-benciloxicarbonilamino-etil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-aliloxi-fenil}-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 2B, sustituyendo 2A por 75B; seguido por las etapas 3C; y 75B. EM (IEP) m/z: 636.5 (M+H)+.

75D. El Ejemplo 75 se preparó siguiendo los procedimientos descritos en la etapa 20D, sustituyendo 20C por 75C; seguido por las etapas 2E/2F; 2G; 1G; y 10H. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.5, 2.5 Hz, 1 H), 7.60 (d, J=8.3 Hz, 1 H), 7.45 (d, J=8.2 Hz, 1 H), 7.40 (s, 1 H), 7.34 (s, 1 H), 7.23 (d, J=15.9 Hz, 1 H), 6.98 - 7.02 (m, 1 H), 6.68 (d, J=15.9 Hz, 1 H), 5.42 (dd, J=7.1, 3.3 Hz, 1 H), 4.14 (s, 2 H), 3.75 (s, 3 H), 3.51 - 3.59 (m, 1 H), 3.42 - 3.49 (m, 1 H), 3.10 - 3.22 (m, 2 H), 1.95 - 2.09 (m, 4 H). EM (IEP) m/z: 578.3 (M+H)+. HPLC analítica: TR= 3.63 min. (Método B).

Ejemplo 76.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(2-acetil-5-cloro-fenil)-acriloilamino]-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA



76A. Éster *terc*-butílico del ácido [(E)-(S)-18-cloro-5-metoxicarbonilamino-9-oxo-17-(2-trimetilsilaniletoximetil)-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il]-carbámico: A una solución de 39A (0.37 g, 0.632 mmol) en acetonitrilo (3 ml)/cloroformo (3 ml) se añadió NCS (0.101 g, 0.758 mmol). La reacción se calentó a 65°C durante 3 h, se enfrió hasta ta y se concentró. La purificación por cromatografía en fase inversa dio 76A (0.205 g, 0.331 mmol, 52.3 %) como un sólido blanco. EM (IEP) m/z: 620.1 (M+H)+.

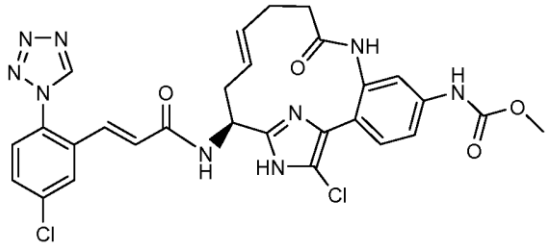
76B. Éster metílico del ácido ((E)-(S)-15-amino-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il)-carbámico, sal 2 HCl: La mezcla de 76A (0.205 g, 0.279 mmol) y HCl 4M en dioxano (2 ml, 8.00 mmol) en un tubo sellado se calentó a 75°C. Después de 2h, la reacción se enfrió hasta ta. El sólido se recogió

por filtración, se aclaró con hexano y luego se secó proporcionando 76B (0.12 g, 93 %) como un sólido blanco. EM (IEP) m/z: 390.1 (M+H)+.

76C. El Ejemplo 76 se preparó siguiendo el procedimiento descrito en la etapa 15D, sustituyendo 15C por 76B, sustituyendo el Intermediario 2 por el Intermediario 4 y sustituyendo la base de Hunig por trietilamina. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.97 (d, *J*=15.4 Hz, 1 H), 7.89 (d, *J*=8.2 Hz, 1 H), 7.67 (d, *J*=2.2 Hz, 1 H), 7.59 (s, 1 H), 7.52 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.41 (s, 2 H), 6.55 (d, *J*=15.9 Hz, 1 H), 5.52 - 5.60 (m, 1 H), 5.34 - 5.42 (m, 1 H), 5.02 (dd, *J*=10.4, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.72 - 2.79 (m, 1 H), 2.59 (s, 3 H), 2.32 - 2.53 (m, 5 H). EM (IEP) m/z: 596.0 (M+H)+. HPLC analítica: TR= 6.86 min.

Ejemplo 77.

Éster metílico del ácido {(E)-(S)-18-cloro-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

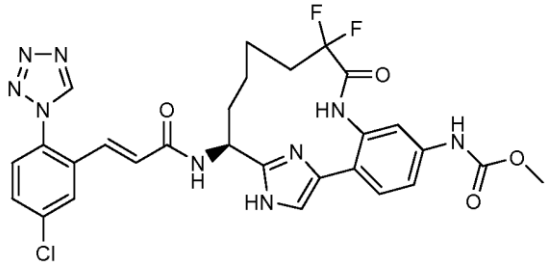


El Ejemplo 77 se preparó siguiendo el procedimiento descrito en 1G, sustituyendo 1F por 76B. ^{1}H NMR (400 MHz,

DMSO-d_6 +2 gotas de D_2O) δ ppm 9.76 (s, 1 H), 7.92 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.64 (d, *J*=8.2 Hz, 1 H), 7.38 (s, 1 H), 7.31 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.26 (d, *J*=8.3 Hz, 1 H), 6.77 - 6.87 (m, 2 H), 5.37 - 5.47 (m, 1 H), 5.12 - 5.21 (m, 1 H), 4.87 (dd, *J*=10.2, 4.1 Hz, 1 H), 3.61 (s, 3 H), 2.12 - 2.33 (m, 6 H). EM (IEP) m/z: 622.0 (M+H)+. HPLC analítica: TR= 6.46 min.

Ejemplo 78.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10,10-difluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 1 TFA

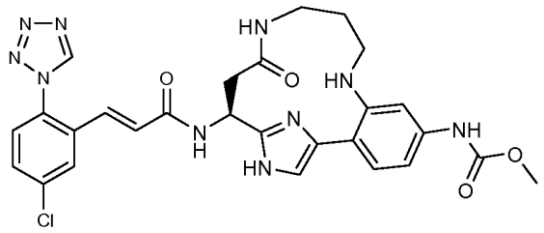


El Ejemplo 78 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2,2-difluoropent-4-enoico; seguido por las etapas 2E/2F; 2G; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.96 (d, J=2.2 Hz, 1 H), 7.67 (d, J=2.2 Hz, 1 H), 7.65 (d, J=2.2 Hz, 1 H), 7.61 (s, 1 H), 7.57 (d, J=8.8 Hz, 1 H), 7.51 (s, 1 H), 7.47 - 7.50 (m, 1 H), 7.11 (d, J=15.9 Hz, 1 H), 6.75 (d, J=15.4 Hz, 1 H), 5.53 - 5.65 (m, 1 H), 3.76 (s, 3 H), 1.95 - 2.29 (m, 4 H), 1.56 (d, J=4.9 Hz, 2

H), 0.68 - 0.94 (m, 2 H). EM (IEP) m/z: 626.3 (M+H)+. HPLC analítica: TR= 4.27 min. (Método B).

Ejemplo 79.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-13-oxo-8,12,17,19-tetraaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 2 TFA



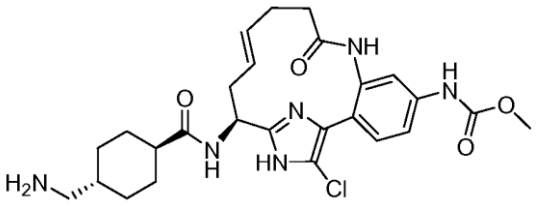
79A. 3-(4-(2-(3-(Benciloxicarbonilamino)propilamino)-4-(metoxicarbonilamino)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)-3-(*terc*-butoxicarbonilamino)propanoato de (S)-bencilo: A una solución de 23A (200 mg, 0.284 mmol) en DMSO se añadieron 3-aminopropilcarbamato de bencilo, sal HCl (83 mg, 0.341 mmol), L-prolina (6.54 mg, 0.057 mmol), CuI (5.41 mg, 0.028 mmol) y K_2CO_3 (118 mg, 0.853 mmol). La reacción se purgó con argón durante 3 min. La reacción se agitó a 80°C durante 16 h. La reacción se enfrió hasta ta y luego se diluyó con EtOAc, se lavó con H_2O, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó por cromatografía en

fase normal dando 79A (47 mg, 20 % de rendimiento) como un sólido color castaño. CL-EM (IEP) m/z: 831.4 (M+H)+.

79B. El Ejemplo 79 se preparó siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E por 79A; seguido por las etapas 23E; 1F, sustituyendo etanol por metanol; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.99 (1 H, d, *J*=2.26 Hz), 7.83 (1 H, s), 7.64 - 7.71 (2 H, m), 7.55 - 7.62 (2 H, m), 7.25 (1 H, dd, *J*=8.53, 2.01 Hz), 7.21 (1 H, d, *J*=15.56 Hz), 6.74 (1 H, d, *J*=15.56 Hz), 5.60 (1 H, dd, *J*=9.29, 4.27 Hz), 3.77 (3 H, s), 3.61 - 3.71 (1 H, m), 3.43 - 3.51 (1 H, m), 3.34 - 3.40 (2 H, m), 2.85 - 2.94 (1 H, m), 2.75 - 2.84 (1 H, m), 2.13 - 2.27 (2 H, m). CL-EM (IEP) m/z: 591.2 (M+H)+. HPLC analítica: TR= 4.836 min.

Ejemplo 80.

Éster metílico del ácido {(E)-(S)-15-[(4-aminometil-ciclohexanocarbonil)-amino]-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 2 TFA

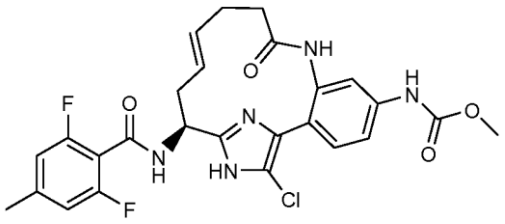


El Ejemplo 80 se preparó siguiendo los procedimientos descritos en la etapa 3B, sustituyendo 3A por 76B y llevando a cabo la reacción a 55°C; seguido por la

etapa 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.53 (d, *J*=1.4 Hz, 1 H), 7.42 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.36 (d, *J*=8.5 Hz, 1 H), 5.46 - 5.54 (m, 1 H), 5.27 - 5.36 (m, 1 H), 4.79 - 4.90 (m, 1 H), 3.75 (s, 3 H), 2.79 (d, *J*=6.9 Hz, 2 H), 2.58 - 2.66 (m, 1 H), 2.26 - 2.48 (m, 6 H), 1.85 - 1.98 (m, 4 H), 1.57 - 1.67 (m, 1 H), 1.42 - 1.55 (m, 2 H), 1.03 - 1.16 (m, 2 H). EM (IEP) m/z: 529.1 (M+H)+. HPLC analítica: TR= 3.31 min.

Ejemplo 82.

Éster metílico del ácido [(E)-(S)-18-cloro-15-(2.6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, sal 1 TFA

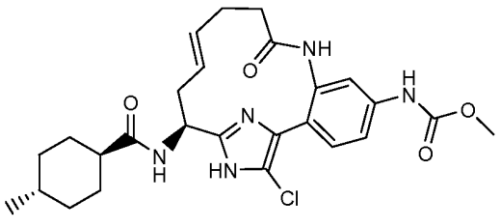


El Ejemplo 82 se preparó siguiendo el procedimiento descrito en la etapa 15D, sustituyendo 15C por 76B, sustituyendo el Intermediario 2 por ácido 2,6-difluoro-4-metil benzoico, sustituyendo la base de Hunig por trietilamina y llevando a cabo la reacción a 55°C. ^{1}H NMR (500 MHz, DMSO-d_6+2 gotas de D_2O) δ ppm 7.39 (d, *J*=1.6 Hz, 1 H), 7.33 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.29 (d, *J*=8.3 Hz, 1 H), 6.93 (d, *J*=8.8 Hz, 2 H), 5.40 - 5.48 (m, 1 H), 5.17 - 5.24 (m, 1 H), 5.06 (dd, *J*=9.1, 4.1 Hz, 1 H), 3.62 (s, 3 H), 2.37

- 2.43 (m, 1 H), 2.24 - 2.36 (m, 6 H), 2.15 - 2.22 (m, 2 H). EM (IEP) m/z: 544.2 (M+H)+. HPLC analítica: TR= 6.67 min.

Ejemplo 83.

Éster metílico del ácido {(E)-(S)-18-cloro-15-[(4-metil-ciclohexanocarbonil)-amino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

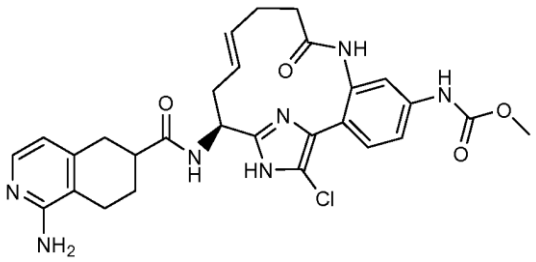


El Ejemplo 83 se preparó siguiendo el procedimiento descrito en la etapa 15D, sustituyendo 15C por 76B, sustituyendo el Intermediario 2 por ácido 4-metilciclohexanocarboxílico, sustituyendo la base de Hunig por trietilamina y llevando a cabo la reacción a 55°C. ^{1}H NMR (500 MHz, DMSO-d_6+2 gotas de D_2O) δ ppm 7.40 (d, *J*=2.2 Hz, 1 H), 7.32 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.27 (d, *J*=8.8 Hz, 1 H), 5.37 - 5.45 (m, 1 H), 5.13 - 5.21 (m, 1 H), 4.81 (dd, *J*=9.6, 4.1 Hz, 1 H), 3.62 (s, 3 H), 2.14 - 2.38 (m, 6 H), 2.03 - 2.11 (m, 1 H), 1.56 - 1.70 (m, 4 H), 1.16 - 1.32 (m, 3 H), 0.75 - 0.89 (m, 5 H). EM (IEP) m/z: 514.2 (M+H)+. HPLC analítica: TR= 6.84 min.

Ejemplo 84.

Éster metílico del ácido {(E)-(S)-15-[(1-amino-5.6.7.8-tetrahidro-isoquinolin-6-carbonil)-amino]-18-cloro-9-oxo-

8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 2 TFA (mezcla de diastereómeros)

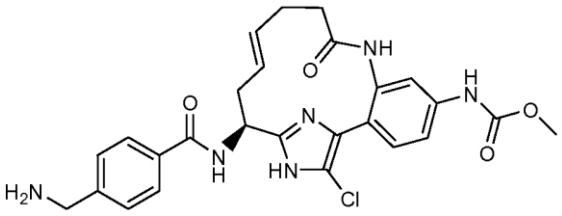


El Ejemplo 84 se preparó siguiendo el procedimiento descrito en 15D, sustituyendo 15C por 76B, sustituyendo el Intermediario 2 por el Intermediario 5, sustituyendo la base de Hunig por trietilamina y llevando a cabo la reacción a 55°C. ^{1}H NMR (500 MHz, DMSO-d_6+2 gotas de D_2O) δ ppm 7.65 - 7.70 (m, 1 H), 7.42 (s, 1 H), 7.35 - 7.39 (m, 1 H), 7.28 - 7.33 (m, 1 H), 6.69 - 6.74 (m, 1 H), 5.42 - 5.51 (m, 1 H), 5.16 - 5.26 (m, 1 H), 4.86 - 4.92 (m, 1 H), 3.65 (s, 3 H), 2.77 - 2.85 (m, 2 H), 2.63 - 2.72 (m, 1 H), 2.45 - 2.53 (m, 1 H), 2.18 - 2.44 (m, 7 H), 2.00 - 2.09 (m, 1 H), 1.63 - 1.78 (m, 1 H). EM (IEP) m/z: 564.2 (M+H)+. HPLC analítica: TR= 3.56 min.

Ejemplo 85.

Éster metílico del ácido [(E)-(S)-15-(4-aminometil-benzoilamino)-18-cloro-9-oxo-8,17,19-triaza-

triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, sal 2 TFA



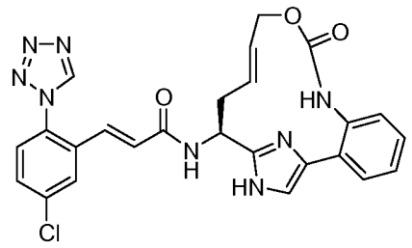
85A. Éster metílico del ácido {(E)-(S)-15-[4-(*terc*-butoxicarbonilamino-metil)-benzoilamino]-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA: Este compuesto se preparó siguiendo el procedimiento descrito en 15D, sustituyendo 15C por 76B, sustituyendo el Intermediario 2 por ácido 4-((*terc*-butoxicarbonilamino)metil)benzoico, sustituyendo la base de Hunig por trietilamina y llevando a cabo la reacción a 55°C. EM (IEP) m/z: 623.3 (M+H)+.

85B. El Ejemplo 85 se preparó siguiendo el procedimiento descrito en 3C, sustituyendo 3B por 85A. ^{1}H NMR (500 MHz, DMSO-d_6+2 gotas de D_2O) δ ppm 7.93 (d, *J*=8.5 Hz, 2 H), 7.54 (d, *J*=8.3 Hz, 2 H), 7.46 (s, 1 H), 7.39 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.32 (d, *J*=8.5 Hz, 1 H), 5.52 - 5.60 (m, 1 H), 5.24 - 5.32 (m, 1 H), 5.15 (dd, *J*=9.4, 4.7 Hz, 1 H), 4.09 (s, 2 H), 3.68 (s, 3 H), 2.23 - 2.54 (m, 6 H). EM (IEP) m/z: 523.1 (M+H)+. HPLC analítica: TR= 3.44 min.

Ejemplo 87.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-9-oxo-10-

oxa-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA

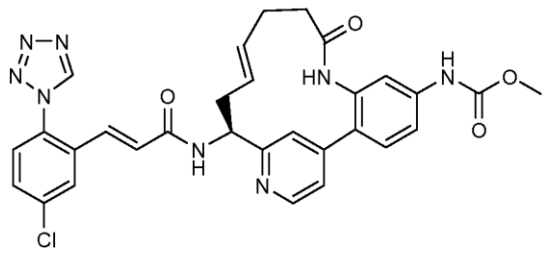


El Ejemplo 87 se preparó siguiendo los procedimientos descritos en la etapa 69A, sustituyendo isocianato de alilo por cloroformiato de alilo; seguido por las etapas 2E; 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.53 - 2.69 (m, 1 H), 2.88 - 2.98 (m, 1 H), 4.28 - 4.43 (m, 2 H), 5.16 (dd, *J*=10.5, 5.2 Hz, 1 H), 5.63 - 5.79 (m, 1 H), 5.84 - 5.94 (m, 1 H), 6.78 (d, *J*=15.7 Hz, 1 H), 7.14 (d, *J*=15.7 Hz, 1 H), 7.25 (d, *J*=7.7 Hz, 1 H), 7.39 (t, *J*=7.4 Hz, 1 H), 7.44 (s, 1 H), 7.48 - 7.54 (m, 2 H), 7.58 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). EM (IEP) m/z: 517.2(M+H)+. HPLC analítica: TR= 5.12 min.

Ejemplo 88.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,12,16,18-heptaen-5-il}-carbámico, sal

1 TFA



88A. (S,E)-N-((4-Cloropiridin-2-il)metilen)-2-metilpropano-2-sulfinamida: Referencia: Liu, G. et al., *J. Org. Chem.*, 64:1278 (1999). A una solución de S-(-)-*t*-butil-sulfinamida (0.856 g, 7.06 mmol) en diclorometano (14.13 ml) se añadió secuencialmente sulfato de cobre (II) (2.481 g, 15.54 mmol) y 4-cloropicolinaldehído [1.0 g, 7.06 mmol, preparado de acuerdo a una modificación descrita por Negi (*Synthesis*, 991 (1996))]. La suspensión blanca se agitó a ta. Después de 3h, la suspensión marrón se filtró a través de CELITE®, eluyendo con DCM, dando un filtrado marrón transparente. La concentración dio un aceite marrón que pesaba 1.85 g. La purificación por cromatografía en fase normal dio 1.31 g de 88A como un aceite amarillo transparente. EM (IEP) m/z: 245.0 (M+H)+.

88B. (S)-N-((S)-1-(4-Cloropiridin-2-il)but-3-enil)-2-metilpropano-2-sulfinamida: Usando un procedimiento modificado descrito por Kuduk (*Tetrahedron Letters*, 45:6641 (2004)). A una solución amarilla transparente enfriada (-78°C) de 88A (2.50 g, 10.21 mmol) en THF (34.0 ml) se

añadió gota a gota bromuro de alilmagnesio (1.0 M en éter dietílico, 14.30 ml, 14.30 mmol) durante 25 min. La suspensión naranja-marrón resultante se agitó a -78°C. Después de 30 min, se añadió más bromuro de alilmagnesio (1.40 ml). Después de 1h, la reacción se interrumpió inactivando con NH_4Cl saturado. La suspensión naranja-marrón resultante se dejó calentar hasta ta. La reacción se repartió entre agua y EtOAc y se separaron las fases. La fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con $NaHCO_3$ saturado, salmuera, se secaron sobre Na2SO4, se filtraron y se concentraron dando un aceite azul que pesó 3.22 g. La purificación por cromatografía en fase normal dio 2.55 g (87 %) de 88B como un sólido naranja-marrón. El exceso diastereomérico basado en HPLC de la mezcla de reacción fue 1:5.7 de diastereómero A:diastereómero B. EM (IEP) m/z: 287.1 (M+H)+.

88C. (S)-N-((S)-1-(4-(2-Amino-4-nitrofenil)piridin-2-il)but-3-enil)-2-metilpropano-2-sulfinamida: A un matraz de fondo redondo se añadió 88B (1.40 g, 4.88 mmol), Intermediario 12 (2.441 g, 9.76 mmol), aducto de $PdCl_2$(dppf)-CH_2Cl_2 (0.399 g, 0.488 mmol), y fosfato potásico, tribásico (2.072 g, 9.76 mmol). El matraz de fondo redondo se equipó con un condensador de reflujo y luego se purgó en aparato con argón durante varios minutos. A continuación, se añadió DMSO desgasificado (24.41 ml) seguido por agua

desgasificada (0.440 ml, 24.41 mmol). La suspensión naranja brillante se calentó hasta 90°C. Después de 5 h, la reacción se interrumpió y se enfrió hasta ta. La mezcla negra se filtró para eliminar el sólido, aclarando con EtOAc. El filtrado se repartió entonces entre EtOAc y agua y se separaron las fases. La fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron dando un aceite negro espeso que pesó 3.8 g. La purificación por cromatografía en fase normal dio 1.70 g como una mezcla de diastereómeros. Los diastereómeros se separaron por cromatografía de fase inversa. Las fracciones puras del diastereómero A se neutralizaron y trataron como se describe en 2D dando 0.139 g de diastereómero A como una espuma naranja. Las fracciones puras de diastereómero B se neutralizaron y trataron como se describe en 2D dando 0.996 g de 88C, como una espuma naranja. Diastereómero B: EM (IEP) m/z: 389.2 (M+H)+.

88D. Éster *terc*-butílico del ácido {(S)-1-[4-(2-amino-4-nitro-fenil)-piridin-2-il]-but-3-enil}-carbámico: A una solución naranja transparente de 88C (1.22 g, 3.14 mmol) en metanol (31.4 ml) se añadió HCl 4 M en dioxano (15.70 ml, 62.8 mmol). La reacción era ligeramente exotérmica al tacto, por lo que se usó un baño de agua. Después de 1 h, la solución naranja se concentró dando un residuo naranja. El

residuo se suspendió en DCM y se concentró. El residuo se suspensión de nuevo en DCM y luego se concentró dando la amina como un sólido naranja. EM (IEP) m/z: 285.2 (M+H)+. El sólido naranja se suspendió en DCM (10.46 ml) y luego se añadió BOC_2O (0.802 ml, 3.45 mmol). A continuación, se añadió trietilamina (1.750 ml, 12.56 mmol) y la reacción se convirtió en una suspensión naranja-marrón. La reacción se agitó a ta. Después de 2 h, la reacción se diluyó con EtOAc y se lavó con $NaHCO_3$ saturado. La fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron dando una espuma marrón oscuro que pesó 1.53 g. La purificación por cromatografía en fase normal dio 1.15 g (95 %) de 88D como una espuma amarilla. EM (IEP) m/z: (M+H)+.

88E. Éster *terc*-butílico del ácido {(S)-1-[4-(4-nitro-2-pent-4-enoilamino-fenil)-piridin-2-il]-but-3-enil}-carbámico: A una solución amarilla transparente enfriada (-5°C) de 88D (0.413 g, 1.074 mmol) y ácido pent-4-enoico (0.220 ml, 2.149 mmol) en acetato de etilo (10.74 ml) se añadió base de Hunig (0.563 ml, 3.22 mmol) y anhídrido del ácido propanofosfónico (1.266 ml, 2.149 mmol). Después de la adición, la reacción se dejó calentar hasta ta y se agitó durante la noche. Después de 17.5 h, se añadieron más ácido pent-4-enoico (2 x 0.220 ml, 2.149 mmol), base de Hunig (2 x 0.563 ml, 3.22 mmol) y anhídrido del ácido propanofosfónico

(2 x 1.266 ml, 2.149 mmol). Después de otras 24 h, la reacción se detuvo, se repartió entre EtOAc y $NaHCO_3$ saturado y se separaron las fases. La fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron dando un aceite naranja que pesó 0.739 g. La purificación por cromatografía en fase normal dio 0.448 g (88 %) de 88E como una espuma amarillo pálido. EM (IEP) m/z: 467.3 (M+H)+.

88F. Éster metílico del ácido {4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-3-pent-4-enoilamino-fenil}-carbámico: A una solución amarilla transparente de 88E (0.330 g, 0.707 mmol) en MeOH (14.15 ml) se añadió polvo de zinc (0.463 g, 7.07 mmol) y cloruro amónico (0.378 g, 7.07 mmol). La suspensión gris se agitó vigorosamente a ta. Después de 2 h, la reacción se interrumpió y luego se filtró a través de un filtro de nylon de 0.45 micrómetros, eluyendo con metanol. El filtrado se concentró dando un residuo amarillo transparente. El residuo se repartió entre EtOAc y HCl 0.25 M (20 ml) y se separaron las fases. La fase orgánica se extrajo con HCl 0.25 M (2 x 10 ml). La fase ácida se basificó con K_2HPO_4 1.5 M y luego se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron dando la anilina como una espuma

amarilla pálida que pesó 0.3047 g. EM (IEP) m/z: 437.3 (M+H)+. A una solución amarilla pálida transparente enfriada (-5°C) de la anilina (0.3047 g, 0.698 mmol) en diclorometano (6.98 ml) se añadió piridina (0.056 ml, 0.698 mmol) y cloroformiato de metilo (0.054 ml, 0.698 mmol). La solución amarillo brillante resultante se agitó a -5°C durante 1h. La reacción se diluyó con EtOAc y se lavó con $NaHCO_3$ saturado. La fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron dando una espuma blanca que pesó 0.345 g. La purificación por cromatografía en fase normal dio 0.312 g (90 %) de 88F, como espuma blanca. EM (IEP) m/z: 495.3 (M+H)+.

88G. Éster metílico del ácido ((E)-(S)-15-*terc*-butoxicarbonilamino-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,12,16,18-heptaen-5-il)-carbámico, sal 1 TFA: A un matraz de fondo redondo de 500 ml secado a la llama se añadió 88F (0.116 g, 0.235 mmol), pTsOH monohidratado (0.049 g, 0.258 mmol) y DCM (235 ml). El matraz se equipó con un condensador de reflujo y la solución incolora transparente se desgasificó con argón durante 30 min. La reacción se calentó entonces hasta 40°C durante 1 h. En un un matraz de fondo redondo secado a la llama separado se añadió Grubbs (II) (0.020 g, 0.023 mmol) y el matraz se purgó con argón durante varios minutos. Se

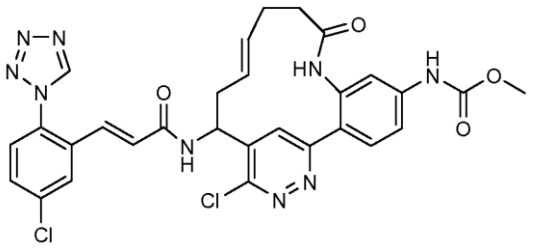
añadió DCM desgasificado (2 ml) dando una solución borgoña transparente. La solución de Grubbs (II) se añadió gota a gota durante 5 min a la reacción anterior. La solución amarilla transparente resultante se agitó a 40°C. La reacción se interrumpió después de un total de 1.5 h. Una vez enfriado hasta ta, la reacción se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre sulfato sódico, se filtró y se concentró dando un sólido marrón oscuro que pesó 0.134 g. La purificación por cromatografía en fase inversa dio 0.102 g (75 %) de 88 G, como un sólido blanquecino. EM (IEP) m/z: 467.3 (M+H)+.

88H. El Ejemplo 88 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 88G; seguido por la etapa 1G. ^{1}H NMR (500 MHz, DMSO-d_6 y D_2O) δ ppm 9.89 (s, 1 H), 9.81 (s, 1 H), 8.63 (d, *J*=5.5 Hz, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.73 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.69 (d, *J*=8.2 Hz, 1 H), 7.38 - 7.48 (m, 3 H), 7.31 (d, *J*=8.2 Hz, 1 H), 7.18 (s, 1 H), 6.98 (d, *J*=15.4 Hz, 1 H), 6.80 (d, *J*=15.4 Hz, 1 H), 5.37 - 5.48 (m, 1 H), 5.18 - 5.28 (m, 1 H), 4.93 (dd, *J*=9.1, 3.6 Hz, 1 H), 3.67 (s, 3 H), 2.50 - 2.55 (m, 1 H), 2.17 - 2.37 (m, 5 H). EM (IEP) m/z: 599.3 (M+H)+. HPLC analítica (Método D): TR= 4.57 min.

Ejemplo 89.

Éster metílico del ácido {(E)-17-cloro-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,18,19-triaza-

triciclo[14.3.1.2.7]icosa-1(20),2,4,6,12,16,18-heptaen-5-il}-carbámico



89A. 1-(3,6-Dicloropiridazin-4-il)but-3-enilcarbamato de *terc*-butilo: A una solución enfriada (-78°C) de (3,6-dicloropiridazin-4-il)metilcarbamato de *terc*-butilo (3.28 g, 11.79 mmol) preparada siguiendo un procedimiento de la bibliografía (Cowden, C.J., *Org. Lett.*, 4497-4499 (2003)) en THF (15 ml) se añadió TMEDA (1.780 ml, 11.79 mmol). A continuación se añadió gota a gota a -78°C sec-butil litio (1.4M en ciclohexano, 21.06 ml, 29.5 mmol). La reacción se calentó hasta -40°C durante 30 min antes de enfriarla hasta -78°C. Se añadió bromuro de alilo (1.496 ml, 17.69 mmol) a -78°C. La reacción se agitó bajo argón a -78°C durante 30 min y luego se inactivó con solución de NH_4Cl. La mezcla de reacción se diluyó con EtOAc, se lavó con HCl 1M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal dando 89A (1.49 g, 40 % de rendimiento) como un sólido. CL-EM (IEP) m/z: 318.1 (M+H)+.

89B. 1-(6-(2-Amino-4-nitrofenil)-3-cloropiridazin-4-il)but-3-enilcarbamato de *terc*-butilo: Se purgó con argón

un matraz que contenía 89A (1.49 g, 4.68 mmol), 2-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-5-nitroanilina (1.756 g, 7.02 mmol) y Cs_2CO_3 (3.81 g, 11.71 mmol). A este se añadieron dioxano (40 ml), tetrafluoroborato de tri-*terc*-butilfosfina (0.204 g, 0.702 mmol) y Pd_2dba_3 (0.429 g, 0.468 mmol) a ta. La reacción se agitó bajo argón a 90°C durante 3 h. La reacción se enfrió hasta ta. El sólido se separó por filtración y el solvente se eliminó dando un sólido oscuro. El producto bruto se purificó por cromatografía en fase normal dando 89B (0.66 g, 34 % de rendimiento) como un sólido marrón oscuro. CL-EM (IEP) m/z: 420.2 (M+H)+.

89C. 1-(3-Cloro-6-(4-nitro-2-pent-4-enamidofenil)piridazin-4-il)but-3-enilcarbamato de *terc*-butilo: A una solución de 89B (0.66 g, 1.572 mmol) en DCM (20 ml) se añadieron TEA (0.438 ml, 3.14 mmol) y cloruro de pent-4-enoilo (0.208 ml, 1.886 mmol) a 0°C. La reacción se agitó bajo argón a 0°C durante 1.5 h. La mezcla de reacción se diluyó con DCM, se lavó con HCl 1M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró dando 89C (0.79 g, 100 % de rendimiento) como un sólido marrón. CL-EM (IEP) m/z: 502.2 (M+H)+.

89D. 1-(6-(4-Amino-2-pent-4-enamidofenil)-3-cloropiridazin-4-il)but-3-enilcarbamato de *terc*-butilo: A una solución de 89C (0.79 g, 1.574 mmol) en metanol (30 ml) se

añadieron polvo de zinc (0.515 g, 7.87 mmol) y cloruro amónico (0.842 g, 15.74 mmol) a 0°C. La reacción se agitó bajo argón a ta durante 4 h. El sólido se filtró a través de una almohadilla de CELITE® y el filtrado se concentró dando 89D (0.74 g, 100 % de rendimiento) como un sólido marrón oscuro. CL-EM (IEP) m/z: 472.4 (M+H)+.

89E. Éster metílico del ácido {4-[5-(1-*terc*-butoxicarbonilamino-but-3-enil)-6-cloro-piridazin-3-il]-3-pent-4-enoilamino-fenil}-carbámico: A una solución de 89D (0.74 g, 1.568 mmol) en DCM (20 ml) y DMF (2 ml) (para hacerlo más soluble) se añadieron piridina (0.254 ml, 3.14 mmol) y cloroformiato de metilo (0.121 ml, 1.568 mmol) a 0°C. La reacción se agitó bajo argón a 0°C durante 30 min. Se añadió agua para inactivar la reacción. Se evaporó la mayor parte del DCM. La mezcla de reacción se diluyó con EtOAc, se lavó con HCl 1M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal dando 89E (501 mg, 60 % de rendimiento) como un sólido marrón. CL-EM (IEP) m/z: 530.3+.

89F. Éster *terc*-butílico del ácido ((E)-17-cloro-5-metoxicarbonilamino-9-oxo-8,18,19-triaza-triciclo[14.3.1.2.7]icosa-1(20),2,4,6,12,16,18-heptaen-15-il)-carbámico: A una solución de 89E (350 mg, 0.660 mmol) en DCM (100 ml) se añadió Grubbs (II) (168 mg, 0.198 mmol)

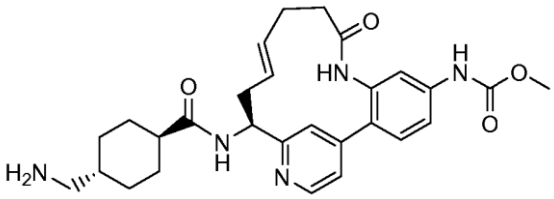
a ta. La solución se purgó con argón durante 3 min y luego se agitó bajo argón a reflujo durante 1 h. Se eliminó el solvente. El residuo se disolvió en EtOAc, que se lavó con agua y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró dando un sólido oscuro. El producto bruto se purificó por cromatografía en fase normal dando 89F (185 mg, 56 % de rendimiento) como un sólido marrón. CL-EM (IEP) m/z: 502.3 (M+H)+.

89G. El Ejemplo 89 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 89F; seguido por la etapa 1G. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.48 (s, 1H), 8.67 (d, *J* = 4.3 Hz, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.92 (s, 1H), 7.64 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.45 (dd, *J* = 14.0, 7.6 Hz, 1H), 7.07 (d, *J* = 15.6 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 5.34 - 5.11 (m, 2H), 4.58 - 4.36 (m, 1H), 3.76 (s, 3H), 3.10 - 2.96 (m, 1H), 2.64 - 2.51 (m, 1H), 2.19 (dd, *J* = 17.9, 11.0 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 1H). CL-EM (IEP) m/z: 634.3 (M+H)+. HPLC analítica: TR= 7.596 min.

Ejemplo 90.

Éster metílico del ácido {(E)-(S)-15-[(4-aminometil-ciclohexanocarbonil)-amino]-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,12,16,18-heptaen-5-

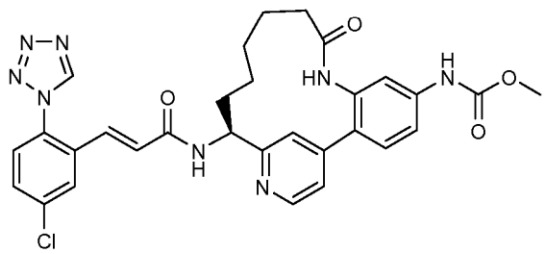
il}-carbámico, sal 2 TFA



El Ejemplo 90 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 88G; seguido por las etapas 3B; y 3C. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.70 (d, *J*=6.0 Hz, 1 H), 7.75 (dd, *J*=6.0, 1.6 Hz, 1 H), 7.53 - 7.63 (m, 2 H), 7.49 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.39 (d, *J*=8.2 Hz, 1 H), 5.46 - 5.59 (m, 1 H), 5.36 (dd, *J*=15.7, 5.5 Hz, 1 H), 4.97 (dd, *J*=9.3, 4.4 Hz, 1 H), 3.75 (s, 3 H), 2.77 (d, *J*=7.1 Hz, 2 H), 2.67 - 2.75 (m, 1 H), 2.44 - 2.58 (m, 2 H), 2.30 - 2.44 (m, 4 H), 1.79 - 1.97 (m, 4 H), 1.51 - 1.65 (m, 1 H), 1.32 - 1.50 (m, 2 H), 0.99 - 1.15 (m, 2 H). EM (IEP) m/z: 506.4 (M+H)+. HPLC analítica (Método C): TR= 6.97 min.

Ejemplo 91.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,16,18-hexaen-5-il}-carbámico, sal 1 TFA



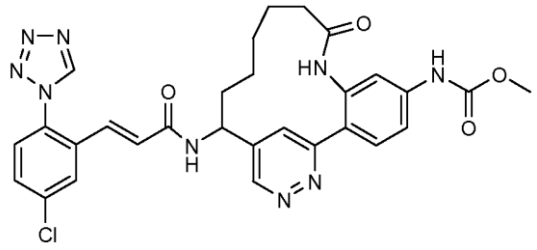
91A. Éster metílico del ácido ((S)-15-amino-9-oxo-

8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,16,18-hexaen-5-il)-carbámico, sal 2 TFA: El compuesto 91A se preparó siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E/2F por 88G; seguido por la etapa 3C. EM (IEP) m/z: 369.1 (M+H)+.

91B. El Ejemplo 91 se preparó siguiendo el procedimiento descrito en la etapa 1G, sustituyendo 1F por 91A. ^{1}H NMR (500 MHz, DMSO-d_6)) δ ppm 9.81 (s, 1 H), 9.78 (s, 1 H), 9.36 (s, 1 H), 8.56 (d, *J*=4.9 Hz, 1 H), 8.53 (d, *J*=7.7 Hz, 1 H), 7.87 (d, *J*=1.6 Hz, 1 H), 7.66 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.64 (d, *J*=8.8 Hz, 1 H), 7.37 - 7.43 (m, 2 H), 7.28 (d, *J*=8.2 Hz, 1 H), 7.21 (dd, *J*=4.9, 1.1 Hz, 1 H), 7.11 (s, 1 H), 6.93 (d, *J*=15.4 Hz, 1 H), 6.73 (d, *J*=15.9 Hz, 1 H), 4.76 - 4.83 (m, 1 H), 3.62 (s, 3 H), 2.09 - 2.20 (m, 2 H), 1.76 - 1.88 (m, 1 H), 1.56 - 1.68 (m, 2 H), 1.30 - 1.42 (m, 1 H), 1.07 - 1.26 (m, 3 H), 0.70 - 0.82 (m, 1 H). EM (IEP) m/z: 601.3 (M+H)+ y 603.2 (M+2+H)+. HPLC analítica (Método D): TR= 4.56 min.

Ejemplo 92.

Éster metílico del ácido {15-[(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,18,19-triaza-triciclo[14.3.1.2.7]icosa-1(20),2,4,6,16,18-hexaen-5-il}-carbámico

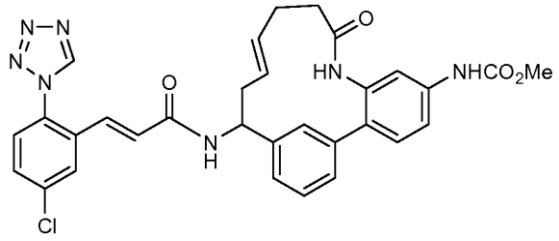


El Ejemplo 92 se preparó siguiendo los

procedimientos descritos en la etapa 2G, sustituyendo 2E por 89F; seguido por las etapas 3C; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.44 (s, 1H), 9.27 (d, *J* = 5.4 Hz, 1H), 8.32 (d, *J* = 1.5 Hz, 1H), 7.99 (d, *J* = 5.4 Hz, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.55 - 7.48 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 15.6 Hz, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 4.76 - 4.64 (m, 1H), 3.76 (s, 3H), 2.37 - 2.23 (m, 2H), 2.04 - 1.91 (m, 1H), 1.82 - 1.70 (m, 1H), 1.58 - 1.17 (m, 6H). CL-EM (IEP) m/z: 602.3 (M+H)+. HPLC analítica: TR= 6.253 min.

Ejemplo 93.

Éster metílico del ácido {(E)-15-[(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8-aza-triciclo[14.3.1.2.7]icosa-1(20),2,4,6,12,16,18-heptaen-5-il}-carbámico



93A. Se añadió solución de éster *terc*-butílico del ácido [1-(3-bromo-fenil)-but-3-enil]-carbámico: hexametidisilazano de litio (1M en THF, 7.30 ml, 7.3 mmol) a una solución enfriada (0°C) en THF (25 ml) del 3-bromobenzaldehído (1.33 g, 7.3 mmol) y se agitó en frío durante 0.5 h. La mezcla de reacción se enfrió hasta -78°C,

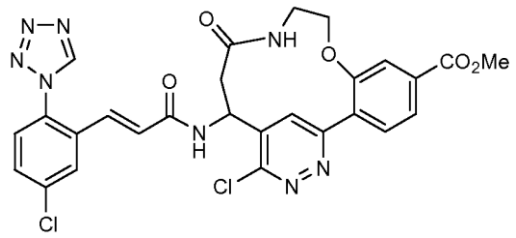
seguido por la adición de MgBr de alilo (1M, 7.30 ml, 7.3 mmol) gota a gota. La mezcla de reacción fría se agitó a esta temperatura durante 1.5 h, luego se inactivó con NH_4Cl saturado y se dejó calentar gradualmente hasta temperatura ambiente. Se extrajeron los materiales orgánicos con EtOAc (2x100 ml), se secó ($MgSO_4$) y se evaporó hasta un aceite (1.1 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (s, 1H), 7.45-7.2 (m, 3H), 5.77-5.68 (m, 1H), 5.15-5.09 (m, 2H), 3.99-3.95 (m, 1H), 2.49-2.30 (m, 2H). EM (IEP) m/z: 326.0 (M+H)+. La mezcla de reacción bruta se disolvió en dioxano (50 ml), y, a esta se añadió Boc_2O (0.74g, 3.4 mmol) seguido por la adición de TEA (1 ml) y se agitó seguidamente a temperatura ambiente durante la noche. Se inactivó la mezcla de reacción con agua (100 ml) y el producto deseado se extrajo con EtOAc (2x100 ml), se secó ($MgSO_4$) y se evaporó hasta una masa semisólida que solidificó gradualmente (1.25 g, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45-7.18 (m, 4H), 5.66-5.61 (m, 1H), 5.17-5.08 (m, 2H), 4.89 (s ancho, 1H), 4.68 (s ancho, 1H), 2.48 (m ancho, 2H), 1.41 (s ancho, 9H)ppm. EM (IEP) m/z: 3499 (M+Na)+.

93B. El Ejemplo 93 se preparó siguiendo los procedimientos descritos en la etapa 88C, sustituyendo 88B por 93A; seguido por las etapas 88E; 88F, sustituyendo metanol por acetona y sustituyendo cloruro amónico sólido por una solución acuosa saturada de cloruro amónico; 88G,

llevando a cabo la reacción sin pTsOH; 3C; y 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.77(s, 1H), 9.68(s ancho, 1H), 9.12(s, 1H), 8.61(d, *J* = 7.7Hz, 1H), 7.98(s, 1H), 7.66(m, 2H), 7.40-7.10(m, 4H), 6.95(s, 1H), 6.81(q, 2H), 5.40-5.20, m, 2H), 4.78(m, 1H), 3.62(s, 3H), 2.25(m, 4H), 1.16(m, 2H)ppm. EM (IEP) m/z: 598.4 (M+H)+. HPLC analítica: TR= 7.851 min.

Ejemplo 94.

Éster metílico del ácido 16-cloro-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-oxo-8-oxa-11.17.18-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-5-carboxílico



94A. Éster metílico del ácido 4-[5-(2-benciloxicarbonil-1-*terc*-butoxicarbonilamino-etil)-6-cloro-piridazin-3-il]-3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etoxi]-benzoico: A una solución de 3-(*terc*-butoxicarbonilamino)-3-(3,6-dicloropiridazin-4-il)propanoato de bencilo (200 mg, 0.469 mmol) preparado siguiendo un procedimiento de la bibliografía (Cowden, C.J., *Org. Lett.*, 4497-4499 (2003)) en dioxano (10 ml) se añadieron Intermediario 13 (308 mg, 0.704 mmol), Cs_2CO_3 (382 mg, 1.173 mmol) y tetrafluoroborato de tri-*terc*-butilfosfina

(13.61 mg, 0.047 mmol). La solución se purgó con argón durante 2 min y luego se añadió Pd_2dba_3 (21.48 mg, 0.023 mmol). La reacción se agitó bajo argón a 90°C durante 2 h. El sólido se separó por filtración y se eliminó el solvente. La mezcla bruta se purificó por cromatografía en fase normal dando 94A (128 mg, 38 % de rendimiento) como un sólido amarillo. CL-EM (IEP) m/z: 715.2 (M+H)+.

94B. Éster metílico del ácido 4-[5-(1-*terc*-butoxicarbonilamino-2-carboxi-etil)-6-cloro-piridazin-3-il]-3-[2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etoxi]-benzoico: A una solución de 94A (128 mg, 0.179 mmol) en MeOH (5 ml) y acetato de etilo (5 ml) (más soluble en EtOAc) se añadió una cantidad catalítica de Pd al 10 %/C. La reacción se agitó bajo un globo de hidrógeno a ta durante 3 horas. El catalizador se separó por filtración y el solvente se eliminó dando 94B (102 mg, 91 % de rendimiento) como un sólido amarillo. CL-EM (IEP) m/z: 625.2 (M+H)+.

94C. Éster metílico del ácido 3-(2-amino-etoxi)-4-[5-(1-*terc*-butoxicarbonilamino-2-carboxi-etil)-6-cloro-piridazin-3-il]-benzoico, sal TFA: A una solución de 94B (102 mg, 0.163 mmol) en EtOH (5 ml) se añadió hidrazina (0.1 ml, 3.19 mmol) a ta. La reacción se agitó bajo argón a reflujo durante 30 min. El solvente se eliminó. La purificación por cromatografía en fase inversa dio 94C (25 mg, 25.2 % de rendimiento) como un sólido. CL-EM (IEP) m/z: 495.1 (M+H)+.

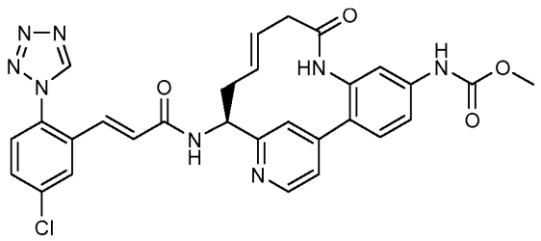
94D. Éster metílico del ácido 14-*terc*-butoxicarbonilamino-16-cloro-12-oxo-8-oxa-11.17.18-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-5-carboxílico: A una solución de reactivo de BOP (36.3 mg, 0.082 mmol), DIEA (0.036 ml, 0.205 mmol) y DMAP (5.02 mg, 0.041 mmol) en DCM (30 ml) se añadió una solución de 94C (25 mg, 0.041 mmol) en DMF (2.0 ml) a través de una bomba de jeringa durante 2 h a ta. Tras la adición, la reacción se agitó durante otros 30 min y se eliminó el solvente. El producto puro se purificó por cromatografía de fase inversa dando 94D (3.0 mg, 15.32 % de rendimiento) como un sólido color castaño. CL-EM (IEP) m/z: 477.1 (M+H)+.

94E. El Ejemplo 94 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 94D; seguido por la etapa 1G. ^{1}H NMR (400 MHz, DMF-d_7) δ ppm 9.84 (1 H, s), 8.80 (1 H, d, *J*=8.03 Hz), 8.33 (1 H, s), 8.19 - 8.28 (1 H, m), 8.11 (1 H, s), 7.83 (1 H, d, *J*=8.28 Hz), 7.73 - 7.80 (4 H, m), 7.00 - 7.09 (1 H, m), 6.90 - 6.99 (1 H, m), 5.47 - 5.63 (1 H, m), 4.24 (2 H, dd, *J*=5.65, 1.88 Hz), 3.94 (3 H, s), 3.61 (2 H, t, *J*=5.90 Hz), 3.03 - 3.14 (2 H, m). CL-EM (IEP) m/z: 609.2 (M+H)+. HPLC analítica: TR= 7.620 min.

Ejemplo 95.

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16-diaza-

triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-il}-carbámico, sal 1 TFA



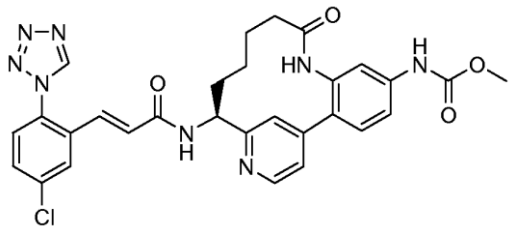
95A. Éster metílico del ácido ((E)-(S)-14-*terc*-butoxicarbonilamino-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-il)-carbámico, sal 1 TFA: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 88E, sustituyendo ácido pent-4-enoico por ácido but-3-enoico; seguido por las etapas 88F; y 88G. EM (IEP) m/z: 453.3 (M+H)+.

95B. El Ejemplo 95 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 95A; seguido por la etapa 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.65 (s, 1 H), 9.49 (s, 1 H), 8.64 (d, *J*=6.0 Hz, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.71 (dd, *J*=6.0, 1.6 Hz, 1 H), 7.66 (dd, *J*=8.8, 2.7 Hz, 1 H), 7.63 (s ancho, 1 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.46 - 7.52 (m, 2 H), 7.38 (s, 1 H), 7.10 (d, *J*=15.4 Hz, 1 H), 6.83 (d, *J*=15.4 Hz, 1 H), 5.79 - 5.90 (m, 1 H), 5.08 (dd, *J*=9.6, 4.1 Hz, 1 H), 4.89 - 4.99 (m, 1 H), 3.76 (s, 3 H), 2.98 (dd, *J*=11.5, 8.8 Hz, 1 H), 2.75 - 2.89 (m, 2 H), 2.40 - 2.53 (m, 1 H). EM (IEP) m/z: 585.3 (M+H)+. HPLC

analítica (Método D): TR= 5.07 min.

Ejemplo 96.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-il}-carbámico, sal 1 TFA



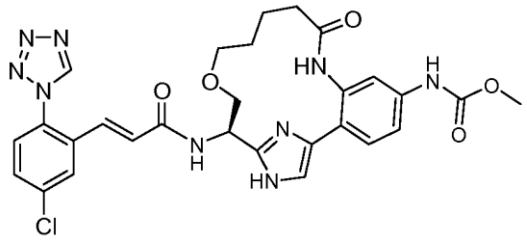
96A. Éster metílico del ácido ((S)-14-amino-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-il)-carbámico, sal 2 TFA: El compuesto 96A se preparó siguiendo los procedimientos descritos en la etapa 2G, sustituyendo 2E/2F por 95A; seguido por la etapa 3C. EM (IEP) m/z: 355.2 (M+H)+.

96B. El Ejemplo 96 se preparó siguiendo los procedimientos descritos en la etapa 1G, sustituyendo 1F por 96A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.66 (s, 1 H), 9.49 (s, 1 H), 8.68 (d, *J*=6.0 Hz, 1 H), 8.04 (s, 1 H), 7.97 (d, *J*=1.6 Hz, 1 H), 7.80 (d, *J*=5.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.61 (d, *J*=8.2 Hz, 1 H), 7.54 - 7.58 (m, 2 H), 7.50 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.10 (d, *J*=15.4 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.06 - 5.15 (m, 1 H), 3.76 (s, 3 H), 2.47 - 2.56 (m, 1 H), 2.08 - 2.19 (m, 1 H), 1.63 - 2.02 (m, 4 H),

1.33 - 1.44 (m, 1 H), 0.66 - 0.81 (m, 1 H). EM (IEP) m/z: 587.3 (M+H)+. HPLC analítica: TR= 4.37 min.

Ejemplo 113.

Éster metílico del ácido {(R)-16-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-14-oxa-8,18,20-triaza-triciclo[15.2.1.2.7]icosa-1(19),2,4,6,17(20)-pentaen-5-il}-carbámico, sal 1 TFA

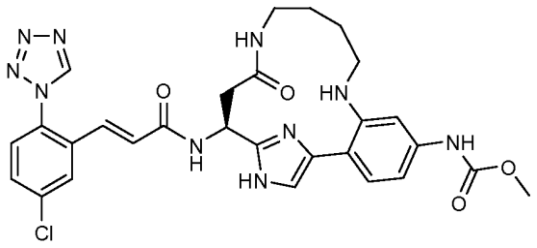


El Ejemplo 113 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo 10C por 52F; seguido por las etapas 2E/2F; 2G; 10H; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.59 (s, 1 H) 9.52 (s, 1 H) 7.97 (d, *J*=2.26 Hz, 1 H) 7.77 (d, *J*=1.76 Hz, 1 H) 7.66 - 7.70 (m, 1 H) 7.56 - 7.61 (m, 1 H) 7.45 - 7.48 (m, 1 H) 7.44 (d, *J*=2.01 Hz, 1 H) 7.36 - 7.42 (m, 1 H) 7.16 (d, *J*=15.81 Hz, 1 H) 6.80 (d, *J*=15.56 Hz, 1 H) 5.29 (t, *J*=4.14 Hz, 1 H) 3.84 - 3.97 (m, 2 H) 3.75 (s, 3 H) 3.58 - 3.69 (m, 1 H) 3.43 - 3.55 (m, 1 H) 2.26 - 2.44 (m, 2 H) 1.54 - 1.75 (m, 4 H). EM (IEP) m/z: 606.3(M+H)+. HPLC analítica: TR= 5.28min.

Ejemplo 115.

Éster metílico del ácido {(S)-16-[(E)-3-(5-cloro-2-tetrazol-

1-il-fenil)-acriloilamino]-14-oxo-8,13,18,20-tetraaza-triciclo[15.2.1.2.7]icosa-1(19),2,4,6,17(20)-pentaen-5-il}-carbámico, sal 2 TFA

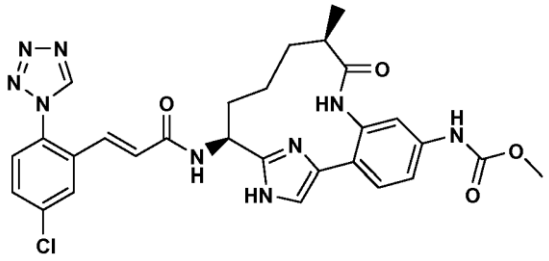


El Ejemplo 115 se preparó siguiendo los procedimientos descritos en Ejemplo 79 sustituyendo 3-aminopropilcarbamato de bencilo, sal HCl por 4-aminobutilcarbamato de bencilo, sal HCl en 79A. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.52 (1 H, s), 8.00 (1 H, d, *J*=2.26 Hz), 7.68 (1 H, dd, *J*=8.53, 2.26 Hz), 7.57 - 7.62 (2 H, m), 7.54 (1 H, d, *J*=8.53 Hz), 7.51 (1 H, s), 7.19 (1 H, d, *J*=15.56 Hz), 7.15 (1 H, dd, *J*=8.53, 2.01 Hz), 6.77 (1 H, d, *J*=15.81 Hz), 5.54 (1 H, dd, *J*=8.53, 5.02 Hz), 3.75 (3 H, s), 3.19 - 3.43 (4 H, m), 2.80 - 2.93 (1 H, m), 1.56 - 1.81 (4 H, m). CL-EM (IEP) m/z: 605.2 (M+H)+. HPLC analítica, TR = 4.950 min.

Ejemplo 116.

Éster metílico del ácido {(10R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10-metil-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1TFA,

diastereómero A



116A. Una solución de Ejemplo 10C (5 g, 9.40 mmol) y trietilamina (1.564 ml, 11.28 mmol) en EtOAc (Volumen: 30 ml) se enfrió hasta 0°C bajo Ar, se añadió gota a gota anhídrido 2,2,2-trifluoroacético (1.458 ml, 10.34 mmol). Después de 1 hora, la mezcla de reacción se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró el sólido y se concentró. La purificación por cromatografía en fase normal dio 5.26 g (97%) de 116A como un sólido amarillo pálido. EM (IEP) *m/z*: 628.1 (M+H)+.

116B. 2-Metilbut-3-enoato de bencilo: A una solución de ácido 2-metilbut-3-enoico (2 g, 18.98 mmol) en CH2Cl2 (38.0 ml) se añadió fenilmetanol (1.966 ml, 18.98 mmol), DCC (3.92 g, 18.98 mmol) y DMAP (0.232 g, 1.898 mmol) (ligera exotermia). La reacción se agitó a ta durante cuatro horas. Se filtró el sólido de la reacción, se aclaró con hexano y se concentró. La purificación por cromatografía en fase normal dio 3.55 g (98%) de 116B como un aceite incoloro.

116C. 6-(*terc*-Butoxicarbonilamino)-6-(4-(4-(metoxicarbonilamino)-2-(2,2,2-trifluoroacetamido)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)-2-metilhex-

3-enoato de (6S,E)-bencilo: A una solución de 116A (0.841 g, 1.340 mmol) en DCM (Volumen 26.8 ml) se añadió pTsOH (0.255 g, 1.340 mmol). La mezcla de reacción se desgasificó burbujeando en Ar durante 30 mins, a continuación la mezcla se agitó bajo Ar a 40°C durante 40 mins, se añadió 116B (1.53 g, 8.04 mmol), seguido por Grubbs(II) (0.341 g, 0.402 mmol) en 2 ml de DCM desgasificado gota a gota. La reacción se agitó a 40°C durante la noche. La reacción se inactivó con $NaHCO_3$ acuoso saturado, se extrajo con DCM, se lavó con salmuera se secó la fase orgánica sobre $MgSO_4$, se separó el sólido por filtración y se concentró. La purificación por cromatografía en fase normal dio 522 mg (49%) de 116C como un aceite pardusco claro. EM (IEP) *m/z*: 790.4 (M+H)+.

116D. Ácido (6S)-6-(*terc*-butoxicarbonilamino)-6-(4-(4-(metoxicarbonilamino)-2-(2,2,2-trifluoroacetamido)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)-2-metilhexanoico: Se hizo varío en una solución de 116C (810 mg, 1.025 mmol) en MeOH (20.5 ml) y se volvió a llenar con Ar, a continuación se añadió Pd al 10% en peso/C (109 mg, 0.103 mmol), se hizo vacío y se volvió a llenar con H_2, se agitó bajo un globo de H_2 a ta durante la noche. La mezcla de reacción se filtró, se aclaró y se concentró dando 116D como una espuma verdosa clara (709 mg, 99%) sin purificación adicional. EM (IEP) *m/z*: 702.5 (M+H)+.

116E. Ácido (6S)-6-(4-(2-amino-4-

(metoxicarbonilamino)fenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)-6-(*terc*-butoxicarbonilamino)-2-metilhexanoico: A una solución de 116D (709 mg, 1.010 mmol) en MeOH (10.100 ml) se añadió hidróxido de litio (2N ac) (3.54 ml, 7.07 mmol), se selló y se calentó a 60°C durante 5 hr. La reacción se enfrió y se concentró. El residuo se ajustó con HCl 1N acuoso hasta pH ~6, se extrajo con EtOAc hasta que no había producto en la fase acuosa. La fase de EtOAc se lavó con salmuera, se secó sobre MgSO4, se separó el sólido por filtración, se concentró dando 116E como una espuma negro oscuro (640 mg, 100%) y se usó en la etapa siguiente sin purificación adicional. EM (IEP) *m/z*: 606.4 (M+H)+.

116F. A una solución de BOP (1.117 g, 2.53 mmol) y DMAP (0.518 g, 4.24 mmol) en CH_2Cl_2 (Relación: 25, Volumen 324 ml) y DMF (Relación: 1.000, Volumen 12.95 ml) se añadió gota a gota mediante una bomba de jeringa una solución de 116E (0.612 g, 1.010 mmol) y DIEA (1.235 ml, 7.07 mmol) en 8 ml DMF durante 8 horas. Se agitó a ta durante la noche. La reacción se transfirió a un frasco sellado y se calentó a 60°C durante 5 hrs y luego se enfrió hasta ta y se agitó a ta durante el fin de semana. Se añadió MeOH para inactivar la reacción. La reacción se concentró, se diluyó con EtOAc, se lavó con H2O (2x), salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por cromatografía en fase

normal dio 116F (287 mg, 48%) como un sólido amarillo claro. La separación de 116F por cromatografía en fase inversa proporcionó dos diastereómeros.

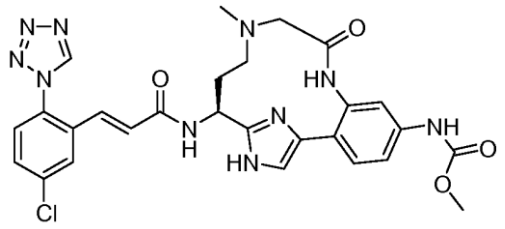
116G. Éster terc-butílico del ácido [(10R,14S)-5-metoxicarbonilamino-10-metil-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: isómero que eluye rápido. EM (IEP) *m/z*: 588.3 (M+H)+.

116H. Éster terc-butílico del ácido [(10S,14S)-5-metoxicarbonilamino-10-metil-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: isómero que eluye lento. EM (IEP) *m/z*: 588.3 (M+H)+.

116I. El Ejemplo 116 se preparó siguiendo los procedimientos descritos en 1F, sustituyendo 1D por 116G; seguido por 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.96 (d, J=2.2 Hz, 1 H), 7.67 (dd, J=8.8, 2.2 Hz, 1 H), 7.58 (d, J=8.8 Hz, 2 H), 7.48 - 7.54 (m, 1 H), 7.41 - 7.48 (m, 2 H), 7.13 (d, J=15.4 Hz, 1 H), 6.74 (d, J=15.9 Hz, 1 H), 5.02 (dd, J=10.4, 6.0 Hz, 1 H), 3.75 (s, 3 H), 2.43 - 2.56 (m, 1 H), 2.16 - 2.29 (m, 1 H), 1.83 - 1.97 (m, 1 H), 1.57 (d, J=9.3 Hz, 1 H), 1.21 - 1.36 (m, 2 H), 1.18 (d, J=7.1 Hz, 3 H), 1.05 - 1.18 (m, 1 H). EM (IEP) *m/z*: 590.3 (M+H)+. HPLC analítica: TR = 4.16 min. (Método B).

Ejemplo 117.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-metil-9-oxo-8,11,16,18-tetraaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



117A. Éster metílico del ácido {3-bromo-4-[2-((S)-1-*terc*-butoxicarbonilamino-3-oxo-propil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico : A una solución de 10B(100 mg, 0.168 mmol) en acetonitrilo (4.00 ml) se añadieron agua (1 ml), peryodato sódico (144 mg, 0.672 mmol) y tetraóxido de osmio (0.105 ml, 8.39 µmol) a 0°C. La mezcla de reacción se agitó y se dejó calentar lentamente hasta ta, luego se diluyó con acetato de etilo, y se lavó con agua y salmuera. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró hasta un sólido marrón. La cromatografía en fase normal dio 117A como un sólido marrón (50 mg, 49.8 % de rendimiento). EM (IEP) m/z: 631.5(M+H)+.

117B. Ácido ({(S)-3-[4-(2-bromo-4-metoxicarbonilamino-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-3-*terc*-butoxicarbonilamino-propil}-metil-amino)-acético: A una solución de 117A (300 mg, 0.502 mmol)

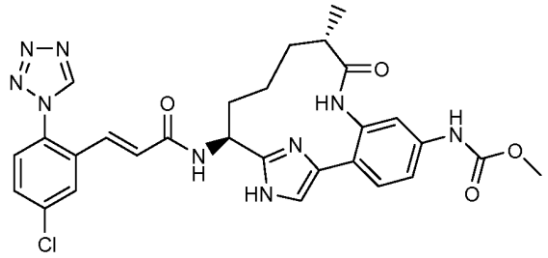
en DCE (6 ml) se añadió ácido 2-(metilamino)acético (67.1 mg, 0.753 mmol) y 1 gota de ácido acético (0.01 ml, 0.175 mmol). La mezcla de reacción se sometió a ultrasonidos y se agitó a temperatura ambiente durante 2 horas. Se añadió triacetoxiborohidruro sódico (319 mg, 1.506 mmol) y la reacción se agitó a temperatura ambiente durante 3 días. La reacción se inactivó con bicarbonato sódico acuoso saturado. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con salmuera y se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando 117B. EM (IEP) m/z: 672.3(M+H)+.

117C. El Ejemplo 117 se preparó siguiendo el procedimiento descrito en la etapa 10C alternativa), sustituyendo 10B por 117B; seguido por las etapas 20F; 10H; y 1G. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 9.52 (s, 1 H) 7.97 (d, *J*=2.2 Hz, 1 H) 7.67 (dd, *J*=8.53, 2.2 Hz, 1 H) 7.59 (m, 2 H) 7.55 (s, 1 H) 7.46 (s, 1 H) 7.37 (dd, *J*=8.52, 2.2 Hz, 1 H) 7.19 (d, *J*=15.68 Hz, 1H) 6.69 (d, *J*=15.41 Hz, 1 H) 5.26 (s ancho, 1 H) 3.93 (m, 1 H) 3.75 (m, 4 H) 3.27 (m, 1 H) 3.00 (m, 1 H) 2.82 (s, 3 H) 2.44 (s ancho, 1 H) 2.37 (s ancho, 1 H). EM (IEP) m/z: 591.3(M+H)+. HPLC analítica: TR= 4.48min.

Ejemplo 118.

Éster metílico del ácido {(10S,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10-metil-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-

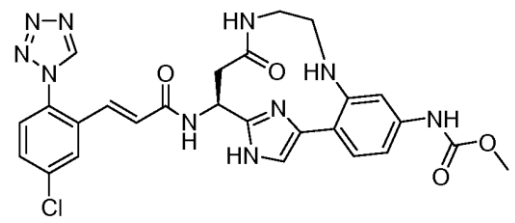
pentaen-5-il}-carbámico, sal 1 TFA,



El Ejemplo 118 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 116H; seguido por la etapa 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.50 (d, *J*=8.2 Hz, 1 H), 7.45 (s, 1 H), 7.35 - 7.42 (m, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.75 (d, *J*=15.4 Hz, 1 H), 5.14 (dd, *J*=9.9, 6.6 Hz, 1 H), 3.76 (s, 3 H), 2.68 - 2.80 (m, 1 H), 2.12 - 2.26 (m, 1 H), 1.90 - 2.05 (m, 1 H), 1.51 - 1.72 (m, 3 H), 1.03 (d, *J*=7.1 Hz, 3 H), 0.70 (s ancho, 1 H). EM (IEP) m/z: 590.3 (M+H)+. HPLC analítica: TR= 4.08 min. (Método B).

Ejemplo 119.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-oxo-8,11,16,18-tetraaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA

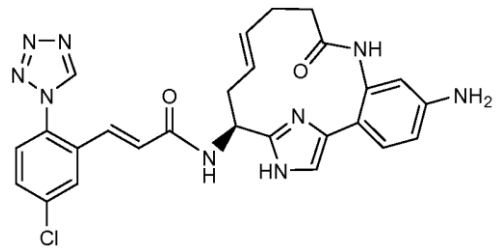


El Ejemplo 119 se preparó siguiendo los

procedimientos descritos en Ejemplo 79 sustituyendo 3-aminopropilcarbamato de bencilo, sal HCl por 2-aminoetilcarbamato de bencilo en 79A. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.99 (1 H, d, *J*=2.26 Hz), 7.92 (1 H, d, *J*=1.51 Hz), 7.75 (1 H, d, *J*=8.53 Hz), 7.67 (1 H, dd, *J*=8.53, 2.26 Hz), 7.55 - 7.61 (2 H, m), 7.34 (1 H, dd, *J*=8.53, 2.01 Hz), 7.21 (1 H, d, *J*=15.81 Hz), 6.76 (1 H, d, *J*=15.56 Hz), 5.48 - 5.64 (1 H, m), 3.78 - 3.93 (1 H, m), 3.77 (3 H, s), 3.33 - 3.72 (3 H, m), 2.81 (2 H, d, *J*=7.03 Hz). CL-EM (IEP) m/z: 577.2 (M+H)+. HPLC analítica: TR= 4.621 min.

Ejemplo 120.

(E)-*N*-((E)-(S)-5-Amino-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 2 TFA

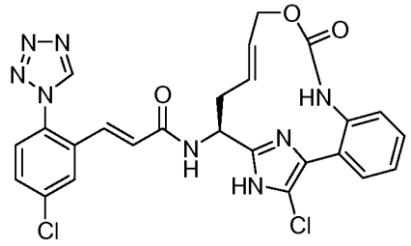


El Ejemplo 120 se preparó siguiendo el procedimiento descrito en la etapa 10H, sustituyendo 10G por 39A y llevando a cabo la reacción a 75°C durante 20 h; seguido por la etapa 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.31 (s, 1 H), 7.24 (d, *J*=8.2 Hz, 1 H), 7.14 (d, *J*=15.4 Hz, 1 H), 6.71 - 6.80 (m, 3 H),

5.50 - 5.60 (m, 1 H), 5.35 - 5.44 (m, 1 H), 5.08 (dd, *J*=9.9, 4.9 Hz, 1 H), 2.74 - 2.83 (m, 1 H), 2.31 - 2.61 (m, 5 H). EM (IEP) m/z: 530.2 (M+H)+. HPLC analítica: TR= 4.24 min.

Ejemplo 121.

(E)-*N*-((E)-(S)-18-Cloro-9-oxo-10-oxa-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

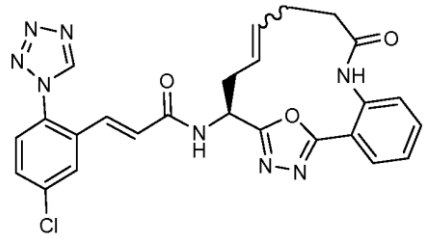


El Ejemplo 121 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 87. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.48 - 2.60 (m, 1 H), 2.81 - 2.93 (m, 1 H), 4.37 (s ancho, 2 H), 5.05 (dd, *J*=10.5, 5.0 Hz, 1 H), 5.60 - 5.73 (m, 1 H), 5.76 - 5.89 (m, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 7.16 (d, *J*=15.4 Hz, 1 H), 7.24 (d, *J*=8.0 Hz, 1 H), 7.40 (td, *J*=7.4, 1.2 Hz, 1 H), 7.49 (td, *J*=7.8, 1.2 Hz, 1 H), 7.52 - 7.56 (m, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.99 (d, *J*=1.9 Hz, 1 H), 9.52 (s, 1 H) EM (IEP) m/z: 551.2 (M+H)+. HPLC analítica: TR= 7.25 min.

Ejemplo 122.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-9-oxo-19-oxa-8,17,18-triaza-triciclo[14.2.1.2.7]nonadeca-

1(18),2,4,6,12,16-hexaen-15-il)-acrilamida y (Z)-3-(5-cloro-2-tetrazol-1-il-fenil)-*N*-((S)-9-oxo-19-oxa-8,17,18-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16-hexaen-15-il)-acrilamida



122A. 1-(2-(2-Nitrobenzoil)hidrazinil)-1-oxopent-4-en-2-ilcarbamato de (S)-*terc*-butilo: Una mezcla de ácido [(S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico (0.500 g, 2.323 mmol), HATU (1.060 g, 2.79 mmol) y DIPEA (1.623 ml, 9.29 mmol) en DCM (15 ml) se agitó a ta bajo nitrógeno durante 3 d. La mezcla de reacción se diluyó con más DCM, luego se lavó con agua, ácido cítrico acuoso al 5 %, $NaHCO_3$ acuoso saturado y salmuera, luego se secó sobre Mg_2SO_4 anhidro, se filtró y se evaporó. El residuo se purificó por cromatografía en fase normal proporcionando la acilhidrazida (0.7 g, 79.6.0 % de rendimiento). EM (IEP) m/z: 379.3 (M+H)+; 323.3 (M+H-tBu)+; 279.3 (M+H-Boc)+.

122B. 1-(5-(2-Nitrofenil)-1,3,4-oxadiazol-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: En un recipiente a presión de 150 ml se cargó una solución de 122A (0.57 g, 1.506 mmol) en THF anhidro (30 ml) y se añadió reactivo de Burgess (1.077 g, 4.52 mmol). El recipiente se selló bajo Ar

y la mezcla se calentó en un baño de aceite a 75°C con agitación detrás de una pantalla frente a ondas expansivas durante 2 horas. La reacción se enfrió hasta temperatura ambiente, se ventiló y se dejó en reposo a temperatura ambiente durante la noche. La mezcla de reacción se transfirió a un matraz de fondo redondo con ayuda de un poco de MeOH y se evaporó hasta sequedad. El residuo se purificó por cromatografía sobre gel de sílice proporcionando oxadiazol producto (0.327 g, 0.907 mmol, 60.2 % de rendimiento) EM (IEP) m/z 383.3 (M+Na)+ 305.3 (M+H-tBu)+.

122C. 1-(5-(2-Aminofenil)-1,3,4-oxadiazol-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: Se disolvió 122B (0.325 g, 0.902 mmol) en etanol (4.5 ml) y se añadió polvo de hierro (1.007 g, 18.04 mmol). La mezcla se agitó a temperatura ambiente durante 1-2 min y luego se añadió HCl 0.1 M (4.51 ml, 0.451 mmol) y la reacción se calentó con agitación bajo nitrógeno en un baño de aceite a 50°C durante 1.5 horas. La reacción se enfrió hasta temperatura ambiente y luego se filtró a través de una almohadilla de CELITE® y se lavaron los sólidos con agua, se descartó el EtOH y EtOAc. El filtrado se evaporó y la fase acuosa que quedó se diluyó con $NaHCO_3$ (hasta pH 8) y se extrajo 3x con EtOAc. Los extractos reunidos se lavaron con solución acuosa saturada de $NaHCO_3$ y salmuera, se secaron sobre Na_2SO_4 anhidro, se filtraron y se evaporaron proporcionando la amina como un sólido blanco

cristalino, (0.216 g, 0.654 mmol, 72.5 % de rendimiento). EM (IEP) m/z: 331.4 (M+H)+; 275.3 (M+H-tBu)+; 231.3 (M+H-Boc)+.

122D. 1-(5-(2-Pent-4-enamidofenil)-1,3,4-oxadiazol-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: Se disolvió 122C en DCM (3.5 ml) y se añadió piridina (0.105 ml, 1.302 mmol). La solución se enfrió en un baño de hielo/agua salada hasta ~ 0°C, luego se añadió cloruro de 4-pentenoilo (0.072 ml, 0.651 mmol) gota a gota con agitación bajo nitrógeno. La mezcla resultante se agitó a 0-5°C durante 1 h y luego se dejó calentar hasta temperatura ambiente. Después de 2h, la reacción se diluyó con EtOAc y se lavó con agua, HCl 1M, $NaHCO_3$ acuoso saturado y salmuera, luego se secó sobre Na_2SO_4 anhidro, se filtró y se evaporó. El residuo se purificó por cromatografía sobre gel de sílice proporcionando la amida (0.242 g, 0.587 mmol, 90 % de rendimiento). EM (IEP) m/z: 413.4 (M+H)+; 357.3 (M+H-tBu)+; 313.4 (M+H-Boc)+.

122E. Éster *terc*-butílico del ácido ((E)-(S)-9-oxo-19-oxa-8,17,18-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16-hexaen-15-il)-carbámico; y Éster *terc*-butílico del ácido ((Z)-(S)-9-oxo-19-oxa-8,17,18-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16-hexaen-15-il)-carbámico: Se dividió 122D (135 mg, 0.327 mmol) entre cinco viales de microondas de 20 ml. Los viales se llenaron entonces con argón durante 10-15 min seguido por la adición de DCM anhidro (4.8 mM) y Grubbs (II) (36 % mol). Todas las

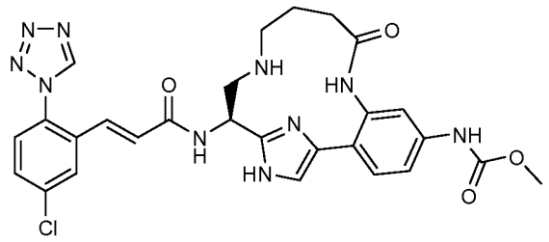
operaciones se llevaron a cabo bajo argón y los viales totalmente cargados se llenaron durante unos minutos más con argón, luego se taparon, sellaron y calentaron durante 90 min a 75° en el microondas, dejando luego reposar durante la noche. Los contenidos de los cinco viales se reunieron y se concentró para eliminar el DCM, se volvió a disolver en MeOH, se filtró y se purificó por HPLC de fase inversa proporcionando el alqueno macrocíclico como una mezcla de isómeros trans/cis (34 mg, 27 %). EM (IEP) m/z: 385.2 (M+H)+; 329.1 (M+H-tBu)+.

122E. Ejemplo 122: Se disolvió 122E (34 mg, 0.088 mmol) en DCM (2 ml) y se añadió TFA (0.5 ml, 6.49 mmol). La mezcla resultante se agitó a temperatura ambiente bajo N_2 durante ~ 5 h, luego se destiló hasta sequedad. El residuo se suspendió en MeOH y se destiló (2X), luego se secó en una bomba de vacío. La sal del ácido trifluoroacético bruta de la amina (EM (IEP) m/z: 285.2 (M+H)+; 33 mg, 0.116 mmol) se disolvió en DMF (1 ml) y se añadieron 3-(5-cloro-2-(1H-tetrazol-1-il)fenil)acrilato de (E)-2.5-dioxopirrolidin-1-ilo (46 mg, 0.132 mmol) y DIPEA (0.1 ml, 0.573 mmol). La solución oscura resultante se agitó bajo una manta de argón durante la noche. La mezcla de reacción se diluyó con agua y se extrajo 3X con EtOAc. Los extractos reunidos se lavaron con solución acuosa al 5 % de ácido cítrico, solución acuosa saturada de $NaHCO_3$ y salmuera, luego se secó sobre sulfato

sódico anhidro, se filtró y se evaporó. El residuo se suspendió en MeOH, se sometió a ultrasonidos y se filtró. El sólido se disolvió en una mezcla 1:1 de DMSO/MeOH, se filtró y se purificó por HPLC de fase inversa proporcionando el compuesto del título (14 mg, 23 %). EM (IEP) m/z: 517.3 (M+H)+ como una mezcla ~ 5:1 de los isómeros trans/cis de doble enlace como se determina por RMN y HPLC. HPLC analítica: isómero trans mayoritario: TR = 7.53 min; isómero minoritario TR = 7.41.

Ejemplo 123.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,13,17,19-tetraaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 2 TFA

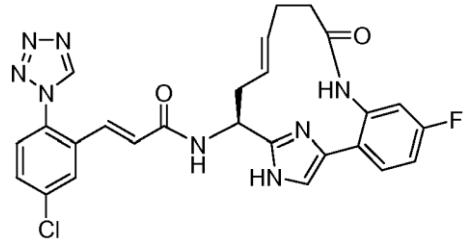


El Ejemplo 123 se preparó siguiendo los procedimientos descritos en la etapa 117B, sustituyendo 117A por ácido 4-oxobutanoico y sustituyendo ácido 2-(metilamino) acético por 20B; seguido por las etapas 20D; 10C (alternativa); 20F; 2G; 1G; y 10H. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 9.54 (s, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.60 (d, *J*=8.8 Hz, 1 H), 7.48 - 7.56 (m, 2 H),

7.44 (s, 1 H), 7.37 - 7.43 (m, 1 H), 7.24 (d, *J*=15.9 Hz, 1 H), 6.69 (d, *J*=15.4 Hz, 1 H), 5.52 (dd, *J*=8.2, 3.8 Hz, 1 H), 3.74 (s, 3 H), 3.42 - 3.61 (m, 2 H), 3.24 - 3.29 (m, 2 H), 2.50 - 2.78 (m, 2 H), 2.02 - 2.33 (m, 2 H). EM (IEP) m/z: 591.3 (M+H)+. HPLC analítica: TR= 3.88min. (Método B).

Ejemplo 124.

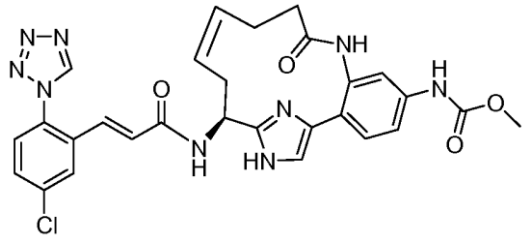
(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-5-fluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal 1 TFA



El Ejemplo 124 se preparó siguiendo los procedimientos descritos en la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 17; seguido por las etapas 2B; 2C; 10C; 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; 2E; 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.33 - 2.62 (m, 5 H), 2.75 - 2.84 (m, 1 H), 5.05 - 5.12 (m, 1 H), 5.37 - 5.47 (m, 1 H), 5.52 - 5.62 (m, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 7.11 - 7.21 (m, 3 H), 7.43 (s ancho, 1 H), 7.50 - 7.56 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.66 - 7.71 (m, 1 H), 7.97 (s ancho, 1 H), 9.51 (s ancho, 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -111.20. EM (IEP) m/z: 533.1 (M+H)+. HPLC analítica: TR= 5.03 min.

Ejemplo 125.

Éster metílico del ácido {(Z)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 1 TFA

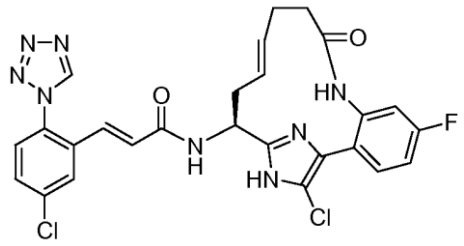


El Ejemplo 125 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; seguido por las etapas 2F; 10H, llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.46 (s, 1 H), 7.95 (d, *J*=2.2 Hz, 1 H), 7.64 - 7.68 (m, 2 H), 7.57 (d, *J*=8.2 Hz, 1 H), 7.41 (d, *J*=8.8 Hz, 1 H), 7.35 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.31 (s, 1 H), 7.18 (d, *J*=15.4 Hz, 1 H), 6.70 (d, *J*=15.4 Hz, 1 H), 5.57 - 5.64 (m, 1 H), 5.42 - 5.50 (m, 1 H), 5.16 - 5.22 (m, 1 H), 3.76 (s, 3 H), 2.87 - 2.97 (m, 1 H), 2.68 - 2.77 (m, 1 H), 2.47 - 2.64 (m, 2 H), 2.31 - 2.43 (m, 2 H). EM (IEP) m/z: 588.2 (M+H)+. HPLC analítica: TR= 4.86 min.

Ejemplo 126.

(E)-*N*-((E)-(S)-18-Cloro-5-fluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-

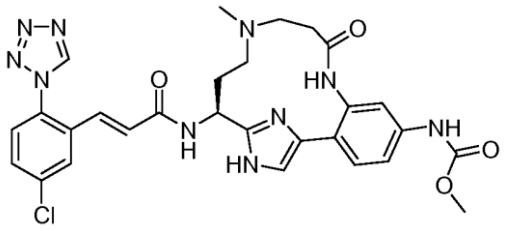
il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA



El Ejemplo 126 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 124. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 2.31 - 2.50 (m, 5 H), 2.66 - 2.74 (m, 1 H), 4.96 (dd, *J*=10.5, 4.4 Hz, 1 H), 5.30 - 5.40 (m, 1 H), 5.50 - 5.59 (m, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 7.11 - 7.18 (m, 3 H), 7.48 - 7.53 (m, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -112.21. EM (IEP) m/z: 567.2 (M+H)+. HPLC analítica: TR= 7.41 min.

Ejemplo 127.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-metil-9-oxo-8,12,17,19-tetraaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal 2 TFA



127A. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-

etoximetil)-1*H*-imidazol-4-il]-3-(2,2,2-trifluoro-acetilamino)-fenil]-carbámico: A una suspensión de 10C (200 mg, 0.376 mmol) en DCM (3 ml) a 0°C se añadió trietilamina (0.157 ml, 1.128 mmol), seguido por anhídrido trifluoracético (0.064 ml, 0.451 mmol). La mezcla de reacción se dejó agitar a ta durante 1 h, luego se diluyó con EtOAc, se lavó con HCl 1 N y salmuera y se secó sobre sulfato de magnesio. El solvente se eliminó a presión reducida dando 127A (271 mg, 0.432 mmol, 115 % de rendimiento) como una espuma amarilla. EM (IEP) m/z: 628.5(M+H)+.

127B. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-3-oxo-propil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(2,2,2-trifluoro-acetilamino)-fenil]-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en 117A, sustituyendo 10B por 127A. EM (IEP) m/z: 630.4(M+H)+.

127C. Ácido 3-({(S)-3-*terc*-butoxicarbonilamino-3-[4-[4-metoxicarbonilamino-2-(2,2,2-trifluoro-acetilamino)-fenil]-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-propil}-metil-amino)-propiónico: A una solución de 127B (97 mg, 0.154 mmol) en MeOH (2 ml) se añadió ácido 3-(metilamino)propanoico (23.83 mg, 0.231 mmol) y 1 gota de ácido acético, luego se añadió cianoborohidruro sódico (4.84 mg, 0.077 mmol) y la reacción se agitó a ta durante la noche. La reacción se inactivó con bicarbonato sódico

saturado, se extrajo con EtOAc y se lavó la fase orgánica con salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró dando 127C (86 mg, 0.120 mmol, 78 % de rendimiento) como un sólido naranja claro. EM (IEP) m/z: 717.5(M+H)+.

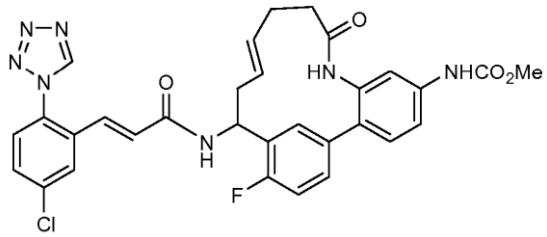
127D. Éster *terc*-butílico del ácido [(S)-5-metoxicarbonilamino-11-metil-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,11,16,18-tetraaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A una mezcla de 127C (86 mg, 0.120 mmol) en metanol (3 ml) se añadió carbonato potásico (116 mg, 0.840 mmol). La mezcla resultante se agitó a ta durante 1 h, luego se almacenó a -10°C durante el fin de semana. Se añadieron agua (0.150 ml) e hidróxido sódico acuoso 1 N (0.4 ml, 0.400 mmol) y la reacción se calentó hasta 50°C durante cuatro horas. La purificación por cromatografía de fase inversa proporcionó 127D (41 mg, 0.066 mmol, 55.0 % de rendimiento) como un sólido naranja oscuro. EM (IEP) m/z: 621.2(M+H)+.

127E. El Ejemplo 127 se preparó siguiendo los procedimientos descritos en la etapa 23E, sustituyendo 23D por 127D; seguido por las etapas 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.96 (1 H, d, *J*=2.5 Hz), 7.66 (1 H, dd, *J*=8.5, 2.2 Hz), 7.58 (2 H, d, *J*=8.5 Hz), 7.53 (1 H, d, *J*=8.5 Hz), 7.48 (1 H, s), 7.33 (1 H, dd, *J*=8.5, 2.2 Hz), 7.19 (1 H, d, *J*=15.7 Hz), 6.69 (1 H, d, *J*=15.7 Hz), 5.40 (1 H, dd,

J=7.4, 3.9 Hz), 3.71 - 3.78 (3 H, m), 3.60 (1 H, s ancho), 3.39 - 3.49 (1 H, m), 3.01 (3 H, s), 2.84 - 2.92 (2 H, m), 2.38 - 2.46 (2 H, m). EM (IEP) m/z: 605.4(M+H)+. HPLC analítica: TR= 4.55 min.

Ejemplo 128.

Éster metílico del ácido {(E)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-fluoro-9-oxo-8-aza-triciclo[14.3.1.2.7]icosa-1(20),2,4,6,12,16,18-heptaen-5-il}-carbámico

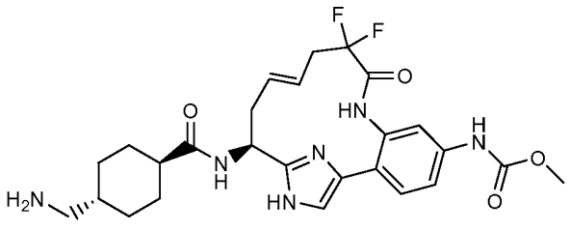


El Ejemplo 128 se preparó siguiendo los procedimientos descritos en la etapa 93A, sustituyendo 3-bromobenzaldehído por 3-bromo-6-fluorobenzaldehído; seguido por las etapas 88C; 88E; 88F, sustituyendo metanol por acetona y sustituyendo cloruro amónico sólido por una solución acuosa saturada de cloruro amónico; 88G, llevando a cabo la reacción sin pTsOH; 3C; y 1G. ^{1}H NMR (400 MHz, MeOD/DMSO-d_6) δ ppm 9.38 (s, 1H), 8.60(s, 1H), 7.01(d, *J* = 2.0Hz, 1H), 6.72-6.63(dd, *J* = 2.0 & 8.3Hz, 3H), 6.63(dd, *J* = 2.0 & 8.2Hz, 1H), 6.32-6.20m, 5H), 6.09-6.05(d, *J* = 15.4Hz, 1H), 5.94-5.91(d, *J* = 15.6Hz, 1H), 4.58(m, 1H), 4.47(m, 2H), 2.80(s, 3H), 1.67(m, 1H), 1.51-1.46(m, 4H)ppm. EM (IEP) m/z:

616.0 (M+H)+. HPLC analítica: TR= 8.55 min.

Ejemplo 129.

Éster metílico del ácido {(E)-(S)-15-[(4-aminometil-ciclohexanocarbonil)-amino]-10,10-difluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal 2 TFA

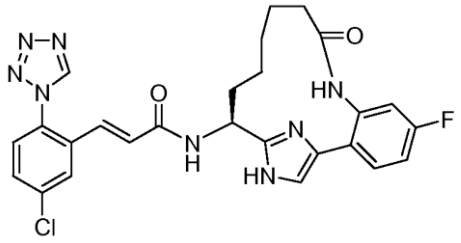


El Ejemplo 129 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2,2-difluoropent-4-enoico; seguido por las etapas 2E; 10H; 3B; y 3C. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.67 (s, 1 H), 7.58 (d, *J*=2.2 Hz, 1 H), 7.53 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.38 - 7.46 (m, 2 H), 5.66 - 5.80 (m, 1 H), 5.20 - 5.31 (m, 1 H), 4.99 (dd, *J*=11.0, 4.4 Hz, 1 H), 3.76 (s, 3 H), 2.73 - 3.00 (m, 5 H), 2.48 - 2.61 (m, 1 H), 2.26 - 2.39 (m, 1 H), 1.83 - 2.00 (m, 3 H), 1.54 - 1.69 (m, 1 H), 1.38 - 1.54 (m, 2 H), 1.01 - 1.19 (m, 2 H). EM (IEP) m/z: 531.3 (M+H)+. HPLC analítica: TR= 1.73 min. (Método B).

Ejemplo 130.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-5-fluoro-9-oxo-

8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-acrilamida, sal 1 TFA

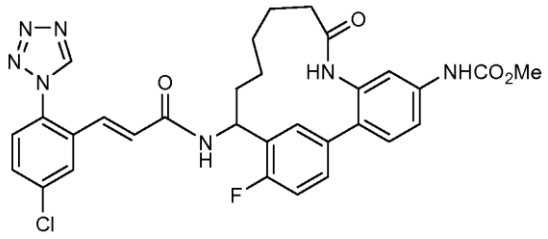


El Ejemplo 130 se preparó siguiendo los procedimientos de la etapa 2A, sustituyendo 2-bromo-1-(2-bromofenil)etanona por el Intermediario 17; seguido por las etapas 2B; 2C; 10C; 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; 2F; 10G, sustituyendo el globo de hidrógeno por hidrógeno (3.791 x 105 Pa); 10H; y 15D. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.81 - 0.91 (m, 1 H), 0.94 - 1.05 (m, 1 H), 1.41 - 1.60 (m, 2 H), 1.61 - 1.78 (m, 2 H), 1.99 - 2.09 (m, 1 H), 2.16 - 2.24 (m, 1 H), 2.30 - 2.42 (m, 2 H), 5.03 (dd, *J*=10.2, 4.7 Hz, 1 H), 6.74 (d, *J*=15.7 Hz, 1 H), 7.10 - 7.19 (m, 2 H), 7.22 (dd, *J*=9.5, 2.3 Hz, 1 H), 7.48 (s, 1 H), 7.55 - 7.62 (m, 2 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.97 (d, *J*=2.2 Hz, 1 H), 9.51 (s, 1 H). RM de 19F (471 MHz, CD3OD) δ ppm -111.56. EM (IEP) m/z: 535.2 (M+H)+. HPLC analítica: TR= 5.18 min.

Ejemplo 131.

Éster metílico del ácido {15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-fluoro-9-oxo-8-aza-

triciclo[14.3.1.2.7]icosa-1(20),2,4,6,16,18-hexaen-5-il}-carbámico

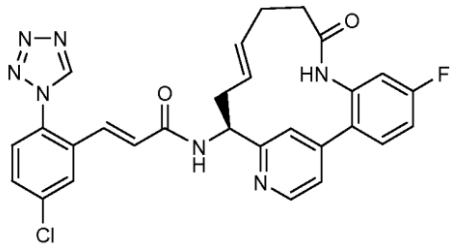


El Ejemplo 131 se preparó siguiendo los procedimientos descritos en la etapa 93A, sustituyendo 3-bromobenzaldehído por 3-bromo-6-fluorobenzaldehído; seguido por las etapas 88C; 88E; 88F, sustituyendo metanol por acetona y sustituyendo cloruro amónico sólido por una solución acuosa saturada de cloruro amónico; 88G, llevando a cabo la reacción sin pTsOH; 2G, sustituyendo el globo de hidrógeno por hidrógeno (3.791 x 105 Pa); 3C, sustituyendo TFA y DCM por HCl 4M en dioxano; y 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.83 (s, 1H), 9.76 (s, 1H), 9.20(s, 1H), 8.77 (s ancho, 1H), 8.54 (d, 1H), 7.90 (s, 1H), 7.73-7.69 (m, 2H), 7.50-7.42 (m, 2H), 7.29-7.23(m, 3H), 6.83 (s, 2H), 4.98 (m, 1H), 3.69 (s, 3H), 2.50-2.25 (m, 4H), 1.90 (m, 1H), 1.7 (m, 1H), 1.50-1.01 (m, 4H). EM (IEP) m/z: 618.1 (M+Na)+. HPLC analítica: TR= 7.95 min.

Ejemplo 132.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((E)-(S)-5-fluoro-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-

1(20),2(7),3,5,12,16,18-heptaen-15-il)-acrilamida, sal 1 TFA



132A. 2-(5,5-Dimetil-1,3,2-dioxaborinan-2-il)-5-fluoro-fenilamina: Este compuesto se preparó siguiendo el procedimiento descrito en Intermediario 12, sustituyendo 2-bromo-5-nitroanilina por 2-bromo-5-fluoroanilina. EM (IEP) m/z: 224.3(M+H)+.

132B. {(S)-1-[4-(2-Amino-4-fluoro-fenil)-piridin-2-il]-but-3-enil}-amida del ácido 2-metil-propano-2-sulfínico: Se cargó un matraz de fondo redondo con 88B (0.377 g, 1.314 mmol), 132A (0.586 g, 2.63 mmol), aducto de $PdCl_2$(dppf)-CH_2Cl_2 (0.107 g, 0.131 mmol) y fosfato potásico, tribásico (0.558 g, 2.63 mmol), luego se vació y se llenó con Ar tres veces. Se añadieron DMSO (6.57 ml) y agua (0.118 ml, 6.57 mmol) y la reacción se vació de nuevo y se llenó con Ar tres veces. La reacción se calentó a 90°C durante 2 horas, luego se dejó a temperatura ambiente durante la noche. La reacción se diluyó con agua y se extrajo tres veces con EtOAc. La fase orgánica reunida se lavó con agua y salmuera, luego se secó sobre $MgSO_4$, se filtró y se condensó dando un residuo marrón. El residuo bruto se volvió a disolver en MeOH, se filtró a través de una pequeña almohadilla de CELITE® y se purificó

por cromatografía de fase inversa. Las fracciones del pico principal se neutralizaron con $NaHCO_3$ saturado, parcialmente condensado para eliminar el MeOH, luego se extrajo tres veces con EtOAc. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro, se filtró y se evaporó proporcionando un residuo naranja, 132B (0.280 g, 0.775 mmol, 58.9 % de rendimiento). EM (IEP) m/z: 362.3(M+H)+.

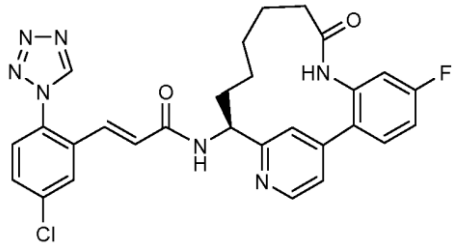
132C. Éster *terc*-butílico del ácido ((E)-(S)-5-fluoro-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,12,16,18-heptaen-15-il)-carbámico: Este compuesto se preparó a partir de 132B en cuatro etapas escindiendo la *t*-butilsulfinamida y mediante la introducción de un grupo protector Boc, reducción del nitro a la anilina correspondiente, acoplamiento con ácido 4-pentenoico y posterior RCM del dieno resultante, siguiendo los procedimientos descritos para los compuestos 88D, 52D, 88E y 88G. EM (IEP) m/z: 412.3(M+H)+.

132D. El Ejemplo 132 se preparó a partir de 132C por eliminación del grupo protector Boc y acoplamiento al Intermediario 1, siguiendo los procedimientos descritos en la etapa s 3C y 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.85 (1 H, s) 9.46 (1 H, s) 8.64 (1 H, d, *J*=7.70 Hz) 8.61 (1 H, d, *J*=4.95 Hz) 7.97 (1 H, d, *J*=1.65 Hz) 7.69 - 7.76 (2 H, m) 7.40 (1 H, dd, *J*=7.97, 6.32 Hz) 7.28 (1 H, d, *J*=4.95 Hz) 7.17 - 7.25 (2 H, m) 7.06 (1 H, d, *J*=15.39 Hz) 7.01 (1 H, s) 6.81 (1 H, d,

J=15.39 Hz) 5.44 (1 H, ddd, *J*=15.12, 7.42, 7.15 Hz) 5.22 (1 H, ddd, *J*=15.53, 5.22, 5.08 Hz) 4.87 - 4.96 (1 H, m) 2.19 - 2.40 (6 H, m). EM (IEP) m/z: 544.3(M+H)+. HPLC analítica: TR= 6.18min.

Ejemplo 133.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-5-fluoro-9-oxo-8,17-diaza-triciclo[14.3.1.2.7]icosa-1(20),2(7),3,5,16,18-hexaen-15-il)-acrilamida, sal 1 TFA

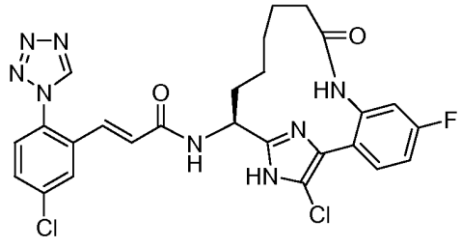


El Ejemplo 133 se preparó a partir de 132C por hidrogenación del doble enlace, desprotección del grupo protector Boc y acoplamiento con el Intermediario 1, siguiendo los procedimientos descritos en la etapa s 2G, 3C y 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.84 (1 H, s) 9.50 (1 H, s) 8.67 (1 H, d, *J*=4.95 Hz) 8.62 (1 H, d, *J*=7.70 Hz) 7.94 (1 H, d, *J*=1.65 Hz) 7.69 - 7.77 (2 H, m) 7.48 (1 H, dd, *J*=9.07, 6.32 Hz) 7.33 (1 H, dd, *J*=4.95, 1.65 Hz) 7.21 - 7.28 (2 H, m) 7.15 (1 H, s) 6.99 (1 H, d, *J*=15.39 Hz) 6.79 (1 H, d, *J*=15.94 Hz) 4.88 (1 H, ddd, *J*=11.54, 7.42, 4.12 Hz) 2.21 (2 H, t, *J*=5.77 Hz) 1.88 (1 H, dd, *J*=13.19, 9.34 Hz) 1.71 (2 H, t, *J*=12.09 Hz) 1.42 (1 H, dd, *J*=13.74, 4.40 Hz) 1.32 (1 H, s ancho) 1.11 -

1.26 (2 H, m) 0.91 (1 H, d, *J*=4.40 Hz). EM (IEP) m/z: 546.4(M+H)+. HPLC analítica: TR= 6.34 min.

Ejemplo 134.

(E)-*N*-((S)-18-Cloro-5-fluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-15-il)-3-(5-cloro-2-tetrazol-1-il-fenil)-acrilamida, sal 1 TFA

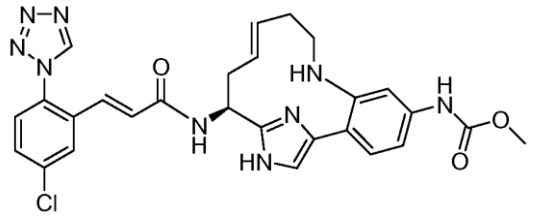


El Ejemplo 134 se preparó siguiendo el procedimiento descrito en 17A, sustituyendo 16A por el Ejemplo 130. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.81 - 0.94 (m, 1 H), 1.04 - 1.21 (m, 1 H), 1.34 - 1.54 (m, 2 H), 1.63 - 1.72 (m, 2 H), 1.90 - 2.01 (m, 1 H), 2.04 - 2.15 (m, 1 H), 2.28 - 2.38 (m, 2 H), 4.91 - 4.95 (m, 1 H), 6.74 (d, *J*=15.4 Hz, 1 H), 7.10 (d, *J*=15.7 Hz, 1 H), 7.13 - 7.20 (m, 2 H), 7.52 - 7.58 (m, 2 H), 7.64 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.93 (d, *J*=2.5 Hz, 1 H), 9.49 (s, 1 H). ^{19}F NMR (471 MHz, CD_3OD) δ ppm -112.04. EM (IEP) m/z: 569.2 (M+H)+. HPLC analítica: TR= 7.54 min.

Ejemplo 135.

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-

triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-5-il}-carbámico, sal 2 TFA

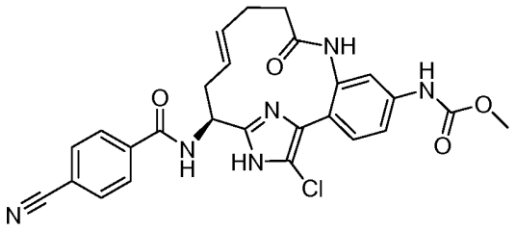


El Ejemplo 135 se preparó siguiendo los procedimientos descritos en la etapa 10C, sustituyendo hidróxido de amonio por but-3-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 10E; 1F, sustituyendo etanol por metanol y llevando a cabo la reacción a 75°C; y 1G. ^{1}H NMR (500 MHz, 50°C, CD_3OD) δ ppm 9.47 (s, 1 H), 7.96 (d, *J*=1.6 Hz, 1 H), 7.79 (s, 1 H), 7.66 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.55 - 7.62 (m, 2 H), 7.41 (s, 1 H), 7.30 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.19 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.9 Hz, 1 H), 5.87 - 5.96 (m, 1 H), 5.20 - 5.28 (m, 1 H), 5.13 (ddd, *J*=15.3, 7.6, 7.4 Hz, 1 H), 3.77 (s, 3 H), 3.29 - 3.35 (m, 2 H), 2.54 - 2.68 (m, 2 H), 2.43 - 2.50 (m, 2 H). EM (IEP) m/z: 560.2 (M+H)+. HPLC analítica: TR= 5.53 min.

Ejemplo 136.

Éster metílico del ácido [(E)-(S)-18-cloro-15-(4-ciano-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-

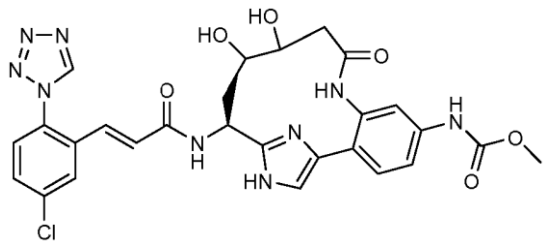
hexaen-5-il]-carbámico, sal 1 TFA



El Ejemplo 136 se preparó siguiendo el procedimiento descrito en la etapa 15D, sustituyendo 15C por 76B, sustituyendo el Intermediario 2 por ácido 4-ciano-benzoico, sustituyendo la base de Hunig por trietilamina y llevando a cabo la reacción a 55°C. ^{1}H NMR (400 MHz, DMSO-d_6, 1 gota de D_2O) δ ppm 8.01 (d, *J*=8.2 Hz, 2 H), 7.93 (d, *J*=8.8 Hz, 2 H), 7.45 (s, 1 H), 7.29 - 7.37 (m, 2 H), 5.51 (ddd, *J*=15.3, 7.6, 7.4 Hz, 1 H), 5.22 - 5.32 (m, 1 H), 5.07 (dd, *J*=9.9, 4.4 Hz, 1 H), 3.65 (s, 3 H), 2.19 - 2.61 (m, 6 H). EM (IEP) m/z: 519.0 (M+H)+. HPLC analítica: TR= 6.12 min.

Ejemplo 137.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11,12-dihidroxi-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA, Diastereómeros A:B (1: 1.3)



137A. Éster metílico del ácido [(S)-11,12-

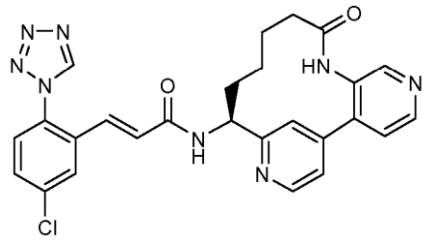
dihidroxi-5-metoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico, sal 1 TFA, Diastereómeros A:B (1:1.3) y 137B. Éster *terc*-butílico del ácido [(S)-11,12-dihidroxi-5-metoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico, sal 1 TFA, Diastereómero C: Se disolvió el contenido de un vial sellado de 1 g de OsO_4 en 200 ml de *t*-butanol. La solución verde pálido se trató con tres gotas de H_2O_2 al 30 % y se dejó reposar durante la noche. Si la solución viraba a color oscuro, se repetía la adición gota a gota de H_2O_2 al 30 %, hasta que persistía el color verde pálido. El compuesto 10E (67 mg, 0.117 mmol) en acetona (1.17 ml) se enfrió hasta 0°C. A continuación, se añadieron H_2O (0.021 ml, 1.172 mmol), NMO (21.23 mg, 0.176 mmol) y tetraóxido de osmio (0.293 ml, 5.86 µmol). La reacción se agitó a 0°C y se calentó gradualmente hasta ta durante la noche. Se añadió $MgSO_4$ a la mezcla de reacción. El sólido se separó por filtración, se aclaró con MeOH y el filtrado se concentró proporcionando un producto bruto oscuro. La purificación por cromatografía de fase inversa proporcionó 9 mg de 137A, como una mezcla. Diastereómeros A:B (1:1.3), como un sólido blanco y 7 mg de 137B (Diastereómero C), como un sólido blanco. Para 137A: EM (IEP) m/z: 606.4 (M+H)+. Para

137B: EM (IEP) m/z: 606.4 (M+H)+.

137C. El Ejemplo 137 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 137A; seguido por la etapa 1G. EM (IEP) m/z: 608.3 (M+H)+. HPLC analítica: TR= 3.90, 4.06 min, ratio 1.3:1. (Método B).

Ejemplo 138.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-9-oxo-5.8.16-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaen-14-il)-acrilamida, sal 2 TFA



138A. [(S)-1-(3'-Amino-[4.4']bipiridinil-2-il)-but-3-enil]-amida del ácido 2-metil-propano-2-sulfínico: Se añadió 088B (591 mg, 2.483 mmol) en un tubo de microondas a dioxano (9 ml) y fosfato potásico tribásico (2.483 ml, 4.97 mmol). La mezcla se desgasificó burbujeando a través de Ar durante varios minutos. Se añadió tetraquis(trifenilfosfina)paladio (0) (191 mg, 0.166 mmol) y se continuó burbujeando durante unos posos minutos. Se tapó y se calentó a 100°C durante la noche. Se añadió más tetraquis(trifenilfosfina)paladio (0) (80 mg) y la reacción se calentó a 100°C durante 5 horas más. La reacción se enfrió

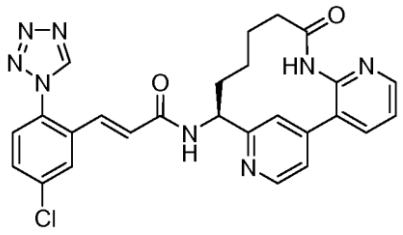
hasta ta y se concentró para eliminar el dioxano, se diluyó con EtOAc/H_2O, se extrajo dos veces más con EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por cromatografía en fase normal dio 350 mg (50 %) de 138A como una espuma ligeramente pardusca. EM (IEP) m/z: 345.2 (M+H)+.

138B. El Ejemplo 138 se preparó siguiendo los procedimientos descritos en la etapa 88D, sustituyendo 88C por 138A; seguido por las etapas 88E, sustituyendo ácido pentenoico por ácido but-3-enoico; 88G, sustituyendo 1.1 eq. de pTsOH por 2.2 eq. de pTsOH; 2G; 3C; y 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.49 (1 H, s), 8.82 (1 H, d, *J*=5.5 Hz), 8.75 (1 H, d, *J*=5.5 Hz), 8.62 (1 H, s), 7.98 (1 H, d, *J*=2.2 Hz), 7.87 - 7.95 (2 H, m), 7.74 (1 H, dd, *J*=5.5, 2.2 Hz), 7.66 (1 H, dd, *J*=8.8, 2.2 Hz), 7.56 (1 H, d, *J*=8.8 Hz), 7.08 (1 H, d, *J*=15.4 Hz), 6.81 (1 H, d, *J*=15.4 Hz), 5.12 (1 H, dd, *J*=11.0, 5.5 Hz), 2.47 - 2.59 (1 H, m), 2.04 - 2.18 (1 H, m), 1.53 - 2.01 (5 H, m), 1.29 - 1.49 (1 H, m), 0.63 (1 H, ninguno). EM (IEP) m/z: 515.5 (M+H)+. HPLC analítica: TR= 4.17 min (Método B).

Ejemplo 144.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-9-oxo-6,8,16-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaen-

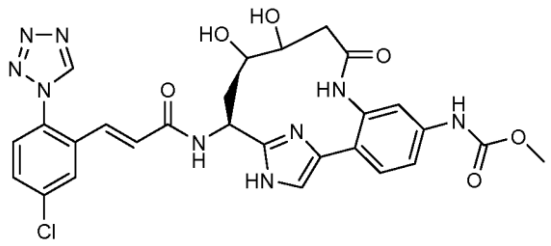
14-il)-acrilamida, sal 2 TFA



El Ejemplo 144 se preparó siguiendo los procedimientos descritos en la etapa 138A, sustituyendo 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-3-ilcarbamato de *terc*-butilo por 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-ilcarbamato de *terc*-butilo; seguido por las etapas 88D; 88E, sustituyendo ácido pentenoico por ácido but-3-enoico; 88G, sustituyendo 1.1 eq. de pTsOH por 2.2 eq. de pTsOH; 2G; 3C; y 1G. EM (IEP) m/z: 515.2(M+H)+.

Ejemplo 145.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11,12-dihidroxi-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA, Diastereómero C.

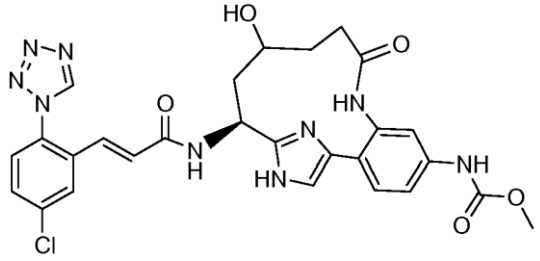


El Ejemplo 145 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por

137B; seguido por la etapa 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.69 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.43 - 7.50 (m, 2 H), 7.38 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.13 (d, *J*=15.4 Hz, 1 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.10 (dd, *J*=10.4, 6.6 Hz, 1 H), 3.91 - 3.97 (m, 1 H), 3.75 (s, 3 H), 3.01 (m, 1 H), 2.63 (dd, *J*=11.6, 3.3 Hz, 1 H), 2.42 - 2.58 (m, 2 H), 2.02 - 2.12 (m, 1 H). EM (IEP) m/z: 608.3 (M+H)+. HPLC analítica: TR= 4.21 min. (Método B).

Ejemplo 152.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-12-hidroxi-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA



152A. Éster metílico del ácido [(S)-11-hidroxi-5-metoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A una solución de 10E/10F (56 mg, 0.098 mmol) en THF (1 ml) se añadió complejo de borano y tetrahidrofurano (0.294 ml, 0.294 mmol) a 0°C gota a gota. Después de la adición, se retiró el baño

de agua y la reacción se calentó hasta temperatura ambiente. Después de 2 horas, la mezcla de reacción se volvió a enfriar hasta 0°C y se añadió solución acuosa de acetato sódico (0.653 ml, 1.959 mmol). Se añadió gota a gota peróxido de hidrógeno (0.300 ml, 2.94 mmol). Después de la adición, la reacción se calentó hasta temperatura ambiente y se agitó a temperatura ambiente durante 2 horas. La reacción se extrajo con EtOAc dos veces. La fase de EtOAc reunida se lavó con salmuera, se secó sobre Na_2SO_4, se separó el sólido por filtración y se concentró. La purificación por cromatografía en fase inversa dio 152A (3.8 mg, sólido amarillo pálido), 152B (3 mg, sólido amarillo pálido) y 152C (7.8 mg, sólido amarillo pálido).

152A: EM (IEP) m/z: 590.4 (M+H)+. HPLC analítica (Método B): TR = 6.09 min.

152B: EM (IEP) m/z: 590.4 (M+H)+. HPLC analítica (Método B): TR = 6.17 min.

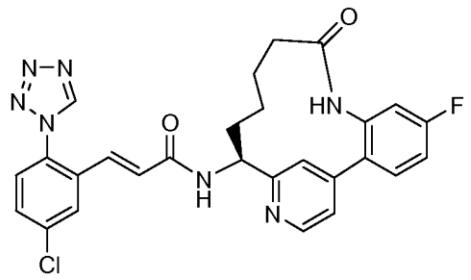
152C: EM (IEP) m/z: 590.4 (M+H)+. HPLC analítica (Método B): TR = 6.44 min.

152D. El Ejemplo 152 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 152A; seguido por la etapa 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.93 - 8.00 (m, 1 H), 7.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.46 - 7.52 (m, 1 H), 7.42 - 7.46 (m, 1 H), 7.41 (s, 1 H), 7.18 (d, *J*=15.7 Hz, 1 H), 6.72 (d,

J=15.4 Hz, 1 H), 5.11 - 5.18 (m, 1 H), 3.75 (s, 3 H), 3.19 - 3.27 (m, 1 H), 2.42 - 2.49 (m, 2 H), 2.16 - 2.24 (m, 2 H), 1.86 - 1.95 (m, 1 H), 1.21 - 1.34 (m, 1 H). EM (IEP) m/z: 592.2 (M+H)+. HPLC analítica: TR= 3.76 min (Método B).

Ejemplo 153.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-*N*-((S)-5-fluoro-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-il)-acrilamida, sal 1 TFA



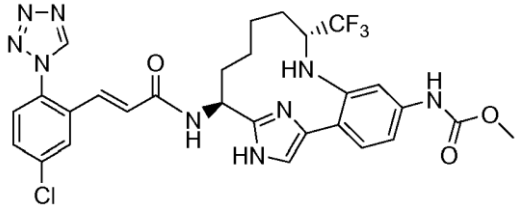
153A. Éster *terc*-butílico del ácido ((E)-(S)-5-fluoro-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-il)-carbámico: Este compuesto se preparó a partir de 132B escindiendo la *t*-butilsulfinamida y por introducción de un grupo protector Boc, acoplamiento con ácido 3-butenoico y posterior RCM del dieno resultante, siguiendo los procedimientos descritos para los compuestos 88D, 88E (reemplazando ácido pentenoico por ácido but-3-enoico) y 88G. EM (IEP) m/z: 398.3(M+H)+.

153B. El Ejemplo 153 se preparó a partir de 153A por hidrogenación, desprotección de Boc y acoplamiento al Intermediario 1 siguiendo los procedimientos descritos para

los compuestos 2G, 3C y 1G. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.85 (1 H, s) 9.84 (1 H, s) 8.74 (1 H, d, *J*=6.60 Hz) 8.71 (1 H, d, *J*=5.23 Hz) 7.93 (1 H, d, *J*=2.20 Hz) 7.70 - 7.77 (2 H, m) 7.62 - 7.68 (2 H, m) 7.53 (1 H, d, *J*=4.40 Hz) 7.31 (1 H, td, *J*=8.46, 2.61 Hz) 7.11 (1 H, dd, *J*=9.77, 2.61 Hz) 6.93 - 6.99 (1 H, m) 6.81 - 6.86 (1 H, m) 4.99 - 5.06 (1 H, m) 2.35 (1 H, dd, *J*=10.32, 6.74 Hz) 1.85 - 1.93 (1 H, m) 1.73 - 1.81 (1 H, m) 1.61 - 1.73 (2 H, m) 1.48 (1 H, ddd, *J*=11.14, 6.74, 4.40 Hz) 1.21 (1 H, dd, *J*=6.33, 4.40 Hz) 0.51 - 0.62 (1 H, m). EM (IEP) m/z: 532.2 (M+H)+. HPLC analítica: TR= 5.90 min.

Ejemplo 154.

Éster metílico del ácido {(9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



154A. Éster metílico del ácido {4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-3-[2,2,2-trifluoro-et-(E)-ilidenamino]-fenil}-carbámico: A una solución de 10C (0.805 g, 1.514 mmol) en DCM (30.3 ml) se añadió 1-etoxi-2,2,2-trifluoroetanol (0.436 g, 3.03 mmol), tamices moleculares de

5 Å (5 g, 1.514 mmol) y ácido p-toluenosulfónico monohidratado (0.014 g, 0.076 mmol). La reacción se calentó hasta 40°C. Después de 2 días se añadió más 1-etoxi-2,2,2-trifluoroetanol (0.436 g, 3.03 mmol). Después de 12 días, la reacción se filtró a través de un filtro GMF de 0.45 micrómetros y la torta del filtro se aclaró con DCM. El filtrado se concentró y luego se añadió tolueno (3 ml) y luego se concentró. Este proceso se repitió una vez más proporcionando 154A (0.926 g, 100 % de rendimiento) como un aceite marrón y como una mezcla de diastereómeros. EM (IEP) m/z: 612.6 (M+H)+. Este se usó en la etapa siguiente sin purificación posterior.

154B. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-3-(1-trifluorometil-but-3-enilamino)-fenil]-carbámico: A una solución enfriada (0°C) de 154A (0.926 g, 1.514 mmol) en THF (30 ml) se añadió bromuro de alil magnesio (1M en Et_2O, 5.00 ml, 5.00 mmol). Después de 30 min, la reacción se dejó calentar hasta ta. Después de 1.5 h, la reacción se inactivó con NH_4Cl saturado. A continuación, la mezcla de reacción se diluyó con EtOAc, se lavó con agua, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por cromatografía en fase normal proporcionó 154B (0.49 g, 49.5 % de rendimiento) como un sólido amarillo y como una mezcla de diastereómeros. EM (IEP)

m/z: 654.5 (M+H)+.

154C. Éster metílico del ácido [(9R,14S)-14-*terc*-butoxicarbonilamino-9-trifluorometil-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il]-carbámico, sal 2 TFA (Diastereómero A) y 154D. Éster metílico del ácido [(9S,14S)-14-*terc*-butoxicarbonilamino-9-trifluorometil-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il]-carbámico, sal 2 TFA (Diastereómero B). Los productos de metátesis de cierre del anillo (una mezcla de isómeros E- y Z-alqueno así como diastereómeros en la alfa amina) se prepararon siguiendo los procedimientos descritos en la etapa 2E/2F, sustituyendo 2D por 154B. A una solución del producto de metátesis de cierre del anillo (1.01 g, 1.614 mmol) en EtOAc (32.3 ml) se añadió TFA (0.249 ml, 3.23 mmol) y paladio al 10 % sobre carbón (0.172 g, 0.161 mmol). El recipiente de reacción se presurizó con hidrógeno hasta 3.791 x 105 Pa. Después de 3 días, la reacción se interrumpió y la reacción se filtró a través de un filtro GMF de 0.45 µm y el catalizador de aclaró con MeOH. El filtrado se concentró. La purificación por cromatografía de fase inversa proporcionó 0.074 g (5.4 %) de 154 C (diastereómero A) y 0.410 g (30 %) de 154 D (diastereómero B). EM (IEP) m/z: 628.4 (M+H)+. De forma alternativa, se puede reemplazar el catalizador de

paladio sobre carbón por óxido de platino.

154E. Éster metílico del ácido ((9R,14S)-14-amino-9-trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico. Se calentó hasta 75°C un vial de alta presión, con un tapón a rosca revestido de teflón, que contenía una mezcla ligeramente turbia de 154D (diastereómero B) (0.0590 g, 0.069 mmol) y ácido 2-amino-3-mercaptopropanoico (0.042 g, 0.345 mmol) en HCl 4M en dioxano (1.551 ml, 6.20 mmol). Se formó un precipitado blanco con el paso del tiempo. Después de 1.5 h, la reacción se interrumpió y se concentró dando un sólido. El sólido se disolvió en $NaHCO_3$ saturado y luego se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron dando 154E como una espuma amarillo pálido. EM (IEP) m/z: 398.1 (M+H)+.

154F. El Ejemplo 154 se preparó siguiendo el procedimiento descrito en 15D, sustituyendo 15C por 154 E. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.94 (d, J=2.2 Hz, 1 H), 7.66 (dd, J=8.8, 2.2 Hz, 1 H), 7.57 (d, J=8.2 Hz, 1 H), 7.50 (s, 1 H), 7.34 (s, 1 H), 7.27 (d, J=8.2 Hz, 1 H), 7.06 - 7.14 (m, 2 H), 6.76 (d, J=15.4 Hz, 1 H), 5.13 (t, J=7.1 Hz, 1 H), 3.73 (s, 3 H), 2.93 - 3.01 (m, 1 H), 2.34 - 2.43 (m, 1 H), 1.95 - 2.04 (m, 1 H), 1.62 - 1.75 (m, 2 H), 1.48 - 1.59 (m, 2 H), 1.35 - 1.46 (m, 1 H), 0.48 - 0.59 (m, 1 H). ^{19}F NMR (470 MHz, CD_3OD) δ ppm -75.22. EM (IEP) m/z: 630.4 (M+H)+.

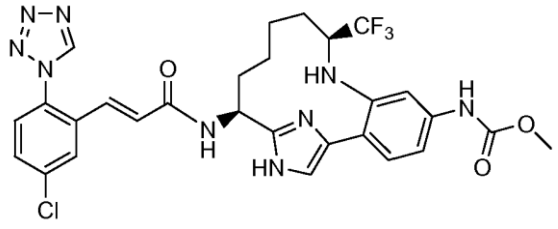
HPLC analítica: TR= 6.13 min.

Como alternativa, se puede condensar 10C con 1-etoxi-2,2,2-trifluoroetanol dando 154G en lugar de la imina (154A) de acuerdo con el siguiente procedimiento. El Compuesto 154G puede sustituir a 154A en la etapa 154B.

154G. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-3-(1-etoxi-2,2,2-trifluoro-etilamino)-fenil]-carbámico: A una solución amarillo yema transparente de 10C (2.0 g, 3.76 mmol) en EtOH (7.52 ml) se añadió 1-etoxi-2,2,2-trifluoroetanol (1.734 ml, 15.05 mmol). La reacción se calentó a 120°C en un microondas durante 3 h. La reacción se enfrió hasta TA y luego se concentró la reacción. La purificación por cromatografía en fase normal dio 1.75 g (66%) de 154A, como una espuma naranja y como una mezcla de diastereómeros. EM (IEP) *m/z*: 658.4 (M+H)+.

Ejemplo 155.

Éster metílico del ácido {(9S,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



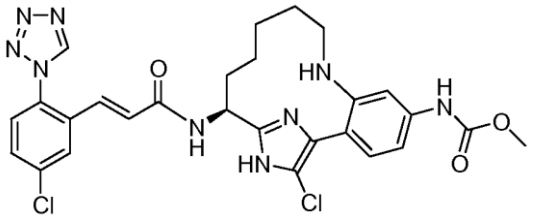
155A. Éster metílico del ácido (9S,14S)-14-amino-9-

trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico. El Compuesto 155A se preparó siguiendo el procedimiento descrito en 154E, sustituyendo 154D por 154 C (diastereómero A). EM (IEP) m/z: 398.1 (M+H)+.

155B. El Ejemplo 155 se preparó siguiendo el procedimiento descrito en 15D, sustituyendo 15C por 155A. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.54 (s, 1 H), 7.39 (s, 1 H), 7.31 (d, *J*=8.2 Hz, 1 H), 7.09 - 7.18 (m, 2 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.24 (dd, *J*=11.0, 7.1 Hz, 1 H), 3.75 (s, 3 H), 2.90 - 2.99 (m, 1 H), 2.24 - 2.37 (m, 1 H), 1.97 - 2.08 (m, 1 H), 1.67 - 1.84 (m, 2 H), 1.43 - 1.63 (m, 3 H), 0.30 - 0.42 (m, 1 H). ^{19}F NMR (470 MHz, CD_3OD) δ ppm -74.66. EM (IEP) m/z: 630.4 (M+H)+. HPLC analítica: TR= 6.29 min.

Ejemplo 156.

Éster metílico del ácido {(S)-17-cloro-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA

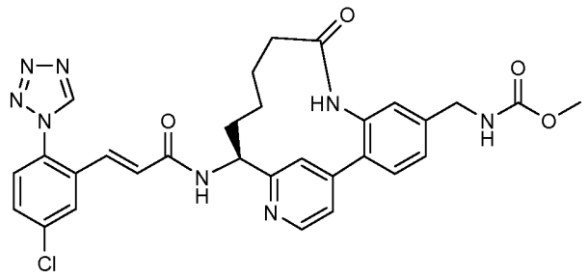


El Ejemplo 156 se sintetizó de acuerdo con el

procedimiento descrito en Ejemplo 7, sustituyendo el Ejemplo 6 por el Ejemplo 11. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 8.02 (d, *J*=2.5 Hz, 1 H), 7.91 (s ancho, 1 H), 7.84 (d, *J*=8.8 Hz, 1 H), 7.69 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.61 (d, *J*=8.5 Hz, 1 H), 7.32 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.26 (d, *J*=15.7 Hz, 1 H), 6.81 (d, *J*=15.7 Hz, 1 H), 5.20 (dd, *J*=11.0, 6.3 Hz, 1 H), 3.72 (s, 3 H), 3.18 - 3.25 (m, 1 H), 2.92 - 3.00 (m, 1 H), 1.97 - 2.19 (m, 3 H), 1.82 - 1.90 (m, 1 H), 1.62 - 1.72 (m, 2 H), 1.33 - 1.43 (m, 1 H), 0.76 - 0.87 (m, 1 H). EM (IEP) m/z: 596.5 (M+H)+. HPLC analítica: TR= 6.01 min.

Ejemplo 159.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-ilmetil}-carbámico



159A. 3-Amino-4-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-benzonitrilo: Este compuesto se preparó siguiendo los procedimientos descritos para el intermediario 12, sustituyendo 2-bromo-5-nitroanilina por 3-amino-4-bromobenzonitrilo. EM (IEP) m/z: 163.1(M+H)+.

159B. Éster *terc*-butílico del ácido ((E)-(S)-5-ciano-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-il)-carbámico: Este compuesto se preparó a partir de 159A en cinco etapas mediante acoplamiento de Suzuki a 88B, escisión de la *t*-butilsulfinamida e introducción de un grupo protector Boc, reducción del nitro a la anilina correspondiente, acoplamiento con ácido 3-butenoico y posterior RCM del dieno resultante, siguiendo los procedimientos descritos para los compuestos 88C, 88D, 88E (sustituyendo ácido 3-butenoico por ácido 4-pentenoico) y 88G. EM (IEP) m/z: 405.2(M+H)+.

159C. Éster *terc*-butílico del ácido ((S)-5-aminometil-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-il)-carbámico: Se disolvió 155B (0.023 g, 0.057 mmol) en MeOH (2.0 ml) y se transfirió a un matraz que contenía una suspensión de Pd al 10 %/C en 1-2 ml de MeOH bajo argón. La mezcla se vació y se volvió a llenar 3 x con argón, luego se agitó bajo 1013300 Pa de hidrógeno durante 3 días. El catalizador se separó por filtración a través de CELITE® y se lavó con MeOH; el filtrado se condensó porporcionando 155C (0.023 g, 99 %), EM (IEP) m/z 411.3(M+H)+.

159D. Éster *terc*-butílico del ácido [(S)-5-(metoxicarbonilamino-metil)-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-

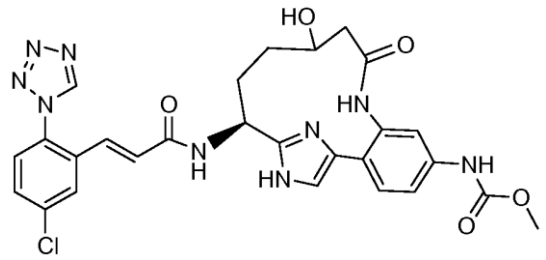
il]-carbámico: Se disolvió 155C (0.023 g, 0.056 mmol) en CH_2Cl_2 (0.5 ml) y se añadió TEA (0.016 ml, 0.112 mmol). Esta mezcla se agitó bajo Ar en un baño de hielo/agua salada. Se añadió gota a gota cloroformiato de metilo (4.56 µl, 0.059 mmol) a la mezcla de reacción. La reacción se dejó llegar gradualmente a la temperatura ambiente durante 2 horas cuando se fundió el baño de hielo. La reacción se inactivó con agua y se diluyó con EtOAc. La fase orgánica se lavó entonces con $NaHCO_3$ saturado y salmuera, se secó rápidamente sobre $MgSO_4$ anhidro, se filtró y se evaporó proporcionando 159D como un vidrio amarillo claro (0.017 g). EM (IEP) m/z: 469.3(M+H)+.

159E. El Ejemplo 159 se preparó a partir de 159D por desprotección de Boc y acoplamiento con el Intermediario 1, siguiendo los procedimientos descritos para las etapas 3C y 1G. ^{1}H NMR (500 MHz, MeOD) δ ppm 9.48 (1 H, s) 8.71 (1 H, d, *J*=5.78 Hz) 7.97 (2 H, d, *J*=1.93 Hz) 7.77 (1 H, dd, *J*=5.64, 1.51 Hz) 7.62 - 7.69 (2 H, m) 7.57 (1 H, d, *J*=8.53 Hz) 7.42 (1 H, d, *J*=7.98 Hz) 7.23 (1 H, s) 7.10 (1 H, d, *J*=15.68 Hz) 6.79 (1 H, d, *J*=15.68 Hz) 5.11 (1 H, dd, *J*=10.87, 5.64 Hz) 4.36 (2 H, s) 3.67 (3 H, s) 2.46 - 2.53 (1 H, m) 2.07 - 2.18 (1 H, m) 1.83 - 2.00 (2 H, m) 1.70 - 1.81 (1 H, m) 1.60 - 1.70 (1 H, m) 1.35 - 1.44 (1 H, m) 0.70 - 0.81 (1 H, m). EM (IEP) m/z: 601.3

(M+H)+. HPLC analítica: TR= 5.54min.

Ejemplo 160.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-hidroxi-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 1 TFA

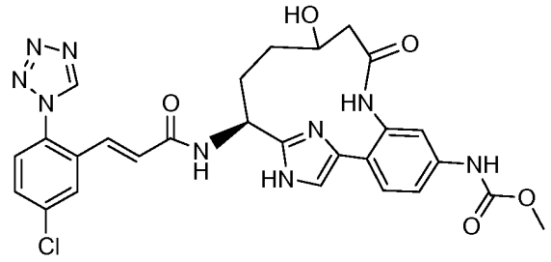


El Ejemplo 160 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 152B; seguido por la etapa 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.49 (s, 1 H), 7.91 - 8.01 (m, 1 H), 7.65 - 7.72 (m, 1 H), 7.55 - 7.63 (m, 2 H), 7.43 - 7.52 (m, 2 H), 7.34 - 7.43 (m, 1 H), 7.15 (d, *J*=15.7 Hz, 1 H), 6.73 (d, *J*=15.7 Hz, 1 H), 5.08 - 5.19 (m, 1 H), 3.85 - 3.95 (m, 1 H), 3.76 (s, 3 H), 2.68 - 2.76 (m, 1 H), 2.40 - 2.54 (m, 1 H), 2.12 - 2.23 (m, 1 H), 1.93 - 2.06 (m, 1 H), 1.39 - 1.51 (m, 1 H), 1.21 - 1.34 (m, 1 H). EM (IEP) m/z: 592.2 (M+H)+. HPLC analítica: TR= 3.86 min (Método B).

Ejemplo 161.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-hidroxi-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-

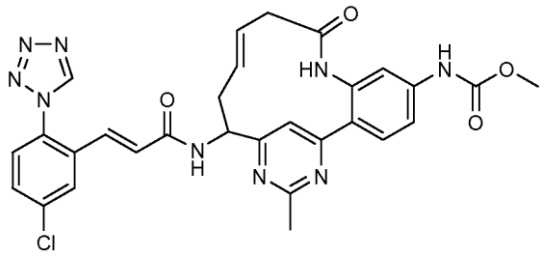
il}-carbámico, sal 1 TFA



El Ejemplo 161 se preparó siguiendo los procedimientos descritos en la etapa 1F, sustituyendo 1D por 152C; seguido por la etapa 1G. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.52 (s, 1 H), 7.92 - 8.04 (m, 1 H), 7.64 - 7.72 (m, 1 H), 7.56 - 7.63 (m, 2 H), 7.50 - 7.56 (m, 1 H), 7.41 - 7.49 (m, 2 H), 7.17 (d, *J*=15.4 Hz, 1 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.26 - 5.38 (m, 1 H), 3.76 (s, 3 H), 3.63 - 3.72 (m, 1 H), 2.51 - 2.64 (m, 1 H), 2.30 - 2.44 (m, 2 H), 1.95 - 2.05 (m, 1 H), 1.65 - 1.78 (m, 1 H), 1.30 - 1.47 (m, 1 H). EM (IEP) m/z: 592.2 (M+H)+. HPLC analítica: TR= 3.69 min (Método B).

Ejemplo 167.

Éster metílico del ácido {(E)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-metil-9-oxo-8,16,18-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,11,15,17-heptaen-5-il}-carbámico



167A. Éster etílico del ácido (S)-4-*terc*-

butoxicarbonilamino-3-oxo-hept-6-enoico. A una solución de ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico (5.0g, 23.23 mmol) en THF (40 ml) se añadió carbonildiimida (4.52 g, 27.9 mmol) a ta. La reacción se agitó bajo argón a ta durante 5 h. A otro matraz que contenía una solución de ácido 3-etoxi-3-oxopropanoico (4.60 g, 34.8 mmol) en THF (40 ml) se añadió gota a gota cloruro de isopropilmagnesio (34.8 ml, 69.7 mmol) a 0°C. Después de la adición, la reacción se agitó a 0°C durante 30 min, a ta durante 30 min y luego a 48°C durante 30 min. La reacción se enfrió hasta ta y se transfirió a la solución enfriada (0°C) preparada en el primer matraz dando una suspensión lechosa. La reacción se dejó agitar a ta durante la noche. La mezcla de reacción se vertió lentamente en HCl 1.0 N (200 ml) a 0°C y se generó gas. La mezcla de reacción se extrajo con EtOAc, se lavó con NaHCO3 saturado y salmuera. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró dando un aceite incoloro transparente. El producto bruto se purificó por cromatografía en fase normal dando 167A (5.36 g, 81 % de rendimiento) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.61 - 5.78 (1 H, m), 5.17 (1 H, d, *J*=3.26 Hz), 5.13 (2 H, d, *J*=2.26 Hz), 4.32 - 4.50 (1 H, m), 4.20 (2 H, q, *J*=7.28 Hz), 3.47 - 3.64 (2 H, m), 2.52 - 2.70 (1 H, m), 2.35 - 2.52 (1 H, m), 1.44 (9 H, s), 1.28 (3 H, t, *J*=7.15 Hz). EM (IEP) m/z: 308.1 (M+Na)+.

167B. Éster *terc*-butílico del ácido [1-(6-hidroxi-2-metil-pirimidin-4-il)-but-3-enil]-carbámico. A una solución de sal HCl de acetimidamida (0.928 g, 9.81 mmol) en MeOH (30 ml) se añadieron solución de metóxido sódico (25 % p/p, 4.49 ml, 19.63 mmol) y una solución de 167A(2.0g, 7.01 mmol) disuelta en MeOH (15 ml) a ta. La reacción se agitó bajo argón a ta durante 3 h. La reacción se neutralizó con HCl 1.0 N. Se eliminó la mayor parte del solvente. La mezcla de reacción se extrajo con cloroformo. La fase orgánica se lavó con salmuera y se secó sobre sulfato sódico, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal dando 167B (1.82 g, 93 % de rendimiento) como un sólido blanco. EM (IEP) m/z: 280.1 (M+H)+.

167C. Éster *terc*-butílico del ácido [1-(6-cloro-2-metil-pirimidin-4-il)-but-3-enil]-carbámico. A un matraz que contenía 167B (1.82 g, 6.52 mmol) se añadió POCl3 (12.15 ml, 130 mmol) a ta. La suspensión se agitó bajo argón a 50°C y la suspensión viró a una solución marrón claro transparente. Después de 2 h, se eliminó el exceso de $POCl_3$ a presión reducida y el residuo se evaporó conjuntamente dos veces con tolueno dando un alquitrán oscuro. Este intermediario se disolvió en acetonitrilo (30 ml), al cual se añadieron Na_2CO_3 (3.46 g, 32.6 mmol) y BOC_2O (1.817 ml, 7.82 mmol) a 0°C. La reacción se agitó bajo argón a 0°C durante 1.5 h. La mezcla de reacción se diluyó con EtOAc, se lavó con H_2O y salmuera.

La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal dando 167C (0.65 g, 34 % de rendimiento) como un sólido amarillo claro. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.30 (1 H, s), 5.70 - 5.88 (1 H, m, *J*=17.13, 10.16, 6.93, 6.93 Hz), 5.02 - 5.15 (2 H, m), 4.63 (1 H, dd, *J*=8.28, 5.27 Hz), 2.64 (3 H, s), 2.54 - 2.62 (1 H, m), 2.36 - 2.49 (1 H, m), 1.43 (9 H, s). EM (IEP) m/z: 298.1 (M+H)+.

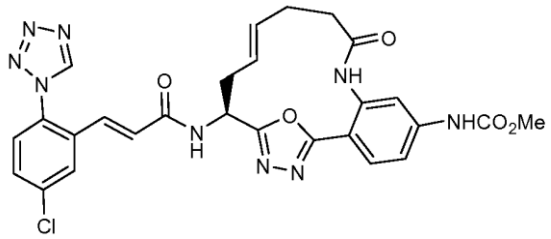
167D. Éster metílico del ácido {3-but-3-enoilamino-4-[6-(1-*terc*-butoxicarbonilamino-but-3-enil)-2-metil-pirimidin-4-il]-fenil}-carbámico: Este compuesto se preparó siguiendo los procedimientos descritos en la etapa 88C, sustituyendo 88B por 167C; seguido por las etapas 88E; y 88F. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23 (1 H, s), 7.63 - 7.72 (2 H, m), 7.40 (1 H, s), 5.92 - 6.07 (1 H, m, *J*=17.07, 10.10, 7.00, 7.00 Hz), 5.61 - 5.72 (1 H, m), 5.19 - 5.30 (2 H, m), 5.08 (2 H, d, *J*=12.05 Hz), 4.62 - 4.78 (1 H, m), 3.75 (3 H, s), 3.18 (2 H, d, *J*=7.03 Hz), 2.73 (3 H, s), 2.45 - 2.64 (2 H, m), 1.40 (9 H, s ancho). EM (IEP) m/z: 496.1 (M+H)+.

167E. Éster *terc*-butílico del ácido ((E)-5-metoxicarbonilamino-17-metil-9-oxo-8,16,18-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,11,15,17-heptaen-14-il)-carbámico. Una solución de 167D (25 mg, 0.050 mmol) en DCM (100 ml) se purgó con argón y luego se añadió HCl 4 M en dioxano (0.1 ml, 0.400 mmol) a ta. La solución se calentó

hasta reflujo y luego se añadió catalizador de Grubbs (II) (17.13 mg, 0.020 mmol). La reacción se agitó bajo argón a reflujo durante 4 h. La reacción se enfrió hasta ta y se eliminó el solvente. La purificación por cromatografía en fase inversa dio 167E (5.1 mg, 22 % de rendimiento) como un sólido marrón oscuro. EM (IEP) m/z: 468.0 (M+H)+.

167F. El Ejemplo 167 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 167E; seguido por la etapa 1G. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.55 (1 H, s), 9.50 (1 H, s), 8.01 (1 H, d, *J*=2.26 Hz), 7.66 (1 H, dd, *J*=8.53, 2.26 Hz), 7.59 - 7.63 (2 H, m), 7.56 (1 H, d, *J*=8.53 Hz), 7.48 (1 H, dd, *J*=8.66, 2.13 Hz), 7.11 (1 H, d, *J*=15.56 Hz), 6.96 (1 H, s), 6.89 (1 H, d, *J*=15.56 Hz), 5.74 - 5.85 (1 H, m), 4.96 - 5.03 (2 H, m), 3.76 (3 H, s), 3.00 (1 H, dd, *J*=11.80, 9.29 Hz), 2.75 - 2.85 (2 H, m), 2.74 (3 H, s), 2.21 - 2.33 (1 H, m). EM (IEP) m/z: 600.1 (M+H)+. HPLC analítica: TR= 6.383 min.

Ejemplo 168.



168A. 4-Amino-2-nitrobenzoato de metilo: Se enfrió una suspensión de ácido 4-amino-2-nitrobenzoico (1.0 g, 5.49 mmol) en MeOH (25 ml) en un baño de hielo/agua salada con

agitación bajo nitrógeno mientras se añadió lentamente $SOCl_2$ (0.601 ml, 8.24 mmol) gota a gota. La solución ámbar resultante se calentó a reflujo durante la noche. La reacción se enfrió hasta temperatura ambiente y se evaporó para eliminar el MeOH. El residuo se repartió entre EtOAc y solución acuosa saturada de $NaHCO_3$ y se volvió a extraer la fase acuosa 2 veces con EtOAc. Los extractos orgánicos reunidos se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro, se filtraron y se evaporaron dando el éster como un sólido amarillo-naranja (0.95 g, 88 %). ^{1}H NMR (500 MHz, DMSO-d_6) d ppm 7.61 (1 H, d, *J*=8.53 Hz) 6.83 (1 H, d, *J*=2.20 Hz) 6.74 (1 H, dd, *J*=8.67, 2.34 Hz) 6.54 (2 H, s) 3.72 (3 H, s).

168B. 4-(Hidrazinacarbonil)-3-nitrofenilcarbamato de metilo: Se suspendió 168A (0.94 g, 4.79 mmol) en DCM (25 ml), se añadió piridina (0.775 ml, 9.58 mmol) y la mezcla se enfrió en un baño de hielo con agitación bajo nitrógeno. Se añadió entonces cloroformiato de metilo (0.390 ml, 5.03 mmol) gota a gota a la mezcla fría. Se continuó agitando durante ~ 30 min en el baño de hielo y luego a temperatura ambiente durante 4 h. La reacción se diluyó con más DCM, se lavó dos veces con HCl 1M, agua y salmuera, luego se secó sobre Na_2SO_4 anhidro, se filtró y se evaporó hasta un sólido naranja claro. El sólido obtenido (1.2 g, 4.72 mmol) se suspendió en etanol (24 ml) y se añadió hidrazina (2.4 ml, 76 mmol). La mezcla se calentó a reflujo bajo nitrógeno con

agitación durante la noche en un baño de aceite a 80°C, luego se enfrió hasta temperatura ambiente y se filtro. Se lavó el sólido amarillo pálido con EtOH y Et2O luego se secó al aire. El filtrado se evaporó y el residuo se suspendió en EtOAc/H_2O. El sólido que se separó se recogió por filtración, se lavó con EtOAc y Et_2O, se secó y se combinó con el sólido inicial. La hidrazina bruta se suspendió en MeOH y se sometió a ultrasonidos durante 10-15, el sólido insoluble se separó por filtración y se lavó con MeOH. La evaporación del filtrado dio el producto, 168B, como un sólido amarillo claro. (0.363 g, 30.2 %). ^{1}H NMR (500 MHz, DMSO-d_6) d ppm 10.28 (1 H, s) 9.60 - 9.71 (1 H, m) 8.13 (1 H, d, *J*=1.93 Hz) 7.71 (1 H, dd, *J*=8.39, 2.06 Hz) 7.51 (1 H, d, *J*=8.53 Hz) 4.45 (2 H, d, *J*=4.13 Hz) 3.72 (3 H, s).

168C. Éster metílico del ácido {4-[5-((S)-1-*terc*-butoxicarbonilamino-but-3-etnil)-1,3,4-oxadiazol-2-il]-3-nitro-fenil}-carbámico: Se disolvieron 168B (0.3 g, 0.393 mmol) y ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico (0.085 g, 0.393 mmol) en DMF (2 ml) en un matraz de fondo redondo de 15 ml y se añadió TEA (0.274 ml, 1.967 mmol). La mezcla se agitó bajo nitrógeno a temperatura ambiente mientras se añadía gota a gota anhídrido del ácido propano fosfónico (T3P), 50 % en EtOAc (0.293 ml, 0.983 mmol). El matraz se conectó a un condensador de reflujo y la mezcla resultante se agitó en un baño de aceite a 80°C durante 5 h.

La mezcla de reacción se vertió en agua helada y se extrajo tres veces con EtOAc. Los extractos reunidos se lavaron con $NaHCO_3$ acuoso saturado, agua y salmuera, se secaron sobre Na_2SO_4 anhidro, se filtraron y se evaporaron proporcionando éster metílico del ácido {4-[N'-((S)-2-*terc*-butoxicarbonilamino-pent-4-enoil)-hidrazinocarbonil]-3-nitro-fenil}-carbámico, (0.46 g, 86%) como un sólido amarillo claro que se usó sin purifiación posterior. El sólido (0.46 g, 1.019 mmol) se disolvió en THF anhidro (20 ml) bajo argón y la solución se transfirió a un matraz de presión de 75 ml. Se añadió reactivo de Burgess (1.33 g, 5.58 mmol), se selló el matraz con un tapón de alivio de presión y luego se calentó en un baño de aceite a 75°C durante 2 horas detrás de una pantalla frente a ondas expansivas y se dejó seguidamente en reposo a temperatura ambiente durante la noche. La mezcla de reacción se evaporó en un evaporador rotatorio. El residuo se purificó por cromatografía en fase ormal dando 168C como una espuma amarillo claro (0.315 g, 71.3 %). EM (IEP) m/z: 434.3 (M+H)+ 378.3 (M+H-tBu)+.

168D. Éster metílico del ácido {3-amino-4-[5-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1,3,4-oxadiazol-2-il]-fenil}-carbámico: Se disolvió 168C (0.315 g, 0.727 mmol) en etanol (4.5 ml) y se añadió polvo de hierro (0.812 g, 14.54 mmol). La mezcla se agitó a temperatura ambiente durante 1-2 min, luego se añadió HCl 0.1 M (3.63 ml, 0.363 mmol) y la

reacción se calentó con agitación bajo nitrógeno en un baño de aceite a 50°C durante 1.5 h. La reacción se enfrió hasta temperatura ambiente y se filtró a través de una almohadilla de CELITE® y se lavaron los sólidos con agua, se descartaron el EtOH y EtOAc. El filtrado se evaporó y la fase acuosa que quedó se diluyó con $NaHCO_3$ hasta pH 8, luego se extrajo tres veces con EtOAc. Los extractos reunidos se lavaron con solución saturada de $NaHCO_3$ y salmuera, se secaron sobre Na2SO4 anhidro y se filtraron. La evaporación de los solventes proporcionó 168D como un sólido cristalino. (0.257 g, 88 %). EM (IEP) m/z: 404.3 (M+H)+ 348.3 (M+H-tBu)+.

168E. Éster metílico del ácido [5-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1,3,4-oxadiazol-2-il]-3-pent-4-enoilamino-fenil}-carbámico: Se disolvió 168D (0.275 g, 0.682 mmol) en DCM (3.5 ml) y se añadió piridina (0.110 ml, 1.363 mmol). La solución se enfrió en un baño de hielo/agua salada hasta ~ 0°C, luego se añadió gota a gota cloruro de 4-pentenoilo (0.075 ml, 0.682 mmol). La mezcla resultante se agitó a 0-5°C durante 1 h y luego se dejó calentar hasta temperatura ambiente. Después de otras 2 horas a temperatura ambiente, la reacción se diluyó con EtOAc y se lavó con agua, HCl 1M, $NaHCO_3$ saturado y salmuera, luego se secó sobre Na2SO4 anhidro, se filtró y se evaporó. El producto bruto se purificó por cromatografía en fase normal proporcionando 168E como un sólido blanco (4 (0.276 g, 83 %). EM (IEP) m/z: 486.3

(M+H)+ 430.3 (M+H-tBu)+

168F. Éster metílico del ácido ((E)-(S)-15-*terc*-butoxicarbonilamino-9-oxo-19-oxa-8,17,18-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16-hexaen-5-il)-carbámico: Se disolvió 168E (0.15 g, 0.309 mmol) en DCE (500 ml) en un matraz de tres bocas de 1 litro secado a la llama provisto de septum, condensador de reflujo y entrada de argón. La solución se desgasificó burbujeando Ar a través de la solución durante 30 min. Se pesó catalizador de Grubbs (II) (0.094 g, 0.111 mmol) bajo argón y se disolvió en 5 ml de DCE desgasificado y la solución rojo oscuro se añadió gota a gota durante 5-10 min a la solución anterior. La mezcla resultante se calentó en un baño de aceite a 75°C durante ~2h. La reacción se enfrió hasta temperatura ambiente y el solvente se eliminó en un evaporador rotatorio. El residuo se volvió a suspender en DCM y se añadieron 0.375 g de tris(hidroximetil)fosfina y 0.78 ml de TEA. La mezcla se agitó durante 10 min, luego se añadió agua y se prolongó la agitación vigorosa durante 15 minutos. Las fases se separaron y la fase orgánica se lavó con salmuera y se secó sobre Na_2SO_4 anhidro. La mezcla de producto bruto se purificó por cromatografía sobre gel de sílice proporcionando 168F, el isómero trans, como producto mayoritario (27 mg, 19.10 %). EM (IEP) m/z: 458.3 (M+H)+ 402.1 (M+H-tBu)+.

168G: El Ejemplo 168 se preparó a partir de 168F por

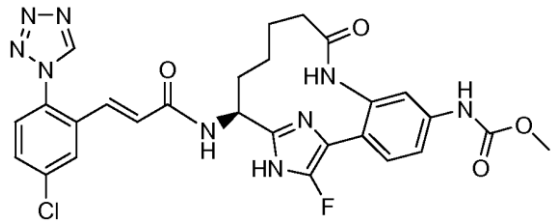
eliminación del grupo protector Boc y acoplamiento con el Intermediario 1, siguiendo los procedimientos descritos para los compuestos 3C y 1G. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.04 (1 H, s) 9.91 (1 H, s) 9.84 (1 H, s) 9.04 (1 H, d, *J*=7.33 Hz) 7.96 (1 H, d, *J*=1.77 Hz) 7.64 - 7.81 (3 H, m) 7.52 (1 H, s) 7.41 (1 H, dd, *J*=8.46, 1.64 Hz) 6.91 (1 H, d, *J*=16.00 Hz) 6.81 (1 H, d, *J*=16.00 Hz) 5.43 - 5.63 (2 H, m) 5.11 - 5.22 (1 H, m) 3.70 (3 H, s) 2.57 - 2.70 (1 H, m) 2.35 - 2.47 (3 H, m) 2.15 - 2.27 (2 H, m). EM (IEP) m/z: 590.2 (M+H)+. HPLC Analítica TR = 5.80 min.

A no ser que se indique de otro modo, los compuestos listados en las tablas siguientes se pueden preparar por un experto en la técnica de síntesis orgánica usando los procedimientos descritos en los Ejemplos 1-168.

Los Ejemplos I-1 a I-17 (Tabla I-1) se prepararon acoplando 10H con derivados ácido carboxílico sustituidos de forma apropiada (R-CO_2H) usando condiciones de acoplamiento descritas en la etapa 15D. En el caso de los Ejemplos I-4, I-12, y I-15, se requirió una etapa adicional de desprotección Boc como se describe en la etapa 3C. El Ejemplo I-18 se preparó acoplando 10H con un derivado ácido carboxílico sustituido de forma apropiada (R-CO_2H) usando condiciones de acoplamiento descritas en la etapa 15D seguido por cloración como se describe en el Ejemplo 7.

Ejemplo I-20.

Éster terc-butílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-fluoro-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal del ácido trifluoracético



I-20A. Éster metílico del ácido ((S)-14-*terc*-butoxicarbonilamino-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico: A una solución marrón de 10H (74.1 mg, 0.178 mmol) en THF (4 ml) y agua (2 ml) se añadió carbonato potásico (98 mg, 0.712 mmol), seguido por dicarbonato de di-*terc*-butilo (0.062 ml, 0.267 mmol). La reacción se agitó a ta durante 12h. A la solución se añadió NH_4Cl acuoso (10 ml) y 100 ul de NH4OH sat. para inactivar la reacción. La mezcla de reacción se extrajo entonces con EtOAc (30 ml x 2). La solución orgánica se secó sobre $MgSO_4$ y se concentró a vacío, proporcionando una mezcla oleosa, que se purificó por cromatografía en columna en fase normal (EtOAc/Hex) proporcionando 40 mg (0.090 mmol, 50.7 % de rendimiento) de I-20A como aceite marrón claro. EM (IEP) *m/z*: 444.2 (M+1)+.

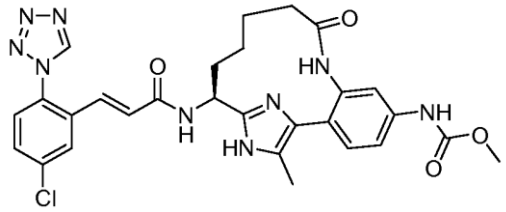
I-20B. Éster metílico del ácido ((S)-14-amino-17-fluoro-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico: A una solución de I-20A (40 mg, 0.090 mmol) en DMF (3 ml) se añadió carbonato sódico (12.43 mg, 0.117 mmol) y 1-fluoro-4-hidroxi-1,4-diazoniabiciclo[2,2,2]octanobis(tetrafluoroborato) (50% en alúmina) (62.9 mg, 0.090 mmol) en una porción, respectivamente y la solución resultante se agitó durante 2h a ta. La mezcla de reacción se diluyó con MeOH y se purificó por cromatografía en fase inversa que dio éster metílico del ácido ((S)-14-*terc*-butoxicarbonilamino-17-fluoro-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico y éster metílico del ácido ((S)-14-Amino-17-fluoro-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico. La mezcla se disolvió en HCl 4N dioxano (10 ml) y se agitó durante la noche a 50°C. La concentración de la solución proporcionó 11 mg de I-20B (34%).

I-20C. El Ejemplo I-20 se preparó siguiendo los procedimientos descritos en la etapa 1G, sustituyendo 1F por I-20B. ^{1}H NMR (400 MHz, CD_3OD) δ

ppm 9.40 - 9.59 (m, 1 H), 7.88 - 8.10 (m, 1 H), 7.62 - 7.85 (m, 1 H), 7.53 - 7.62 (m, 1 H), 7.31 - 7.52 (m, 2 H), 7.07 - 7.22 (m, 1 H), 6.71 - 6.94 (m, 1 H), 4.92 - 5.03 (m, 1 H), 2.36 - 2.50 (m, 1 H), 1.94 - 2.30 (m, 2 H), 1.75 (s ancho, 2 H), 1.45 (s ancho, 2 H), 0.99 (s ancho, 1 H). MS(ESI) *m/z*: 594.2 (M+H)+. HPLC analítica: TR = 6.79 min.

Ejemplo I-22.

N-[(14S)-14-[(2E)-3-[5-Cloro-2-(1H-1,2,3,4-tetrazol-1-il)fenil]prop-2-enamido]-17-metil-9-oxo-8,16,18-triazatriciclo[13.2.1.2.7]octadeca-1(17),2(7),3,5,15(18)-pentaen-5-il]carbamato de metilo, ácido trifluoracético.



I-22A. N-[(14S)-17-Bromo-5-[(metoxicarbonil)amino]-9-oxo-16-{[2-(trimetilsilil)etoxi]metil}-8,16,18-triazatriciclo[13.2.1.2.7]octadeca-1(17),2(7),3,5,15(18)-pentaen-14-il]carbamato de terc-butilo: A una solución enfriada (< 0°C) de 10G (0.53 g, 0.924 mmol) en $CHCl_3$ (10 ml) se añadió NBS (0.164 g, 0.924 mmol). La reacción se agitó bajo argón a 0°C durante 30 min. Se eliminó el solvente. El producto bruto se purificó por cromatografía en fase normal dando I-22A (0.58 g, 96%) como un sólido. EM (IEP) *m/z*: 652.2 (M+H)+ y 654.2 (M+2+H)+.

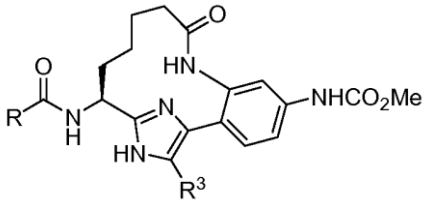
I-22B. N-[(14S)-5-[(metoxicarbonil)amino]-17-metil-

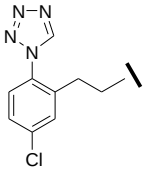
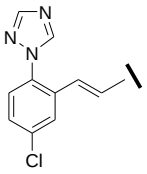
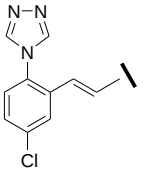
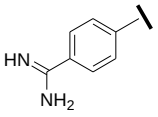
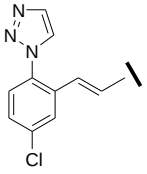
9-oxo-16-{[2-(trimetilsilil)etoxi]metil}-8,16,18-triazatriciclo[13.2.1.2.7]octadeca-1(17),2(7),3,5,15(18)-pentaen-14-il]carbamato de terc-butilo: A una solución de I-22A (0.53g, 0.812 mmol) en dioxano (15 ml) se añadieron Na_2CO_3 (0.430 g, 4.06 mmol), ácido metilborónico (0.097 g, 1.624 mmol) y bis(tri-*t*-butilfosfina) paladio(0) (0.042 g, 0.081 mmol) a TA. La mezcla de reacción se purgó con argón y luego la reacción se agitó bajo argón a 80°C durante 5 h. La reacción se enfrió hasta TA. La mezcla de reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ sat. y salmuera. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró. Con el fin de eliminar el subproducto de des-Br para una mejor purificación se convirtió éste de nuevo en el material de partida de bromoimidazol siguiendo el procedimiento descrito en I-22A. El producto bruto se purificó por cromatografía en fase inversa dando I-22B (44 mg, 10% de rendimiento). EM (IEP) *m/z*: 588.4 (M+H)+.

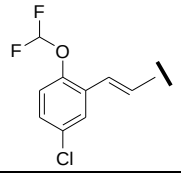
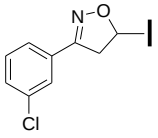
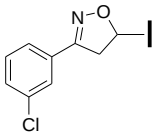
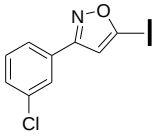
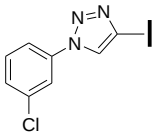
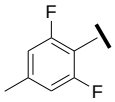
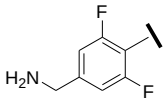
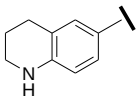
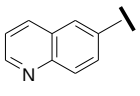
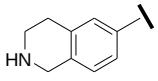
I-22C. El Ejemplo I-22 se preparó siguiendo los procedimientos descritos en 10H, sustituyendo 10G por I-22B; seguido por la etapa 1G. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.57 (1 H, s, br), 9.50 (1 H, s), 7.96 (1 H, d, J=2.01 Hz), 7.68 (1 H, dd, J=8.53, 2.26 Hz), 7.55 - 7.61 (2 H, m), 7.39 - 7.47 (2 H, m), 7.14 (1 H, d, J=15.56 Hz), 6.73 (1 H, d, J=15.81 Hz), 5.03 (1 H, dd, J=10.16, 6.40 Hz), 3.76 (3 H, s), 2.37 - 2.48 (1 H, m), 2.31 (3 H, s), 2.15 - 2.28 (1 H, m), 2.00 - 2.12 (1

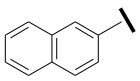
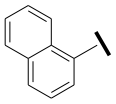
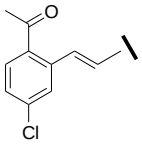
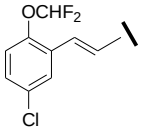
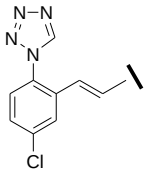
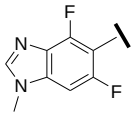
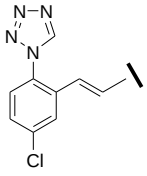
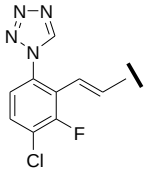
H, m), 1.84 - 1.97 (1 H, m), 1.41 - 1.66 (3 H, m), 0.96 - 1.18 (1 H, m). EM (IEP) *m/z*: 590.2 (M+H)+. HPLC analítica: TR = 4.38 min.

Tabla I-1: Ejemplos I-1 a I-23



Ej. nº	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-1		H	578.2	4.7
I-2		H	575.2	4.5
I-3		H	575.2	4.2
I-4		H	490.1	2.0 (B)
I-5		H	575.2	5.0

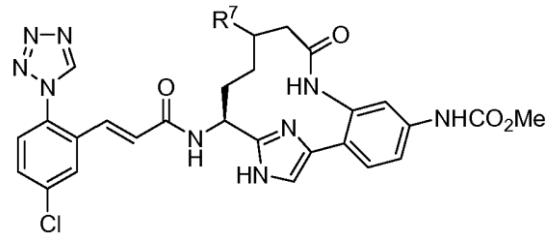
Ej. nº	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-6		H	574.2	6.1
I-7		H	551.1	5.0 4.8 (B)
I-8		H	551.1	5.0 4.9 (B)
I-9		H	549.2	6.2
I-10		H	549.2	5.6
I-11		H	498.2	4.0
I-12		H	513.2	6.2 (C)
I-13		H	503.4	5.2
I-14		H	499.2	3.7
I-15		H	503.3	4.0

Ej. n°	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-16		H	498.3	5.9
I-17		H	498.3	5.6
I-18		Cl	584.3	5.9 (B)
I-19		Cl	608.2	8.0
I-20		F	594.2	6.8
I-21		F	556.2	4.9
I-22		Me	590.2	4.4
I-23		Me	608.2	5.2

Los Ejemplos I-24 e I-25 (Tabla I-2) se prepararon

siguiendo los procedimientos descritos en el Ejemplo 116 y 118 sustituyendo ácido 2-metilbut-3-enoico por ácido 3-metilbut-3-enoico.

Tabla I-2: Ejemplos I-24 y I-25

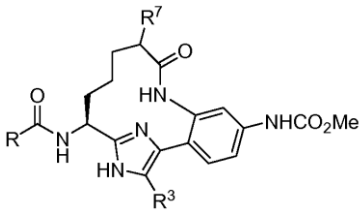


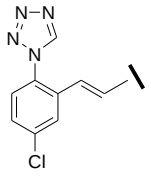
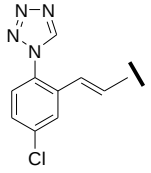
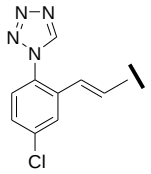
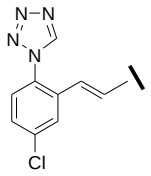
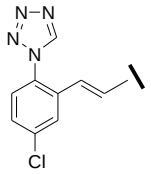
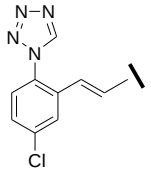
Ej. n°	R^7	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-24	Me (homoquiral)	590.3	5.0
I-25	Me (homoquiral)	590.3	5.0

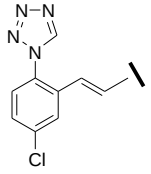
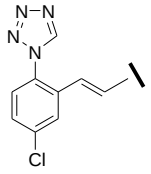
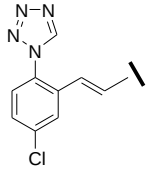
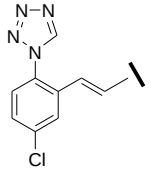
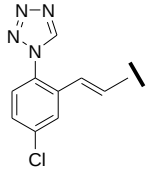
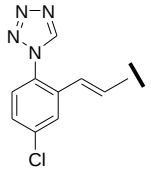
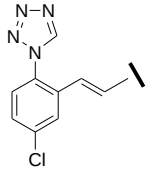
Los Ejemplos I-26 a I-34 (Tabla I-3) se prepararon siguiendo los procedimientos generales descritos en los Ejemplos 116 y 118. Los Ejemplos I-26 y I-27 se prepararon sustituyendo 2-metilbut-3-enoato de bencilo por 2-hidroxibut-3-enoato de metilo como se describe en el Ejemplo 116C, seguido por 116D, etapa adicional de sustitución del grupo hidroxilo con fluoruro por DAST; seguido por las etapas 116E; 116F; y 116I. Los Ejemplos I-30 y I-31 se prepararon

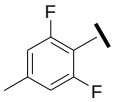
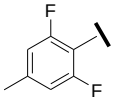
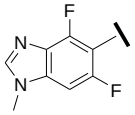
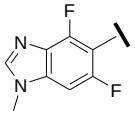
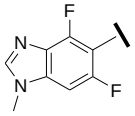
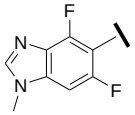
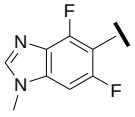
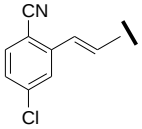
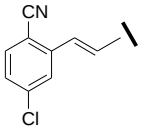
sustituyendo 2-metilbut-3-enoato de bencilo por 2-metoxibut-3-enoato de metilo como se describe en el Ejemplo 116C. Los Ejemplos I-28, I-29 y I-33 se prepararon sustituyendo 2-metilbut-3-enoato de bencilo por 2-etilbut-3-enoato de bencilo o 2-isopropilbut-3-enoato de bencilo como se describe en el Ejemplo 116C. El Ejemplo I-32 se preparó sustituyendo 2-metilbut-3-enoato de bencilo por 2-hidroxibut-3-enoato de metilo como se describe en el Ejemplo 116C; seguido por 116D; etapa adicional de oxidación del grupo hidroxilo a la cetona por reactivo de Dess-Martin seguido por fluoración con DAST; seguido por las etapas 116E; 116F; y 116I. Los Ejemplos I35-I38 se prepararon por cloración de los Ejemplos 116G, 116H, I-33, y I-34 como se describe en el Ejemplo 7. Los Ejemplos I-39 a I-59 se prepararon acoplando los núcleos macrocíclicos con derivados de ácido carboxílico sustituidos de forma apropiada (R-CO_2H) usando condiciones de acoplamiento descritas en la etapa 15D. Los Ejemplos I-40, I-44, I-49 a I-51, I-54, I-55, I-57, I-59 se prepararon acoplando el núcleo macrocíclico con un derivado de ácido carboxílico sustituido de forma apropiada (R-CO_2H) usando condiciones de acoplamiento descritas en la etapa 15D seguido por cloración como se describe en el Ejemplo 7.

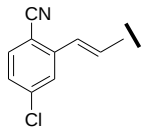
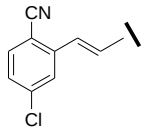
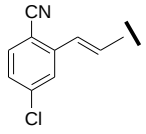
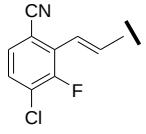
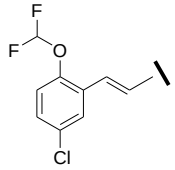
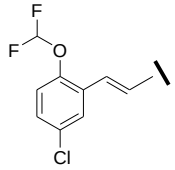
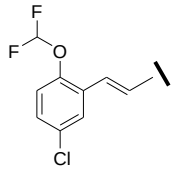
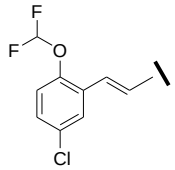
Tabla I-3: Ejemplos I-26 a I-59

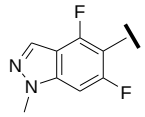
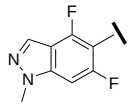
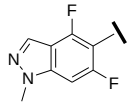
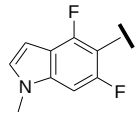


Ej. nº	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-26		F (homoquiral)	H	593.9	3.7 (B)
I-27		F (homoquiral)	H	593.9	3.6 (B)
I-28		Et	H	604.1	4.2 (B)
I-29		Et	H	604.1	4.2 (B)
I-30		OMe (homoquiral)	H	606.2	5.3
I-31		OMe (homoquiral)	H	606.3	6.0

Ej. nº	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-32		Bis-F	H	612.1	3.8 (B)
I-33		 (diastereómero A)	H	618.3	4.5 (B)
I-34		 (diastereómero B)	H	618.3	4.5 (B)
I-35			Cl	624.3	7.0
I-36			Cl	624.3	6.7
I-37		 (diastereómero B)	Cl	652.3	5.8 (B)
I-38		 (diastereómero A)	Cl	652.3	5.8 (B)

Ej. nº	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-39			H	512.2	4.8
I-40			Cl	546.2	6.9
I-41			H	552.2	3.5
I-42		Me (mezcla de diastereómeros)	H	552.4	3.3
I-43		 (diastereómero A)	H	580.3	4.3
I-44		Me (mezcla de diastereómeros)	Cl	586.3	4.7 4.9
I-45			H	552.3	2.9
I-46			H	547.3	5.2
I-47			H	561.3	5.7

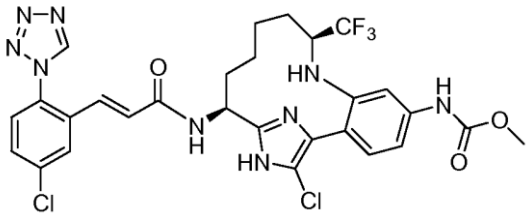
Ej. nº	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-48		 (diastereómero A)	H	575.3	5.3 (B)
I-49			Cl	581.3	7.5
I-50			Cl	595.3	7.7
I-51			Cl	599.2	7.8
I-52			H	602.3	6.4
I-53			H	588.2	5.9
I-54			Cl	622.3	7.9
I-55			Cl	636.3	8.4

Ej. nº	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-56			H	552.3	3.8 (B)
I-57			Cl	586.2	4.9 (B)
I-58			H	566.4	4.6
I-59			Cl	585.4	7.7

El Ejemplo I-60 se preparó siguiendo los procedimientos descritos en Ejemplo 7, sustituyendo el Ejemplo 6 por el Ejemplo 154.

Ejemplo I-61.

Éster metílico del ácido {(9S,14S)-17-cloro-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



I-61A e I-61AA. Éster *terc*-butílico del ácido

[(9S,14S)-17-cloro-5-metoxicarbonilamino-9-trifluorometil-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico, sal 2TFA (I-61A) y éster *terc*-butílico del ácido [(9S,14S)-4,17-dicloro-5-metoxicarbonilamino-9-trifluorometil-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico, sal 2TFA (I-61AA): A la solución de 154C (diastereómero A) (0.124 g, 0.145 mmol) en acetonitrilo (1 ml)/cloroformo (1.000 ml) se añadió NCS (0.029 g, 0.217 mmol) y DIPEA (0.076 ml, 0.435 mmol). La mezcla de reacción se agitó a ta durante 44 h. Se añadió más NCS (0.029 g, 0.217 mmol). Después de otras 2.5 h, la mezcla de reacción se concentró. La purificación por cromatografía en fase inversa dio 0.024 g (18.6 %) de I-61A como un sólido amarillo y 0.010 g (7.5%) de I-61AA como un sólido blanco. Para I-61A: EM (IEP) m/z: 662.4 (M+H)+. Para I-61AA: EM (IEP) m/z: 696.3 (M+H)+.

I-61B. Éster metílico del ácido ((9S,14S)-14-amino-17-cloro-9-trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico, sal 3TFA: A la solución de I-61A (0.032 g, 0.036 mmol) en MeOH (0.5 ml) se añadió HCl 5 N (0.5 ml, 2.5 mmol) y clorhidrato de metoxilamina (25-30 % en peso en agua, 0.055 ml, 0.180 mmol). La mezcla de reacción se calentó

hasta 75°C durante 1 h y luego se enfrió hasta ta. La purificación por cromatografía en fase inversa dio I-61B (0.02 g, 71.9 %) como un sólido blanco. EM (IEP) m/z: 432.2 (M+H)+.

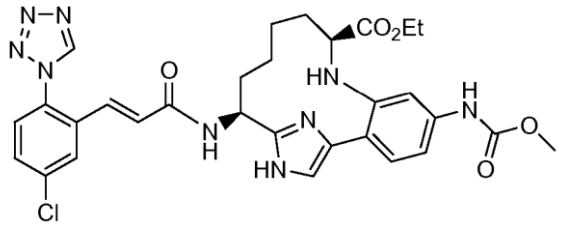
I-61C. El Ejemplo I-61 se preparó siguiendo el procedimiento descrito en 15D, sustituyendo 15C por I-61B. 1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 7.98 (d, *J*=2.5 Hz, 1 H), 7.66 (dd, *J*=8.5, 2.5 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.30 - 7.34 (m, 2 H), 7.12 (d, *J*=15.7 Hz, 1 H), 7.07 (dd, *J*=8.3, 2.2 Hz, 1 H), 6.77 (d, *J*=15.7 Hz, 1 H), 5.14 (dd, *J*=10.6, 7.0 Hz, 1 H), 3.74 (s, 3 H), 2.84 - 2.92 (m, 1 H), 2.13 - 2.22 (m, *J*=13.0, 13.0, 7.1, 2.9 Hz, 1 H), 1.87 - 1.95 (m, 1 H), 1.63 - 1.81 (m, 2 H), 1.39 - 1.55 (m, 3 H), 0.44 - 0.55 (m, 1 H). 19F NMR (471MHz, CD_3OD) δ -74.96, -77.49. (471 MHz, CD EM (IEP) m/z: 664.3 (M+H)+. HPLC analítica, Tr = 8.89 min.

Los Ejemplos I-62 a I-64 se sintetizaron acoplando la amina 155A, con derivados ácido carboxílico sustituidos de forma apropiada (R-CO_2H) usando condiciones de acoplamiento descritas en la etapa 15D. En el caso de los Ejemplos I-62 y I-63 se requirió una etapa de desprotección Boc adicional como se describe en la etapa 3C.

Ejemplo I-67.

Éster etílico del ácido (9S,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-

8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 2 TFA



I-67A. Éster etílico del ácido 2-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-5-metoxicarbonilamino-fenilamino}-pent-4-enoico. A una solución amarillenta-marrón transparente de 10C (4.50 g, 8.46 mmol) y ácido maleico (0.982 g, 8.46 mmol) en acetonitrilo (33.9 ml) se añadió una solución al 50 % de 2-oxoacetato de etilo en tolueno (2.52 ml, 12.69 mmol) seguido por alil tributil estaño (4.72 ml, 15.23 mmol). La solución naranja resultante se agitó vigorosamente. Después de 18 h, la reacción se diluyó con EtOAc y luego se lavó la reacción con NaOH 1.0 N (75 ml x 2), salmuera, se secó sobre Na_2SO_4, se filtró y se concentró dando un aceite naranja viscoso. La purificación por cromatografía en fase normal dio 3.96 g (76 %) de I-67A como una espuma naranja. La 1H NMR indicó aproximadamente una mezcla 1:1 de diastereómeros. EM (IEP) m/z: 658.4 (M+H)+.

I-67B. Éster etílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-

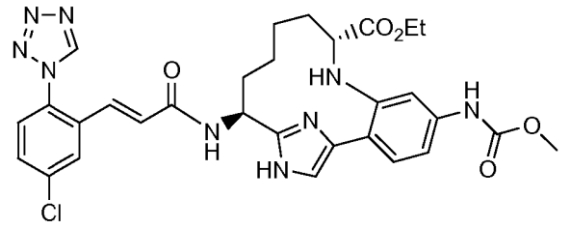
triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico (Diastereómero A), sal 2 TFA y I-67C. Éster etílico del ácido (9S,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico (Diastereómero B), sal 2 TFA.

Los Compuestos I-67B (diastereómero A) y I-67C (diastereómero B) se prepararon siguiendo los procedimientos descritos en I-74C, sustituyendo I-74B por I-67A; seguido por la etapa I-74D. Los diastereósmeros se separaron por cromatografía de fase inversa. EM (IEP) m/z: 632.5 (M+H)+.

I-67D. El Ejemplo I-67 se preparó siguiendo los procedimientos descritos en 154E, sustituyendo 154D por I-67C (diastereómero B); seguido por la etapa 15D. 1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (s, 1 H), 9.39 (s, 1 H), 7.94 (d, *J*=2.2 Hz, 1 H), 7.67 (dd, *J*=8.2, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 1 H), 7.51 (s, 1 H), 7.41 (s, 1 H), 7.28 - 7.35 (m, *J*=8.2 Hz, 1 H), 7.09 - 7.15 (m, 2 H), 6.77 (d, *J*=15.4 Hz, 1 H), 5.15 (t, *J*=6.6 Hz, 1 H), 3.96 - 4.12 (m, 2 H), 3.73 (s, 3 H), 3.09 (d, *J*=10.4 Hz, 1 H), 2.31 - 2.42 (m, 1 H), 1.94 - 2.07 (m, 1 H), 1.56 - 1.79 (m, 2 H), 1.44 - 1.55 (m, 3 H), 1.14 (t, *J*=7.2 Hz, 3 H), 0.54 - 0.66 (m, 1 H). EM (IEP) m/z: 634.3 (M+H)+ y 636.2 $(M+2+H)^+$. HPLC analítica (Método D): Tr = 4.9 min.

Ejemplo I-68.

Éster etílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 2 TFA



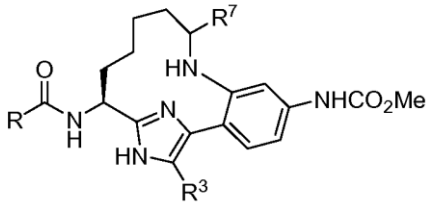
I-68A. Éster etílico del ácido (9R,14S)-14-amino-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: El compuesto I-68A se preparó siguiendo el procedimiento descrito en 154E, sustituyendo 154D por I-67B (diastereómero A). EM (IEP) m/z: 632.5 (M+H)+.

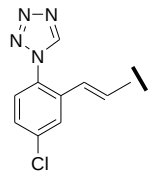
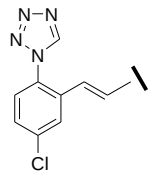
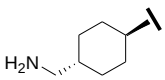
I-68B. El Ejemplo I-68 se preparó siguiendo los procedimientos descritos en 15D, sustituyendo 15C por I-68A. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 9.41 (s, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.68 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.56 (s, 1 H), 7.44 (s, 1 H), 7.35 (d, *J*=8.2 Hz, 1 H), 7.12 - 7.19 (m, 2 H), 6.77 (dd, *J*=15.4, 2.2 Hz, 1 H), 5.20 - 5.30 (m, 1 H), 3.94 - 4.11 (m, 2 H), 3.74 (s, 3 H), 3.05 (d, *J*=10.4 Hz, 1 H), 2.22 - 2.37 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.72 - 1.93 (m, 2 H), 1.37 - 1.62 (m, 3

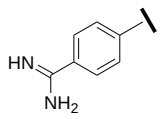
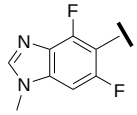
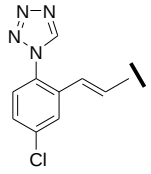
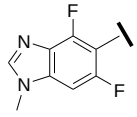
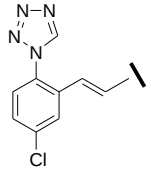
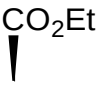
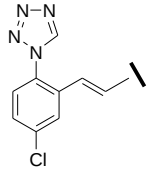
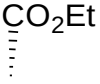
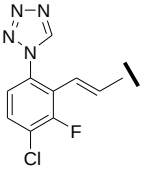
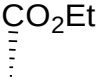
H), 1.12 (t, *J*=7.2 Hz, 3 H), 0.30 - 0.43 (m, 1 H). EM (IEP) m/z: 634.3 (M+H)+ y 636.2 (M+2+H)+. HPLC Analítica (Método D): RT = 5.2 min.

El Ejemplo I-69 se preparó siguiendo el procedimiento descrito en 15D, sustituyendo 15C por I-68A y sustituyendo el Intermediario 2 por el Intermediario 3A.

Tabla I-4: Ejemplos I-60 a I-69



Ej. n°	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-60			Cl	664.1	8.6
I-61			Cl	664.3	8.9
I-62			H	537.2	3.8

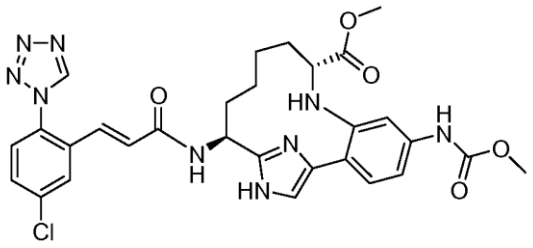
Ej. n°	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-63			H	544.4	4.1
I-64			H	592.3	4.4 (D)
I-65			F	648.2	8.8
I-66			F	610.2	7.1
I-67			H	634.3	4.9 (D)
I-68			H	634.3	5.2 (D)
I-69			H	652.3	5.7 (D)

Los Ejemplos I-72 e I-73 se prepararon de acuerdo con los procedimientos descritos para el Ejemplo I-76, sustituyendo 2-oxoacetato de etilo por los aldehídos

sustituidos de forma apropiada.

Ejemplo I-74.

Éster metílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 2 TFA



I-74A. Ácido (R)-2-(2-(2-((S)-1-(*terc*-butoxicarbonilamino)but-3-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-4-il)-5-(metoxicarbonilamino)fenilamino)pent-4-enoico: Se cargó un matraz de paredes gruesas con 10B (5 g, 8.39 mmol), yoduro de cobre(I) (0.160 g, 0.839 mmol), carbonato potásico (2.90 g, 20.99 mmol), ácido (R)-2-aminopent-4-enoico (1.160 g, 10.07 mmol) y DMSO (16.8 ml). El matraz se llevó a vacío y se volvió a llenar con argón tres veces y luego se selló el matraz con un tapón a rosca de teflón. La reacción se calentó tapada hasta 90°C durante 18 h y luego se enfrió la reacción hasta TA. La mezcla de reacción se diluyó con acetato de etilo y agua y se separaron las fases. La fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se

concentraron dando I-74A (5.5 g, 83 %) como un sólido amarillo. EM (IEP) m/z: 630.4 (M+H)+. El material se llevó a la etapa siguiente sin purificación posterior.

I-74B. Éster metílico del ácido (R)-2-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-5-metoxicarbonilamino-fenilamino}-pent-4-enoico: A una solución de I-74A (5.5 g, 6.99 mmol) en DMF (100 ml) se añadió K_2CO_3 (0.966 g, 6.99 mmol) y MeI (0.437 ml, 6.99 mmol). La reacción se agitó a ta durante 24 h. La reacción se repartió entre EtOAc y agua y se separaron las fases. La fase acuosa se extrajo con EtOAc (1x). Las fases orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por cromatografía en fase normal dio I-74B (2.36 g, 52.5 %) como sólido marrón. EM (IEP) m/z: 644.5 (M+H)+.

I-74C. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaeno-9-carboxílico: Una solución de I-74B (0.4 g, 0.621 mmol), Grubbs (II) (0.211 g, 0.249 mmol) en DCE (15.53 ml) se calentó en un microondas a 120°C durante 20 min. La reacción se enfrió hasta TA. La misma reacción se repitió ocho veces más. Se reunieron las nueve reacciones, se lavó con $NaHCO_3$

saturado, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por cromatografía en fase normal dio I-74C (1.03 g, 30 %) como un sólido marrón. EM (IEP) m/z: 616.5 (M+H)+.

I-74D. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico (diastereómero A), sal 2 TFA y I-74C. Éster metílico del ácido (9S,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico (diastereómero B), sal 2 TFA.

A la solución de I-74E (1.03 g, 1.673 mmol) en EtOAc (15 ml)/EtOH (5.00 ml) se añadió TFA (0.258 ml, 3.35 mmol) y paladio al 10 % sobre carbón (0.178 g, 0.167 mmol). Se burbujeó hidrógeno a través de la mezcla de reacción durante 5 min. La reacción se agitó bajo un globo de hidrógeno durante 4 días. La reacción se filtró a través de un GMF de 0.45 µm que contenía Celite®. El sólido se aclaró con MeOH, y el filtrado se concentró. El residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró concentraron. La purificación por cromatografía en fase normal dio I-74D (0.3

g, 29.0 % de rendimiento) como un sólido amarillo. EM (IEP) m/z: 618.4 (M+H)+. Se obtuvo también una mezcla de I-74D y I-74E (0.55 g) como un sólido amarillo. Esta mezcla se purificó por cromatografía de fase inversa dando 0.325 g (23.0 %) de I-74D (diastereómero A) como un sólido blanco y 0.23 g (16.3 %) I-74E (diastereómero B) como un sólido blanco. Para I-74D: EM (IEP) m/z: 618.5 (M+H)+. 1H NMR (500 MHz, CD_3OD) δ ppm 7.73 (s, 1 H), 7.37 (d, J=1.9 Hz, 1 H), 7.30 (d, J=8.3 Hz, 1 H), 7.17 (dd, J=8.4, 2.1 Hz, 1 H), 5.66 (d, J=10.5 Hz, 1 H), 5.53 (d, J=10.5 Hz, 1 H), 5.12 (t, J=9.1 Hz, 1 H), 3.65 - 3.77 (m, 5 H), 3.51 (s, 3 H), 3.03 (d, J=10.7 Hz, 1 H), 2.07 - 2.16 (m, 2 H), 1.68 - 1.81 (m, 2 H), 1.31 - 1.55 (m, 12 H), 0.90 - 1.04 (m, 2 H), 0.26 - 0.38 (m, 1 H), 0.01 (s, 9 H). [α] = -6.9 (c = 1.23, MeOH).

Para I-74E: EM (IEP) m/z: 618.4 (M+H)+. 1H NMR (500 MHz, CD_3OD) δ ppm 7.71 (s, 1 H), 7.39 (s, 1 H), 7.32 (d, J=8.3 Hz, 1 H), 7.13 - 7.17 (m, 1 H), 5.85 (d, J=10.7 Hz, 1 H), 5.51 (d, J=11.0 Hz, 1 H), 5.13 (t, J=6.3 Hz, 1 H), 3.70 - 3.76 (m, 5 H), 3.52 - 3.57 (m, 3 H), 3.09 (dd, J=9.4, 3.3 Hz, 1 H), 2.27 - 2.36 (m, 1 H), 1.91 - 2.00 (m, 1 H), 1.70 - 1.79 (m, 1 H), 1.31 - 1.69 (m, 13 H), 0.89 - 1.07 (m, 2 H), 0.43 - 0.54 (m, 1 H), 0.00 (s, 9 H).

I-74F. Éster metílico del ácido (9R,14S)-14-amino-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: El compuesto I-74F se preparó siguiendo el procedimiento descrito en 154E, sustituyendo 154D por I-74D (diastereómero A). EM (IEP) m/z: 388.1 (M+H)+.

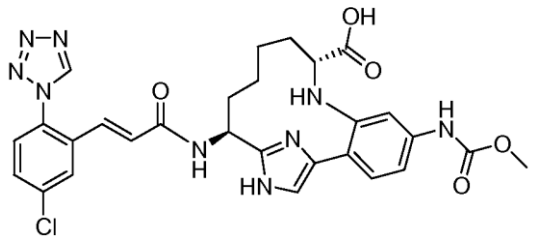
I-74G. El Ejemplo I-74 se preparó siguiendo el procedimiento descrito en 1G, sustituyendo 1F por I-74F. 1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.8, 2.2 Hz, 1 H), 7.55 - 7.60 (m, 2 H), 7.41 (d, J=2.2 Hz, 1 H), 7.35 (d, J=8.2 Hz, 1 H), 7.12 - 7.21 (m, 2 H), 6.76 (d, J=15.4 Hz, 1 H), 5.25 (dd, J=11.0, 7.1 Hz, 1 H), 3.75 (s, 3 H), 3.57 (s, 3 H), 3.07 (d, J=10.4 Hz, 1 H), 2.25 - 2.36 (m, 1 H), 1.97 - 2.06 (m, 1 H), 1.72 - 1.90 (m, 2 H), 1.38 - 1.62 (m, 3 H), 0.30 - 0.43 (m, 1 H). EM (IEP) m/z: 620.3 (M+H)+. HPLC analítica: TR= 5.66 min.

El Ejemplo I-75 se preparó siguiendo el procedimiento descrito en el Ejemplo 7, sustituyendo el Ejemplo 6 por el Ejemplo I-74 y llevando a cabo la reacción a ta en acetonitrilo.

Ejemplo I-76.

Ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-

acriloilamino]-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 2 TFA



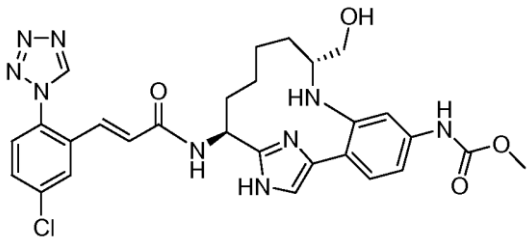
I-76A. Ácido (9R,14S)-14-amino-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 3 HCl: A una solución amarilla pálida transparente de I-74F (0.079 g, 0.204 mmol) en MeOH (2.0 ml) se añadió hidróxido sódico 1N (0.408 ml, 0.408 mmol). La solución se agitó vigorosamente a 55°C durante 1.5 h, se enfrió hasta TA, se acidificó con HCl 1.0 N (1 ml) y se concentró dando I-76A (0.098 g, 0.187 mmol, 92 % de rendimiento) como un sólido blanquecino. EM (IEP) m/z: 374.1 (M+H)+. El material se llevó a la etapa siguiente sin purificación posterior.

I-76B. El Ejemplo I-76 se preparó siguiendo el procedimiento descrito en 1G, sustituyendo 1F por I-76A. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.5, 2.2 Hz, 1 H), 7.58 (d, J=8.5 Hz, 1 H), 7.55 (s, 1 H), 7.40 (d, J=1.9 Hz, 1 H), 7.36 (d, J=8.5 Hz, 1 H), 7.21 (dd, J=8.4, 2.1 Hz, 1 H), 7.16 (d, J=15.7 Hz, 1 H),

6.76 (d, J=15.7 Hz, 1 H), 5.26 (dd, J=11.0, 7.2 Hz, 1 H), 3.74 (s, 3 H), 3.04 (d, J=10.2 Hz, 1 H), 2.26 - 2.35 (m, J=13.3, 13.3, 7.2, 3.0 Hz, 1 H), 1.98 - 2.06 (m, 1 H), 1.73 - 1.94 (m, 2 H), 1.44 - 1.63 (m, 3 H), 0.35 - 0.46 (m, 1 H). EM (IEP) m/z: 606.3 (M+H)+. HPLC analítica: TR= 5.47 min.

Ejemplo I-77.

Éster metílico del ácido {(9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-hidroximetil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



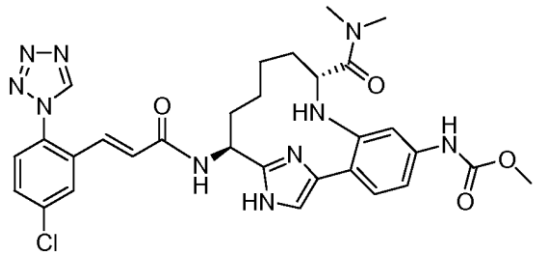
I-77A. Éster metílico del ácido [(9R,14S)-14-*terc*-butoxicarbonilamino-9-hidroximetil-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il]-carbámico: A una solución enfriada (0°C) de I-74D (0.22 g, 0.356 mmol) en THF (5 ml) se añadió LAH (0.178 ml, 0.356 mmol) (2M en THF). La reacción se dejó agitar a 0°C. Después de 1 h, se añadió más LAH (0.05 ml, 0.1 mmol) (2M en THF). Después de 1 hora más, la reacción se inactivó con HCl 1N (ac, 1 ml). La reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró dando 0.217 g

(103 %) de I-77A como un sólido amarillo. EM (IEP) m/z: 590.5 (M+H)+. El material se llevó a la etapa siguiente sin purificación posterior.

I-77B. El Ejemplo I-77 se preparó siguiendo los procedimientos descritos en 154E, sustituyendo 154D por I-77A; seguido por la etapa 15D. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.99 (d, J=2.2 Hz, 1 H), 7.65 - 7.71 (m, 2 H), 7.53 - 7.61 (m, 2 H), 7.49 (s, 1 H), 7.30 (dd, J=8.5, 2.2 Hz, 1 H), 7.16 (d, J=15.7 Hz, 1 H), 6.77 (d, J=15.7 Hz, 1 H), 5.29 (dd, J=11.1, 6.7 Hz, 1 H), 3.76 (s, 3 H), 3.52 (dd, J=11.6, 4.7 Hz, 1 H), 3.39 - 3.43 (m, 1 H), 2.82 - 2.88 (m, 1 H), 2.16 - 2.26 (m, J=13.0, 13.0, 6.9, 3.4 Hz, 1 H), 1.98 - 2.09 (m, 2 H), 1.86 - 1.94 (m, 1 H), 1.44 - 1.64 (m, 3 H), 0.58 - 0.69 (m, 1 H). EM (IEP) m/z: 592.4 (M+H)+. HPLC analítica: TR= 5.62 min.

Ejemplo I-78.

Éster metílico del ácido {(9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-dimetilcarbamoil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



I-78A. Ácido (9R,14S)-14-*terc*-butoxicarbonilamino-

5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 2 HCl: El compuesto I-78A se preparó siguiendo el procedimiento descrito en I-76A, sustituyendo I-74F por I-74D.

EM (IEP) m/z: 604.5 (M+H)+. El material se llevó a la etapa siguiente sin purificación posterior.

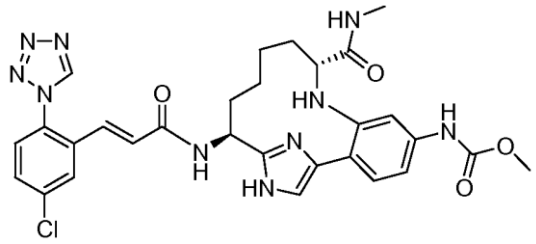
I-78B. Éster *terc*-butílico del ácido [(9R,14S)-9-dimetilcarbamoil-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A la solución de I-78A (0.088 g, 0.074 mmol) en DMF (2 ml) se añadió EDC (0.028 g, 0.148 mmol), HOBT (0.023 g, 0.148 mmol), dimetilamina, HCl (7.26 mg, 0.089 mmol) y TEA (0.041 ml, 0.297 mmol). La reacción se agitó a ta. Después de18h, la reacción se diluyó con EtOAc y luego se lavó con agua, $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró dando 0.047 g (100 %) de I-78B como un sólido marrón. EM (IEP) m/z: 631.5 (M+H)+. El material se llevó a la etapa siguiente sin purificación posterior.

I-78C. El Ejemplo I-78 se preparó siguiendo los procedimientos descritos en 154E, sustituyendo 154D por I-78B; seguido por la etapa 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.5, 2.2 Hz, 1 H), 7.56 - 7.63 (m, 2 H), 7.38 (d, J=8.5 Hz, 1 H), 7.29

(dd, J=8.3, 1.9 Hz, 1 H), 7.24 (d, J=1.4 Hz, 1 H), 7.16 (d, J=15.7 Hz, 1 H), 6.76 (d, J=15.7 Hz, 1 H), 5.27 (dd, J=11.3, 7.2 Hz, 1 H), 3.75 (s, 3 H), 3.52 (d, J=10.7 Hz, 1 H), 2.80 (s, 3 H), 2.66 (s, 3 H), 2.26 - 2.36 (m, 1 H), 1.87 - 2.06 (m, 2 H), 1.68 - 1.77 (m, 1 H), 1.56 - 1.66 (m, 1 H), 1.43 - 1.54 (m, 1 H), 1.25 - 1.33 (m, 1 H), 0.32 - 0.43 (m, 1 H). EM (IEP) m/z: 633.5 (M+H)+. HPLC analítica: TR= 6.64 min.

Ejemplo I-79.

Éster metílico del ácido {(9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-metilcarbamoil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA

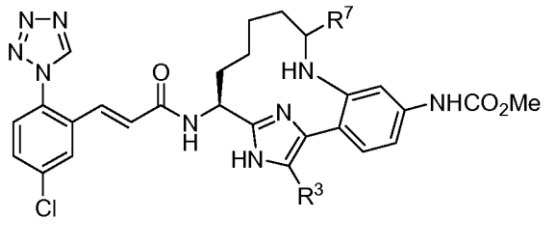


El Ejemplo I-79 se preparó siguiendo el procedimiento descrito en 15D, sustituyendo el Intermediario 2 por el Ejemplo I-76 y sustituyendo 15C por clorhidrato de metanamina. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, J=2.5 Hz, 1 H), 7.68 (dd, J=8.5, 2.2 Hz, 1 H), 7.58 (d, J=8.5 Hz, 1 H), 7.53 (s, 1 H), 7.37 - 7.41 (m, 1 H), 7.25 - 7.29 (m, 2 H), 7.16 (d, J=15.7 Hz, 1 H), 6.76 (d, J=15.7 Hz, 1 H), 5.26 (dd, J=11.1, 7.0 Hz, 1 H), 3.74 (s, 3 H), 3.03 (dd, J=11.7, 1.5 Hz, 1 H), 2.57 (s, 3 H), 2.24 - 2.33 (m, 1 H), 1.76 - 2.03 (m, 3 H), 1.41 - 1.58 (m, 2 H), 1.26 - 1.34

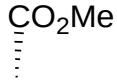
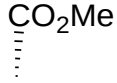
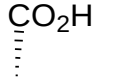
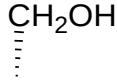
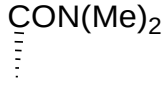
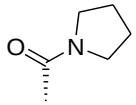
(m, 1 H), 0.43 - 0.54 (m, 1 H). EM (IEP) m/z: 619.4 (M+H)+. HPLC analítica: TR= 4.78 min.

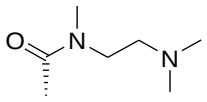
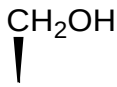
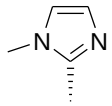
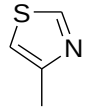
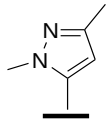
Los Ejemplos I-80 y I-81 se prepararon de acuerdo con el Ejemplo I-79 sustituyendo clorhidrato de metanamina por las aminas sustituidas de forma apropiada. Los Ejemplos I-82 a I-85 se prepararon de acuerdo con los procedimientos descritos para los Ejemplos I-74 a I-77. Los Ejemplos I-86 a I-100 se prepararon de acuerdo con los procedimientos descritos para el Ejemplo I-67, sustituyendo 2-oxoacetato de etilo por los aldehídos sustituidos de forma apropiada. Para la preparación de los compuestos I-99 e I-100 se llevó a cabo la desprotección Boc y SEM sustituyendo el HCl 4M en dioxano, cisteína a 75°C, por H_2SO_4 acuoso 5M, cisteína en metanol a 75°C.

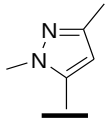
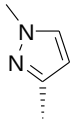
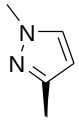
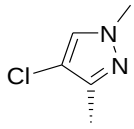
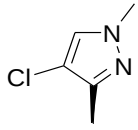
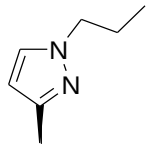
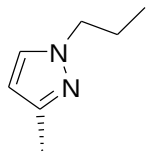
Tabla I-5: Ejemplos I-70 a I-100

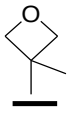
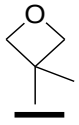


Ej. n°	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-70		Me	644.4	6.3
I-71		Me	644.4	6.5

Ej. nº	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-72		H	612.2	6.0
I-73		H	612.2	6.1
I-74		H	620.3	5.6
I-75		Cl	654.3	6.9 (D)
I-76		H	606.3	4.6
I-77		H	592.4	5.6
I-78		H	633.3	5.5
I-79		H	619.4	4.8
I-80		H	659.4	6.5 (D)

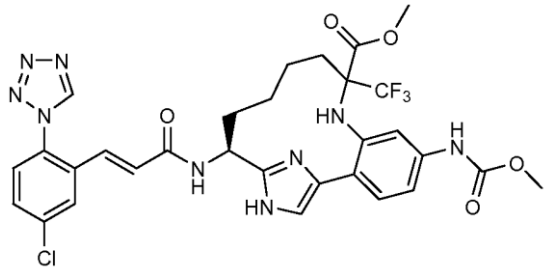
Ej. nº	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-81		H	690.4	5.6 (D)
I-82		H	620.2	5.6
I-83		Cl	654.2	7.5
I-84		H	606.3	5.1
I-85		H	592.3	4.3
I-86		H	642.3	4.6
I-87	 (mezcla de diastereómeros)	H	645.2	5.4 6.0
I-88	 (homoquiral)	H	656.3	5.4

Ej. nº	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-89	 (homoquiral)	H	656.4	5.4
I-90		H	642.3	5.3
I-91		H	642.3	5.8
I-92		H	642.3	5.7
I-93		H	676.3	7.2
I-94		H	676.3	7.1
I-95		H	670.4	7.3
I-96		H	670.3	7.3
I-97	Me (diastereómero A)	H	576.3	5.6

Ej. nº	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-98	Me (diastereómero B)	H	576.3	5.5
I-99	 (diastereómero B)	H	632.4	6.8
I-100	 (diastereómero A)	H	632.3	9.3

Ejemplo I-103.

Éster metílico del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-9-trifluorometil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico



I-103A. Éster metílico del ácido 2-{(E)-2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-

etoximetil)-1*H*-imidazol-4-il]-5-metoxicarbonilamino-fenilimino}-3,3,3-trifluoro-propiónico: A una solución del Ejemplo 10C (164 mg, 0.308 mmol), 3,3,3-trifluoro-2-oxopropanoato de metilo (39 mg, 0.250 mmol) y trietilamina (95 µl, 0.679 mmol) en 1 ml de tolueno (Volumen 1028 µl) a 0°C bajo Ar se añadió cloruro de titanio(IV) (1M en DCM) (308 µl, 0.308 mmol) gota a gota. Después de la adición, se retiró el baño de hielo y la reacción se agitó a TA durante la noche. La mezcla de reacción se inactivó con NaOH 1N (ac), se repartió entre agua y DCM, se secó la fase de DCM sobre Na_2SO_4, se separó el sólido por filtración, se concentró proporcionando un aceite naranja. La purificación por cromatografía en fase normal dio I-103A (95 mg, 46%) como un aceite naranja. EM (IEP) *m/z*: 670.4 (M+H)+.

I-103B. Éster metílico del ácido 2-{2-[2-((S)-1-amino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-5-metoxicarbonilamino-fenilamino}-2-trifluorometil-pent-4-enoico: A una solución de I-103A (87 mg, 0.130 mmol) en CH_2Cl_2 (Volumen 2 ml) se añadió aliltrimetilsilano (0.15 ml, 0.940 mmol). La reacción se enfrió hasta -78°C bajo Ar. Se añadió gota a gota percloroestanano (1M en DCM) (0.162 ml, 0.162 mmol). Después de la adición, se retiró el baño de acetona y hielo seco y la reacción se calentó hasta ta y se agitó durante 2 días. La mezcla de reacción se concentró a vacío proporcionando un

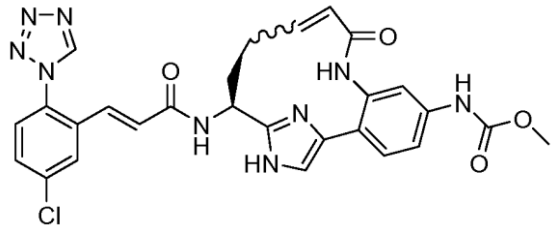
producto sólido bruto. La purificación por cromatografía en fase inversa dio I-103B (35 mg, 44%) como un sólido amarillo pálido. EM (IEP) *m/z*: 612.3 (M+H)+.

I-103C. Éster metílico del ácido 2-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-5-metoxicarbonilamino-fenilamino}-2-trifluorometil-pent-4-enoico: A una solución de I-103B (35 mg, 0.057 mmol) en dioxano (Volumen 0.3 ml) se añadió dicarbonato de di-*terc*-butilo (0.020 ml, 0.086 mmol) e hidróxido sódico (1N ac) (0.229 ml, 0.229 mmol). La reacción se agitó a ta durante 3 horas, se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por cromatografía en fase normal dio I-103C (20 mg, 49%) como un sólido amarillo pálido. EM (IEP) *m/z*: 712.5 (M+H)+.

I-103D. El Ejemplo I-103 se preparó siguiendo los procedimientos descritos en I-74C sustituyendo I-74B por I-103C; seguido por las etapas I-74D/I-74E; I-74F; I-74G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 7.98 (d, *J*=1.9 Hz, 1 H), 7.67 (d, *J*=2.2 Hz, 1 H), 7.54 - 7.61 (m, 1 H), 7.36 (s, 3 H), 7.11 - 7.22 (m, 2 H), 6.71 - 6.81 (m, 1 H), 5.03 - 5.12 (m, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H), 2.77 - 2.90 (m, 1 H), 1.99 - 2.17 (m, 2 H), 1.55 - 1.73 (m, 2 H), 1.42 - 1.54 (m, 1 H), 0.93 - 1.07 (m, 1 H), 0.80 - 0.93 (m, 1 H). EM (IEP) *m/z*: 688.3 (M+H)+.

Ejemplo I-106.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,10.15(18)-hexaen-5-il}-carbámico (90755-098)



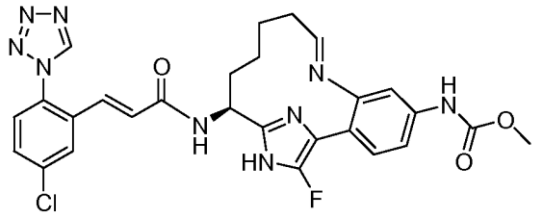
I-106A. Éster terc-butílico del ácido [(S)-5-metoxicarbonilamino-9-oxo-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,10.15(18)-hexaen-14-il]-carbámico: A una solución de mezcla de 152A,152B y 152C (20 mg, 0.034 mmol) en 0.5 ml DCM a -78°C bajo Ar se añadió cloruro de metanosulfonilo (5.83 mg, 0.051 mmol) en 0.5 ml de DCM gota a gota. Después de 5 mins, se añadió gota a gota trietilamina (10.29 mg, 0.102 mmol). El baño de reacción se sustituyó por un baño de hielo-sal y se calentó gradualmente hasta 0°C. La mezcla de reacción se repartió entre agua y DCM. La fase de DCM se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por cromatografía en fase inversa dio I-106A (5.3 mg, 27%) como un sólido amarillo pálido. EM (IEP) *m/z*: 572.3 (M+H)+.

I-106B. El Ejemplo I-106 se preparó siguiendo los

procedimientos descritos en 1F, sustituyendo 1D por I-106A; seguido por la etapa 1G. RMN 1H (500 MHz, CD_3OD) δ ppm 9.65 - 9.77 (m, 1 H), 9.51 - 9.56 (m, 1 H), 7.92 - 8.06 (m, 1 H), 7.65 - 7.74 (m, 1 H), 7.56 - 7.64 (m, 2 H), 7.36 - 7.55 (m, 3 H), 7.18 - 7.28 (m, 1 H), 6.61 - 6.76 (m, 1 H), 5.21 - 5.48 (m, 1 H), 4.40 - 4.64 (m, 1 H), 3.74 - 3.80 (m, 3 H), 2.09 - 2.61 (m, 4 H). EM (IEP) *m/z*: 574.1 (M+H)+. HPLC analítica: Tr = 3.91 min. (Método B).

Ejemplo I-107.

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-fluoro-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,8,15(18)-hexaen-5-il}-carbámico, sal del ácido trifluoracético



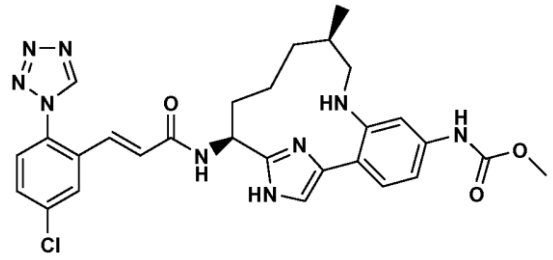
I-107A. Éster metílico del ácido ((E)-(S)-14-amino-17-fluoro-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,8,15(18)-hexaen-5-il)-carbámico: A una suspensión amarilla de I-20B (18.67 mg, 0.043 mmol) en THF (4 ml) se añadió complejo de borano-THF (1M) (0.430 ml, 0.430 mmol) gota a gota. Se selló y se calentó a 60°C durante 1 hr y luego se enfrió hasta ta. A la solución se añadió MeOH, seguido por 0.5 ml de HCl (4M en dioxano). La mezcla de reacción se selló y se guardó a TA durante la

noche. La mezcla de reacción se concentró a continuación y se purificó por cromatografía en fase inversa proporcionando I-107A (4 mg, 25%). 1H NMR (400 MHz, CD_3OD) δ ppm 7.31 (d, *J*=8.34 Hz, 1 H) 7.16 (d, *J*=1.52 Hz, 1 H) 6.79 (dd, *J*=8.46, 2.15 Hz, 1 H) 5.69 (dd, *J*=9.98, 3.41 Hz, 1 H) 4.69 (dd, *J*=11.37, 4.04 Hz, 1 H) 3.68 - 3.77 (m, 3 H) 2.11 - 2.32 (m, 1 H) 1.43 - 2.03 (m, 6 H) 0.68 - 0.97 (m, 1 H). EM (IEP) *m/z*: 329.3 (M+H-NH3)+.

I-107B. El Ejemplo 1-107 se preparó siguiendo los procedimientos descritos en la etapa 1G, sustituyendo 1F por I-107A. 1H NMR (400 MHz, CD_3OD) δ ppm 9.52 (s, 1 H) 8.02 (d, *J*=2.26 Hz, 1 H) 7.66 (dd, *J*=8.53, 2.26 Hz, 1 H) 7.50 - 7.59 (m, 1 H) 7.27 (d, *J*=8.03 Hz, 1 H) 7.13 (d, *J*=15.56 Hz, 2 H) 6.73 - 6.90 (m, 2 H) 5.74 (s ancho, 1 H) 5.18 (s ancho, 1 H) 3.72 (s, 3 H) 2.03 - 2.19 (m, 1 H) 1.55 - 1.97 (m, 5 H) 1.07 - 1.23 (m, 2 H). 19F NMR (376 MHz, CD_3OD) δ ppm -139.71 (s ancho, 1 F). MS(ESI) *m/z*: 578.3 (M+H)+.

Ejemplo I-109.

Éster metílico del ácido {(10R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-10-metil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2TFA



I-109A. Éster metílico del ácido ((10R,14S)-14-

amino-10-metil-9-oxo-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico, sal 3 HCl: I-109A se preparó siguiendo el procedimiento descrito en 1F, sustituyendo 1D por 116G.

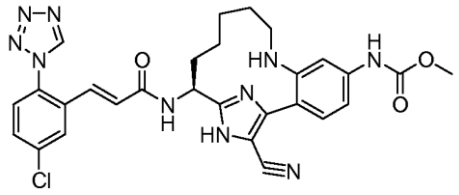
I-109B. Éster metílico del ácido ((10R,14S)-14-amino-10-metil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il)-carbámico, sal 3 TFA: A una suspensión amarilla de I-109A sal HCl (0.05 g, 0.116 mmol) en tetrahidrofurano (5 ml) se añadió Complejo de borano-THF (1M) (1.162 ml, 1.162 mmol), La reacción se volvió incolora y transparente. Se selló y se calentó a 60°C durante 1 hr antes de enfriarse hasta ta. Se añadió MeOH seguido por adición de 1 ml de HCl (4M en dioxano). La reacción se selló y se calentó a 60°C durante la noche. La mezcla de reacción se concentró, se disolvió en MeOH, se separó el sólido por filtración. La purificación por cromatografía en fase inversa dio I-109B (5.3 mg, 27%) como un sólido amarillo pálido. EM (IEP) *m/z*: 344.3 (M+H)+.

I-109C. El Ejemplo I-109 se preparó siguiendo los procedimientos descritos en 1G, sustituyendo 1F por I-109B. 1H NMR (500 MHz, CD_3OD) δ ppm 9.54 (s, 1 H), 8.03 (d, *J*=2.5 Hz, 1 H), 7.71 - 7.76 (m, 1 H), 7.69 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.61 (d, *J*=8.5 Hz, 1 H), 7.43 - 7.49 (m, 1 H), 7.23 - 7.32 (m, 3 H), 6.83 (d, *J*=15.7 Hz, 1 H), 5.31 (dd, *J*=11.3, 6.3 Hz, 1 H), 3.69 (s, 3 H), 3.02 - 3.04 (m, 1 H), 2.99 -

3.02 (m, 1 H), 2.67 - 2.74 (m, 1 H), 2.24 - 2.39 (m, 2 H), 2.05 - 2.15 (m, 1 H), 1.83 - 1.92 (m, 1 H), 1.54 - 1.65 (m, 1 H), 1.40 - 1.51 (m, 1 H), 0.96 (d, *J*=7.2 Hz, 3 H). EM (IEP) *m/z*: 576.2 (M+H)+. HPLC analítica: Tr = 6.26 min.

Ejemplo I-115.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciano-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal 2 TFA



I-115A. Éster *terc*-butílico del ácido [(S)-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: Se preparó I-115A a partir de 10B siguiendo los procedimientos descritos en la etapa 10C, sustituyendo hidróxido de amonio por but-3-enilamina y llevando a cabo la reacción a 90°C; seguido por las etapas 2E/F; y 10G, añadiendo 2 equivalentes de TFA y sustituyendo la mezcla metanol/EtOAc por EtOAc. EM (IEP) *m/z:* 560.5 (M+H)+.

I-115B. Éster *terc*-butílico del ácido [(S)-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-

trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: Se enfrió hasta 0°C bajo argón una mezcla de 115A (1.21 g, 2.162 mmol) y TEA (0.362 ml, 2.59 mmol) en EtOAc (10.81 ml) y luego se añadió gota a gota TFAA (0.336 ml, 2.378 mmol). Después de ~2 h a 0°C, la mezcla de reacción se diluyó con EtOAc, se lavó con agua (2x) y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía en columna ultrarrápida proporcionando I-115B como una espuma blanquecina (1.14 g, 80 %). EM (IEP) *m/z:* 656.5 (M+H)+.

I-115C. Éster *terc*-butílico del ácido [(S)-17-bromo-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: A una solución enfriada (< 0°C) de I-115B (1.14 g, 1.738 mmol) en $CHCl_3$ (5.79 ml) se añadió NBS (0.325 g, 1.825 mmol). La reacción se agitó bajo argón a 0°C durante 20 min. La mezcla de reacción se evaporó y el residuo se purificó por cromatografía en columna ultrarrápida proporcionando I-115C como una espuma color durazno claro (1.3 g, 102 %). EM (IEP) *m/z:* 734.5 (M+H)+.

I-115D. Éster *terc*-butílico del ácido [(S)-17-ciano-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-

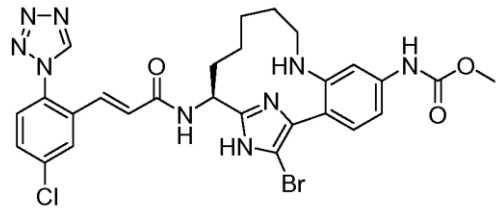
triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: En un vial de microondas, se añadió I-115C (0.1 g, 0.136 mmol) a una solución de cianuro de zinc (0.016 g, 0.136 mmol) en DMF (2.72 ml). La mezcla se evacuó/llenó con Ar tres veces y luego se añadió tetraquis(trifenilfosfina)paladio(0) (7.86 mg, 6.81 µmol). El vial se evacuó/llenó de nuevo con Ar tres veces, luego se tapó y se calentó a 120°C en el microondas durante 120 minutos. Se añadieron otros 0.05 equivalentes de catalizador (7.86 mg), el vial de reacción se tapó y se evacuó/llenó con Ar tres veces, luego se calentó a 120°C en el microondas durante otros 20 minutos. La reacción se evaporó hasta sequedad y el residuo se purificó por cromatografía en fase normal proporcionando I-115D como una espuma blanca, (0.088 g, 95 %). EM (IEP) *m/z:* 681.5 (M+H)+.

I-115E. El Ejemplo I-115 se preparó a partir de I-115D siguiendo los procedimientos descritos en la etapa I-61B y 1G proporcionando el Ejemplo 115 como un sólido blanco (0.0077 g, 19.8%). 1H NMR (500 MHz, CD_3OD) δ ppm 9.91 (1 H, s) 9.55 (1 H, d, *J*=1.10 Hz) 8.07 (1 H, s ancho) 8.02 (1 H, d, *J*=2.20 Hz) 7.97 (1 H, dd, *J*=8.25, 4.40 Hz) 7.69 (1 H, dd, *J*=8.80, 2.20 Hz) 7.59 - 7.63 (1 H, m) 7.41 (1 H, dd, *J*=8.80, 2.20 Hz) 7.19 - 7.25 (1 H, m) 6.83 (1 H, dd, *J*=15.95, 2.20 Hz) 5.29 (1 H, dd, *J*=11.00, 6.05 Hz) 3.76 (3 H, s) 3.28 (1 H, s ancho) 2.99 - 3.07 (1 H, m) 2.14 - 2.23 (1 H, m) 2.04 -

2.14 (2 H, m) 1.85 - 1.93 (1 H, m) 1.69 (2 H, t, *J*=12.92 Hz) 1.42 (1 H, t, *J*=9.62 Hz) 0.88 (1 H, q, *J*=11.18 Hz). EM (IEP) *m/z:* 587.3 (M+H)+. HPLC analítica: TR= 5.83 min.

Ejemplo I-116.

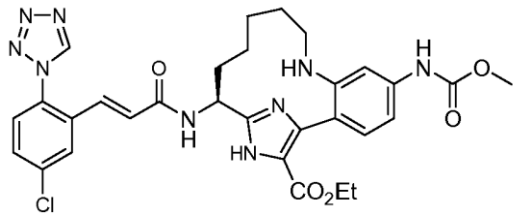
Éster metílico del ácido {(S)-17-bromo-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, 2 TFA



El Ejemplo I-116 se preparó a partir de I-115C siguiendo los procedimientos descritos en la etapa I-61B y 1G, como un sólido blanco (0.046 g, 78 % de rendimiento). 1H NMR (500 MHz, CD_3OD) δ ppm 9.75 (1 H, s) 9.55 (1 H, s) 8.88 (1 H, d, *J*=4.40 Hz) 8.02 (1 H, d, *J*=2.20 Hz) 7.98 (1 H, d, *J*=8.80 Hz) 7.96 (1 H, s ancho) 7.70 (1 H, dd, *J*=8.80, 2.20 Hz) 7.60 - 7.64 (1 H, m) 7.33 (1 H, dd, *J*=8.80, 2.20 Hz) 7.24 (1 H, d, *J*=15.40 Hz) 6.81 (1 H, d, *J*=15.40 Hz) 5.22 (1 H, dd, *J*=11.00, 6.60 Hz) 3.73 (3 H, s) 3.19 - 3.25 (1 H, m) 2.95 (1 H, t, *J*=12.10 Hz) 2.10 - 2.19 (1 H, m) 1.97 - 2.09 (2 H, m) 1.82 - 1.91 (1 H, m) 1.68 (2 H, t, *J*=12.37 Hz) 1.37 (1 H, s ancho) 0.72 - 0.84 (1 H, m). EM (IEP) *m/z:* 640.3 (M+H)+. HPLC analítica: TR= 6.34 min.

Ejemplo I-118.

Éster etílico del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-17-carboxílico, 2 TFA

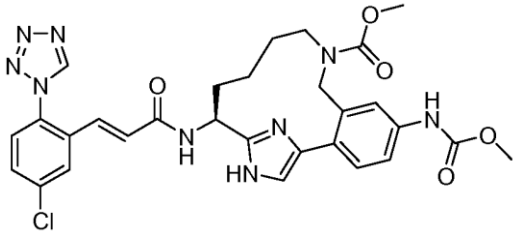


I-118A. Éster etílico del ácido (S)-14-amino-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-17-carboxílico, 3TFA: Se disolvió I-115D (0.086 g, 0.126 mmol) en EtOH (0.5 ml) y luego se añadió H2SO4 concentrado (10.10 µl, 0.189 mmol) a temperatura ambiente. La reacción se llevó a reflujo a 90°C bajo Ar durante la noche. Se añadieron más EtOH (2 ml) y H_2SO_4 concentrado (0.2 ml) y la reacción se calentó a 90°C durante otras 18 horas más, luego se enfrió hasta temperatura ambiente y se vertió en agua fría. La fase acuosa se ajustó a pH ~10 con NaOH 1N y se extrajo 3x con EtOAc; las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y evaporaron. El residuo se purificó por HPLC de fase inversa proporcionando I-118A (0.019 g, 20.2%). EM (IEP) *m/z:* 402.3 (M+H)+.

I-118B. El Ejemplo I-118 se obtuvo como un sólido amarillo claro a partir de I-118A siguiendo el procedimiento descrito en la Etapa 1G (0.014 g, 58.5 %). 1H NMR (500 MHz, CD_3OD) δ ppm 9.78 (1 H, s) 9.52 (1 H, s) 8.32 (1 H, dd, *J*=8.67, 1.51 Hz) 8.03 (1 H, d, *J*=2.20 Hz) 8.01 (1 H, d, *J*=2.20 Hz) 7.68 (1 H, dd, *J*=8.39, 2.34 Hz) 7.60 (1 H, d, *J*=8.53 Hz) 7.32 (1 H, d, *J*=8.80 Hz) 7.19 (1 H, d, *J*=15.41 Hz) 6.80 (1 H, d, *J*=15.41 Hz) 5.32 (1 H, dd, *J*=10.04, 6.46 Hz) 4.32 - 4.41 (2 H, m) 3.77 (3 H, s) 3.21 (1 H, ddd, *J*=12.52, 4.13, 3.99 Hz) 2.93 - 3.03 (1 H, m) 2.09 - 2.19 (1 H, m) 1.81 - 2.05 (3 H, m) 1.68 (2 H, t, *J*=12.24 Hz) 1.37 (3 H, t, *J*=7.15 Hz) 1.30 (1 H, d, *J*=6.88 Hz) 0.69 - 0.81 (1 H, m). EM (IEP) *m/z:* 634.4 (M+H)+. HPLC analítica: TR= 6.46 min.

Ejemplo I-119.

Éster metílico del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-9,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal 1 TFA



I-119A. Éster metílico del ácido {4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-

formil-fenil}-carbámico: A una solución de 10B (351 mg, 0.589 mmol) en THF (3 ml) a -78°C se añadió metil litio (0.786 ml, 1.179 mmol). La reacción se agitó a -78°C durante 30 min, a continuación se añadió gota a gota butil litio (0.552 ml, 0.884 mmol) en hexanos. Después de 30 mins, se añadió a la mezcla de reacción DMF (0.055 ml, 0.707 mmol). La reacción se agitó a -78°C, antes se inactivó con NH4Cl concentrado (ac), se extrajo con éter (2x), las fases de éter combinadas se lavaron salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron proporcionando un aceite amarillo. La purificación por cromatografía en fase normal dio I-119A como una espuma amarillo pálido (187 mg, 58%). EM (IEP) *m/z*: 545.2 (M+H)+.

1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: A una solución de I-119A (187 mg, 0.343 mmol) en DCM (3.433 ml) se añadió prop-2-en-1-amina (19.60 mg, 0.343 mmol) y una gota de AcOH. La reacción se agitó a ta durante 30 min, se añadió triacetoxiborohidruro sódico (109 mg, 0.515 mmol). Después de 3 hrs, la reacción se diluyó con DCM, se lavó con Na_2CO_3 saturado, salmuera, se secó sobre $MgSO_4$. Se filtró y se concentró. La purificación por cromatografía en fase normal dio I-119B como una

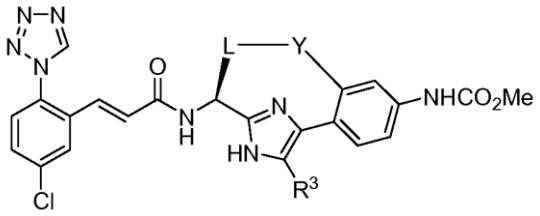
espuma blanca (145 mg, 72%). EM (IEP) *m/z*: 586.5 (M+H)+.

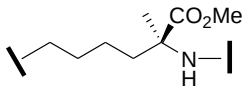
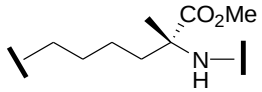
I-119C. Éster terc-butílico del ácido [(S)-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-9,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: Se preparó I-119C siguiendo los procedimientos descritos en 2E/2F, sustituyendo 2D por I-119B; seguido por 2G. EM (IEP) *m/z*: 560.4 (M+H)+.

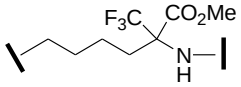
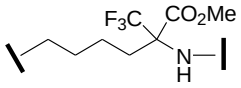
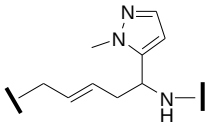
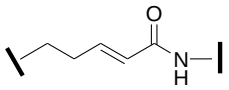
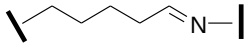
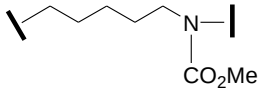
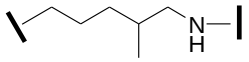
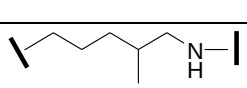
I-119D. Éster metílico del ácido (S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-9,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: A una solución de I-119C (14 mg, 0.021 mmol) en CH2Cl2 (Volumen 1 ml) se añadió cloroformiato de metilo (1.967 µl, 0.025 mmol) en 0.4 ml DCM, seguido por TEA (0.014 ml, 0.099 mmol). La reacción se agitó a TA durante 30 min. La mezcla de reacción se concentró, se volvió a disolver en EtOAc, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se separó el sólido por filtración, se concentró. La purificación por cromatografía en fase normal dio I-119D como un sólido blanco (7 mg, 55%). EM (IEP) *m/z*: 618.5 (M+H)+.

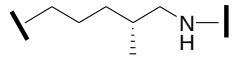
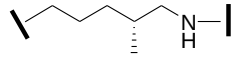
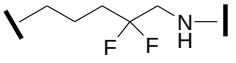
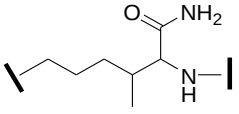
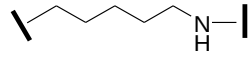
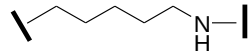
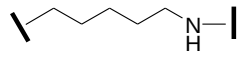
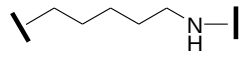
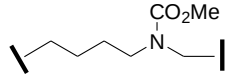
I-119E. El Ejemplo I-119 se preparó siguiendo los procedimientos descritos en 1F, sustituyendo 1D por I-119D; seguido por 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 - 9.53 (m, 1 H), 7.98 (d, *J*=2.5 Hz, 1 H), 7.67 - 7.72 (m, 2 H), 7.55 - 7.61 (m, 2 H), 7.49 (s, 1 H), 7.40 (d, *J*=8.2 Hz, 1 H), 7.18 (d, *J*=15.7 Hz, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 4.92 - 4.98 (m, 1 H), 4.31 - 4.52 (m, 1 H), 3.77 (s, 3 H), 3.62 - 3.65 (m, 2 H), 3.61 (s, 3 H), 3.04 - 3.18 (m, 1 H), 2.98 - 3.01 (m, 1 H), 2.13 - 2.28 (m, 1 H), 1.77 - 1.92 (m, 1 H), 1.51 - 1.69 (m, 1 H), 1.20 - 1.43 (m, 2 H). EM (IEP) *m/z*: 620.3 (M+H)+. HPLC analítica: Tr = 4.56 min. (Método B).

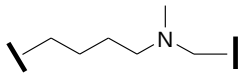
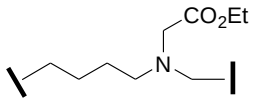
Tabla I-6: Ejemplos I-101 a I-121



Ej. n°	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-101		H	634.3	4.5 (B)
I-102		H	634.3	5.0 (B)

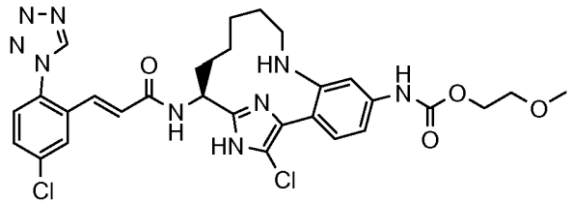
Ej. nº	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-103	 (homoquiral)	H	688.3	5.1 (B)
I-104	 (homoquiral)	H	688.3	5.8 (B)
I-105	 (mezcla de diastereómeros)	H	640.2	5.4
I-106		H	573.9	3.9 (B)
I-107		F	578.3	8.6
I-108		H	620.2	5.5
I-109	 (mezcla de diastereómeros)	H	576.3	4.8 (B)
I-110	 (mezcla 2:1 de diastereómeros)	H	576.2	6.2

Ej. nº	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-111		H	576.3	6.3
I-112		Cl	610.3	5.7 (B)
I-113		H	598.2	4.9 (B)
I-114	 (mezcla de diastereómeros)	H	619.3	5.0
I-115		CN	587.3	5.8
I-116		Br	640.3	6.3
I-117		Me	576.4	5.8
I-118		CO_2Et	634.4	6.5
I-119		H	620.3	4.6 (B)

Ej. nº	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-120		H	576.4	7.2
I-121		H	648.5	7.6

Ejemplo I-123.

Éster 2-metoxi-etílico del ácido {(S)-17-cloro-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, 2 TFA



I-123A. Éster *terc*-butílico del ácido {(S)-1-[4-(4-amino-2-bromo-fenil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-but-3-enil}-carbámico: A una solución agitada de 10B (1.5 g, 2.52 mmol) disuelto en MeOH (36 ml) se añadió NaOH 1N (50.4 ml, 50.4 mmol) gota a gota a temperatura ambiente. La reacción se agitó a 85°C bajo un condensador de reflujo durante la noche. El solvente se eliminó a presión reducida y el residuo se repartió entre

EtOAc/agua. La fase acuosa se extrajo con EtOAc 3x, las fases orgánicas combinadas se lavaron con salmuera, se secaron con sulfato sódico, se filtraron y evaporaron proporcionando el producto bruto, I-123A (1.42 g, 105 %), como un sólido amarillo. EM (IEP) *m/z:* = 537.2 (M+H)+.

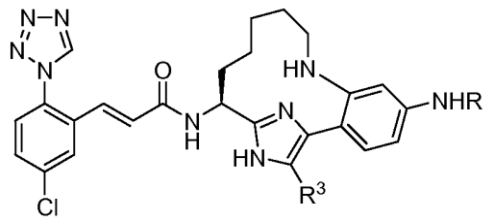
I-123B. Éster 2-metoxi-etílico del ácido {3-bromo-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: Se disolvió I-123A (1.42 g, 2.64 mmol) en DCM (26.4 ml). Se añadió piridina (0.855 ml, 10.57 mmol) seguido por la adición gota a gota de carbonocloridato de 2-metoxietilo a 0°C. La reacción se dejó calentar hasta TA y se agitó. Se añadieron otros 2 equivalentes de carbonocloridato de 2-metoxietilo (0.439 g, 3.17 mmol) y se continuó agitando a ta durante 2 horas. La reacción se inactivó con bicarbonato sódico saturado y se extrajo con EtOAc 3x. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto bruto se purificó por cromatografía sobre gel de sílice proporcionando I-123B (1.23 g, 72.8 % de rendimiento) como un sólido oleoso amarillo. EM (IEP) *m/z:* = 639.3/641.3 (M+H)+.

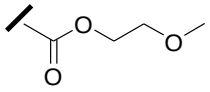
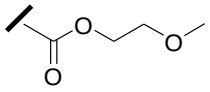
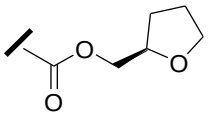
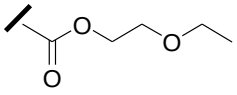
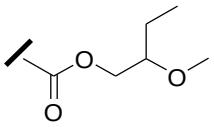
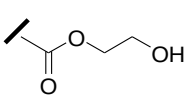
I-123C. Éster 2-metoxi-etílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-

1(17),2,4,6,15(18)-pentaen-5-il}-carbámico: Se preparó I-123C a partir de I-123B usando los procedimientos descritos para 115A, 61B y 1G. Se usó producto bruto sin purificación en la etapa siguiente. EM (IEP) *m/z:* = 606.4 (M+H)+.

I-123D. El Ejemplo I-123: I-123C (.085 g, 0.140 mmol) se disolvió en acetonitrilo (1 ml)/cloroformo (1 ml) y se añadió TFA (0.086 ml, 1.122 mmol) seguido por NCS (0.022 g, 0.168 mmol) y la mezcla se agitó a 65°C bajo Ar durante 1.75 h. La reacción se diluyó con agua y se extrajo con EtOAc 2x. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto bruto se purificó por cromatografía de fase inversa proporcionando el Ejemplo I-123 (0.056 g, 44.6 %) como un sólido amarillo. 1H NMR (500 MHz, *CD_3OD*) δ ppm 9.79 (1 H, s ancho), 9.54 (1 H, s), 8.90 (1 H, d, *J*=5.50 Hz), 8.02 (1 H, d, *J*=2.20 Hz), 7.93 (1 H, s ancho), 7.86 (1 H, d, *J*=8.80 Hz), 7.67 - 7.72 (1 H, m), 7.58 - 7.64 (1 H, m), 7.32 (1 H, dd, *J*=8.80, 2.20 Hz), 7.18 - 7.28 (1 H, m), 6.81 (1 H, d, *J*=15.95 Hz), 5.20 (1 H, dd, *J*=11.27, 6.32 Hz), 4.17 - 4.29 (2 H, m), 3.61 (2 H, t, *J*=4.67 Hz), 3.37 (3 H, s), 3.18 - 3.26 (1 H, m), 2.90 - 3.02 (1 H, m), 1.94 - 2.21 (3 H, m), 1.78 - 1.91 (1 H, m), 1.62 - 1.74 (2 H, m), 1.30 - 1.45 (1 H, m), 0.72 - 0.91 (1 H, m). EM (IEP) *m/z:* = 640.3 (M+H)+. HPLC analítica: TR= 5.9 min.

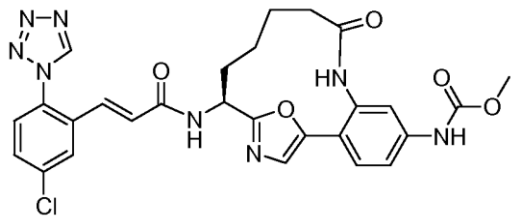
Tabla I-7: Ejemplos I-122 a I-127



Ej. n°	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
I-122		H	606.3	6.2
I-123		Cl	640.3	5.9
I-124		H	632.4	5.9
I-125		H	620.4	5.9
I-126		H	634.4	6.3
I-127		H	592.4	5.2

Ejemplo I-134.

N-[(14S)-14-[(2E)-3-[5-Cloro-2-(1H-1,2,3.4-tetrazol-1-il)fenil]prop-2-enamido]-9-oxo-18-oxa-8,16-diazatriciclo[13.2.1.2.7]octadeca-1(17),2(7),3,5,15-pentaen-5-il]carbamato de metilo, sal del ácido trifluoracético



I-134A. 4-(2-Aminoacetil)-3-bromofenilcarbamato de metilo: A una solución de Intermediario 8 (3.0 g, 8.55 mmol) en acetonitrilo (40 ml) se añadió diformilamida de sodio (0.975 g, 10.26 mmol). La suspensión se agitó bajo argón a ta durante 5 hrs. La mezcla se filtró y el sólido se lavó con MeCN caliente. El filtrado se concentró dando un sólido castaño. A continuación se añadió HCl 4 N acuoso (25 ml) y la suspensión resultante se calentó a reflujo. Después de 2 h, se enfrió la reacción transparente hasta ta y la solución se concentró dando 2.45 g (100%) de I-134A como un sólido castaño claro. EM (IEP) *m/z*: 287.0 (M+H)+ y 288.9 (M+2+H)+.

I-134B. N-[(1S)-1-[(2-{2-Bromo-4-[(metoxicarbonil)amino]fenil}-2-oxoetil)carbamoil]but-3-en-1-il]carbamato de terc-butilo: A una solución de ácido (S)-2-(*terc*-butoxicarbonilamino)pent-4-enoico (515 mg, 2.393 mmol)

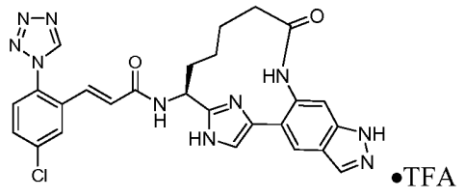
en DMF (15 ml) se añadió HOBt (476 mg, 3.11 mmol) y EDC (596 mg, 3.11 mmol). Después de 5 min, se añadió una solución de I-134A (774 mg, 2.393 mmol) y DIEA (0.418 ml, 2.393 mmol) en DMF (5 ml). La reacción se agitó bajo argón a ta durante 2 h. La mezcla de reacción se diluyó con EtOAc, se lavó con HCl 1M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró. La purificación por cromatografía en fase normal dio 1.05 g (91%) de I-134B como un sólido color castaño. EM (IEP) *m/z*: 484.0 (M+H)+ y 485.9 (M+2+H)+.

I-134C. N-[(1S)-1-(5-{2-Bromo-4-[(metoxicarbonil)amino]fenil}-1,3-oxazol-2-il)but-3-en-1-il]carbamato de terc-butilo: Se sometió a microondas a 120°C durante 12 minutos una solución de I-134B (900 mg, 1.858 mmol) y reactivo de Burgess (1771 mg, 7.43 mmol) en THF(10 ml). La mezcla de reacción se diluyó con EtOAc, se lavó con H2O y salmuera. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal que dio 398 mg (46%) de I-134C como un sólido. EM (IEP) *m/z*: 466.0 (M+H)+ y 468.0 (M+2+H)+.

I-134D. El Ejemplo I-134 se preparó siguiendo los procedimientos descritos en 10C (alternativo), sustituyendo 10B por I-134C; seguido por las etapas 10D; 2E/2F, sustituyendo DCM por DCE y llevando a cabo la reacción a

70°C; 2G; 3C; y 1G. 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.72 (1 H, s), 9.70 (1 H, s), 9.59 (1 H, s), 8.64 (1 H, d, J=7.53 Hz), 7.78 (1 H, d, J=2.01 Hz), 7.60 (1 H, dd, J=8.53, 2.26 Hz), 7.57 (1 H, d, J=8.53 Hz), 7.38 (1 H, d, J=8.53 Hz), 7.27 (1 H, dd, J=8.66, 1.88 Hz), 7.16 (1 H, d, J=1.76 Hz), 7.13 (1 H, s), 6.75 (1 H, d, J=15.56 Hz), 6.68 (1 H, d, J=15.56 Hz), 4.91 - 5.02 (1 H, m), 3.53 (3 H, s), 1.84 - 1.94 (1 H, m), 1.73 - 1.84 (1 H, m), 1.60 - 1.73 (2 H, m), 1.40 - 1.54 (1 H, m), 1.12 - 1.25 (1 H, m), 0.73 - 0.91 (1 H, m). EM (IEP) *m/z*: 577.2 (M+H)+. HPLC analítica: Tr = 6.39 min.

Ejemplo I-136.



I-136A. 5-Bromo-6-nitro-1H-indazol: Una solución de nitrito sódico (2.189 g, 31.7 mmol) en agua (6.29 ml) se añadió gota a gota a una solución de 4-bromo-2-metil-5-nitroanilina preparada de acuerdo con *J. Org. Chem.*, 44:4609 (1979) (7.33 g, 31.7 mmol) en ácido acético glacial (793 ml), y la mezcla de reacción se agitó bajo argón a temperatura ambiente durante la noche. La mezcla se concentró dando un residuo oleoso. Se añadió agua para precipitar el producto bruto que se recogió por filtración y se lavó con agua, a continuación se secó a vacío proporcionando un sólido

naranja. El sólido se secó por liofilización proporcionando I-136A (6.77 g, 88%). (M+H)+ EM (IEP) *m/z*: 242.1 (M+H)+.

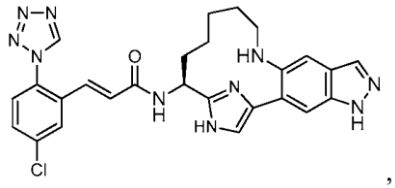
I-136B. 5-(1-Etoxivinil)-6-nitro-1H-indazol: Una solución de I-136A (7.65 g, 31.6 mmol), tributil(1-etoxivinil)estanano (12.81 ml, 37.9 mmol), y $(Ph_3P)_2PdCl_2$ (1.109 g, 1.580 mmol) en tolueno (63.2 ml) se calentó a 115°C bajo Ar. La reacción se enfrió hasta temperatura ambiente y se filtró. El filtrado se concentró y secó a vacío proporcionando un aceite marrón oscuro, que se disolvió en DCM y se absorbió en una almohadilla seca de gel de sílice. La almohadilla se lavó secuencialmente con Hex y EtOAc. La fracción de EtOAc se condensó a un aceite marrón oscuro, que luego se purificó por cromatografía en fase normal proporcionando una mezcla ~3:1 de SM a producto. Esta mezcla se disolvió en dioxano y se añadieron tributil(1-etoxivinil)estanano (3.46 ml, 10.23 mmol), CuI (0.162 g, 0.852 mmol), y tetraquis(trifenilfosfina)paladio(0) (0.492 g, 0.426 mmol). La mezcla se desgasificó y luego se calentó a 110°C bajo Ar durante 3 hrs, a continuación se dejó asentar a TA durante la noche. La mezcla de reacción se filtró y los sólidos se lavaron con EtOAc. El filtrado se destiló hasta un aceite marrón que se purificó por cromatografía ultrarrápida proporcionando I-136B como un aceite naranja, (1.93 g, 61.1%). EM (IEP) *m/z*: 234.1 (M+H)+.

I-136C. 2-Bromo-1-(6-nitro-1H-indazol-5-il)etanona:

A una solución de I-136B (1.39 g, 5.96 mmol) en THF (8.83 ml) y agua (3.09 ml) se añadió NBS (1.061 g, 5.96 mmol). La reacción se agitó a ta durante ~45 min, a continuación se repartió entre EtOAc/salmuera. La fase de salmuera se volvió a extraer con EtOAc, y la fase orgánica reunida se secó sobre MgSO4, se filtró, se concentró, y secó a vacío proporcionando 2.01 g de un sólido naranja que se combinó con 0.698 g de una segunda preparación y se disolvió en una pequeña cantidad de cloruro de metileno. El sólido castaño insoluble se filtró proporcionando 0.381 g (16.6%) de producto. El filtrado se purificó por cromatografía en fase normal proporcionando y otros 0.783 de I-136C (34%). EM (IEP) *m/z*: 284.1 (M+H)+.

Ejemplo I-136D. El compuesto del título se preparó a partir de I-136C siguiendo los procedimientos descritos para 2A; 1B; 10B; 122C; 10D; 2E; 2G; 10H; y 1G. 1H NMR (500 MHz, DMSO-d_6) δ ppm 14.27 (1 H, s ancho) 13.26 (1 H, s) 9.86 (1 H, s) 9.63 (1 H, s ancho) 8.89 (1 H, s ancho) 8.17 (1 H, s) 7.99 (1 H, s) 7.92 (1 H, d, *J*=2.20 Hz) 7.72 - 7.80 (2 H, m) 7.64 (1 H, s ancho) 7.43 (1 H, s ancho) 6.91 - 6.97 (1 H, m) 6.80 - 6.85 (1 H, m) 5.04 (1 H, dt, *J*=9.83, 4.85 Hz) 2.34 - 2.40 (1 H, m) 2.10 (1 H, s ancho) 2.00 (1 H, s ancho) 1.82 (1 H, s ancho) 1.63 (1 H, s ancho) 1.39 (1 H, s ancho) 1.28 (1 H, s ancho) 0.89 (1 H, s ancho). EM (IEP) *m/z*: 543.3 (M+H)+. HPLC analítica: Tr = 4.8 min.

Ejemplo I-140.



, 2TFA

I-140A. 3-Amino-N-metoxi-N,4-dimetilbenzamida: Se disolvió ácido 3-amino-4-metilbenzoico (5.0 g, 33.1 mmol) en DMF (165 ml) y se añadieron TEA (23.05 ml, 165 mmol), EDC (7.93 g, 41.3 mmol), HOBT (6.33 g, 41.3 mmol) y clorhidrato de N,O-dimetilhidroxilamina (8.07 g, 83 mmol). La reacción se agitó bajo Ar a temperatura ambiente durante la noche. La mezcla se diluyó con EtOAc y se lavó 3x con agua. Las aguas de lavado acuosas combinadas se volvieron a extraer con EtOAc. Las fases orgánicas se reunieron y se lavaron con salmuera, a continuación se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo naranja resultante se purificó por cromatografía en fase normal proporcionando el producto como un aceite incoloro (2.87 g, 44.7%). EM (IEP) *m/z*: 195.1 *m/z* (M+H)+.

I-140B. 5-Amino-2-bromo-N-metoxi-N,4-dimetilbenzamida: Se añadió NBS (2.52 g, 14.16 mmol) a una solución de I-140A (2.75 g, 14.16 mmol) en DMF (28.3 ml), y la mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con H_2O y se extrajo 3x con EtOAc. Los extractos orgánicos se reunieron y se lavaron con

salmuera, a continuación se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se disolvió en una pequeña cantidad de cloruro de metileno y el precipitado se separó por filtración proporcionando el producto como un sólido blanco (1.53 g, 39.6%). El filtrado se purificó por cromatografía en fase normal proporcionando más producto (1.13g, 29.2%). EM (IEP) *m/z*: 273.1 *m/z* (M+H)+.

I-140C. 5-Bromo-N-metoxi-N-metil-1H-indazol-6-carboxamida: Este compuesto se preparó a partir de I-140B (2.66 g, 9.74 mmol) siguiendo el procedimiento descrito para la etapa I-136A. El producto se aisló como un sólido amarillo (2.55g, 92%). EM (IEP) *m/z*: 284.1 *m/z* (M+H)+.

I-140D. 5-Bromo-6-(metoxi(metil)carbamoil)-1H-indazol-1-carboxilato de terc-butilo: Una solución de I-140C (2.55 g, 8.98 mmol), $(Boc)O_2$ (4.79 ml, 20.64 mmol), TEA (5.00 ml, 35.9 mmol), y DMAP (0.658 g, 5.39 mmol) en THF (44.9 ml) se agitó bajo Ar a TA durante la noche. La mezcla de reacción se concentró para eliminar el THF y se repartió entre EtOAc y solución acuosa saturada de NH4Cl. Las fases se separaron y la fase acuosa se volvió a extraer con EtOAc. Las fases orgánicas se reunieron y se lavaron con salmuera, a continuación se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal proporcionando I-140D como una espuma amarillo claro (3.23 g, 94%). EM (IEP) *m/z*: 384.1 *m/z* (M+H)+

I-140E. 1-(5-Bromo-1H-indazol-6-il)etanona: A una solución de I-140D (3.1 g, 8.07 mmol) en THF (81 ml) en un matraz de fondo redondo de tres bocas a 0°C se añadieron 4 eq. de bromuro de metilmagnesio (1.4 M en THF:Tolueno, 23.05 ml, 32.3 mmol) gota a gota durante 20min. La solución amarilla resultante se agitó bajo argón a 0°C. Después de ~1.5 horas desde comenzar la adición se añadieron gota a gota a la solución fría otros 3 eq de bromuro de metilmagnesio (1.4 M en THF:Tolueno, 17.29 ml, 24.20 mmol). La mezcla se agitó entonces bajo Ar durante la noche dejando que la reacción volviera gradualmente a temperatura ambiente. Se añadieron entonces gota a gota durante aproximadamente 10 minutos a TA otros 1.5 eq. de bromuro de metilmagnesio (1.4 M en THF:Tolueno. 8.64 ml, 12.10 mmol) y la reacción se agitó a TA bajo Ar durante otras 3 h antes del tratamiento. La reacción se inactivó a 0°C con MeOH seguido por un poco de agua, a continuación se diluyó con EtOAc. La suspensión se ajustó a pH5 para disolver los sólidos y luego se evaporó para eliminar el THF. Se añadió más EtOAc, y los orgánicos se lavaron con ácido acuoso diluido (pH ~5), $NaHCO_3$ saturado y salmuera, a continuación se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó por cromatografía en fase normal proporcionando I-140E como un sólido blanco (1.45 g, 75%). EM (IEP) *m/z*: 239.1 *m/z* (M+H)+

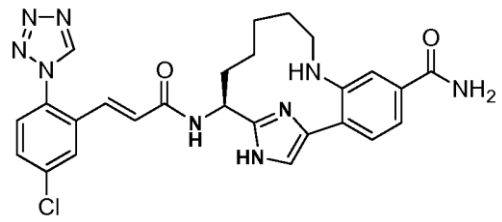
I-140F. 2-Bromo-1-(5-bromo-1H-indazol-6-il)etanona:

Se suspendió I-140E (1.45 g, 6.07 mmol) en THF (30.3 ml) y se añadió tribromuro de piridinio (1.959 g, 6.13 mmol). La mezcla se agitó bajo Ar a ta durante 15 min y luego 40°C durante 20 min. La reacción se evaporó y el sólido amarillo pálido resultante se repartió entre EtOAc/agua. La fase orgánica se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida proporcionando el producto monobromado deseado, I-140F (1.14 g, 59%). EM (IEP) *m/z*: 319.0 *m/z* (M+H)+

Ejemplo I-140. El compuesto del título se preparó a partir de I-140F siguiendo los procedimientos descritos para las etapas 2A; 1B; 10B; 10C sustituyendo 3-butenamina por hidróxido amónico; 2E/F; 154C/D; I-61B; y 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.56 (1 H, s) 8.18 (1 H, d, *J*=1.10 Hz) 8.02 (1 H, d, *J*=2.75 Hz) 7.79 (1 H, s) 7.69 (1 H, dd, *J*=8.80, 2.20 Hz) 7.62 (1 H, d, *J*=8.25 Hz) 7.60 (1 H, s ancho) 7.51 (1 H, s) 7.25 (1 H, d, *J*=15.40 Hz) 6.85 (1 H, d, *J*=15.95 Hz) 5.28 (1 H, dd, *J*=11.00, 6.60 Hz) 3.20 (1 H, d, *J*=12.65 Hz) 2.94 (1 H, t, *J*=12.37 Hz) 2.13 - 2.22 (1 H, m) 2.09 (2 H, t, *J*=12.65 Hz) 1.86 - 1.94 (1 H, m) 1.61 - 1.79 (2 H, m) 1.30 - 1.40 (1 H, m) 0.73 (1 H, d, *J*=12.65 Hz). EM (IEP) *m/z*: 529.4 *m/z* (M+H)+. HPLC analítica: Tr = 5.43 min.

Ejemplo I-141.

Amida del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-5-carboxílico, 2 TFA



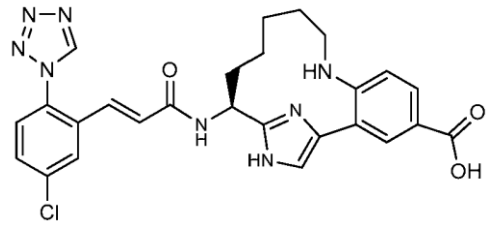
I-141-A. Ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-5-carboxílico, 2 TFA: Se preparó I-141A siguiendo los procedimientos descritos para el Ejemplo 142 sustituyendo ácido 3-bromo-4-metilbenzoico por ácido 4-bromo-3-metilbenzoico. EM (IEP) *m/z*: 533.3 *m/z* (M+H)+.

Ejemplo I-141. Se disolvió I-141A (.012 g, 0.016 mmol) en DMF (1 ml). Se añadió base de Hunig (0.028 ml, 0.158 mmol), seguido por cloruro de amonio (8.43 mg, 0.158 mmol), HOBT (2.90 mg, 0.019 mmol) y EDC (3.63 mg, 0.019 mmol). La reacción se agitó a temperatura ambiente durante 48 h, se destiló hasta sequedad y el residuo se purificó por cromatografía en fase inversa proporcionando el compuesto del título como un sólido blanco. 1H NMR (500 MHz, CD_3OD) δ ppm 9.53 (1 H, s), 8.87 (1 H, d, *J*=5.50 Hz), 8.00 (1 H, d, *J*=2.20

Hz), 7.91 - 7.98 (2 H, m), 7.86 (1 H, d, *J*=7.70 Hz), 7.65 - 7.70 (2 H, m), 7.59 (1 H, d, *J*=8.25 Hz), 7.18 (1 H, d, *J*=15.40 Hz), 6.80 (1 H, d, *J*=15.95 Hz), 5.30 (1 H, dd, *J*=10.72, 6.32 Hz), 3.24 - 3.29 (1 H, m), 2.95 - 3.06 (1 H, m), 1.98 - 2.22 (3 H, m), 1.80 - 1.96 (1 H, m), 1.58 - 1.78 (2 H, m), 1.24 - 1.44 (1 H, m), 0.76 - 1.00 (1 H, m). EM (IEP) *m/z*: 532.4 (M+H)+. HPLC analítica: Tr = 4.94 min.

Ejemplo I-142.

Ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-4-carboxílico, 2TFA



I-142A. 4-Bromo-3-metilbenzoato de terc-butilo: A una suspensión de ácido 4-bromo-3-metilbenzoico (2.8 g, 13.02 mmol) en THF (20 ml) y hexano (20 ml) en un baño de hielo bajo N2, se añadió 2,2,2-tricloroacetimidato de terc-butilo (3.50 ml, 19.53 mmol). Después de 10 min, se añadió BF_3•OEt_2 (0.165 ml, 1.302 mmol). La mezcla resultante se dejó calentar lentamente hasta ta y se agitó durante la noche. La mezcla se diluyó con Et_2O, se lavó con solución 1.5 M de K_2HPO_4, se secó sobre Na_2SO_4 anhidro, se filtró y se evaporó. El residuo se trituró con Et_2O al 20%/hexano, y el sólido se filtró. El

filtrado se evaporó. El residuo se purificó por cromatografía ultrarrápida proporcionando I-142A como un aceite color durazno claro (2.141 g, 60.6%). EM (IEP) *m/z*: 293.1/295.1 (M+Na)+ 271.2/273.1 (M+H)+ 215.1/217.1 (M+H-tBu)+.

I-142B. 4-Bromo-3-formilbenzoato de terc-butilo: Se disolvió I-142A (2.14 g, 7.89 mmol) en CCl_4 (39.5 ml) y se añadieron NBS (3.09 g, 17.36 mmol) y peróxido de benzoilo (0.191 g, 0.789 mmol). La mezcla se agitó bajo nitrógeno a reflujo en un baño de aceite a 90°C durante la noche. La reacción se diluyó con EtOAc y se lavó con agua y salmuera, se secó sobre Na_2SO_4 anhidro, se filtró y se evaporó. El producto bruto (3.39 g, 7.90 mmol) se disolvió en morfolina (10 ml, 115 mmol), y la mezcla se calentó con agitación en un baño de aceite a 60°C bajo nitrógeno durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con EtOAc, a continuación se agitó durante ~30 min. Los sólidos se separaron por filtración y se lavó con EtOAc. El filtrado se transfirió a un embudo de separación y se lavó 3X con ácido cítrico acuoso al 5% y una vez con salmuera, a continuación se secó sobre Na_2SO_4 anhidro, se filtró y se evaporó. El residuo se purificó por cromatografía ultrarrápida proporcionando I-142B como un sólido blanco (1.885 g, 84%). RMN de 1H NMR (500 MHz, $CDCl_3$) δ ppm 10.39 (1 H, s) 8.47 (1 H, d, J=2.20 Hz) 8.05 (1 H, dd, J=8.25, 2.20 Hz) 7.73 (1 H, d, J=8.53 Hz) 1.61 (9 H, s).

I-142C. 4-Bromo-3-(1-hidroxietil)benzoato de terc-butilo: Se disolvió I-142B en THF (50 ml) y se enfrió en un baño de hielo seco/acetona. A la solución fría se añadió cloruro de metilmagnesio (3.0 M en THF, 2.86 ml, 8.59 mmol) gota a gota durante 10-15 min. Se continuó agitando a -78°C durante 1 h momento en el cual la reacción se inactivó con solución acuosa al 10% de $KHSO_4$ y se calentó hasta temperatura ambiente. La mezcla se diluyó con agua y se extrajo 3x con EtOAc. Los extractos se reunieron y se lavaron con agua y salmuera, se secaron sobre Na_2SO_4 anhidro, se filtraron y se evaporaron. El residuo se purificó por cromatografía ultrarrápida proporcionando el producto deseado (1.18 g, 59.6%) junto con material de partida recuperado (0.425 g, 22%). EM (IEP) *m/z*: 301.1/303.1 (M+H)+ 245.1/247.1 (M+H-tBu)+.

I-142D. 3-Acetil-4-bromobenzoato de terc-butilo: Se disolvió I-142C (1.186 g, 3.94 mmol) en DCM (50 ml) y se trató con PCC (1.02 g, 4.73 mmol) con agitación bajo nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 4 h y luego se filtró a través de una almohadilla de CELITE®. El filtrado se evaporó hasta sequedad, y el residuo se purificó por cromatografía ultrarrápida proporcionando el producto como un líquido incoloro (0.938g, 80%). 1H NMR (500

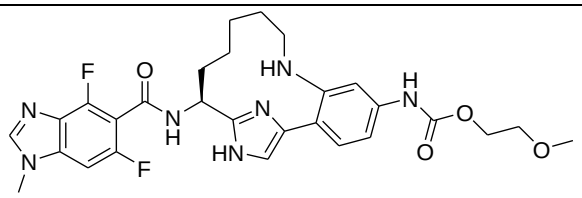
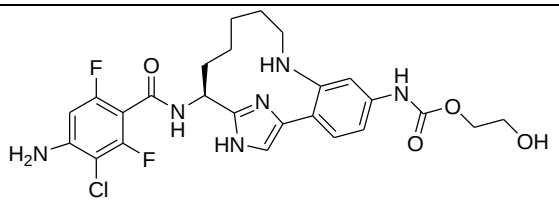
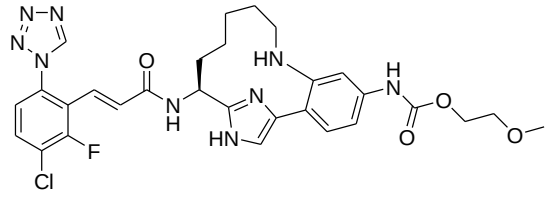
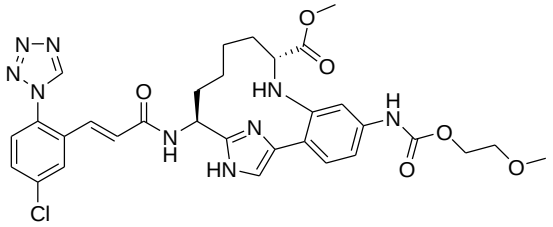
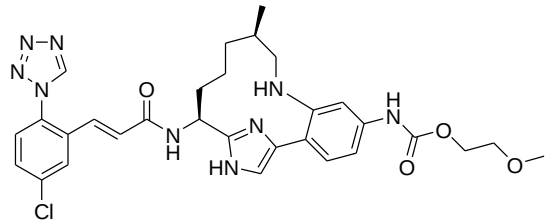
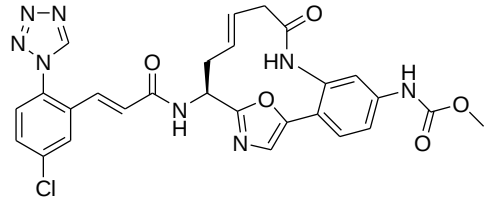
MHz, $CDCl_3$) δ ppm 8.04 (1 H, d, *J*=2.20 Hz) 7.88 (1 H, dd, *J*=8.25, 2.20 Hz) 7.67 (1 H, d, *J*=8.25 Hz) 2.65 (3 H, s) 1.59 (9 H, s).

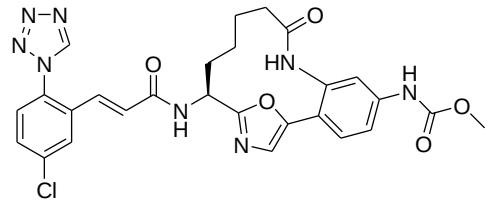
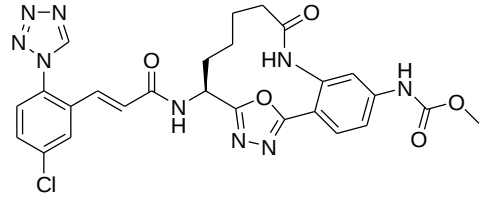
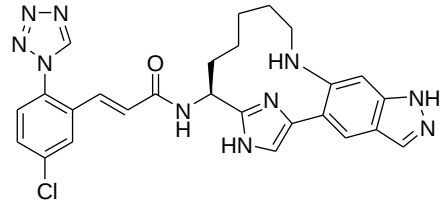
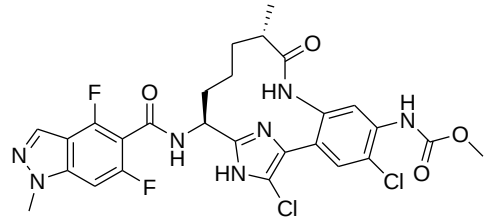
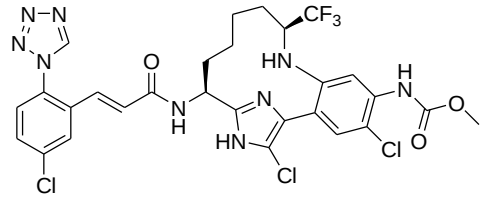
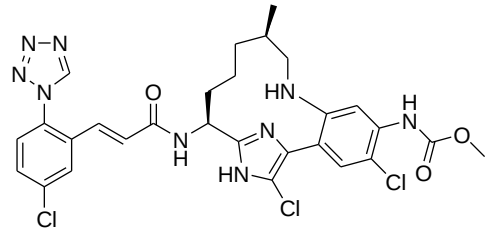
I-142E. 4-Bromo-3-(2-bromoacetil)benzoato de terc-butilo: Se disolvió I-142D (0.209 g, 0.699 mmol) en THF (3.5 ml) y tribromuro de piridinio (0.226 g, 0.706 mmol) se añadió con agitación bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante ~ 30 min. La reacción se diluyó con EtOAc y se lavó con salmuera, se secó sobre Na_2SO_4 anhidro, se filtró y se evaporó. El residuo se purificó por cromatografía ultrarrápida proporcionando I-142E (0.214g, 81%) contaminado con una pequeña cantidad de material de partida. EM (IEP) *m/z*: 323.0 (M+H-tBu)+.

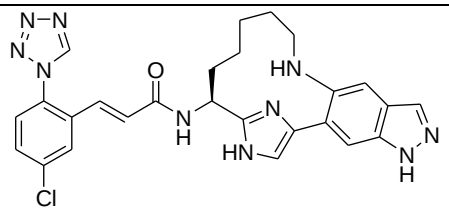
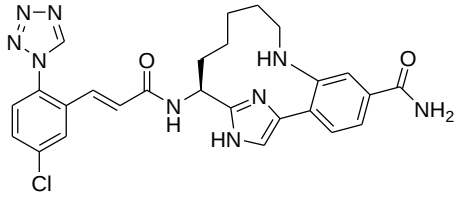
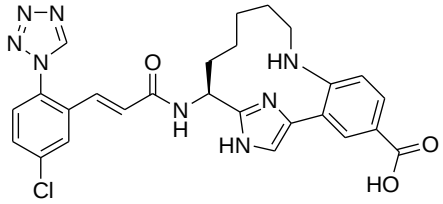
Ejemplo 142. Se convirtió I-142E en el compuesto del título usando la misma serie de etapas descrita para la conversión de I-140F en el Ejemplo 140. 1H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s) 8.29 (1 H, d, *J*=1.65 Hz) 7.95 - 8.03 (2 H, m) 7.64 - 7.74 (2 H, m) 7.59 (1 H, d, *J*=8.53 Hz) 7.43 (1 H, d, *J*=8.53 Hz) 7.18 (1 H, d, *J*=15.68 Hz) 6.78 (1 H, d, *J*=15.68 Hz) 5.28 (1 H, dd, *J*=10.45, 6.33 Hz) 3.07 - 3.17 (1 H, m) 2.83 - 2.94 (1 H, m) 2.10 - 2.26 (1 H, m) 1.86 - 2.05 (3 H, m) 1.55 - 1.72 (2 H, m) 1.32 - 1.45 (1 H, m) 0.78 - 0.95 (1 H, m). EM (IEP) *m/z*: 533.2 (M+H)+ HPLC

analítica: Tr = 5.71 min.

Tabla I-8: Ejemplos I-128 a I-142

Ej. nº	Estructura	LCMS $[M+H]^+$	HPLC Tr (min)
I-128		568.4	4.2
I-129		549.3	4.7
I-130		624.3	5.7
I-131		664.4	6.2
I-132		620.3	6.0
I-133		575.2	7.2

Ej. n°	Estructura	LCMS $[M+H]^+$	HPLC Tr (min)
I-134		577.2	6.4
I-135		578.0	7.2
I-136		543.3	4.8
I-137		586.2	5.7 (B)
I-138		698.1	10.0
I-139		644.3	5.9

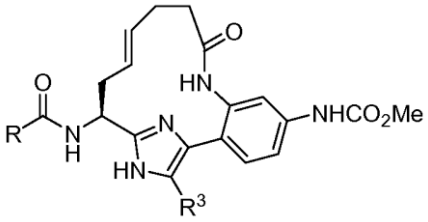
Ej. n°	Estructura	LCMS $[M+H]^+$	HPLC Tr (min)
I-140		529.4	5.4
I-141		532.4	4.9
I-142		533.0	5.7

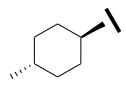
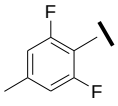
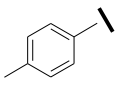
Los Ejemplos I-143 a I-147 se prepararon siguiendo la secuencia de procedimientos descrita en la etapa 10H, sustituyendo 10G por 39A; seguido por la etapa 15D, sustituyendo el Intermediario 2 por derivados ácido carboxílico apropiadamente sustituidos ($R-CO_2H$). Los Ejemplos I-148 a I-157 se prepararon siguiendo la secuencia de procedimientos descrita en la etapa 10H, sustituyendo 10G por 39A; seguido por la etapa 15D, sustituyendo el Intermediario 2 por derivados ácido carboxílico apropiadamente sustituidos ($R-CO_2H$); y finalmente desprotección Boc de acuerdo con el procedimiento

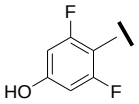
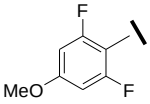
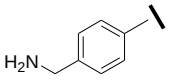
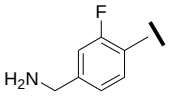
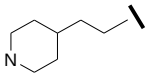
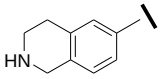
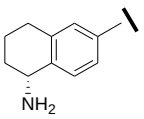
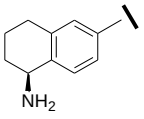
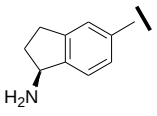
descrito en 3C. Los Ejemplos I-158 a I-161 se prepararon acoplando 76B con derivados ácido carboxílico sustituidos de forma apropiada (R-CO_2H) usando condiciones de acoplamiento descritas en la etapa 15D. En el caso del Ejemplo I-158, se requirió una etapa adicional de desprotección Boc como se describe en la etapa 3C.

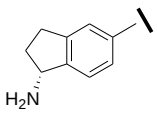
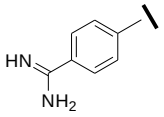
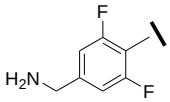
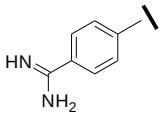
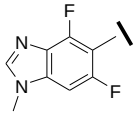
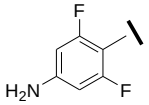
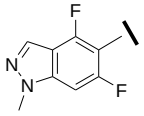
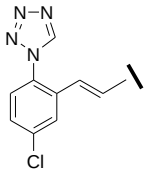
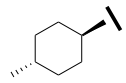
Los Ejemplos I-162 a I-176 se prepararon de una forma similar a como se ha descrito antes.

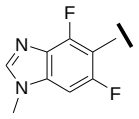
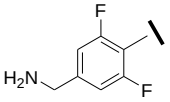
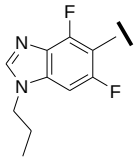
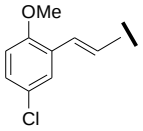
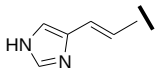
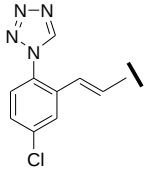
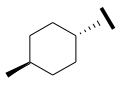
Tabla I-9: Ejemplos I-143 a I-176

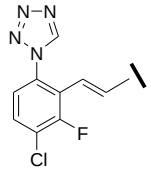
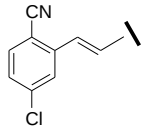
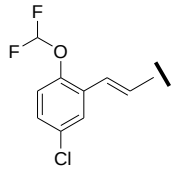
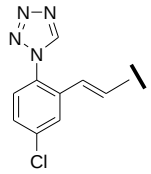


Ej. n°	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-143		H	480.2	4.2 (D)
I-144		H	510.1	3.6 (D)
I-145		H	474.1	3.8 (D)

Ej. nº	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-146		H	512.1	3.8
I-147		H	526.2	4.4
I-148		H	489.2	3.0 (D)
I-149		H	507.1	3.0 (D)
I-150		H	495.2	6.3 (C)
I-151		H	515.2	7.4 (C)
I-152		H	529.2	8.3 (C)
I-153		H	529.2	8.3 (C)
I-154		H	515.2	7.7 (C)

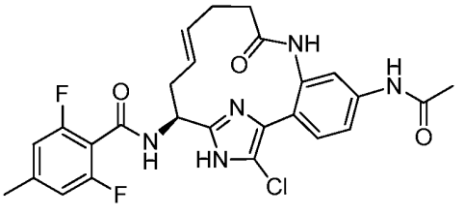
Ej. nº	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-155		H	515.2	7.7 (C)
I-156		H	502.2	6.4 (C)
I-157		H	525.2	6.7 (C)
I-158		Cl	536.1	3.5
I-159		Cl	584.0	5.0
I-160		Cl	545.2	5.2
I-161		Cl	584.0	6.1
I-162		F	606.0	7.1
I-163		F	498.2	7.7

Ej. nº	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
I-164		F	568.2	5.3
I-165		F	543.1	3.5
I-166		F	600.2	10.1
I-167		F	568.2	8.1
I-168		F	602.1	6.4
I-169		F	494.3	4.0
I-170		F	584.4 $[M-H]+$	6.1
I-171		Me	602.2	4.8
I-172		Me	494.3	5.3

Ej. n°	R	R^3	LCMS [M+H]+	HPLC Tr (min) (MÉTODO)
I-173		Me	620.3	5.2
I-174		Me	559.3	6.4
I-175		Me	600.3	6.0
I-176		CN	613.2	6.9

Ejemplo I-177.

N-((E)-(S)-5-Acetilamino-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-2,6-difluoro-4-metil-benzamida, TFA



I-177A y 177-B. (E)-(S)-5,15-Diamino-18-cloro-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-9-ona y éster etílico del ácido

((E)-(S)-15-amino-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il)-carbámico: Se disolvió 76B (0.377g, 0.815 mmol) en una mezcla de etanol (3.3 ml), agua (9.8 ml) y THF (3.3 ml) y se añadió LiOH (0.156 g, 6.52 mmol). La reacción se agitó a 60°C durante 48 h, se enfrió hasta temperatura ambiente, se neutralizó con HCl 1M y se concentró. Los productos brutos se aislaron por cromatografía en fase inversa proporcionando I-177A (0.559 g) y I-177B (30 mg) que se usaron sin purificación adicional.

I-177C. 2,6-Difluoro-4-metilbenzoato de 2.5-dioxopirrolidin-1-ilo: A una solución de ácido 2,6-difluoro-4-metilbenzoico (2.0 g, 11.62 mmol) en THF (61.8 ml) se añadió 1-hidroxipirrolidin-2,5-diona (1.471 g, 12.78 mmol) y 1,3-diisopropilcarbodiimida (2.00 ml, 12.78 mmol) a TA. La mezcla de reacción se agitó bajo N_2 a TA durante la noche. La mezcla de reacción se filtró y el filtrado se evaporó. El residuo se volvió a suspender en MeOH, se filtró y se lavó varias veces con MeOH. El sólido blanco que quedó se secó a vacío proporcionando I-177C (2.80 g, 90%). EM (IEP) *m/z*: 155.1 (M+H)+.

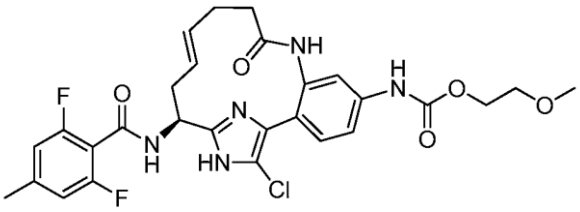
I-177D (Ejemplo I-184. *N*-((E)-(S)-5-Amino-18-cloro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-2,6-difluoro-4-metil-benzamida): Se

preparó I-177D a partir de I-177A siguiendo el procedimiento descrito en la etapa 1G, sustituyendo el Intermediario 1 por I-177C. 1H NMR (500 MHz, CD_3OD) δ ppm 7.17 (1 H, d, *J*=8.25 Hz), 6.89 (2 H, d, *J*=8.80 Hz), 6.68 (1 H, dd, *J*=8.25, 2.20 Hz), 6.60 (1 H, d, *J*=2.20 Hz), 5.49 - 5.61 (1 H, m), 5.23 - 5.34 (1 H, m), 5.14 (1 H, dd, *J*=9.35, 3.85 Hz), 2.55 - 2.66 (1 H, m), 2.41 - 2.52 (1 H, m), 2.33 - 2.41 (7 H, m). EM (IEP) *m/z*: 486.1 (M+H)+. HPLC analítica: Tr = 4.92 min.

Ejemplo I-177. Se disolvió I-177D (0.03 g, 0.062 mmol) en DCM (0.5 ml) y se añadió gota a gota una solución de anhídrido acético (6.30 mg, 0.062 mmol) en DCM (0.1 ml). La reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró, y el residuo se purificó por cromatografía en fase inversa proporcionando el compuesto del título (12.6 mg, 31.6%) como un sólido blanco. 1H NMR (500 MHz, DMSO-d_6) δ ppm 11.45 (1 H, s ancho), 10.08 - 10.13 (1 H, m), 9.32 (1 H, s ancho), 9.21 (1 H, d, *J*=7.70 Hz), 7.63 (1 H, s ancho), 7.44 (1 H, d, *J*=10.45 Hz), 7.33 (1 H, d, *J*=8.25 Hz), 6.98 (2 H, d, *J*=8.80 Hz), 5.41 - 5.61 (1 H, m), 5.20 - 5.35 (1 H, m), 5.04 - 5.19 (1 H, m), 2.39 - 2.45 (1 H, m), 2.32 (3 H, s), 2.29 - 2.40 (2 H, m), 2.16 - 2.31 (2 H, m), 2.04 (3 H, s). EM (IEP) *m/z*: 528.2 (M+H)+. HPLC analítica: Tr = 6.05 min.

Ejemplo I-178.

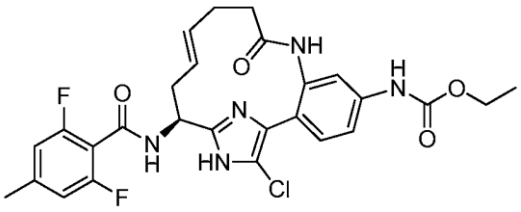
Éster 2-metoxi-etílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, TFA



Se disolvió I-177C en DCM (5 ml) y se añadió piridina (0.02 ml, 0.247 mmol), seguido por la adición gota a gota de una solución de carbonocloridato de 2-metoxietilo (8.55 mg, 0.062 mmol) en DCM (0.5 ml). La mezcla resultante se agitó durante la noche a temperatura ambiente. La reacción se concentró hasta y el residuo purificó por HPLC de fase inversa proporcionando el Ejemplo I-178 como un sólido blanco (10.6 mg, 24.21%). 1H NMR (500 MHz, DMSO-d_6) δ ppm 11.38 (1 H, s ancho), 9.96 (1 H, s ancho), 9.33 (1 H, s ancho), 9.22 (1 H, d, *J*=8.25 Hz), 7.45 (1 H, s ancho), 7.35 - 7.41 (1 H, m), 7.27 - 7.35 (1 H, m), 6.99 (2 H, d, *J*=8.25 Hz), 5.45 - 5.58 (1 H, m), 5.20 - 5.34 (1 H, m), 5.05 - 5.18 (1 H, m), 4.17 - 4.27 (2 H, m), 3.47 - 3.61 (2 H, m), 3.27 (3 H, s), 2.43 - 2.50 (2 H, m), 2.31 - 2.38 (2 H, m), 2.33 (3 H, s), 2.18 - 2.28 (2 H, m). EM (IEP) *m/z*: 588.3 (M+H)+. HPLC analítica: Tr = 6.8 min.

Ejemplo I-179.

Éster etílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, TFA

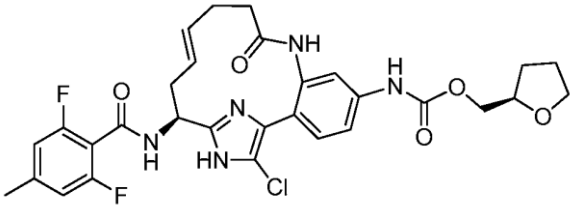


El Ejemplo I-179 se preparó siguiendo el procedimiento descrito para I-177D sustituyendo I-177A por I-177B. 1H NMR (500 MHz, DMSO-d_6) δ ppm 11.26 (1 H, s ancho), 9.65 (1 H, s), 9.19 (1 H, s ancho), 9.00 (1 H, d, J=7.70 Hz), 7.50 (1 H, s ancho), 7.38 - 7.45 (1 H, m), 7.31 - 7.36 (1 H, m), 6.92 - 7.03 (2 H, m), 5.49 - 5.62 (1 H, m), 5.23 - 5.36 (1 H, m), 5.07 - 5.22 (1 H, m), 4.16 (2 H, q, J=6.97 Hz), 2.40 - 2.50 (2 H, m), 2.33 - 2.43 (5 H, m), 2.25 - 2.33 (2 H, m), 1.27 (3 H, t, J=7.02 Hz). EM (IEP) *m/z*: 558.2 (M+H)+. HPLC analítica: Tr = 7.35 min.

Ejemplo I-180.

Éster (R)-1-(tetrahidro-furan-2-il)metílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-

1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, TFA



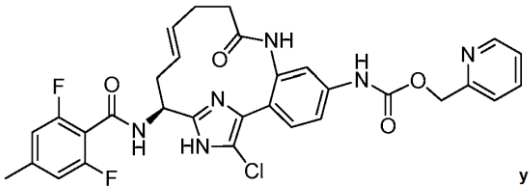
I-180A. (Tetrahidrofuran-2-il)metil carbonato de (R)-4-nitrofenilo: Una solución de carbonocloridato de 4-nitrofenilo (0.2 g, 1.998 mmol) en DCM (8 ml) se añadió gota a gota a una solución de (R)-hidroxi(tetrahidrofuran-2-il)metilio (0.2 g, 1.998 mmol) en DCM (6.66 ml)/piridina (0.162 ml, 1.998 mmol) a 0°C. La reacción se mantuvo a 0°C durante 2 horas y luego se dejó calentar hasta TA durante la noche. La reacción se inactivó con agua y se diluyó con DCM. La fase orgánica se lavó 3x con bicarbonato sódico saturado, y una vez con salmuera, se secó sobre sulfato sódico, se filtró y se concentró. Se obtuvo I-180A (0.442 g, 83%) como un sólido blanco. EM (IEP) *m/z*: 290.2 (M+Na)+

Ejemplo I-180. Se disolvió I-177D (0.026 g, 0.054 mmol) en piridina. Se añadió I-180A (0.029 g, 0.107 mmol) seguido por DMAP (6.54 mg, 0.054 mmol). La reacción se agitó a TA durante la noche. Se añadieron otros 2 equiv. de I-180A y la mezcla se agitó durante 2 horas más y a continuación se evaporó. El residuo se purificó por cromatografía en fase inversa proporcionando el compuesto del título (5.6 mg, 13.80%) como un sólido blanco. 1H NMR (500 MHz, CD_3OD) δ ppm

9.63 (1 H, s ancho), 7.55 (1 H, s), 7.36 - 7.46 (2 H, m), 6.91 (2 H, d, *J*=8.80 Hz), 5.45 - 5.64 (1 H, m), 5.29 - 5.46 (1 H, m), 5.06 - 5.23 (1 H, m), 4.04 - 4.32 (3 H, m), 3.85 - 3.96 (1 H, m), 3.70 - 3.84 (1 H, m), 2.70 - 2.84 (1 H, m), 2.21 - 2.62 (8 H, m), 2.00 - 2.14 (1 H, m), 1.81 - 2.01 (2 H, m), 1.52 - 1.80 (1 H, m). EM (IEP) *m/z*: 614.2 (M+H)+. HPLC analítica: Tr = 7.65 min.

Ejemplo I-181.

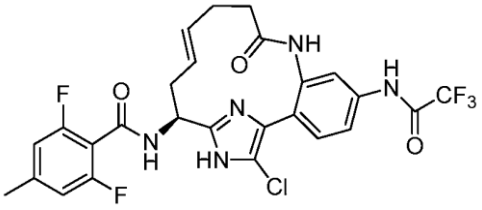
Éster piridin-2-ilmetílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, TFA



y

Ejemplo I-182.

N-[(E)-(S)-18-Cloro-9-oxo-5-(2,2,2-trifluoro-acetilamino)-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il]-2,6-difluoro-4-metil-benzamida, TFA



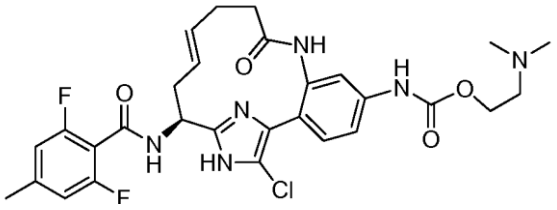
Se disolvió I-177D (0.013 g, 0.018 mmol) en DCM

(0.5 ml). Se añadió TEA (0.018 ml, 0.127 mmol), seguido por trifosgeno (10.81 mg, 0.036 mmol). La mezcla se agitó durante 30 min a TA, y luego se añadió una solución de piridin-2-ilmetanol (9.93 mg, 0.091 mmol) en DCM (0.1 ml). Se continuó agitando a TA durante la noche. La mezcla de reacción se evaporó y el residuo se purificó por cromatografía en fase inversa proporcionando Ejemplo I-181 (1.6 mg, 9.83%). 1H NMR (500 MHz, CD_3OD) δ ppm 8.68 (1 H, d, J=4.95 Hz), 8.22 (1 H, td, J=7.84, 1.37 Hz), 7.82 (1 H, d, J=7.70 Hz), 7.64 - 7.70 (1 H, m), 7.56 - 7.60 (1 H, m), 7.43 - 7.46 (2 H, m), 6.91 (2 H, d, J=8.80 Hz), 5.47 - 5.61 (1 H, m), 5.41 (2 H, s), 5.26 - 5.40 (1 H, m), 5.08 - 5.17 (1 H, m), 2.67 - 2.80 (1 H, m), 2.26 - 2.55 (8 H, m). EM (IEP) *m/z*: 623.1 (M+H)+. HPLC analítica: Tr = 5.31 min., y Ejemplo I-182 (5.6 mg, 43.8%). 1H NMR (500 MHz, CD_3OD) δ ppm 7.79 (1 H, d, J=2.20 Hz), 7.65 (1 H, dd, J=8.53, 2.20 Hz), 7.56 (1 H, d, J=8.53 Hz), 6.91 (2 H, d, J=8.80 Hz), 5.48 - 5.60 (1 H, m), 5.32 - 5.44 (1 H, m), 5.09 - 5.19 (1 H, m), 2.69 - 2.79 (1 H, m), 2.29 - 2.57 (8 H, m). EM (IEP) *m/z*: 582.3 (M+H)+. HPLC analítica: Tr = 8.06 min.

Ejemplo 183.

Éster 2-dimetilamino-etílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-

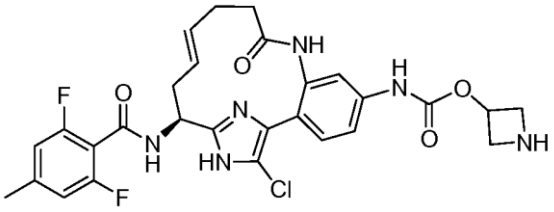
il]-carbámico, 2 TFA



El Ejemplo I-183 se preparó usando el procedimiento descrito para el Ejemplo I-181 sustituyendo piridin-2-ilmetanol por 2-(dimetilamino)etanol. 1H NMR (500 MHz, CD_3OD) δ ppm 8.10 (1 H, s), 7.58 (1 H, s), 7.44 - 7.47 (2 H, m), 6.90 (2 H, d, *J*=8.80 Hz), 5.49 - 5.59 (1 H, m), 5.28 - 5.41 (1 H, m), 5.07 - 5.15 (1 H, m), 4.49 - 4.55 (2 H, m), 3.46 - 3.56 (2 H, m), 3.00 (6 H, s), 2.60 - 2.75 (2 H, m), 2.25 - 2.56 (7 H, m). EM (IEP) *m/z*: 601.3 (M+H)+. HPLC analítica: Tr = 4.66 min.

Ejemplo 185.

Éster azetidin-3-ílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, 2 TFA

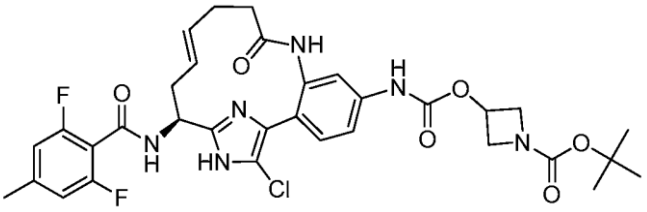


El Ejemplo 186 se disolvió en DCM (1 ml) y TFA (0.25 ml) se añadió. Después de agitar durante 1h a TA, la

mezcla de reacción se evaporó hasta sequedad proporcionando el compuesto del título. 1H NMR (500 MHz, CD_3OD) δ ppm 7.44 - 7.50 (1 H, m), 7.33 - 7.41 (2 H, m), 6.80 - 6.86 (2 H, m), 5.38 - 5.52 (1 H, m), 5.23 - 5.34 (2 H, m), 5.00 - 5.07 (1 H, m), 4.33 - 4.43 (2 H, m), 4.09 - 4.19 (2 H, m), 2.61 - 2.73 (1 H, m), 2.17 - 2.49 (8 H, m). EM (IEP) *m/z*: 585.2 (M+H)+. HPLC analítica: Tr = 4.53 min.

Ejemplo 186.

Éster terc-butílico del ácido 3-[(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-ilcarbamoiloxi]-azetidin-1-carboxílico, TFA

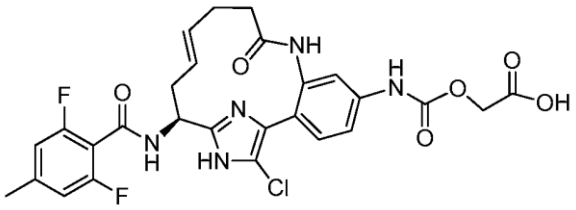


El Ejemplo 186 se preparó usando los procedimientos descritos para el Ejemplo I-180, sustituyendo (R)-hidroxi(tetrahidrofuran-2-il)metilio por 3-hidroxiazetidin-1-carboxilato de terc-butilo en la etapa I-180A. 1H NMR (500 MHz, CD_3OD) δ ppm 9.81 (1 H, s ancho), 7.52 - 7.58 (1 H, m), 7.37 - 7.48 (2 H, m), 6.90 (2 H, d, *J*=8.80 Hz), 5.45 - 5.59 (1 H, m), 5.29 - 5.41 (1 H, m), 5.16 - 5.24 (1 H, m), 5.07 - 5.16 (1 H, m), 4.23 - 4.35 (2 H, m), 3.85 - 3.99 (2 H, m), 2.68 - 2.78 (1 H,

m), 2.25 - 2.56 (8 H, m), 1.44 (9 H, s). EM (IEP) *m/z*: 685.3 (M+H)+. HPLC analítica: Tr = 8.63 min.

Ejemplo I-187.

Ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-ilcarbamoiloxi]-acético, TFA

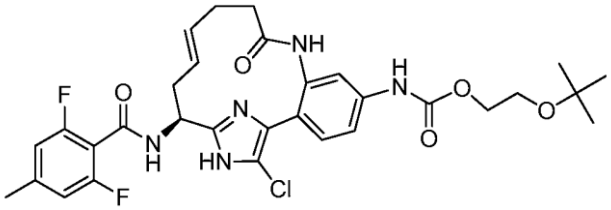


El Ejemplo I-187 se preparó siguiendo el procedimiento descrito para el Ejemplo 181, sustituyendo piridin-2-ilmetanol por 2-hidroxiacetato de etilo, seguido por hidrólisis del éster etílico bruto con LiOH en THF. 1H NMR (500 MHz, CD_3OD) δ ppm 9.80 (1 H, s ancho), 7.57 (1 H, s), 7.43 (2 H, s), 6.90 (2 H, d, *J*=8.80 Hz), 5.47 - 5.62 (1 H, m), 5.29 - 5.41 (1 H, m), 5.01 - 5.20 (1 H, m), 4.66 (2 H, s), 2.68 - 2.79 (1 H, m), 2.25 - 2.56 (8 H, m). EM (IEP) *m/z*: 588.2 (M+H)+. HPLC analítica: Tr = 6.08 min.

Ejemplo I-188.

Éster 2-terc-butoxi-etílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-

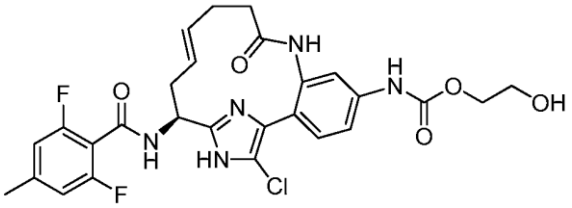
il]-carbámico, TFA



El Ejemplo 188 se preparó de forma similar al Ejemplo I-180, sustituyendo (R)-hidroxi(tetrahidrofuran-2-il)metilo por 2-*terc*-butoxietanol en la etapa I-180A. 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (1 H, s ancho), 7.50 (1 H, s), 7.37 (2 H, s), 6.86 (2 H, d, *J*=8.80 Hz), 5.40 - 5.58 (1 H, m), 5.22 - 5.33 (1 H, m), 5.08 (1 H, dd, *J*=10.17, 4.12 Hz), 4.13 - 4.21 (2 H, m), 3.56 - 3.64 (2 H, m), 2.59 - 2.70 (1 H, m), 2.34 (8 H, s), 1.17 (9 H, s). EM (IEP) *m/z*: 630.3 (M+H)+. HPLC analítica: Tr = 8.0 min.

Ejemplo I-189.

Éster 2-hidroxi-etílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, TFA



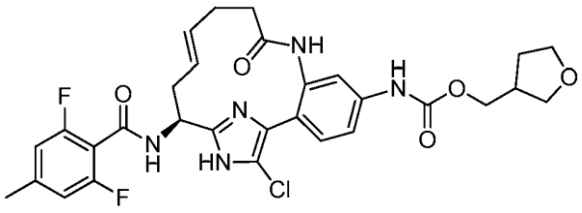
I-189A. Carbonocloridato de 2-*terc*-butoxietilo: A una solución de 2-*terc*-butoxietanol (0.444 ml, 3.38 mmol) y piridina (0.274 ml, 3.38 mmol) en éter (10 ml) se añadió trifosgeno (0.331 g, 1.117 mmol)

disuelto en 2 ml de éter. La mezcla de reacción se mantuvo a 0°C durante una hora. La mezcla de reacción se filtró y se concentró proporcionando el carbonocloridato de 2-*terc*-butoxietilo bruto (0.424 g, 69.3%), como un aceite transparente. 1H NMR (500 MHz, $CDCl_3$) δ ppm 4.38 - 4.43 (2 H, m), 3.60 - 3.65 (2 H, m), 1.20 (9 H, s).

Ejemplo I-189. Este compuesto se preparó a partir de I-177D de acuerdo con el procedimiento descrito para la etapa I-123B, sustituyendo carbonocloridato de 2-metoxietilo por I-189A, seguido por desprotección del éter t-butílico bruto con TFA/DCM. 1H NMR (500 MHz, CD_3OD) δ ppm 9.57 (1 H, s ancho), 7.55 - 7.66 (1 H, m), 7.39 - 7.51 (2 H, m), 6.94 (2 H, d, *J*=8.80 Hz), 5.48 - 5.61 (1 H, m), 5.32 - 5.46 (1 H, m), 5.16 (1 H, dd, *J*=10.59, 4.54 Hz), 4.21 - 4.34 (2 H, m), 3.77 - 3.86 (2 H, m), 2.74 - 2.84 (1 H, m), 2.31 - 2.59 (8 H, m). EM (IEP) *m/z*: 574.2 (M+H)+. HPLC analítica: Tr = 5.77 min.

Ejemplo 190.

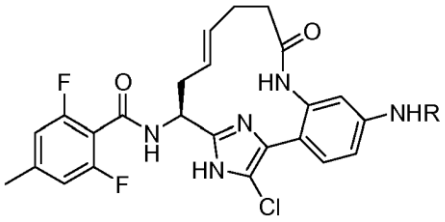
Éster tetrahidrofuran-3-ilmetílico del ácido [(E)-(S)-18-cloro-15-(2,6-difluoro-4-metil-benzoilamino)-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il]-carbámico, TFA

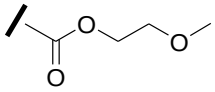


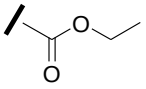
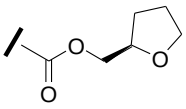
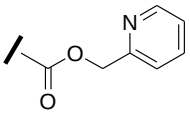
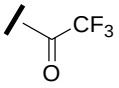
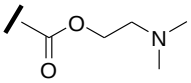
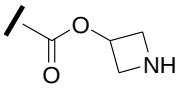
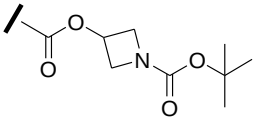
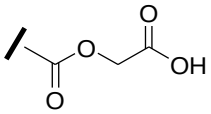
El Ejemplo I-190 se preparó siguiendo los procedimientos descritos para el Ejemplo I-189, sustituyendo

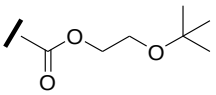
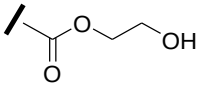
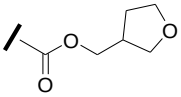
2-*terc*-butoxietanol por (tetrahidrofuran-3-il)metanol en la etapa I-189A y omitiendo el tratamiento con TFA. 1H NMR (500 MHz, CD_3OD) δ ppm 9.54 (1 H, s ancho), 8.25 (1 H, d, *J*=9.35 Hz), 7.47 - 7.53 (1 H, m), 7.24 - 7.45 (2 H, m), 6.85 (2 H, d, *J*=8.80 Hz), 5.41 - 5.57 (1 H, m), 5.24 - 5.35 (1 H, m), 5.06 (1 H, dd, *J*=10.72, 4.12 Hz), 4.06 - 4.28 (1 H, m), 3.94 - 4.04 (1 H, m), 3.74 - 3.87 (2 H, m), 3.63 - 3.73 (1 H, m), 3.53 - 3.62 (1 H, m), 2.62 - 2.74 (1 H, m), 2.53 - 2.63 (1 H, m), 2.20 - 2.50 (8 H, m), 1.90 - 2.10 (1 H, m), 1.58 - 1.75 (1 H, m). EM (IEP) *m/z*: 614.3 (M+H)+. HPLC analítica: Tr = 6.86 min.

Tabla I-10: Ejemplos I-177 a I-190



Ej. n°	R	LCMS $[M+H]^+$	HPLC Tr (min)
I-177		528.2	6.1
I-178		588.3	6.8

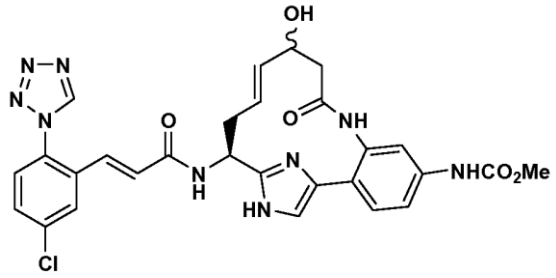
Ej. n°	R	LCMS $[M+H]^+$	HPLC Tr (min)
I-179		558.2	7.3
I-180		614.2	7.7
I-181		621.3	5.3
I-182		582.3	8.1
I-183		601.3	4.7
I-184	H	486.1	4.9
I-185		585.2	4.5
I-186		685.3	8.6
I-187		588.2	6.1

Ej. nº	R	LCMS $[M+H]^+$	HPLC Tr (min)
I-188		630.3	8.0
I-189		574.2	5.8
I-190		614.3	6.9

El Ejemplo I-192 se preparó siguiendo el procedimiento descrito en Ejemplo 47. Los Ejemplos I-193 a I-195 se prepararon siguiendo los procedimientos descritos en Ejemplo 53, sustituyendo 15B por 10C.

Ejemplo I-196.

Éster metílico del ácido {(E)-(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-hidroxi-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-5-il}-carbámico, sal del ácido trifluoracético



I-196A. Se disolvió éster metílico del ácido {3-amino-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-

trimetilsilanil-etoximetil)-1H-imidazol-4-il]-fenil}-carbámico (0.15g, 0.28 mmol) en DMF (3 ml). A esta solución se añadió ácido 3-hidroxi-pent-4-enoico (0.064g, 0.55 mmol), seguido por T3P (0.326g, 0.423 mmol) y base de Hunig (0.073g, 0.56 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La reacción se inactivó con agua (100ml), y se extrajeron los orgánicos con EtOAc (2x100 ml), se secaron ($MgSO_4$) y evaporaron hasta una masa semisólida verdosa. Se purificó el compuesto bruto por cromatografía en fase normal. Las fracciones puras se recogieron y concentraron hasta un sólido amarillo pálido (0.11g, 62%). 1H NMR (500 MHz, CD_3OD) δ ppm 8.39 (m, 1H), 7.58-7.43 (m, 2H), 7.21 (s, 1H), 5.80 (m, 1H), 5.55-5.05 (m, 8H), 3.76 (s, 3H), 3.54 (m. 2H), 2.80 (m, 2H), 1.46 (s, 9H), 0.94 (m, 2H), 0.00 (s, 9H). EM (IEP) *m/z*: 630.3 (M+H)+.

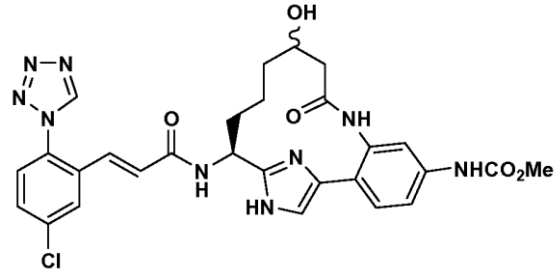
I-196 B. El producto de I-196A se disolvió en DCM (35 ml) y se desgasificó. Después de 0.5 h se añadió pTsOH (0.03g, 0.18 mmol) y la mezcla de reacción se agitó durante otras 0.5 horas mientras se desgasificaba. A esta solución se añadió catalizador de Grubbs II (0.06g, 0.07 mmol) y la mezcla de reacción se calentó hasta 40°C durante la noche. La mezcla de reacción se enfrió y se inactivó con solución en fase de sodio (10%, 50 ml) y se separó la fase orgánica. La fase acuosa se extrajo adicionalmente con EtOAc (2x100ml), y se secaron los extractos reunidos ($MgSO_4$) y se evaporaron y

hasta un aceite marrón. El material bruto se purificó por cromatografía en fase normal proporcionando el macrociclo deseado como un aceite incoloro. EM (IEP) *m/z*: 602.2 (M+H)+.

I-196C. La retirada de los grupos protectores Boc y Sem como en el Ejemplo 1 (etapa 1F) del producto de I-196B, seguida por acoplamiento del macrociclo amino bruto con el Intermediario 1 como se describe para el Ejemplo 1 (etapa 1G) proporcionó el compuesto del título como un sólido blanco (10 mg, 23%). 1H NMR (500 MHz, CD_3OD) δ ppm 9.55 (s, 1H), 9.50 (d, *J* = 2.5Hz, 1H), 7.98 (m, 1H), 7.69 (dd, *J* = 2.3 & 8.5Hz, 1H), 7.60-7.57 (m, 2H), 7.41-7.37 (m, 2H), 7.18-7.13 (dd, *J* = 4.3 & 8.7Hz, 1H), 6.77 (d, *J* = 15.8Hz, 1H), 5.84-5.73 (m, 1H), 5.55-5.43 (m, 1H), 5.17-5.09 (m, 1H), 4.44 (m, 1H), 3.75 (s, 3H), 2.9-2.45 (m, 5H). EM (IEP) *m/z*: 604.3 (M+H)+. HPLC analítica: Tr = 5.12 min.

Ejemplo I-197.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-hidroxi-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal del ácido trifluoracético

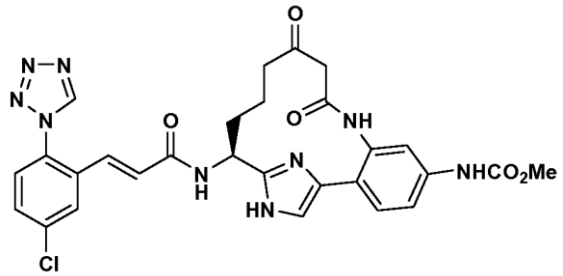


La reducción de I-196B como en el Ejemplo 2 (etapa

2G), desprotección de los grupos protectores Boc y Sem como en el Ejemplo 1 (etapa 1F), y acoplamiento con el Intermediario 1 como se describe para el Ejemplo 1 (etapa 1G) proporcionó el compuesto del título como un sólido marrón (7 mg, 13%). 1H NMR (500 MHz, CD_3OD) δ ppm 9.51 (s, 1H), 9.51 (s, 1H), 7.98 (dd, *J* = 2.3 & 8.3Hz, 1H), 7.69-7.66 (m, 1H), 7.61-7.56 (m, 1H), 7.44-7.41 (m, 2H), 7.16-7.10 (t, 1H), 6.79-6.69 (dd, *J* = 15.6Hz, 2H), 5.05-4.97 (m, 1H), 4.00 (m, 1H), 3.76 (s, 3H), 2.66-2,63 (m, 1H), 2.34-2.22 (m, 2H), 2.05 (m, 1H), 1.80 (m, 1H), 1.62 (m, 1H), 1.58 (m, 1H), 1.38-1.22 (m, 2H), 1.00-0.74 (m, 2H). EM (IEP) *m/z*: 606.4 (M+H)+. HPLC analítica: Tr = 4.36 min.

Ejemplo I-198.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9,11-dioxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, sal del ácido trifluoracético

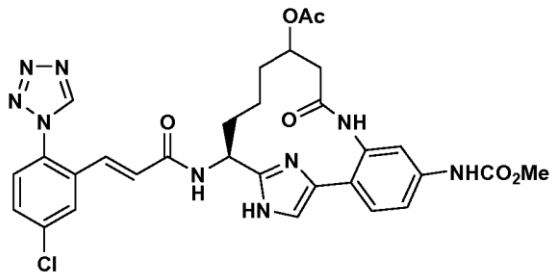


La reducción de I-196B como en el Ejemplo 2 (etapa 2G), seguido por la oxidación del producto reducido (0.04 g, 0.06 mmol) con peryodinano de Dess-Martin (0.03 g, 0.076 mmol) en DCM (5 ml), desprotección de los grupos protectores

Boc y SEM como en el Ejemplo 1 (etapa 1F), y acoplamiento con el Intermediario 1 como se describe para el Ejemplo 1 (etapa 1G) proporcionó el compuesto del título como un sólido marrón (6 mg, 15%). 1H NMR (500 MHz, CD_3OD) δ ppm 9.41(s, 1H), 7.87 (d, *J* = 2.7Hz, 1H), 7.52-7.45 (m, 4H), 7.40-7.30 (m, 4H), 7.04 (d, *J* = 16.4Hz, 1H), 6.65 (d, *J* = 15.4Hz, 1H), 4.97 (m, 1H), 3.66 (s, 3H), 3.63 (t, 1H). 3.18-3.10 (m, 1H), 2.25-2.05 (m, 2H), 1.75 (bm, 2H). EM (IEP) *m/z*: 604.2 (M+H)+. HPLC analítica: Tr = 5.79 min.

Ejemplo I-199.

Éster (S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-11-ílico del ácido acético, sal del ácido trifluoracético



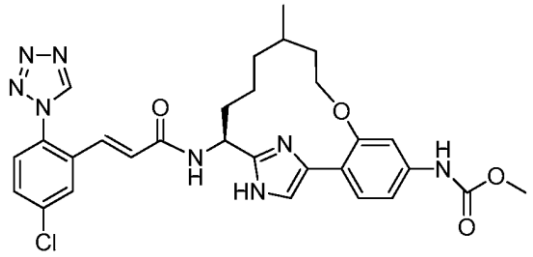
La reducción de I-196B como en el Ejemplo 2 (etapa 2G), seguido por la acetilación con anhídrido acético del producto reducido, desprotección de los grupos protectores Boc y SEM como en el Ejemplo 1 (etapa 1F), y acoplamiento con el Intermediario 1 como se describe para el Ejemplo 1 (etapa 1G) proporcionó el compuesto del título como un sólido marrón (4 mg, 5%). 1H NMR (500 MHz, CD_3OD) δ ppm 9.39 (s, 1H), 7.88-

7.85 (dd, *J* = 2.3 & 8.8Hz, 1H), 7.63-7.56 (m, 1H), 7.54-7.47 (m, 2H), 7.48-7.39 (m, 2H), 7.08-7.03 (m, 1H), 6.69-6.57 (q, 2H), 5.12-4.98 (m, 1H), 4.48 (m, 1H), 3.66 (s, 3H), 2.78 (dd, 2H), 2.40-2.30 (m, 1H), 2.12 (bm, 1H), 1.95 (s, 3H), 1.51-1.00 (m, 4H). EM (IEP) *m/z*: 648.2 (M+H)+. HPLC analítica: Tr = 4.93 min.

Los Ejemplos I-200 y I-201 se prepararon siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2-metilpent-4-enoico; seguido por las etapas 2E/2F; 10H; y 1G. Los Ejemplos I-202 y I-203 se prepararon siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2-metilpent-4-enoico; seguido por las etapas 2E/2F; 2G; 10H; y 1G.

Ejemplos I-205 y I-206.

Éster metílico del ácido {(S)-15-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-11-metil-8-oxa-17,19-diaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,16(19)-pentaen-5-il}-carbámico, TFA, Diastereómero A y Diastereómero B



I-205A. 2-Hidroxi-4-(metoxicarbonilamino)benzoato de metilo: Se disolvió 4-amino-2-hidroxibenzoato de metilo

(10 g, 59.8 mmol) en DCM (120 ml), y se añadió piridina (5.32 ml, 65.8 mmol). La mezcla se enfrió hasta 0°C, y se añadió gota a gota cloroformiato de metilo (4.87 ml, 62.8 mmol). La reacción se agitó durante 1.5h, a continuación se inactivó con solución 1.5M de fosfato potásico dibásico, y se extrajo 2x con DCM. Las fases orgánicas combinadas se lavaron 2x con HCl 1M y 1x con salmuera, se secaron con sulfato sódico, se filtraron y se concentraron proporcionando I-205A (14.2 g) que se usó sin purificación adicional en la etapa siguiente. EM (IEP) *m/z*: 226.2 (M+H)+.

I-205B. 2-(Aliloxi)-4-(metoxicarbonilamino)benzoato de metilo: Se disolvió I-205A (14.22 g, 63.1 mmol) en acetona (210 ml). Se añadió bromuro de alilo (16.39 ml, 189 mmol) seguido por carbonato potásico (43.6 g, 316 mmol). La reacción se calentó a 60°C bajo Ar y en un condensador de reflujo durante 8 horas. La reacción se concentró a presión reducida y se diluyó con EtOAc/agua. La fase acuosa se lavó con EtOAc 2x, a continuación se lavaron las fases orgánicas combinadas con salmuera y se secaron con sulfato sódico y se concentraron. El residuo se purificó por cromatografía en fase normal proporcionando I-205B (8.03 g, 47.9%), como un sólido amarillo. EM (IEP) *m/z*: 266.1 (M+H)+

I-205C. 3-(Aliloxi)-4-(2-cloroacetil)fenilcarbamato de metilo: A cloruro de trimetilsulfoxonio (12.12 g, 94 mmol) y t-butóxido potásico 1 M (99 ml, 99 mmol) se añadieron otros

80 ml de THF. La mezcla se llevó a reflujo durante 2 horas, a continuación se dejó enfriar hasta temperatura ambiente. Se añadió gota a gota una solución de I-205B (5 g, 18.85 mmol) disuelta en 100 ml de THF. La reacción se dejó agitar a TA durante la noche bajo Ar. La mezcla de reacción se concentró, y el residuo se repartió entre EtOAc y agua. La fase acuosa se extrajo 2x con EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, se secaron con sulfato sódico, se filtraron y se concentraron. El residuo se suspendió en cloruro de metileno y se filtró. El filtrado se purificó por cromatografía en fase normal, y las fracciones que contenían producto se reunieron con el sólido insoluble anterior proporcionando la especie sulfonio intermedia (5.76 g, 94%, EM (IEP) *m/z*: 326.1 (M+H)+), que se disolvió en THF (89 ml). Se añadió una solución de HCl 4M HCl en dioxano (8.85 ml, 35.4 mmol) y la mezcla se agitó a 70°C durante la noche en un tubo sellado. La mezcla de reacción se concentró, y el residuo se purificó por cromatografía en fase normal proporcionando I-205C (2.01 g, 40.0%) como un sólido amarillo. EM (IEP) *m/z*: 284.1 (M+H)+.

I-205D. Éster metílico del ácido {3-aliloxi-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: Se preparó I-205D en tres etapas siguiendo los procedimientos descritos para las etapas 2A, sustituyendo 2-

bromo-1-(2-bromofenil)etanona por I-205C; 2B; y 10B. EM (IEP) *m/z*: 573.4 (M+H)+.

I-205E. Éster metílico del ácido {4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-hidroxi-fenil}-carbámico: Se disolvió I-205D (0.663 g, 1.158 mmol) en metanol (5.79 ml) y se añadió a un matraz de fondo redondo de tres bocas junto con carbonato potásico (0.480 g, 3.47 mmol). El matraz se desgasificó y se volvió a llenar con Ar 3x. Se añadió (Ph3P)4Pd (0.134 g, 0.116 mmol) bajo una corriente de Ar. La mezcla se desgasificó y se volvió a llenar tres veces más con Ar. La reacción se agitó durante 10 min a TA, a continuación se añadió bajo una corriente de Ar una porción adicional de carbonato potásico (0.480 g, 3.47 mmol) y la mezcla se agitó durante 1 hr bajo Ar. La reacción se diluyó con EtOAc/agua; se extrajo la fase acuosa 2x con EtOAc; Las fases orgánicas combinadas se lavaron con salmuera, se secaron con sulfato sódico concentrado. El residuo se purificó por cromatografía ultrarrápida proporcionando I-205E (0.45 g, 0.845 mmol, 73.0%) como un sólido blanco. EM (IEP) *m/z*: 533.4 (M+H)+.

I-205F. 5-yodo-3-metilpent-1-eno: A una solución enfriada (0°C) de hidruro de litio y aluminio 1M en Et2O (21.90 ml, 21.90 mmol) y 10 ml de éter adicionales, se añadió gota a gota ácido 3-metilpent-4-enoico (1.064 ml, 8.76 mmol) disuelto en 15 ml de éter. Se dejó calentar la reacción hasta

TA y se agitó durante la noche. La reacción se vertió cuidadosamente sobre hielo en pequeñas porciones y se añadieron 15 ml de H_2SO_4 5M para disolver la mayor parte de las sales. La fase acuosa se extrajo 2 veces con éter y las fases orgánicas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron proporcionando el 3-metilpent-4-en-1-ol bruto, que se recogió sin purificación adicional. El alcohol (0.877 g, 8.76 mmol) se disolvió en 20 ml de DCM anhidro y se añadieron trifenilfosfina (2.99 g, 11.38 mmol) y imidazol (0.894 g, 13.13 mmol). La mezcla de reacción se enfrió hasta 0°C, y se añadió gota a gota una solución de yodo (2.89 g, 11.38 mmol) en 20 ml de DCM. Después de 30 min a 0°C, la reacción se calentó hasta TA y se agitó durante la noche. La reacción se lavó 3x con sulfito sódico acuoso al 10% y 1x con salmuera, se secó con sulfato sódico, se filtró y se concentró. El residuo se purificó en una almohadilla de gel de sílice eluido con pentano, proporcionando el yoduro (0.937 g, 4.46 mmol, 50.9%) como un aceite transparente.

I-205G. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(3-metil-pent-4-eniloxi)-fenil]-carbámico: Se disolvió I-205E (.206 g, 0.335 mmol, 79%) en acetona (3 ml) y se añadieron carbonato potásico (0.292 g, 2.112 mmol) y I-205F (0.444 g, 2.112 mmol). La

mezcla de reacción se agitó a 55°C en un vial sellado durante 1h, a continuación a 70°C durante la noche. La reacción se concentró y se repartió entre agua y EtOAc. La fase acuosa se volvió a extraer 2x con EtOAc, y los extractos orgánicos reunidos se lavaron con salmuera, se secaron con sulfato sódico, se filtraron y se concentraron. El residuo se purificó por cromatografía en fase normal proporcionando I-205G (0.206 g, 79%) como un sólido blanco. EM (IEP) *m/z*: 615.5 (M+H)+.

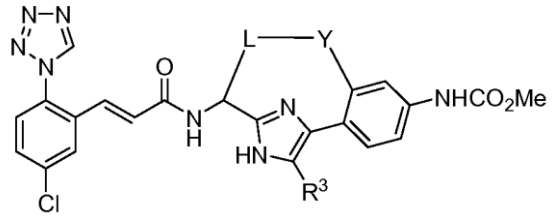
Ejemplos I-205 y I-206. Los compuestos del título se prepararon en cuatro etapas a partir de I-205G usando procedimientos descritos en las etapas 2E/F y 2G, momento en el cual se separaron los diastereómeros por cromatografía en fase inversa y se trataron individualmente mediante etapas de desprotección y acoplamiento de amida usando procedimientos descritos en las etapas 10H y 1G. El Ejemplo I-205 (Diastereómero A): 1H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 7.99 (1 H, d, J=2.20 Hz), 7.69 (1 H, dd, J=8.53, 2.48 Hz), 7.60 (1 H, d, J=8.53 Hz), 7.40 (1 H, s), 7.33 - 7.40 (2 H, m), 7.19 (1 H, d, J=15.41 Hz), 7.02 - 7.09 (1 H, m), 6.80 (1 H, d, J=15.41 Hz), 5.14 (1 H, dd, J=8.80, 4.40 Hz), 3.99 - 4.13 (2 H, m), 3.76 (3 H, s), 2.22 - 2.41 (1 H, m), 1.71 - 1.91 (3 H, m), 1.55 - 1.71 (2 H, m), 1.41 - 1.55 (1 H, m), 0.94 - 1.05 (2 H, m), 0.95 (3 H, d, J=6.60 Hz). EM (IEP) *m/z*: 591.2 (M+H)+. HPLC analítica: Tr = 6.98 min. El Ejemplo I-206

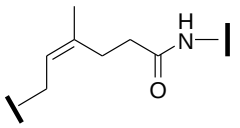
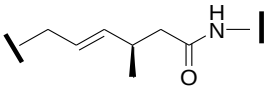
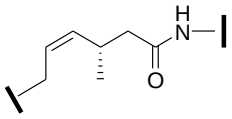
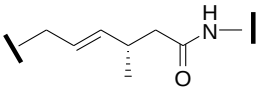
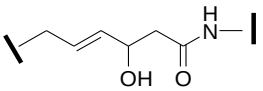
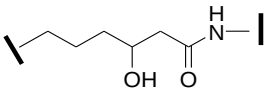
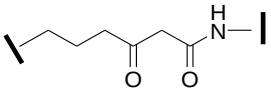
(Diastereómero B): 1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (1 H, s), 7.95 (1 H, d, J=2.20 Hz), 7.67 (1 H, dd, J=8.79, 2.20 Hz), 7.52 - 7.62 (1 H, m), 7.40 - 7.43 (1 H, m), 7.37 - 7.40 (1 H, m), 7.36 (1 H, d, J=8.25 Hz), 7.14 (1 H, d, J=15.39 Hz), 7.05 (1 H, dd, J=8.25, 1.65 Hz), 6.70 (1 H, d, J=15.94 Hz), 5.01 (1 H, dd, J=9.89, 4.95 Hz), 3.94 - 4.12 (2 H, m), 3.75 (3 H, s), 1.99 - 2.25 (2 H, m), 1.47 - 1.81 (4 H, m), 0.96 - 1.34 (3 H, m), 0.94 - 1.03 (3 H, m). EM (IEP) *m/z*: 591.2 (M+H)+. HPLC analítica: Tr = 6.976 min.

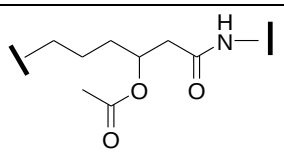
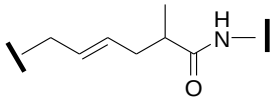
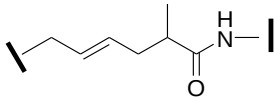
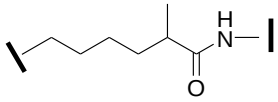
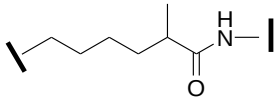
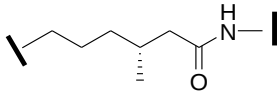
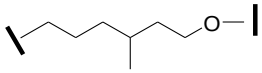
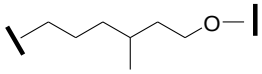
Los Ejemplos I-207 y I-208 se prepararon de una forma similar a los Ejemplos I-205 y I-206 partiendo del Intermediario I-205E y sustituyendo ácido 2-metilpent-4-enoico por ácido 3-metilpent-4-enoico en la etapa I-205F.

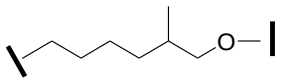
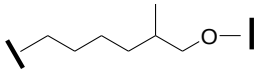
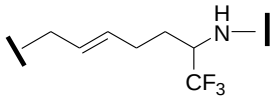
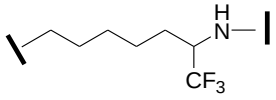
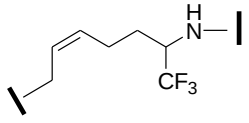
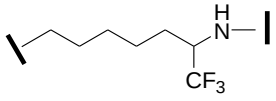
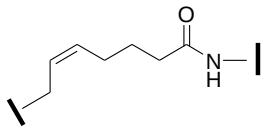
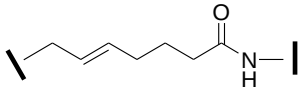
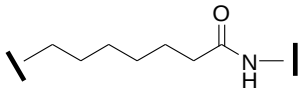
Los Ejemplos I-209 a I-212 se prepararon siguiendo los procedimientos descritos para la preparación de los Ejemplos 154 y 155, sustituyendo bromuro de alilmagnesio por bromuro de but-3-enilmagnesio. Los Ejemplos I-213 a I-215 se prepararon siguiendo los procedimientos descritos para la preparación de los Ejemplos 125, 39, y 34, sustituyendo ácido pent-4-enoico por ácido hex-5-enoico.

Tabla I-11: Ejemplos I-191 a I-215



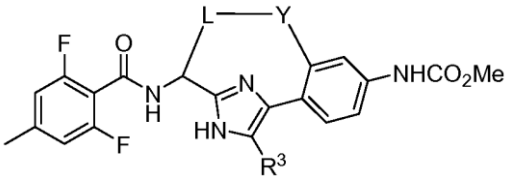
Ej. nº	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
I-191	-(CH2)5-C(O)NH-	F	608.3	7.0
I-192		H	602.0	5.4
I-193		H	602.2	5.5
I-194		H	602.2	5.4
I-195		H	602.2	5.4
I-196	 (mezcla de diastereómeros)	H	604.2	5.1
I-197	 (mezcla de diastereómeros)	H	604.4 [M-H]+	4.4
I-198		H	604.2	5.8

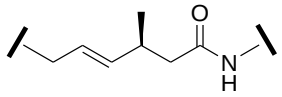
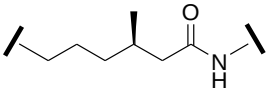
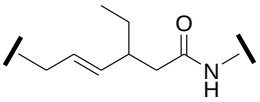
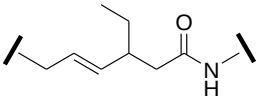
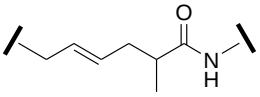
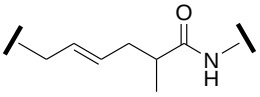
Ej. nº	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
I-199	 (mezcla de diastereómeros)	H	648.2	4.9
I-200	 (diastereómero B)	H	602.2	5.4
I-201	 (diastereómero A)	H	602.3	5.3
I-202	 (diastereómero B)	H	604.3	4.9
I-203	 (diastereómero A)	H	604.3	4.9
I-204		Cl	638.2	6.9
I-205	 (homoquiral)	H	591.2	7.0
I-206	 (homoquiral)	H	591.2	7.0

Ej. n°	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
I-207	 (homoquiral)	H	591.3	6.8
I-208	 (homoquiral)	H	591.2	6.8
I-209	 (homoquiral)	H	642.3	7.3
I-210	 (homoquiral)	H	644.3	7.2
I-211	 (homoquiral)	H	642.3	5.7
I-212	 (homoquiral)	H	644.3	6.3
I-213		H	602.1	5.3
I-214		H	602.2	5.6
I-215		H	604.2	5.5

El Ejemplo I-216 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 3-metil-4-pentenoico; seguido por las etapas 2E; 10H; y 15D, sustituyendo el Intermediario 2 por ácido 2,6-difluoro-4-metilbenzoico. El Ejemplo I-217 se preparó siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 3-metil-4-pentenoico; seguido por las etapas 2E/2F; 10G; 10H; y 15D, sustituyendo el Intermediario 2 por ácido 2,6-difluoro-4-metilbenzoico. Los Ejemplos I-218 a I-219 se prepararon siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 3-etil pent-4-enoico; seguido por las etapas 2E/2F; 10H; y 15D, sustituyendo el Intermediario 2 por ácido 2,6-difluoro-4-metilbenzoico. Los Ejemplos I-220 y I-221 se prepararon siguiendo los procedimientos descritos en la etapa 10D, sustituyendo ácido but-3-enoico por ácido 2-metil-4-pentenoico; seguido por las etapas 2E/2F; 10H; y 15D, sustituyendo el Intermediario 2 por ácido 2,6-difluoro-4-metilbenzoico.

Tabla I-12: Ejemplos I-216 a I-221

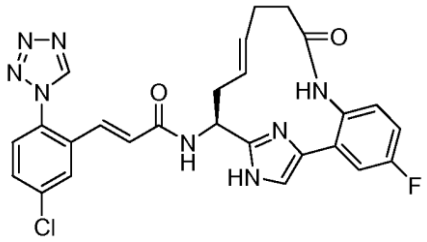


Ej. nº	L-Y	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
I-216		Cl	558.1	7.5
I-217		Cl	560.0	7.1
I-218	 (diastereómero A)	H	538.2	4.9
I-219	 (diastereómero B)	H	538.2	4.9
I-220	 (diastereómero B)	H	524.3	5.1
I-221	 (diastereómero A)	H	524.2	5.0

Ejemplo I-226.

(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-N-((E)-(S)-4-fluoro-9-oxo-8,17,19-triaza-triciclo[14.2.1.2.7]nonadeca-1(18),2,4,6,12,16(19)-hexaen-15-il)-acrilamida, sal del ácido

trifluoracético.



I-226A. {(S)-1-[4-(5-Fluoro-2-nitro-fenil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-but-3-enil}-amida del ácido 2-metil-propano-2-sulfínico: Se desgasificó con argón durante 5 minutos un vial de microondas que contenía una mezcla del Intermediario 37 (409.6 mg, 0.909 mmol), ácido 5-fluoro-2-nitrofenilborónico (336 mg, 1.818 mmol) y carbonato potásico (251 mg, 1.818 mmol) en dioxano (5.82 ml) y agua (1.46 ml). A continuación, se añadió bis(tri-*t*-butilfosfina)paladio (0) (23.23 mg, 0.045 mmol) y el vial se selló y se calentó en un microondas hasta 130°C durante 10 min. Se añadió más ácido 5-fluoro-2-nitrofenilborónico (1 eq) y carbonato potásico (1 eq) al vial y el vial se desgasificó con argón durante 5 min. Se añadió más bis(tri-*t*-butilfosfina)paladio (0) (23.23 mg, 0.045 mmol) se añadió y el vial se selló y se calento en un microondas a 130°C durante 10 min. Se añadió más ácido 5-fluoro-2-nitrofenilborónico (1 eq) y carbonato potásico (1 eq) al vial y el vial se desgasificó con argón durante 5 min. Se añadió más bis(tri-*t*-butilfosfina)paladio (0) (23.23 mg, 0.045 mmol) y el vial se selló y se calentó en un microondas a 130°C

durante 10 min. La reacción se repartió entre agua y acetato de etilo y se separaron las fases. La fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas combinadas $NaHCO_3$ (ac) saturado, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron hasta un aceite marrón espeso. La purificación por cromatografía en fase normal dio 168.4 mg (36.3 %) de I-226A como un aceite amarillo. EM (IEP) *m/z*: 511.2 (M+H)+.

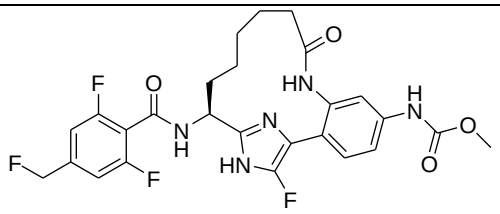
I-226B. Éster terc-butílico del ácido {(S)-1-[4-(5-fluoro-2-nitro-fenil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-but-3-enil}-carbámico: A una solución amarillo oscuro de I-226A (314.6 mg, 0.616 mmol) en MeOH (6.16 ml) se añadió gota a gota HCl 4M en dioxano (0.77 ml, 3.08 mmol). La reacción se dejó agitar a TA. Después de 30 min, la reacción se inactivó con la adición gota a gota $NaHCO_3$ (ac) saturado y luego se concentró dando un aceite marrón claro. El aceite se repartió entonces entre $NaHCO_3$ (ac) saturado y DCM y se separaron las fases. La fase acuosa se extrajo con DCM (1x). Las fases orgánicas se reunieron, se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron dando 204.7 mg (82 %) de la amina como un aceite naranja. EM (IEP) *m/z*: 407.1 (M+H)+.

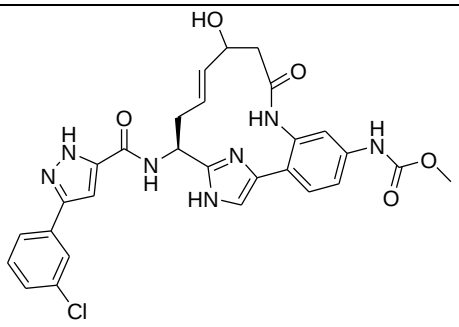
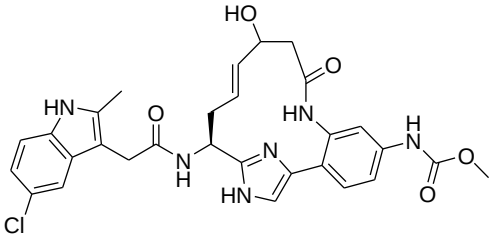
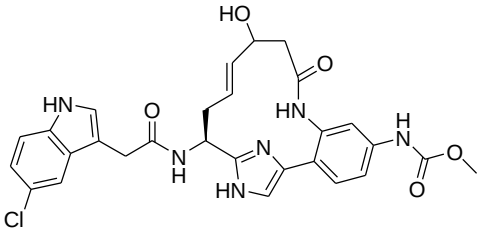
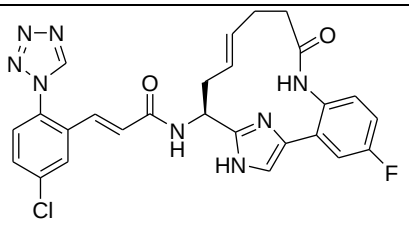
A una solución de amina (196.9 mg, 0.444 mmol) en DCM (1.4 ml) se añadió trietilamina (0.248 ml, 1.778 mmol). A continuación, se añadió BOC_2O (0.114 ml, 0.489 mmol). Después de 30min, la reacción se repartió entre DCM y $NaHCO_3$ (ac)

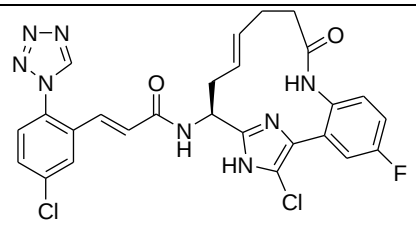
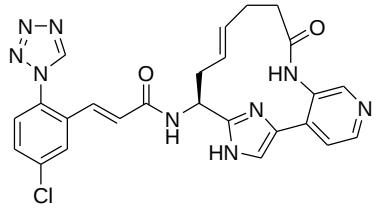
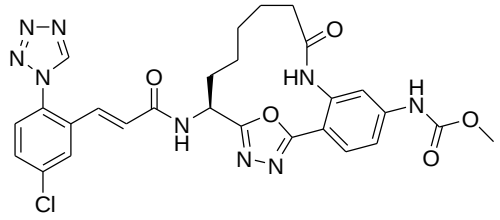
saturado y se separaron las fases. La fase acuosa se extrajo con DCM. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron hasta un aceite naranja. La purificación por cromatografía en fase normal dio 195.7 mg (87 %) de I-226B como un residuo amarillo-verde. EM (IEP) *m/z*: 507.3 (M+H)+.

I-226C. El Ejemplo I-226 se preparó siguiendo los procedimientos descritos en 15B, sustituyendo 15A por I-226B; seguido por las etapas 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; 2E/2F; 10H; y 15D. EM (IEP) *m/z*: 533.1 (M+H)+. 1H NMR (500 MHz, CD_3OD) δ: 2.33 - 2.51 (m, 4 H), 2.53 - 2.61 (m, 1 H), 2.77 - 2.86 (m, 1 H), 5.09 (dd, *J*=9.9, 4.7 Hz, 1 H), 5.37 - 5.46 (m, 1 H), 5.52 - 5.60 (m, 1 H), 6.76 (d, *J*=15.7 Hz, 1 H), 7.15 (d, *J*=15.7 Hz, 1 H), 7.27 - 7.38 (m, 3 H), 7.49 (s, 1 H), 7.59 (d, *J*=8.5 Hz, 1 H), 7.68 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.98 (d, *J*=2.5 Hz, 1 H), 9.51 (s, 1 H).

Tabla I-13: Ejemplos I-222 a I-230

Ej. n°	Estructura	LCMS $[M+H]^+$	HPLC Tr (min)
I-222		548.1	6.9

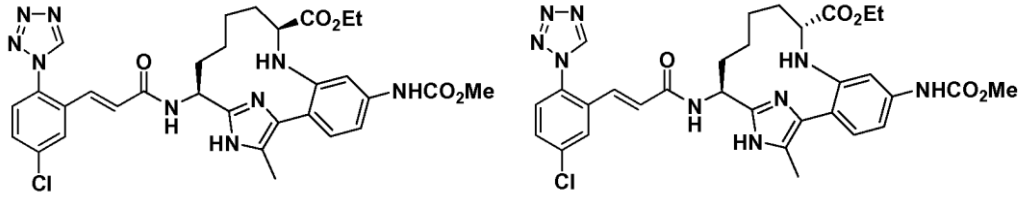
Ej. nº	Estructura	LCMS $[M+H]^+$	HPLC Tr (min)
I-223	 (mezcla de diastereómeros)	576.2	5.4
I-224	 (mezcla de diastereómeros)	577.2	4.3
I-225	 (mezcla de diastereómeros)	563.2	4.1
I-226		533.1	5.2

Ej. n°	Estructura	LCMS $[M+H]^+$	HPLC Tr (min)
I-227		567.0	7.5
I-228		516.1	5.4
I-229		592.0	7.6

Ejemplos I-241 y I-242.

Éster etílico del ácido (9S,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-17-metil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, bis-sal del ácido trifluoracético, y éster etílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-17-metil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, bis-sal

del ácido trifluoracético



Estos compuestos se prepararon usando una variación de los procedimientos empleados para preparar los compuestos I-67 y I-68.

I-241A. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(2,2,2-trifluoro-acetilamino)-fenil]-carbámico: A una suspensión del Ejemplo 10C (3 g, 5.64 mmol) en CH_2Cl_2 (40 ml) a 0°C se añadió Et_3N (0.944 ml, 6.77 mmol), seguido por $(CF_3CO)_2O$ (0.797 ml, 5.64 mmol). Se eliminó el solvente a vacío y el residuo se purificó por cromatografía en fase normal dando una espuma amarilla (3.0 g, 4.54 mmol, 80 % de rendimiento): EM (IEP) *m/z*: 628.5.

I-241B. Éster metílico del ácido [4-[5-bromo-2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(2,2,2-trifluoro-acetilamino)-fenil]-carbámico: A una solución de Ejemplo I-241A (1.0 g, 1.593 mmol) en $CHCl_3$ (10 ml) a 0°C se añadió 1-bromopirrolidin-2,5-diona (0.284 g, 1.593 mmol) y se agitó a la misma temperatura durante 10 min. La mezcla de

reacción se concentró a vacío y se purificó por cromatografía en fase normal: EM (IEP) *m/z*:708.

I-241C. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-5-metil-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(2,2,2-trifluoro-acetilamino)-fenil]-carbámico: A una mezcla del Ejemplo I-241C (200 mg, 0.283 mmol), ácido metilborónico (85 mg, 1.415 mmol) y K3PO4 (148 mg, 0.849 mmol) en un vial de microondas se añadió dioxano (5 ml), que se había desgasificado burbujeando argón a su través durante 30 min. La mezcla de reacción se desgasificó de nuevo durante 15 minutos. A esta mezcla se añadió entonces aducto de $PdCl_2$(dppf)-CH_2Cl_2 (46.2 mg, 0.057 mmol) y se selló inmediatamente y se sometió a calentamiento en microondas durante 25 minutos a 150°C. La mezcla de reacción se diluyó con EtOAc y se lavó con salmuera. El secado sobre Na_2SO_4, filtración, eliminación del solvente a vacío y purificación del residuo por cromatografía en fase normal dio un aceite: EM (IEP) *m/z* = 642.3.

I-241D. Éster metílico del ácido {3-amino-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-5-metil-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-fenil}-carbámico: A una solución de I-241C (420 mg, 0.654 mmol) en MeOH (5 ml) se añadió una solución de LiOH (7 ml, 7 mmol) y se agitó a 60°C durante 1.5 h. La mezcla de reacción se acidificó hasta pH 6 con HCl 1N y se extrajo con EtOAc tres

veces. Las fases orgánicas combinadas se secaron sobre Na2SO4, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía en fase normal dando un aceite. EM (IEP) *m/z*: 546.3.

Ejemplos I-241 y I-242. La síntesis siguió los procedimientos para I-67 y I-68 usando el Ejemplo I-241D en lugar del Ejemplo 10C. Esto dio lugar a diastereómeros éster etílico en lugar de diastereómeros éster metílico. Cada diastereómero se trató por separado a través del resto de la secuencia como se describe para los Ejemplos I-67 y I-68.

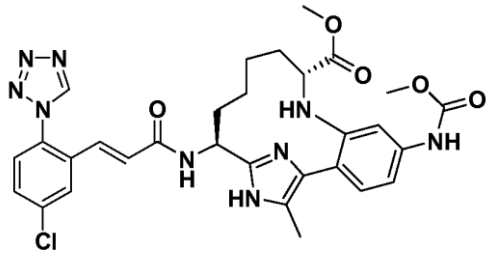
Para el Ejemplo I-241: 1H NMR (500MHz, CD_3CN) δ 9.11 (s, 1H), 8.81 (d, *J* = 6.1 Hz, 1H), 7.85 - 7.79 (m, 2H), 7.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 2.2 Hz, 1H), 7.20 - 7.16 (m, 1H), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.98 (d, *J* = 15.4 Hz, 1H), 6.66 (d, *J* = 15.7 Hz, 1H), 5.33 (m, 1H), 4.09 - 3.94 (m, 2H), 3.70 (s, 3H), 3.07 (dd, *J* = 9.8, 2.9 Hz, 1H), 2.30 - 2.21 (m, 5H), 1.94 (m, 1H), 1.85 (s ancho, 1H), 1.63 - 1.50 (m, 2H), 1.45 - 1.31 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 4H), 0.75 - 0.65 (m, 1H).

Para el I-242, 1H NMR (500MHz, CD_3CN) δ: 10.02 (d, *J* = 8.5 Hz, 1H), 9.08 (s, 1H), 7.82 (d, *J* = 2.2 Hz, 1H), 7.66 (s, 1H), 7.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.21 - 7.15 (m, 2H), 7.15 - 7.10 (m, 1H), 6.79 - 6.72 (m, 1H), 6.63 - 6.58 (m, 1H), 5.84 (dt, *J* = 10.9, 8.2 Hz, 1H), 4.02 - 3.88 (m, 2H), 3.74 - 3.67 (m, 3H), 2.96 (d, *J* =

11.3 Hz, 1H), 2.39 - 2.31 (m, 4H), 2.17 - 2.02 (m, 2H), 1.94 (m, 1H), 1.76 - 1.63 (m, 2H), 1.56 - 1.44 (m, 2H), 1.44 - 1.32 (m, 1H), 1.11 - 1.02 (m, 3H), 0.44 - 0.32 (m, 1H).

Ejemplo I-243.

Éster metílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-17-metil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, bis-sal del ácido trifluoracético



I-243A. 2-(N-(2-(2-((S)-1-(*terc*-butoxicarbonilamino)but-3-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-4-il)-5-(metoxicarbonilamino)fenil)-2,2,2-trifluoroacetamido)pent-4-enoato de (R)-metilo: El Ejemplo I-74B (3.66 g, 5.68 mmol) se disolvió en EtOAc (50 ml) y la mezcla de reacción se enfrió hasta 0°C. Se añadió Et_3N (1.585 ml, 11.37 mmol) seguido por $(CF_3CO)_2O$ (0.964 ml, 6.82 mmol). La mezcla de reacción se dejó calentar hasta TA durante 72h. La mezcla de reacción se diluyó con agua y se extrajo tres veces con EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío.

El residuo se purificó por cromatografía en fase normal: Peso = 500 mg; EM (IEP) *m/z*: 740.

I-243B. Éster metílico del ácido (E)-(9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaeno-9-carboxílico: El Ejemplo I-243A (500 mg, 0.676 mmol) se disolvió en DCE (15 ml) y se hizo reaccionar con catalizador de Grubbs II de acuerdo con el procedimiento descrito para I-74C. El tratamiento y purificación por cromatografía en fase normal proporcionó un sólido (Peso = 730 mg): EM (IEP) *m/z*: 712.5.

I-243C. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: El Ejemplo I-243C se preparó de acuerdo con el procedimiento descrito para I-74D usando el precursor I-243B (730 mg). El tratamiento y cromatografía en fase normal proporcionaron el intermediario deseado (Peso = 520 mg): EM (IEP) *m/z*: 714.

I-243D. Éster metílico del ácido (9R,14S)-17-bromo-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-

pentaeno-9-carboxílico: El Ejemplo I-243C (520 mg, 0.628 mmol) se disolvió en $CHCl_3$ (10 ml). La mezcla de reacción se enfrió hasta 0°C y se añadió NBS (123 mg, 0.691 mmol). La reacción se dejó agitar a 0°C. La mezcla de reacción se concentró a vacío y el residuo se purificó por cromatografía en fase normal. (Peso = 225 mg): EM (IEP) *m/z*: 795, 793. 1H NMR (500 MHz, MeOH-d_3) δ ppm 9.57 (1 H, s ancho), 7.83 - 7.95 (1 H, m), 7.60 (1 H, dd, J=8.25, 1.65 Hz), 7.39 (1 H, d, J=8.25 Hz), 5.75 (1 H, d, J=11.55 Hz), 5.42 (1 H, d, J=11.00 Hz), 4.97 - 5.02 (1 H, m), 4.48 - 4.62 (1 H, m), 3.80 (3 H, s), 3.78 (3 H, s), 3.58 - 3.71 (1 H, m), 2.22 - 2.36 (1 H, m), 1.84 - 1.97 (1 H, m), 1.64 - 1.81 (2 H, m), 1.44 (9 H, s), 0.84 - 1.05 (3 H, m), 0.00 (9 H, s).

I-243E. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-17-metil-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: A una mezcla del Ejemplo I-243D (78 mg, 0.098 mmol), ácido metilborónico (10.57 mg, 0.177 mmol) y K3PO4 (18.46 mg, 0.106 mmol) en un vial de microondas se añadió dioxano (1 ml) que se desgasificó burbujeando argón a su través durante 30 min. La mezcla de reacción se desgasificó de nuevo durante 15 mins. A esta mezcla se añadió entonces aducto de $PdCl_2$(dppf)-CH_2Cl_2 (5.77 mg, 7.06 µmol) y el vial de reacción se selló inmediatamente y se sometió a

calentamiento en microondas durante 15 minutos a 150°C. La mezcla de reacción se diluyó con acetato de etilo y se lavó con salmuera. La fase orgánica se separó, se secó sobre Na2SO4, se filtró y se concentró a vacío. La cromatografía sobre fase normal proporcionó un sólido (Peso = 33 mg): EM (IEP) *m/z*: 696.4.

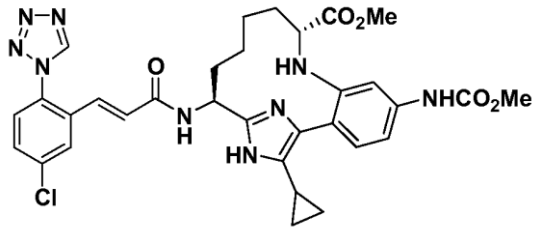
I-243F. Éster metílico del ácido (9R,14S)-14-amino-5-metoxicarbonilamino-17-metil-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal diclorhidrato: El Ejemplo I-243F se preparó a partir de Ejemplo I-243E (42.7 mg, 0.227 mmol) usando el procedimiento descrito para el Ejemplo I-61B. El tratamiento y cromatografía sobre fase inversa proporcionó un sólido que era una sal del ácido trifluoracético (Peso = 11 mg): EM (IEP) *m/z*: 402.3.

Ejemplo I-243. El Ejemplo I-243F (11 mg, 0.015) y 3-(5-cloro-2-(1H-tetrazol-1-il)fenil)acrilato de (E)-2,5-dioxopirrolidin-1-ilo (5.2 mg, 0.015 mmol) se hicieron reaccionar de acuerdo con el procedimiento para el Ejemplo 1G. El tratamiento y cromatografía sobre fase inversa dio el producto deseado como una bis-sal del ácido trifluoracético (Peso = 6 mg): EM (IEP) *m/z*: 634.4. 1H NMR (500MHz, CD_3CN) δ 9.91 (d, J = 8.3 Hz, 1H), 9.08 (s, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.74 - 7.42 (m, 3H), 7.26 - 7.06 (m, 3H), 6.77 (d, J = 15.7 Hz, 1H), 6.65 - 6.57 (m, 1H), 5.80 (dt, J = 11.3, 7.8

Hz, 1H), 3.76 - 3.65 (m, 3H), 3.55 - 3.46 (m, 3H), 3.01 (d, J=11.6 Hz, 1H), 2.39 - 2.31 (m, 3H), 2.19 - 2.02 (m, 2H), 1.94 (m, 2 H) 1.77 - 1.62 (m, 2H), 1.56 - 1.32 (m, 3H), 0.46 - 0.29 (m, 1H).

Ejemplo I-244.

Éster metílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciclopropil-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, bis-sal del ácido trifluoracético

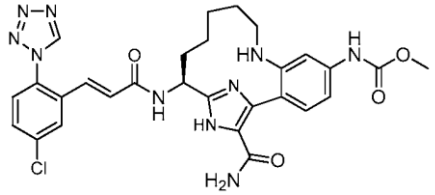


La síntesis para este compuesto siguió el procedimiento para el Ejemplo I-243 usando ácido ciclopropilborónico en lugar de ácido metil borónico en la etapa para preparar el Ejemplo I-243E. El Ejemplo I-244 se aisló como una bis-sal del ácido trifluoracético. EM (IEP) *m/z*: 660.3; 1H NMR (500MHz, CD_3CN) δ 10.36 (d, *J* = 8.8 Hz, 1H), 9.08 (s, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.65 - 7.54 (m, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.18 - 6.98 (m, 2H), 6.63 - 6.56 (m, 2H), 5.97 - 5.86 (m, 1H), 3.71 (s, 3H), 3.48 (s, 3H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.14 - 2.02 (m, 2H), 1.75 - 1.42 (m, 6H), 1.34 (t, *J* = 13.2 Hz, 2H),

1.08 - 0.98 (m, 1H), 0.94 - 0.77 (m, 3H), 0.32 - 0.16 (m, 1H).

Ejemplo I-245.

Éster metílico del ácido {(S)-17-carbamoil-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, 2 TFA

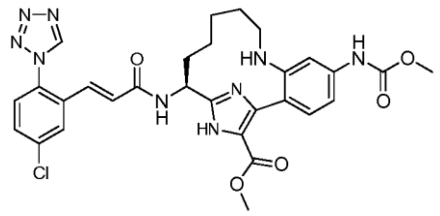


Se disolvió I-115D (0.050 g, 0.073 mmol) en DMSO (0.367 ml) y se añadió K_2CO_3 (0.030 g, 0.220 mmol) seguido por adición gota a gota de peróxido de hidrógeno al 30% (0.083 ml, 0.808 mmol). Se formó un precipitado blanco espeso. La reacción se agitó a temperatura ambiente durante 5.5 h bajo Ar. La mezcla de reacción se diluyó con EtOAc y se lavó con agua (3x) y salmuera, a continuación se secó sobre $MgSO_4$, se filtró y se concentró proporcionando una mezcla de producto, producto parcialmente desprotegido (pérdida de trifluoroacetamida) y material de partida. Esta mezcla se purificó por HPLC de fase inversa para eliminar el material de partida que no ha reaccionado, y la mezcla del producto se desprotegió totalmente usando el procedimiento descrito para la etapa I-61B, seguido por acoplamiento de la amina resultante con Intermediario 1 usando el procedimiento

descrito en la etapa 1G proporcionando Ejemplo I-245 como un sólido blanco. 1H NMR (500 MHz, CD_3OD) δ ppm 9.71 (1 H, s) 9.55 (1 H, s) 7.94 (1 H, d, *J*=1.65 Hz) 7.89 (1 H, d, *J*=8.25 Hz) 7.86 (1 H, s ancho) 7.61 - 7.67 (1 H, m) 7.55 - 7.60 (1 H, m) 7.26 (1 H, dd, *J*=8.52, 1.92 Hz) 7.23 (1 H, d, *J*=15.40 Hz) 6.79 (1 H, d, *J*=15.40 Hz) 5.15 (1 H, dd, *J*=10.45, 6.60 Hz) 3.73 (3 H, s) 3.20 (1 H, d, *J*=12.65 Hz) 2.97 (1 H, t, *J*=12.65 Hz) 2.09 - 2.18 (1 H, m) 2.00 (1 H, t, *J*=11.27 Hz) 1.79 - 1.92 (2 H, m) 1.61 (2 H, t, *J*=13.75 Hz) 1.32 (1 H, s ancho) 0.62 (1 H, d, *J*=12.65 Hz). EM (IEP) *m/z*: 605.4 (M+H)+. HPLC analítica: Tr = 4.98 min.

Ejemplo I-246.

Éster metílico del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-17-carboxílico, 2TFA



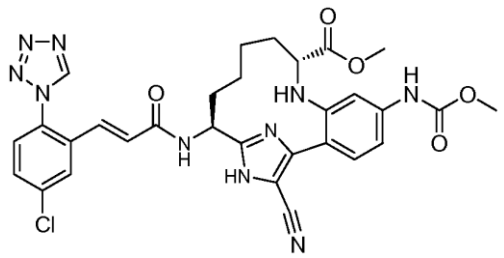
Se disolvió I-115D (0.025 g, 0.037 mmol) en MeOH (0.5 ml), y luego se añadió H_2SO_4 concentrado (0.050 ml) a TA. La reacción se calentó a 75°C bajo Ar durante la noche, momento en donde se obtuvo el producto deseado, Éster metílico del ácido (S)-14-amino-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-

1(17),2,4,6,15(18)-pentaeno-17-carboxílico (I-246A) junto con Éster metílico del ácido (S)-5.14-diamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-17-carboxílico (I-246B) a partir de la ruptura del carbamato de metilo. La mezcla de reacción se enfrió hasta ta y se diluyó con MeOH, a continuación se filtró y se purificó por HPLC de fase inversa. Se desprotegió I-246A usando el procedimiento descrito en la etapa I-61B, y la amina resultante se acopló con el Intermediario 1 usando el procedimiento descrito para la etapa 1G proporcionando el Ejemplo I-246. 1H NMR (500 MHz, DMSO-d_6) δ ppm 13.28 (1 H, s ancho) 10.76 (1 H, s ancho) 10.18 (1 H, s ancho) 9.86 (1 H, s) 8.43 (1 H, d, *J*=5.50 Hz) 8.03 (1 H, d, *J*=7.15 Hz) 7.99 (1 H, d, *J*=2.20 Hz) 7.95 (1 H, s ancho) 7.69 - 7.79 (2 H, m) 7.44 (1 H, d, *J*=7.70 Hz) 6.84 - 6.93 (2 H, m) 5.19 - 5.28 (1 H, m) 3.80 (3 H, s) 3.72 (3 H, s) 3.05 (1 H, d, *J*=11.00 Hz) 2.83 (1 H, t, *J*=11.28 Hz) 1.91 - 2.00 (1 H, m) 1.79 (2 H, s ancho) 1.66 (1 H, q, *J*=10.73 Hz) 1.36 - 1.49 (2 H, m) 1.17 (1 H, s ancho) 0.61 (1 H, d, *J*=13.75 Hz). EM (IEP) *m/z*: 620.4 (M+H)+. HPLC analítica: Tr = 5.55 min.

Ejemplo I-247.

Éster metílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciano-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-

carboxílico, 2TFA



I-247A. 2-(N-(2-(2-((S)-1-(*terc*-Butoxicarbonilamino)but-3-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-4-il)-5-(metoxicarbonilamino)fenil)-2,2,2-trifluoroacetamido)pent-4-enoato de (R)-metilo: Se disolvió I-74B (12 g, 13.98 mmol) en acetato de etilo (100 ml). Se añadió piridina (1.357 ml, 16.77 mmol), y la reacción se enfrió hasta 0°C. Se añadió TFAA (2.172 ml, 15.38 mmol) gota a gota con agitación y se dejó que la reacción llegara a TA, a continuación se agitó a temperatura ambiente bajo Ar durante la noche. La reacción se diluyó con EtOAc y agua. Se extrajo la fase acuosa 3x con EtOAc, y las fases orgánicas combinadas se secaron con sulfato sódico, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida proporcionando la trifluoroacetamida deseada que contiene impurezas minoritarias que no se separan sobre gel de sílice. Este producto bruto se recogió sin purificación adicional.

I-247B. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8-(2,2,2-trifluoroacetil)-16-(2-trimetilsilaniletoximetil)-8,16,18-

triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: Se disolvió I-247A (6.15 g, 8.31 mmol) en DCE (208 ml) en un matraz de fondo redondo equipado con una entrada de argón y condensador de reflujo. La solución se desgasificó burbujeando con Ar durante 15 minutos. La mezcla de reacción se calentó hasta 84°C, y se añadió una solución de Grubbs II (1.059 g, 1.247 mmol) disuelta en 15 ml de DCE. La mezcla de reacción se agitó a 84°C bajo Ar durante 15 horas. La reacción se inactivó por adición de una solución saturada de $NaHCO_3$ y se diluyó con DCM. La fase orgánica se extrajo una vez más con solución saturada de $NaHCO_3$ y una vez con salmuera. La fase orgánica se secó con Na_2SO_4, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida proporcionando el producto RCM con ~37% de rendimiento como una mezcla de isómeros cis/trans. Se recogió una porción de este intermediario (1.9 g, 2.67 mmol) en MeOH (26.7 ml) y se añadió Pd/C (0.284 g, 0.267 mmol). La mezcla se agitó entonces a temperatura ambiente bajo 3.446 x 105 Pa de H2 durante 48 h proporcionando I-127-B (1.66g, 87%) después de separar el catalizador y evaporar el solvente. EM (IEP) *m/z*: 714.3 (M+H)+.

I-247C. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-17-ciano-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-

triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: Éster metílico del ácido (9R,14S)-17-bromo-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8-(2,2,2-trifluoro-acetil)-16-(2-trimetilsilanil-etoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, preparado a partir de I-247B usando el procedimiento descrito para I-115C, (2.0 g, 2.52 mmol) se disolvió en DMF (12.61 ml). Se añadió cianuro de zinc (0.178 g, 1.514 mmol) y la reacción se desgasificó burbujeando con Ar durante 15 minutos. Se añadió (Ph3)4Pd (0.292 g, 0.252 mmol) y la mezcla se agitó a 120°C durante 10 horas bajo Ar. La mezcla de reacción se diluyó con EtOAc, se lavó 4x con LiCl al 10%, salmuera, se secó con sulfato sódico, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida proporcionando 1.44 g de una mezcla 3:1 de producto ciano a bromuro de partida. Esta mezcla se volvió a someter a las condiciones anteriores de reacción y aislamiento proporcionando I-247C con un ~60% de rendimiento después de cromatografía. EM (IEP) *m/z*: 739.3 (M+H)+.

I-247D. Éster metílico del ácido (9R,14S)-14-amino-17-ciano-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, 3TFA: Se disolvió I-247C (0.106 g, 0.143 mmol) en MeOH (2 ml) y se añadió una solución de O-

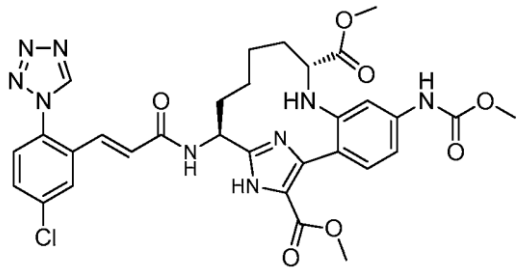
metilhidroxilamina en H_2O (25% p/p, 0.135 ml, 0.717 mmol) seguido por HCl 6M (2 ml). La mezcla se calentó con agitación en un tubo sellado a 75°C durante la noche. La mezcla de reacción se concentró, y se añadieron HCl/dioxano (0.5 ml) y MeOH (2 ml) seguido por agitación durante la noche a temperatura ambiente. La mezcla se concentró y el residuo purificó por HPLC de fase inversa proporcionando I-247D (0.031 g, 28.6%) como un sólido blanco. EM (IEP) *m/z*: 413.3 (M+H)+.

I-247E. El Ejemplo I-247 se preparó a partir de I-247D por acoplamiento con el Intermediario 1 usando el procedimiento descrito para la etapa 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (1 H, s ancho), 8.00 (1 H, d, *J*=2.20 Hz), 7.65 (1 H, dd, *J*=8.80, 2.20 Hz), 7.56 (1 H, d, *J*=8.80 Hz), 7.46 (1 H, d, *J*=8.25 Hz), 7.42 - 7.45 (1 H, m), 7.16 (1 H, dd, *J*=8.52, 1.92 Hz), 7.10 (1 H, d, *J*=15.40 Hz), 6.80 (1 H, d, *J*=15.95 Hz), 5.19 (1 H, dd, *J*=10.72, 6.87 Hz), 3.74 (3 H, s), 3.58 (3 H, s), 3.01 - 3.07 (1 H, m), 2.05 - 2.17 (1 H, m), 1.80 - 1.92 (2 H, m), 1.69 - 1.80 (1 H, m), 1.32 - 1.53 (4 H, m), 0.33 - 0.51 (1 H, m). EM (IEP) *m/z*: 645.4 (M+H)+. HPLC analítica: Tr = 8.23 min.

Ejemplo I-248.

Éster dimetílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-

1(17),2,4,6,15(18)-pentaeno-9,17-dicarboxílico, 2TFA



I-248A. Éster metílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-17-carbamoil-5-metoxicarbonilamino-8-(2,2,2-trifluoroacetil)-16-(2-trimetilsilaniletoximetil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico: Se pesaron I-247C (60 mg, 0.081 mmol), oxima de acetaldehído (9.90 µl, 0.162 mmol), trifenilfosfina (4.26 mg, 0.016 mmol) y acetato de paladio(II) (1.823 mg, 8.12 µmol) en un vial de presión de 3.696 ml y se añadieron etanol (0.2 ml) y agua (0.050 ml). El vial se llenó con argón y se tapón y la mezcla de reacción se calentó a 80°C con agitación durante ~1 h. La reacción se enfrió hasta temperatura ambiente, se filtró a través de un filtro de jeringa que luego se lavó con una mezcla de MeOH/CH_2Cl_2, y el filtrado se destiló hasta sequedad. El residuo se purificó por cromatografía ultrarrápida proporcionando I-248A (42.1 mg, 68.5 %). EM (IEP) *m/z*: 757.4 (M+H)+

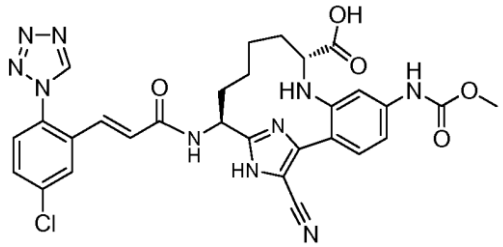
I-248B. Éster dimetílico del ácido (9R,14S)-14-amino-5-metoxicarbonilamino-8,16,18-triaza-

triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9,17-dicarboxílico, 3TFA: Se obtuvo I-248B a partir de I-248A usando el procedimiento descrito para la etapa I-61B y se aisló como la sal tris-TFA después de HPLC de fase inversa.

I-248C. El Ejemplo I-248 se preparó a partir de I-248B por acoplamiento con el Intermediario 1 usando el procedimiento descrito para la etapa 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.50 (1 H, s), 7.98 (1 H, d, *J*=2.2 Hz), 7.67 (1 H, dd, *J*=8.8, 2.2 Hz), 7.59 (1 H, s), 7.57 (1 H, s), 7.45 (1 H, s), 7.09 - 7.16 (2 H, m), 6.76 (1 H, d, *J*=15.4 Hz), 5.18 (1 H, dd, *J*=11.0, 7.1 Hz), 3.88 (3 H, s), 3.75 (3 H, s), 3.59 (3 H, s), 3.05 (1 H, d, *J*=11.5 Hz), 2.21 - 2.33 (1 H, m), 1.99 - 2.08 (1 H, m), 1.67 - 1.78 (2 H, m), 1.51 - 1.62 (1 H, m), 1.37 - 1.50 (2 H, m), 0.40 - 0.55 (1 H, m). EM (IEP) *m/z*: 678.1 (M+H)+. HPLC analítica: Tr = 6.52 min.

Ejemplo I-250.

Ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciano-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, 2 TFA



I-250A. Ácido (9R,14S)-14-amino-17-ciano-5-

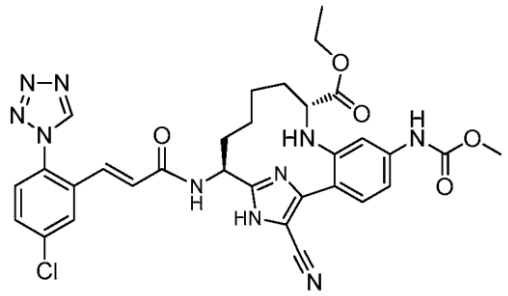
metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, 3 TFA: Una mezcla de I-247C (165 mg, 0.193 mmol), clorhidrato de O-metoxiamina (30% en agua, 0.245 ml, 0.967 mmol), HCl 6M (1.29 ml, 7.74 mmol) y MeOH (1.6 ml) se calentó con agitación en un baño de aceite a 75°C durante la noche en un vial de presión sellado de 5 ml. La reacción se enfrió hasta temperatura ambiente y se determinó por LCMS que era una mezcla ~ 1:1 de éster metílico y productos ácidos. La mezcla se destiló hasta sequedad, y el residuo se volvió a disolver en una mezcla de 4 ml de THF, 2.5 ml de LiOH 1M LiOH y ~0.5 ml de MeOH, a continuación se agitó durante la noche a temperatura ambiente bajo nitrógeno. La mezcla de reacción se neutralizó con HCl 1M y se destiló hasta sequedad. El residuo se purificó por HPLC de fase inversa proporcionando I-250A (29.3 mg, 29.6 %) y el éster metílico correspondiente, I-247D (23.2 mg, 22.78 %). I-250A EM (IEP) *m/z*: 399.2 (M+H)+.

I-250B. El Ejemplo I-250 se preparó a partir de I-250A por acoplamiento con el Intermediario 1 usando el procedimiento descrito para la etapa 1G. 1H NMR (500 MHz, DMSO-d_6) δ ppm 12.98 (1 H, s ancho), 9.86 (1 H, s), 9.79 (1 H, s), 8.76 (1 H, d, *J*=7.7 Hz), 7.93 (1 H, d, *J*=2.2 Hz), 7.67 - 7.80 (2 H, m), 7.34 (1 H, s ancho), 7.28 (1 H, d, *J*=8.2 Hz), 7.10 (1 H, d, *J*=8.2 Hz), 6.82 - 6.96 (2 H, m), 5.14 - 5.27 (1 H, m), 5.00 (1 H, s ancho), 3.67 (3 H, s), 2.68 -

2.85 (1 H, m), 1.99 (1 H, s ancho), 1.59 - 1.79 (3 H, m), 1.17 - 1.36 (3 H, m), 0.33 (1 H, s ancho). EM (IEP) *m/z*: 631.4 (M+H)+ HPLC analítica: Tr = 7.66 min.

Ejemplo I-251.

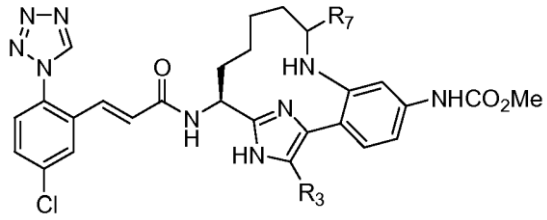
Éster metílico del ácido (9R,14S)-14-[(E)-3-(5-Cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciano-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, 2 TFA

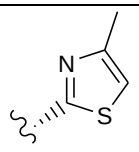


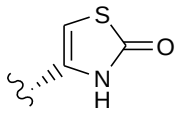
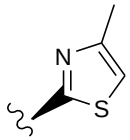
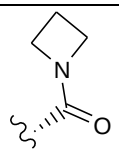
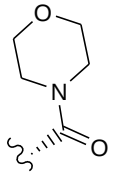
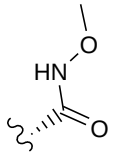
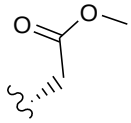
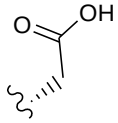
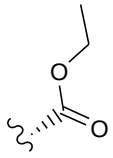
Ejemplo I-251. El Ejemplo I-250 (15.8 mg, 0.018 mmol) se disolvió en EtOH (0.5 ml) y se añadió TMS-Cl (5.64 µl, 0.044 mmol) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Solo se observó una pequeña cantidad del producto deseado, por tanto, la solución se transfirió a un vial de presión usando ~ 0.2 ml más de EtOH para aclarar. Se añadieron otros 20 µl de TMS-Cl, y el vial se tapó y calentó con agitación a 75°C durante 4 h. La LCMS mostró conversión completa a éster etílico. La mezcla de reacción se destiló hasta sequedad y el producto bruto se volvió a disolver en MeOH, se filtró y se purificó

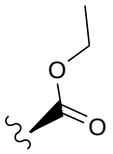
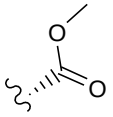
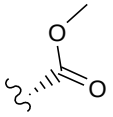
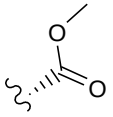
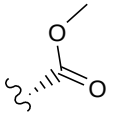
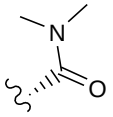
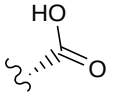
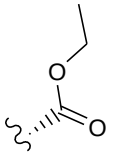
por HPLC de fase inversa proporcionando el Ejemplo I-251 (6.8 mg, 40.4 %) como un sólido blanco. 1H NMR (500 MHz, CD_3CN) δ ppm 9.10 (1 H, s), 7.88 (1 H, d, *J*=2.2 Hz), 7.86 (1 H, s), 7.61 (1 H, dd, *J*=8.5, 2.2 Hz), 7.52 (2 H, dd, *J*=11.8, 8.5 Hz), 7.41 (1 H, d, *J*=1.9 Hz), 7.36 (1 H, d, *J*=7.4 Hz), 7.17 (1 H, dd, *J*=8.3, 2.2 Hz), 7.01 (1 H, d, *J*=15.4 Hz), 6.65 (1 H, d, *J*=15.7 Hz), 5.30 (1 H, ddd, *J*=10.9, 7.0, 6.9 Hz), 3.92 - 4.07 (2 H, m), 3.71 (3 H, s), 2.94 - 3.05 (1 H, m), 2.05 - 2.16 (1 H, m), 1.66 - 1.83 (3 H, m), 1.32 - 1.57 (3 H, m), 1.10 (3 H, t, *J*=7.2 Hz), 0.42 (1 H, d, *J*=12.7 Hz). EM (IEP) *m/z*: 659.2 (M+H)+. HPLC analítica: Tr = 9.00 min.

Tabla I-14: Ejemplos I-231 a I-251



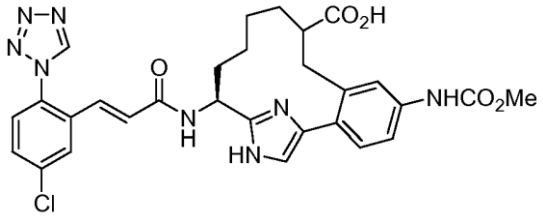
Ej. n°	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min.)
I-231	CH_2OMe (homoquiral)	H	606.3	9.1
I-232	CH_2OMe (homoquiral)	H	606.3	9.0
I-233		H	659.3	5.9

Ej. n°	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min.)
I-234		H	661.2	5.8
I-235		H	659.2	5.8
I-236		H	645.3	5.1
I-237		H	675.3	5.1
I-238		H	635.2	5.4
I-239		H	634.2	6.8
I-240		H	620.1	5.3
I-241		Me	648.4	6.1

Ej. n°	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min.)
I-242		Me	648.4	5.9
I-243		Me	634.4	5.8
I-244			660.3	6.2
I-245	H	CONH2	605.4	5.0
I-246	H	CO2Me	620.4	5.5
I-247		CN	645.4	8.2
I-248		CO2Me	678.3	6.1
I-249		CN	658.4	7.8
I-250		CN	631.4	7.7
I-251		CN	659.2	9.0

Ejemplo I-252.

Éster terc-butílico del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal del ácido trifluoracético



I-252A. Éster terc-butílico del ácido 3-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-5-metoxicarbonilamino-fenil}-propiónico: (Molander, G.A., *Organic Letters*, 10(9):1795 (2008).) Se purgó con argón durante varios minutos un matraz con boca a rosca de 150 ml y paredes gruesas que contenía 3-trifluoroboratopropionato potásico, éster terc-butílico (2.180 g, 9.23 mmol), 10B (5.0 g, 8.39 mmol), acetato de paladio (0.141 g, 0.630 mmol), 2-diciclohexilfosfino-2',6'-di-i-propoxi-1,1'-bifenilo (Ru-Phos) (0.588 g, 1.259 mmol) y carbonato potásico (3.48 g, 25.2 mmol). A continuación se añadieron tolueno (33.6 ml) y agua desgasificada(8.4 ml) y bajo una capa de argón se reemplazó el septum por un tapón a rosca de teflón que poseía una junta tórica Viton. La mezcla naranja bifásica se calentó hasta 85°C. Después de 24 h, la reacción se detuvo y se enfrió hasta TA. Las fases se

separaron y la fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron dando una espuma amarilla que pesaba 6.63 g. La purificación por cromatografía en fase normal (elución con gradiente 0-20% EtOAc/DCM) dio 1.45 g (27%) de I-252A, como una espuma blanca. EM (IEP) *m/z*: 645.4 (M+H)+.

I-252B. Éster terc-butílico del ácido 2-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-4-il]-5-metoxicarbonilamino-bencil}-pent-4-enoico: A una solución enfriada (-78°C) de diisopropilamina (1.167 ml, 8.19 mmol) en THF desgasificado (14 ml) se añadió gota a gota n-BuLi (4.65 ml, 7.44 mmol). La solución amarilla pálida transparente resultante se agitó a -78°C durante 45 min. A continuación, se añadió gota a gota durante 30 minutos una solución amarilla pálida de I-252A (1.20 g, 1.86 mmol) en THF (desgasificado, 9 ml). La suspensión amarilla resultante se agitó intensamente a -78°C. Después de 1.5 h, se añadió bromuro de alilo (0.161 ml, 1.861 mmol) gota a gota. La mezcla de reacción se agitó a -78°C. Después de 1 h, la solución amarilla pálida transparente se dejó calentar lentamente hasta -15°C. La reacción se inactivó con la adición gota a gota de cloruro de amonio saturado y la reacción se dejó calentar hasta TA. La reacción se repartió entre agua y EtOAc y se separaron las fases. La fase acuosa

se extrajo con EtOAc (2x). Las fases orgánicas combinadas se lavaron con NaHCO3 saturado, salmuera, se secó sobre Na2SO4, se filtró y se concentró dando una espuma amarilla. La purificación por cromatografía en fase normal (elución con gradiente 0-20% EtOAc/DCM) dio 1.04 g (70%) como una mezcla 1:2.6 de I-252A:I-252B. El Compuesto I-252B es una mezcla de diastereómeros. EM (IEP) *m/z*: 686.7 (M+H)+.

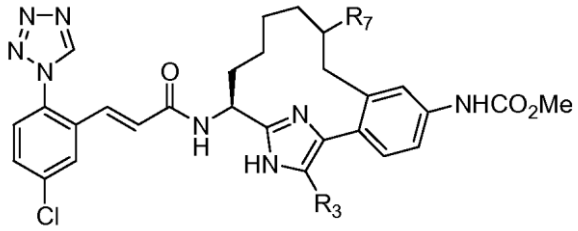
I-252C. Éster terc-butílico del ácido (S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal del ácido trifluoracético (Diastereómero A) y I-252D. Éster terc-butílico del ácido (S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, sal del ácido trifluoracético (Diastereómero B). Los compuestos del título I-252C (Diastereómero A) y I-252D (Diastereómero B) se prepararon siguiendo los procedimientos descritos en 2E/2F, sustituyendo 2D por la mezcla 1:2.6 de I-253A:I-253B; seguido por la etapa 2G, sustituyendo metanol por etanol. Los diastereómeros se separaron por cromatografía en fase inversa.

I-252E. El Ejemplo I-252 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G

por I-252C (diastereómero A) y llevando a cabo la reacción a 75°C; seguido por la etapa 1G. 1H NMR (500 MHz, CD_3OD) 50°C, δ ppm 9.46 (s, 1 H), 7.94 (d, J=2.2 Hz, 1 H), 7.68 (dd, J=8.8, 2.2 Hz, 1 H), 7.57 (d, J=8.8 Hz, 1 H), 7.45 - 7.52 (m, 3 H), 7.38 (d, J=8.2 Hz, 1 H), 7.17 (d, J=15.9 Hz, 1 H), 6.74 (d, J=15.9 Hz, 1 H), 5.18 (t, J=6.0 Hz, 1 H), 3.74 (s, 3 H), 2.79 - 2.91 (m, 2 H), 2.18 - 2.27 (m, 2 H), 1.97 - 2.06 (m, 1 H), 1.30 - 1.67 (m, 4 H), 1.05 - 1.16 (m, 1 H), 0.40 - 0.55 (m, 1 H). EM (IEP) *m/z*: 605.3 (M+H)+. HPLC analítica: Tr = 8.82 min.

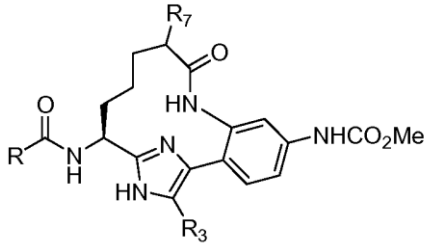
Los Ejemplos I-253 a I-255 se prepararon a partir de I-252C (diastereómero A) de acuerdo con los procedimientos descritos en los ejemlos anteriores. Los Ejemplos I-256 a I-259 se prepararon a partir de I-252D (diastereómero B) de acuerdo con los procedimientos descritos en los ejemplos anteriores.

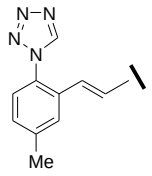
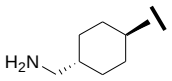
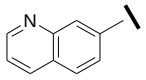
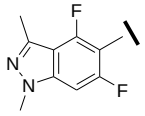
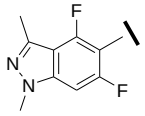
Tabla I-15: Ejemplos I-252 a I-259



Ej. nº	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min.)
I-252	CO_2H (homoquiral)	H	605.3	8.8
I-253	CO_2Me (homoquiral)	H	619.4	9.2
I-254	$CONMe_2$ (homoquiral)	H	632.5	8.7
I-255	$CONMe_2$ (homoquiral)	Cl	666.2	7.4
I-256	CO_2H (homoquiral)	H	605.3	8.8
I-257	CONHMe (homoquiral)	H	618.5	8.6
I-258	$CONMe_2$ (homoquiral)	H	632.5	8.7
I-259	$CONH_2$ (homoquiral)	H	604.4	8.5

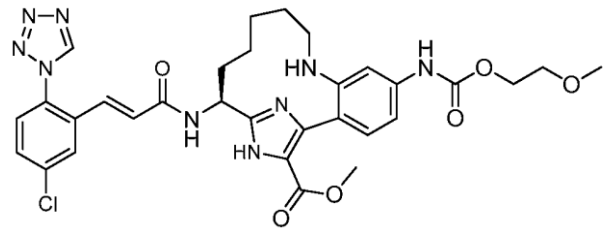
Tabla I-16: Ejemplos I-260 a I-264



Ej. nº	R	R^7	R^3	LCMS $[M+H]^+$	HPLC Tr (min.)
I-260		H	H	556.3	8.1
I-261		H	H	483.4	6.5 (C)
I-262		H	H	499.3	3.1
I-263			H	566.3	8.0
I-264			Cl	600.3	7.5

Ejemplo 266.

Éster metílico del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-(2-metoxi-etoxicarbonilamino)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-17-carboxílico, 2TFA

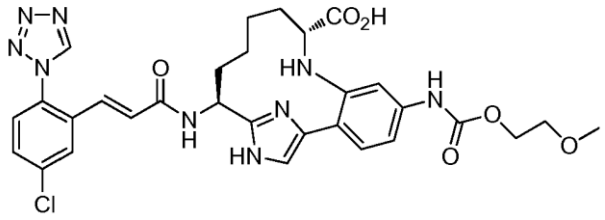


El Ejemplo I-266 se preparó a partir de anilina, I-246B siguiendo un procedimiento similar al descrito para la

etapa I-123B. 1H NMR (500 MHz, CD_3OD) δ ppm 9.53 (1 H, s) 8.34 (1 H, d, *J*=8.80 Hz) 8.03 (1 H, s ancho) 8.02 (1 H, d, *J*=2.20 Hz) 7.67 - 7.71 (1 H, m) 7.59 - 7.62 (1 H, m) 7.31 (1 H, dt, *J*=8.80, 1.10 Hz) 7.19 (1 H, d, *J*=15.95 Hz) 6.80 (1 H, d, *J*=15.40 Hz) 5.31 (1 H, dd, *J*=10.17, 6.32 Hz) 4.26 - 4.32 (2 H, m) 3.89 (3 H, s) 3.65 (2 H, t, *J*=4.67 Hz) 3.39 (3 H, s) 3.18 - 3.24 (1 H, m) 2.98 (1 H, t, *J*=11.27 Hz) 2.09 - 2.19 (1 H, m) 1.99 (1 H, s ancho) 1.83 - 1.96 (2 H, m) 1.67 (2 H, t, *J*=12.10 Hz) 1.31 (1 H, s ancho) 0.69 - 0.82 (1 H, m). EM (IEP) *m/z*: 664.4 (M+H)+. HPLC analítica: Tr = 5.65 min.

Ejemplo I-267.

Ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-(2-metoxi-etoxicarbonilamino)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico, 2 TFA

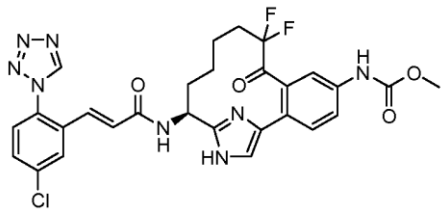


El Ejemplo I-131 (13 mg, 0.015 mmol) se disolvió en HCl 4M/dioxano (2 ml)/agua (0.5 ml) y se calentó hasta 55°C en un vial sellado durante 1.5 horas y luego a 45°C durante 9h. La mezcla de reacción se filtró y el residuo se purificó por HPLC de fase inversa proporcionando el Ejemplo I-267 (4.41 mg, 32.7 %) como un sólido amarillo. 1H NMR (500 MHz,

CD_3CN) δ ppm 9.43 (1 H, s ancho), 9.09 (1 H, s), 7.73 - 7.89 (2 H, m), 7.60 (1 H, dd, *J*=8.25, 2.20 Hz), 7.47 (1 H, d, *J*=8.25 Hz), 7.39 (1 H, s), 7.21 - 7.29 (2 H, m), 7.09 - 7.18 (1 H, m), 6.82 - 6.93 (1 H, m), 6.62 (1 H, d, *J*=15.95 Hz), 5.59 - 5.76 (1 H, m), 4.13 - 4.31 (2 H, m), 3.58 (2 H, t, *J*=4.40 Hz), 3.33 (3 H, s), 3.26 (1 H, s), 3.01 (1 H, d, *J*=11.55 Hz), 2.08 - 2.18 (1 H, m), 1.97 - 2.08 (1 H, m), 1.64 - 1.77 (2 H, m), 1.35 - 1.55 (3 H, m), 0.21 - 0.37 (1 H, m). EM (IEP) *m/z*: 650.4 (M+H)+. HPLC analítica: Tr = 5.18 min.

Ejemplo I-270.

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9,9-difluoro-8-oxo-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il}-carbámico, sal TFA



I-270A. 2,2-Difluoro-1-morfolinopent-4-en-1-ona: A una solución de ácido 2,2-difluoropent-4-enoico (701 mg, 5.15 mmol) en diclorometano (10 ml) se añadió una cantidad catalítica de DMF (0.05ml, 0.646 mmol). A continuación, la mezcla de reacción se enfrió en un baño de hielo. A la solución se añadió cloruro de oxalilo (0.460 ml, 5.15 mmol) gota a gota. La solución resultante se agitó durante 2 horas a TA.

La mezcla de reacción se enfrió entonces en un baño de hielo, se añadió TEA (1.436 ml, 10.30 mmol) y morfolina (0.497 ml, 5.7 mmol). La solución resultante se agitó durante 1.5 h a TA. La mezcla de reacción se diluyó entonces con EtOAc (30 ml) y se lavó con NH_4Cl acuoso. La solución orgánica se secó sobre $MgSO_4$ y se concentró a vacío, proporcionando un residuo oleoso, que se purificó por cromatografía en fase normal proporcionando 633 mg (3.1 mmol, 60 % de rendimiento) de I-270A como aceite marrón claro. EM (IEP) *m/z*: 206.1 (M+1)+.

I-270B. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-4-il]-3-(2,2-difluoro-pent-4-enoil)-fenil]-carbámico: A una solución de 10B (0.145 g, 0.243 mmol) en THF (2 ml) bajo N_2 se añadió BuLi 2.5M en hex (0.487 ml, 1.217 mmol) a -78°C. La solución resultante se agitó durante 0.5h y a la solución se añadió I-270A en 3 ml de THF gota a gota durante 10 min. La mezcla de reacción se dejó calentar hasta TA. La reacción se inactivó entonces añadiendo NH_4Cl acuoso (2 ml). La mezcla de reacción se diluyó entonces con EtOAc (30 ml) y se lavó con NH_4Cl acuoso (10 ml). La solución orgánica se secó sobre $MgSO_4$ y se concentró a vacío, proporcionando residuo oleoso, que se

purificó por cromatografía en fase normal proporcionando I-270B. TFA proporcionando I-270B. TFA (43 mg, 0.057 mmol, 23.6%).

I-270C. Éster terc-butílico del ácido [(E)-(S)-9,9-difluoro-5-metoxicarbonilamino-8-oxo-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,11,15(18)-hexaen-14-il]-carbámico: El Compuesto I-270C se preparó siguiendo el procedimiento descrito en la etapa 2E/2F, sustituyendo 2D por I-270B. EM (IEP) *m/z* : 607.2 (M+1)+.

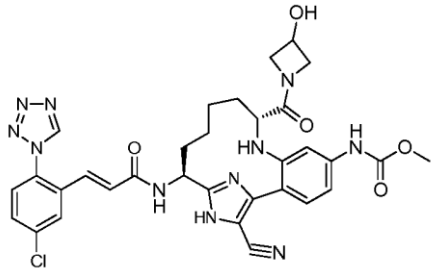
I-270D. Éster terc-butílico del ácido [(S)-9,9-difluoro-5-metoxicarbonilamino-8-oxo-16-(2-trimetilsilanil-etoximetil)-16,18-diaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-14-il]-carbámico: Una solución de I-270C (14 mg, 0.023 mmol) y PtO_2 (3 mg, 0.013 mmol) en EtOAc (5 ml) y MeOH (5ml) se agitó bajo H_2 (3.44 x 105 Pa) durante 14h. La mezcla de reacción se filtró y se concentró a vacío proporcionando I-270D (14 mg, 100%), que se sometió a la siguiente reacción sin purificación adicional. EM (IEP) *m/z*: 609.3 (M+H)+.

I-270E. El Ejemplo I-270 se preparó siguiendo los procedimientos descritos en la etapa 10H, sustituyendo 10G por I-270D; seguido por la etapa 1G. 19F NMR (376 MHz, acetonitrilo-d_3) δ ppm -76.47 (2 F, s

ancho). EM (IEP) *m/z*: 611.2 (M+H)+. HPLC analítica: Tr = 5.59 min.

Ejemplo I-280.

Éster metílico del ácido [(9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciano-9-(3-hidroxi-azetidin-1-carbonil)-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaen-5-il]-carbámico, 2TFA

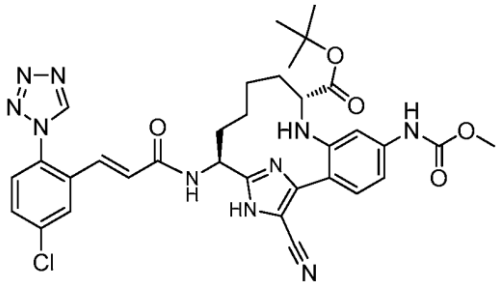


Una mezcla del Ejemplo I-250 (0.020 g, 0.023 mmol), clorhidrato de azetidin-3-ol (3.83 mg, 0.035 mmol) y reactivo BOP (0.015 g, 0.035 mmol) en DMF (0.5 ml) se trató con DIPEA (0.020 ml, 0.116 mmol) y luego se agitó a temperatura ambiente bajo Ar durante la noche. La reacción se evaporó para eliminar el DMF, y el residuo se purificó por HPLC de fase inversa proporcionando el Ejemplo I-280 (0.0196 g, 92 %) como un sólido blanco. 1H NMR (500 MHz, CD_3OD) δ ppm 9.52 (1 H, s), 8.00 (1 H, d, *J*=2.2 Hz), 7.67 (1 H, dd, *J*=8.8, 2.2 Hz), 7.55 - 7.61 (2 H, m), 7.40 (1 H, dd, *J*=17.9, 1.9 Hz), 7.28 - 7.33 (1 H, m), 7.14 (1 H, dd, *J*=15.7, 1.4 Hz), 6.80 (1 H, d, *J*=15.9 Hz),

5.22 (1 H, dd, *J*=11.0, 6.6 Hz), 4.33 - 4.47 (1 H, m), 4.04 - 4.12 (1 H, m), 3.79 - 4.06 (1 H, m), 3.59 - 3.67 (1 H, m), 3.38 - 3.62 (1 H, m), 3.13 - 3.18 (1 H, m), 2.12 - 2.21 (1 H, m), 1.77 - 2.01 (3 H, m), 1.45 - 1.56 (2 H, m), 1.31 (1 H, t, *J*=14.0 Hz), 0.42 - 0.55 (1 H, m). EM (IEP) *m/z*: 686.1 (M+H)+. HPLC analítica: Tr = 6.98 min.

Ejemplo I-283.

Éster terc-butílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-17-ciano-5-metoxicarbonilamino-8,16,18-triaza-triciclo[13.2.1.2.7]octadeca-1(17),2,4,6,15(18)-pentaeno-9-carboxílico

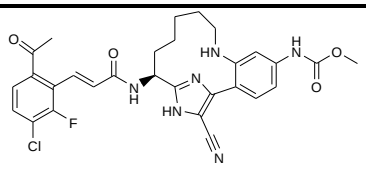
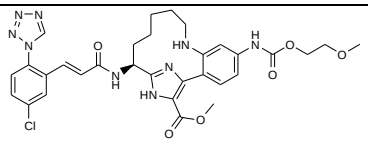
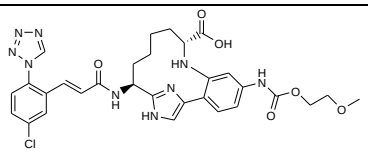
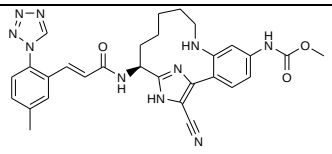
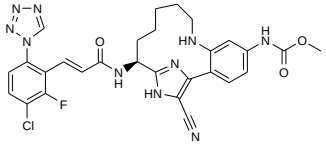
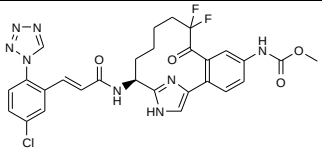
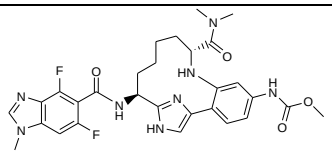
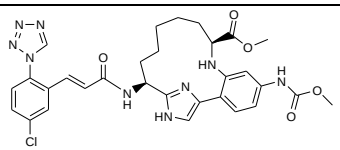


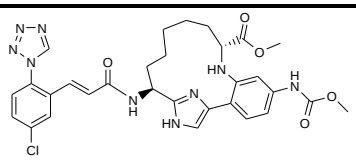
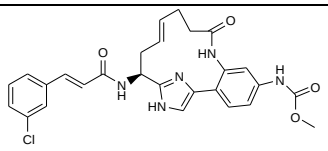
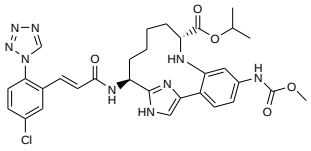
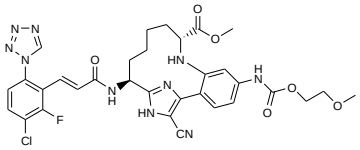
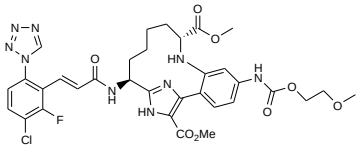
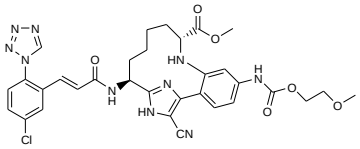
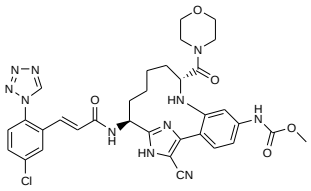
A una solución del Ejemplo I-250 (0.03 g, 0.048 mmol) en THF (0.5 ml)/diclorometano (0.5 ml) a TA se añadió *t*-BuOH (0.500 ml) y una solución de N,N'-diisopropilcarbamimidato de (E)-terc-butilo (0.048 g, 0.238 mmol) disuelta en DCM (0.3 ml). La reacción se dejó agitar a TA durante la noche. La reacción se concentró y el residuo se purificó por HPLC de fase inversa. Las fracciones que contenían

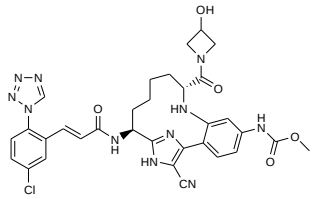
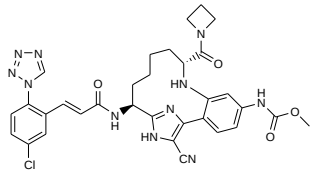
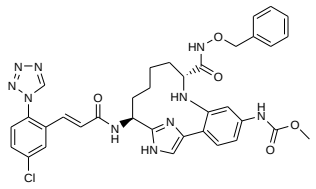
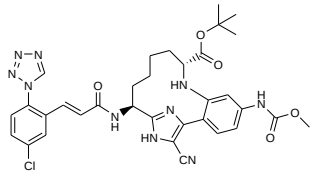
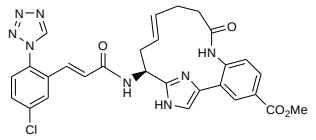
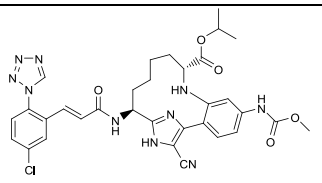
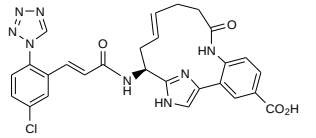
producto se neutralizaron haciéndolas pasar a través de un cartucho PL-HCO_3 MP SPE antes de evaporar hasta sequedad proporcionando el Ejemplo I-283 (12 mg, 36.4 %) como un sólido blanco. 1H NMR (500 MHz, CD_3OD) δ ppm 9.53 (1 H, s), 8.02 (1 H, d, *J*=2.48 Hz), 7.68 (1 H, dd, *J*=8.53, 2.20 Hz), 7.59 (1 H, d, *J*=8.53 Hz), 7.46 (2 H, d, *J*=8.25 Hz), 7.05 - 7.18 (2 H, m), 6.83 (1 H, d, *J*=15.68 Hz), 5.22 (1 H, dd, *J*=10.73, 6.88 Hz), 3.77 (3 H, s), 2.77 - 2.87 (1 H, m), 2.09 - 2.19 (1 H, m), 1.78 - 1.96 (2 H, m), 1.64 - 1.78 (1 H, m), 1.40 - 1.53 (2 H, m), 1.28 - 1.40 (10 H, m), 0.39 - 0.55 (1 H, m). EM (IEP) *m/z*: 687.2 (M+H)+. HPLC analítica: Tr = 9.28 min.

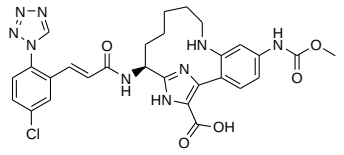
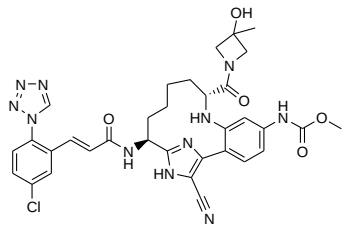
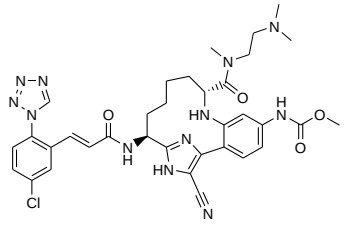
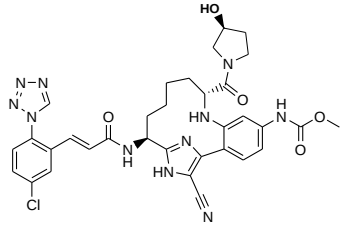
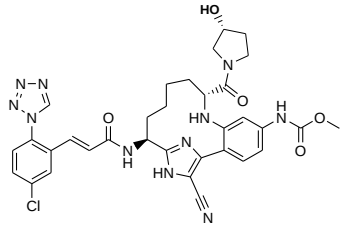
El Ejemplo I-284 se preparó de acuerdo con el procedimiento descrito en 88C, sustituyendo 88B por el Intermediario 37 y sustituyendo el Intermediario 12 por el Intermediario 39; seguido por las etapas I-226B; 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; 2E/2F; 10H; y 1G. Los Ejemplos I-286 se prepararon de acuerdo con el procedimiento descrito en 88C, sustituyendo 88B por el Intermediario 37 y sustituyendo el Intermediario 12 por el Intermediario 39; seguido por las etapas I-226B; 10D, sustituyendo ácido but-3-enoico por ácido pent-4-enoico; 2E/2F; 10H; saponificación del éster metílico con hidróxido sódico acuoso 1.0 M en metanol a 45°C; y 1G.

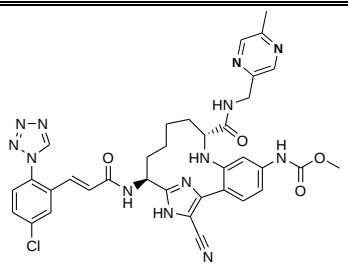
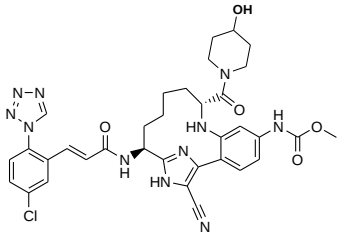
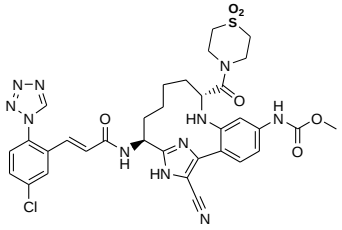
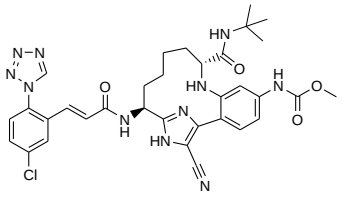
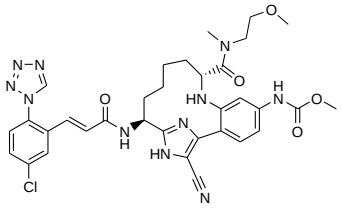
Tabla I-17: Ejemplos I-265 a I-334

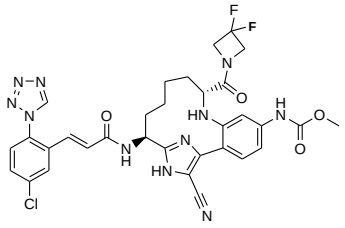
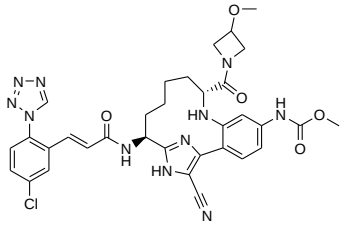
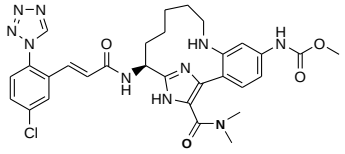
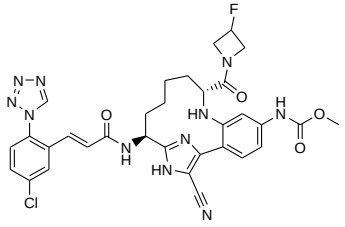
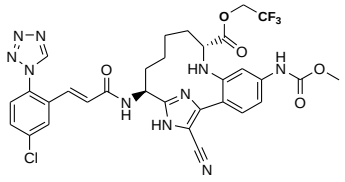
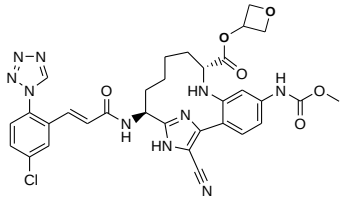
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-265		579.2	6.4
I-266		664.4	5.7
I-267		650.4	5.2
I-268		567.4	5.8
I-269		605.4	5.9
I-270		611.2	6.9
I-271		595.2	5.1
I-272		634.2	6.2

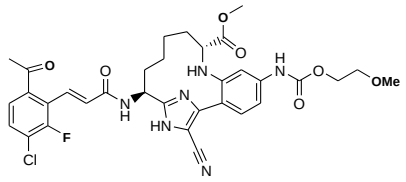
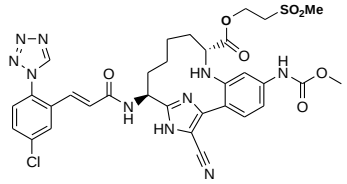
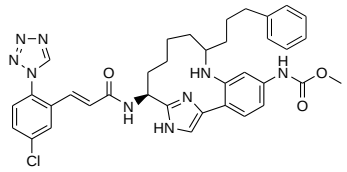
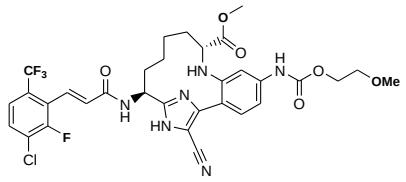
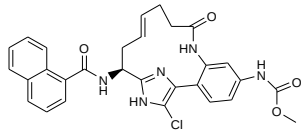
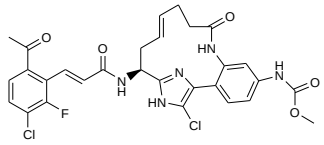
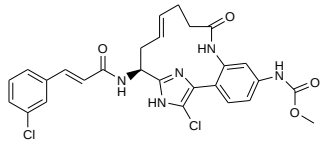
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-273		634.2	7.0
I-274		520.3	5.4
I-275		648.1	7.4
I-276		707.3	8.8
I-277		740.3	6.7
I-278		689.4	8.6
I-279		700.3	7.7

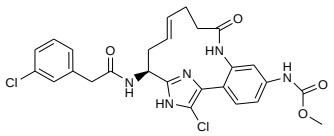
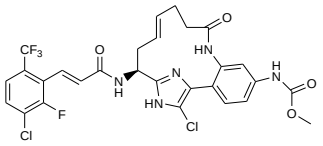
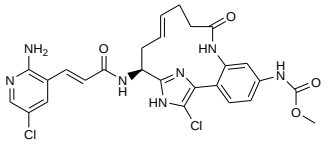
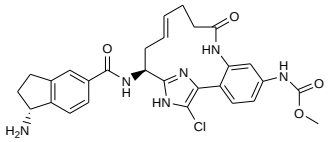
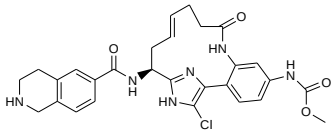
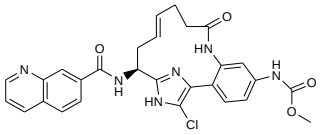
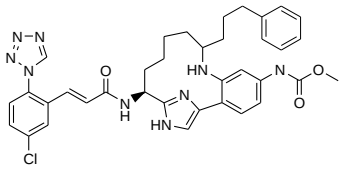
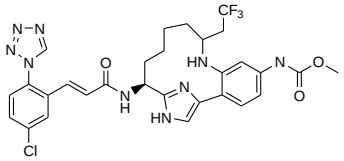
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-280		686.1	6.9
I-281		670.1	7.7
I-282		711.2	6.2
I-283		687.2	9.3
I-284		573.0	5.25 (D)
I-285		673.1	8.9
I-286		559.0	7.50 (D)

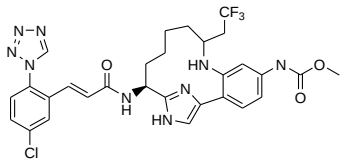
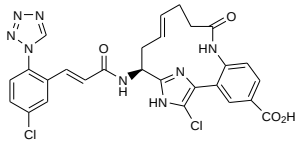
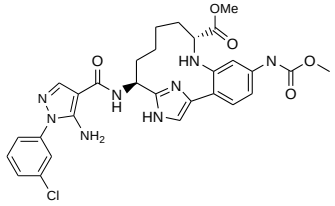
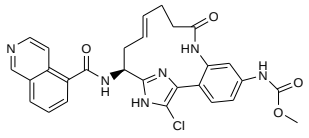
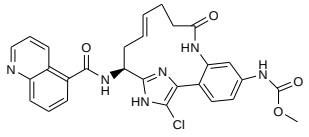
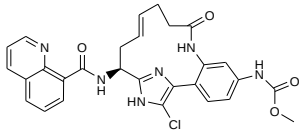
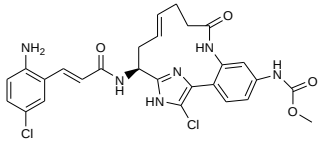
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-287		606.1	5.55
I-288		700.1	7.16
I-289		715.2	5.35
I-290		700.1	7.01
I-291		700.1	7.00

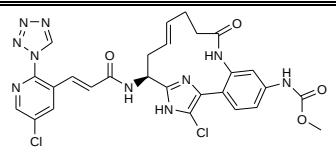
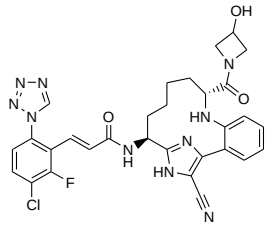
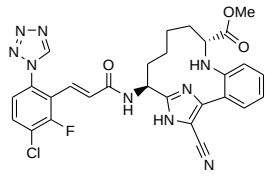
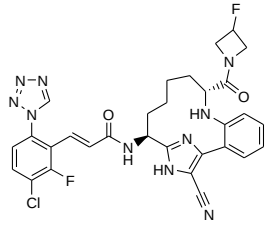
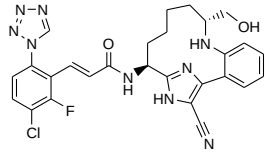
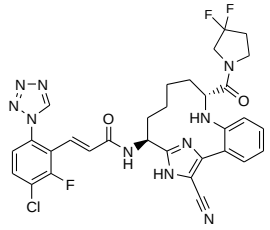
Ej. nº		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-292		736.1	6.87
I-293		714.2	7.01
I-294		748.1	7.77
I-295		686.1	8.01
I-296		702.2	7.42

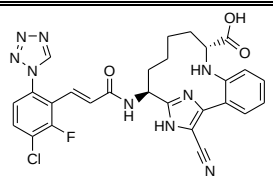
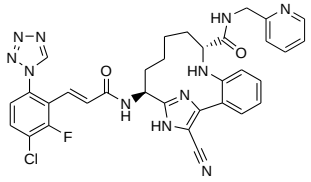
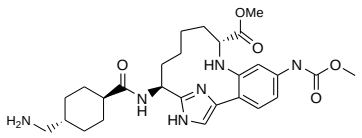
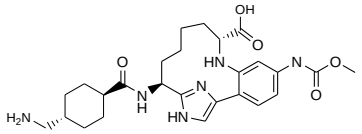
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-297		706.2	8.45
I-298		700.2	7.75
I-299		633.1	5.50
I-300		688.1	7.93
I-301		713.1	9.13
I-302		687.1	7.87

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-303		681.1	8.89
I-304		737.0	7.68
I-305		680.3	7.07
I-306		707.0	9.92
I-307		544.0	6.8
I-308		615.9	7.1
I-309		554.0	7.4

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-310		542.0	6.9
I-311		639.9	8.3
I-312		570.0	4.5
I-313		549.0	3.5
I-314		549.0	6.5
I-315		545.0	4.2
I-316		680.2	7.44
I-317		644.0	6.61

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-318		644.0	6.37
I-319		592.9	6.41
I-320		607.0	6.67
I-321		545.0	3.61
I-322		545.0	3.75
I-323		544.9	5.37
I-324		568.9	7.38

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-325		622.9	6.05
I-326		631.0	7.09
I-327		590.0	9.21
I-328		633.0	8.21
I-329		562.0	6.05
I-330		665.0	8.97

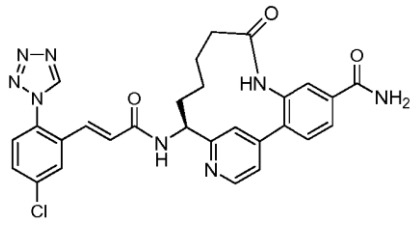
Ej. nº		LCMS $[M+H]^+$	HPLC Tr (min.) (MÉTODO)
I-331		575.9	8.01
I-332		666.1	6.02
I-333		527.1	4.51
I-334		513.1	3.88

Los Ejemplos II-1 y II-2 se prepararon en dos etapas acoplando 91A con un derivado ácido carboxílico sustituido de forma apropiada ($R-CO_2H$) usando condiciones de acoplamiento descritas en la etapa 15D, seguido por una desprotección Boc como se describe en la etapa 3C. El Ejemplo II-3 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por 88G; seguido por la etapa 15D, sustituyendo el Intermediario 2 por un ácido carboxílico sustituido de forma apropiada; seguido por una etapa de desprotección Boc 3C. Los Ejemplos II-4 y II-5 se prepararon

acoplando 96A con un derivado ácido carboxílico sustituido de forma apropiada usando condiciones de acoplamiento descritas en la etapa 15D. En el caso de II-5 se requirió una etapa adicional de desprotección Boc como se describe en la etapa 3C.

Ejemplo II-6.

Amida del ácido (S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaeno-5-carboxílico, TFA



II-6A. 1-(4-Cloropiridin-2-il)but-3-enilcarbamato de (S)-bencilo: Se suspendió 88B (1.135 g, 3.96 mmol) en MeOH (39.6 ml) y se añadió HCl 4M en dioxano (19.79 ml, 79 mmol). La reacción se agitó a TA bajo Ar durante ~2 horas y luego se evaporó para eliminar el MeOH y se trituró con Et_2O 2x proporcionando (S)-1-(4-cloropiridin-2-il)but-3-en-1-amina, 2 HCl (1.005 g, 99%, EM (IEP) *m/z*: 183.1 (M+H)+), que se suspendió en MeOH (13.11 ml) y se trató con 2.5-dioxopirrolidin-1-il carbonato de bencilo (1.078 g, 4.33 mmol) y DIPEA (2.060 ml, 11.80 mmol). La mezcla resultante se agitó a ta durante 5 min y luego se destiló hasta sequedad, se diluyó con EtOAc y se lavo con salmuera, se secó sobre

MgSO4, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida proporcionando II-6A (1.19 g, 96%) como un aceite incoloro. EM (IEP) *m/z*: 317.2 (M+H)+

II-6B. Ácido (S)-2-(1-(benciloxicarbonilamino)but-3-enil)piridin-4-ilborónico, TFA: Una mezcla de II-6A (0.75 g, 2.368 mmol), bis(neopentil glicolato)diboro (0.802 g, 3.55 mmol), acetato potásico (0.697 g, 7.10 mmol), aducto de $PdCl_2$(dppf)-CH_2Cl_2 (1:1) (0.193 g, 0.237 mmol) y DMSO (7.89 ml) en un tubo sellado se desgasificó vaciando y volviendo a llenar con Ar 3x, y luego la reacción se calentó a 80°C durante 6-8 h, a continuación se dejó a temperatura ambiente durante la noche. Se llevó a cabo una segunda reacción de forma idéntica. Las dos reacciones se reunieron y se diluyeron con EtOAc, a continuación se filtró a través de una pequeña almohadilla de CELITE® que se aclaró varias veces con EtOAc. El filtrado se transfirió a un embudo de separación y se lavó 3x con H_2O, se volvió a filtrar a través de CELITE®, a continuación se lavó con salmuera, se secó y se concentró proporcionando un aceite marrón oscuro que se purificó por HPLC de fase inversa proporcionando II-6B como una espuma blanca (1.325 g, 63.6%). EM (IEP) *m/z*: 327.3 (M+H)+.

II-6C. 1-(4-(2-Amino-4-cianofenil)piridin-2-il)but-3-enilcarbamato de (S)-bencilo, 2 TFA: A II-6B (0.44 g, 1.000 mmol), 3-amino-4-bromobenzonitrilo (0.164 g, 0.833 mmol) (81378-051-01), bromuro de tetrabutilamonio (0.013 g, 0.042

mmol) y carbonato sódico 2M (1.249 ml, 2.499 mmol) en un tubo de microondas de 20 ml se añadió tolueno (6.92 ml) y EtOH (2.88 ml), y la solución se desgasificó vaciando/llenando con Ar 3x. Se añadió $(Ph_3P)_4Pd$ (0.048 g, 0.042 mmol) y el vial se volvió a llenar/variar de nuevo 3 veces con Ar. Se prepararon de forma idéntica dos viales más. Los tres viales se taparon y se calentaron a 95°C en un baño de aceite durante la noche. A continuación la reacción se dejó agitar a ta durante 3 días. Se reunieron los contenidos de los viales y se diluyó con EtOAc y se lavó agua, $NaHCO_3$ saturado y salmuera, a continuación se secó sobre sulfato de magnesio anhidro, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida proporcionando II-6C (0.758 g, 48.4%) como una espuma amarillo claro. EM (IEP) *m/z*: 399.3 (M+H)+.

II-6D. Éster bencílico del ácido ((E)-(S)-5-ciano-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-il)-carbámico: Se preparó II-6D en dos etapas a partir de II-6C usando los procedimientos descritos para las etapas 10D y 2E/F. EM (IEP) *m/z*: 439.2(M+H)+.

II-6E. Éster bencílico del ácido ((E)-(S)-5-carbamoil-9-oxo-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-14-il)-carbámico: Se disolvió II-6D (0.015 g, 0.034 mmol) (81378-069-01) en DMSO (0.171 ml)

y se añadió K_2CO_3 (0.014 g, 0.103 mmol). A continuación, se añadió H_2O_2 al 30% (0.038 ml, 0.376 mmol) gota a gota. La suspensión amarillo claro se agitó durante ~1 h a temperatura ambiente bajo nitrógeno. La mezcla de reacción se diluyó con agua y se extrajo 3x con EtOAc. La fase orgánica se secó sobre $MgSO_4$, se filtró y se condensó proporcionando la amida bruta como un residuo incoloro (0.022 g) que se recogió para la etapa siguiente sin purificación adicional. EM (IEP) *m/z*: 457.3 (M+H)+.

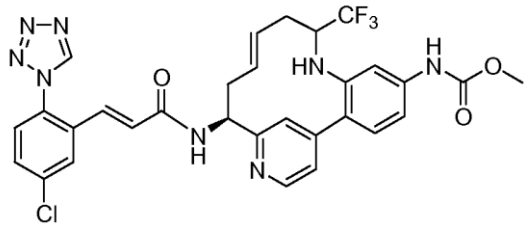
Ejemplo II-6. El compuesto del título se preparó a partir de II-6E usando los procedimientos descritos para las etapas 10F y 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.49 (1 H, s) 8.76 (1 H, d, *J*=5.78 Hz) 8.00 (1 H, d, *J*=1.10 Hz) 7.95 - 7.99 (2 H, m) 7.82 (1 H, dd, *J*=5.78, 1.65 Hz) 7.80 (1 H, d, *J*=1.65 Hz) 7.77 (1 H, d, *J*=8.25 Hz) 7.66 (1 H, dd, *J*=8.39, 2.34 Hz) 7.57 (1 H, d, *J*=8.53 Hz) 7.10 (1 H, d, *J*=15.41 Hz) 6.79 (1 H, d, *J*=15.68 Hz) 5.12 (1 H, dd, *J*=10.73, 5.78 Hz) 2.50 (1 H, ddd, *J*=12.52, 6.74, 1.93 Hz) 2.07 - 2.19 (1 H, m) 1.93 - 2.01 (1 H, m) 1.82 - 1.92 (1 H, m) 1.70 - 1.80 (1 H, m) 1.60 - 1.69 (1 H, m) 1.33 - 1.42 (1 H, m) 0.71 - 0.86 (1 H, m). EM (IEP) *m/z*: 557.3 (M+H)+. HPLC analítica: Tr = 4.95 min.

El Ejemplo II-7 se preparó a partir de 88B siguiendo los procedimientos descritos para las etapas II-6A, sustituyendo 2.5-dioxopirrolidin-1-il carbonato de bencilo por dicarbonato de di-*t*-butilo; 88C, sustituyendo 88B por

ácido (S)-2-(1-(*terc*-butoxicarbonilamino)but-3-enil)piridin-4-ilborónico e Intermediario 12 por 4-amino-3-bromobenzoato de metilo; 10D; 2E/F; y 2G; seguido por hidrólisis del éster metílico con LiOH 1 M en THF; luego las etapas 3A y 1G. El Ejemplo II-8 se preparó de igual forma siguiendo los procedimientos descritos para las etapas II-6C, sustituyendo ácido (S)-2-(1-(*terc*-butoxicarbonilamino)but-3-enil)piridin-4-ilborónico por II6-B y 4-amino-3-bromobenzonitrilo por 3-amino-4-bromobenzonitrilo; 10D, 2E/F, 3C y 1G.

Ejemplo II-11

Éster metílico del ácido {(E)-(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-trifluorometil-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-il}-carbámico, sal 2 TFA



II-11A. 1-(4-(2-Amino-4-nitrofenil)piridin-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: El compuesto II-11A se preparó siguiendo el procedimiento descrito en la etapa 88C, sustituyendo 88B por 1-(4-cloropiridin-2-il)but-3-enilcarbamato de (S)-*terc*-butilo. EM (IEP) 385.1 (M+H)+.

II-11B. 1-(4-(2,4-Diaminofenil)piridin-2-il)but-3-enilcarbamato de (S)-*terc*-butilo: A una solución naranja

transparente de II-11A (2.9 g, 7.54 mmol) en metanol (75 ml) se añadió secuencialmente polvo de zinc (4.93 g, 75 mmol) y cloruro amónico (4.04 g, 75 mmol). La suspensión resultante suspensión se agitó vigorosamente durante 4 h. La reacción se interrumpió y se filtró a través de un GMF de 0.45 micrómetros eluyendo con metanol dando un filtrado amarillo transparente. La concentración del filtrado dio un residuo amarillo-negro. El residuo se repartió entre EtOAc y HCl 0.25 M (50 ml) y se separaron las fases. La fase orgánica se extrajo con HCl 0.25 M (1 x 50 ml). Las fases acuosas combinadas se basificaron con K_2HPO_4 1.5 M y luego se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron dando II-11B (2.63 g, 98 %) como una espuma marrón. EM (IEP) m/z: 355.2 (M+H)+.

II-11C. Éster metílico del ácido {3-amino-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-fenil}-carbámico: A una solución marrón transparente enfriada (-78°C) de II-11B (2.63 g, 7.42 mmol) y piridina (0.600 ml, 7.42 mmol) en diclorometano (74.2 ml) se añadió gota a gota durante 30 min cloroformiato de metilo (0.516 ml, 6.68 mmol). La reacción se agitó a -78°C. Después de 1.5 h, la reacción se inactivó con NH_4Cl saturado y se dejó calentar la reacción hasta TA. La reacción se diluyó con DCM y agua y se separaron las fases. La fase acuosa se extrajo con DCM (1x).

Las fases orgánicas combinadas se lavaron con NaHCO3 saturado, salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se disolvió en DCM (~10 ml) y luego se añadió hexano (~300 ml) dando una suspensión marrón con una sustancia pegajosa y gomosa marrón en el fondo. La mezcla se sometió a ultrasonidos dando una solución en su mayor parte transparente con la sustancia marrón en el fondo. La solución se decantó y la sustancia del fondo se aclaró con hexano, se secó dando II-11C (2.7 g, 88 %) como una espuma ligeramente marrón. LCMS (ES) 413.2 (M+H)+.

II-11D. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-3-(1-etoxi-2,2,2-trifluoro-etilamino)-fenil]-carbámico: Se trató en microondas a 120°C durante 2 horas una solución amarilla transparente de II-11C (2.296 g, 5.57 mmol), pTsOH (0.053 g, 0.278 mmol) y hemiacetal de etil trifluoroacetaldehído (2.63 ml, 22.27 mmol) en etanol (11.13 ml). La reacción se concentró, se purificó por cromatografía en fase normal que dio II-11D (1.61 g, 53.7 %) como un sólido amarillo y como una mezcla de diastereómeros. EM (IEP) m/z: 539.2 (M+H)+.

II-11E. Éster metílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-3-(1-trifluorometil-but-3-enilamino)-fenil]-carbámico: A una solución enfriada (-20°C) de II-11D (1.816 g, 3.37 mmol) en THF (33.7 ml) se añadió gota a gota bromuro de alilmagnesio

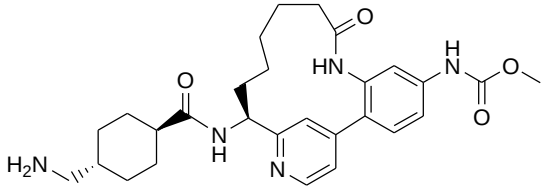
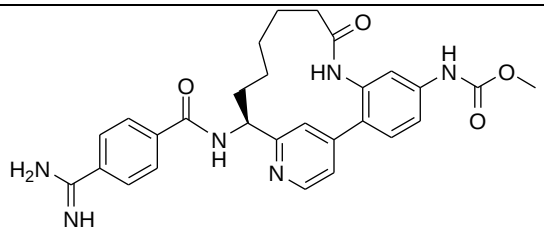
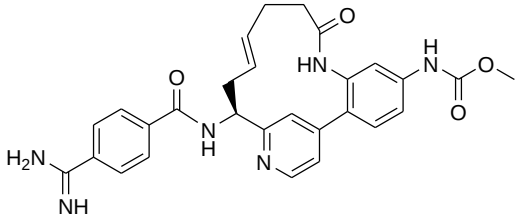
(1M en Et_2O, 15.17 ml, 15.17 mmol). La mezcla de reacción roja turbia resultante se agitó a -20°C. Después de 3h, se añadió más bromuro de alilmagnesio (0.8 ml, 0.8 mmol). Después de otros 20 min, la mezcla de reacción se inactivó con NH4Cl saturado y la reacción se calentó hasta TA. La reacción se repartió entre agua y EtOAc y se separaron las fases. La fase acuosa se extrajo con EtOAc (2x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por cromatografía en fase normal dio II-11E (1.45 g, 80 %) como una espuma amarilla y como una mezcla de diastereómeros. EM (IEP) m/z: 535.3 (M+H)+.

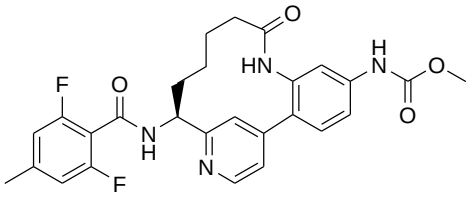
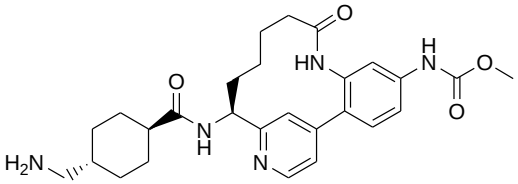
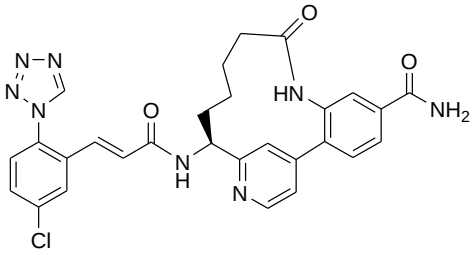
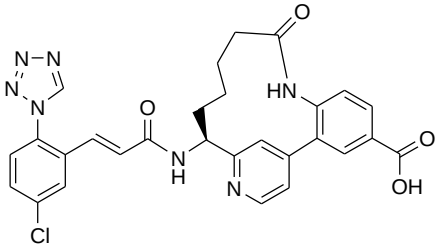
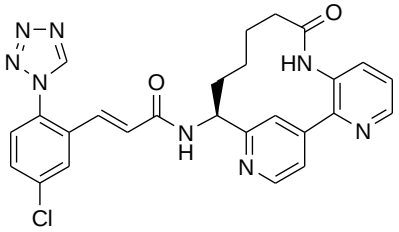
II-11F y II-11G. Éster metílico del ácido ((E)-(S)-14-*terc*-butoxicarbonilamino-9-trifluorometil-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaen-5-il)-carbámico: Los Compuestos II-11F (diastereómero A) y II-11G (diastereómero B) se prepararon siguiendo el procedimiento descrito en 88G, sustituyendo 88F por II-11E. Para II-11F: EM (IEP) m/z: 507.2 (M+H)+. Para II-11G: EM (IEP) m/z: 507.3 (M+H)+.

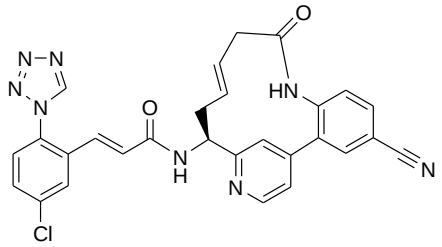
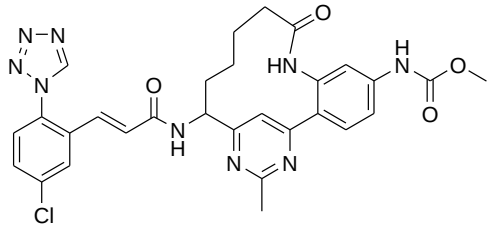
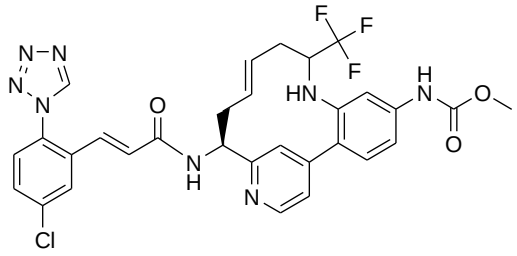
II-11H. El Ejemplo II-11 se preparó siguiendo los procedimientos descritos en la etapa 3C, sustituyendo 3B por II-11F (diastereómero A); seguido por la etapa 1G. 1H NMR (400 MHz, CD_3OD) δ ppm 9.51 (s, 1 H), 8.64 (d, *J*=5.5 Hz, 1 H), 8.06 (d, *J*=1.1 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.77

(dd, *J*=6.1, 1.6 Hz, 1 H), 7.67 (dd, *J*=8.3, 2.2 Hz, 1 H), 7.58 (d, *J*=8.8 Hz, 1 H), 7.33 (s ancho, 1 H), 7.27 (d, *J*=8.2 Hz, 1 H), 7.09 - 7.18 (m, 2 H), 6.76 (d, *J*=15.4 Hz, 1 H), 5.59 - 5.72 (m, 1 H), 5.06 - 5.24 (m, 2 H), 3.75 (s, 3 H), 3.43 - 3.57 (m, 1 H), 2.83 - 2.94 (m, 1 H), 2.47 - 2.65 (m, 2 H), 2.26 - 2.39 (m, 1 H). 19F NMR (471MHz, CD_3OD) δ -75.49, -77.15. EM (IEP) m/z: 639.2 $(M+H)^+$. HPLC analítica, Tr = 6.74 min.

Tabla II-1: Ejemplos II-1 a II-11:

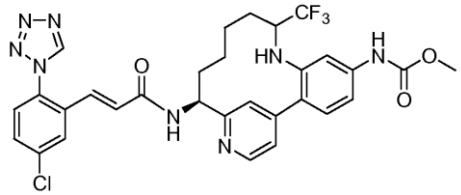
Ej. n°	Estructura	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
II-1		508.2	6.5 (C)
II-2		515.1	6.3 (C)
II-3		513.1	6.3 (C)

Ej. nº	Estructura	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
II-4		509.1	4.9
II-5		494.4	6.5 (C)
II-6		557.3	5.0
II-7		558.2	5.2
II-8		515.2	4.1 (B)

Ej. nº	Estructura	LCMS $[M+H]^+$	HPLC Tr (min) (MÉTODO)
II-9		537.2	6.2
II-10	 (Racemato)	602.1	6.4
II-11	 (homoquiral)	639.2	6.7

Ejemplo II-12

Éster metílico del ácido {(S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-9-trifluorometil-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-il}-carbámico, sal 2 TFA



II-12A. Éster *terc*-butílico del ácido ((S)-5-

metoxicarbonilamino-9-trifluorometil-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-14-il)-carbámico: A la solución II-11F (diastereómero A) (0.46 g, 0.908 mmol) en EtOH (6 ml) se añadió TFA (0.070 ml, 0.908 mmol) y paladio al 10 % sobre carbón (0.097 g, 0.091 mmol). Se burbujeó hidrógeno desde un globo a través de la reacción durante unos pocos minutos, luego se agitó la reacción bajo un globo de hidrógeno durante 24 h. Se añadió más TFA (0.070 ml, 0.908 mmol), y la reacción se agitó bajo un globo de H2 durante otras 24 h. La reacción se filtró a través de un filtro GMF de 0.45 µm aclarando con MeOH. El filtrado se concentró. El residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por cromatografía en fase normal dio II-12A (0.4 g, 87 % de rendimiento) como un sólido amarillo. EM (IEP) m/z: 509.3 (M+H)+.

II-12B. Éster metílico del ácido ((S)-14-amino-9-trifluorometil-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaen-5-il)-carbámico, sal 3 TFA: El compuesto II-12B se preparó siguiendo el procedimiento descrito en 3C, sustituyendo 3B por II-12A. EM (IEP) m/z: 409.1 (M+H)+.

II-12C. El Ejemplo II-12 se preparó siguiendo

el procedimiento descrito en la etapa 1G sustituyendo 1F por II-12B. 1H NMR (500 MHz, CD_3OD) δ ppm 9.48 (s, 1 H), 8.73 (d, *J*=1.4 Hz, 1 H), 8.66 (d, *J*=6.1 Hz, 1 H), 7.98 (d, *J*=2.2 Hz, 1 H), 7.89 (dd, *J*=6.2, 1.8 Hz, 1 H), 7.67 (dd, *J*=8.4, 2.3 Hz, 1 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.48 (d, *J*=8.5 Hz, 1 H), 7.40 (d, *J*=1.7 Hz, 1 H), 7.22 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (d, *J*=15.7 Hz, 1 H), 6.79 (d, *J*=15.4 Hz, 1 H), 5.17 (dd, *J*=11.7, 6.5 Hz, 1 H), 3.76 (s, 3 H), 2.95 - 3.05 (m, 1 H), 2.20 - 2.31 (m, 1 H), 1.84 - 1.99 (m, 2 H), 1.71 - 1.80 (m, 1 H), 1.51 - 1.62 (m, 2 H), 1.41 - 1.50 (m, 1 H), 0.33 - 0.45 (m, 1 H). 19F NMR (471MHz, CD_3OD) δ -75.06, -77.30. EM (IEP) m/z: 641.3 (M+H)+. HPLC analítica: TR= 7.06 min.

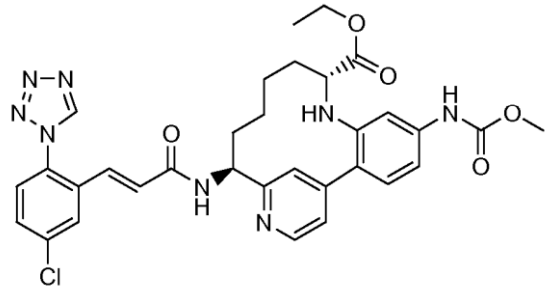
Los Ejemplos II-13 y II-14 se prepararon en dos etapas acoplando II-12B con un derivado ácido carboxílico sustituido de forma apropiada ($R-CO_2H$) usando condiciones de acoplamiento descritas en la etapa 15D, seguido por una desprotección Boc como se describe en la etapa 3C.

El Ejemplo II-15 se preparó de acuerdo con los procedimientos descritos en II-12 y II-14, sustituyendo II-11F por II-11G; seguido por II-14.

Ejemplo II-17

Éster etílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-

metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaeno-9-carboxílico, diastereómero A, sal 2 TFA



II-17A. Éster etílico del ácido 2-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-5-metoxicarbonilamino-fenilamino}-pent-4-enoico: El compuesto II-17A se preparó siguiendo el procedimiento descrito en I-67A, sustituyendo 10C por II-11C. EM (IEP) m/z: 539 (M+H)+.

II-17B. Éster etílico del ácido (E)-(9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaeno-9-carboxílico (diastereómero A) y II-17C. éster etílico del ácido (E)-(9S,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,11,15,17-heptaeno-9-carboxílico (diastereómero B): Los Compuestos II-17B (diastereómero A) y II-17C (diastereómero B) se prepararon siguiendo el procedimiento descrito en 88G, sustituyendo 88F por II-17A. Los diastereómeros se separaron por HPLC quiral (columna OJ, EtOH:MeOH:heptano 20:20:60). Para II-17B (diastereómero A):

EM (IEP) m/z: 512, 511 (M+H)+. 1H NMR (MeOH-d_4, 400 MHz): δ ppm 8.56 (d, 1H, J = 5), 7.62 (s, 1H), 7.24 (d, 1H, J = 5), 7.20 (d, 1H, J = 8), 7.03 (s, 1H), 6.98 (d, 1H, J = 9), 5.44 (m, 1H), 5.07 (m, 1H), 4.71 (m, 1H), 4.12 (q, 2H, J = 7), 3.73 (s, 3H), 3.31 (m, 3H), 2.72 (m, 1H), 2.35 (m, 4H), 1.44 (s, 9H), 1.20 (m, 3H). Para II-17C (diastereómero B): EM (IEP) m/z: 512, 511 (M+H)+; 1H NMR (MeOH-d_4, 400 MHz): δ ppm 8.56 (d, 1H, J = 5), 7.49 (s, 1H), 7.21 (m, 2H), 6.99 (s, 1H), 6.94 (d, 1H, J = 9), 5.66 (m, 1H), 5.03 (m, 1H), 4.12 (m, 3H), 3.72 (s, 3H), 3.31 (m, 3H), 2.69 (m, 1H), 2.54 (m, 1H), 2.37 (m, 2H), 1.44 (s, 9H), 1.14 (t, 3H, J = 7).

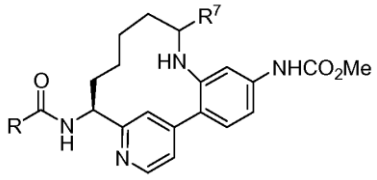
II-17D. Éster etílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaeno-9-carboxílico: El compuesto II-17D se preparó siguiendo el procedimiento descrito en II-12A, sustituyendo II-11F por II-17B (diastereómero A). EM (IEP) m/z: 514, 513 (M+H)+.

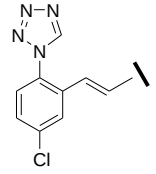
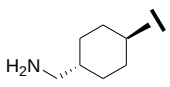
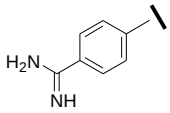
II-17E. Éster etílico del ácido (9R,14S)-14-amino-5-metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3.5.5.17-hexaeno-9-carboxílico, sal 3HCl: Se agitó a temperatura ambiente durante una hora una mezcla de II-17D (175 mg, 0.341 mmol) y cloruro de hidrógeno (1.71 ml, 6.83 mmol) (4 M en dioxano) y acetato de etilo (2 ml). Se eliminó el solvente a vacío dando un sólido amarillo castaño claro (130 mg): EM (IEP) m/z: 414, 413 (M+H)+. El producto se suspendió sin

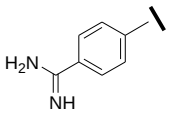
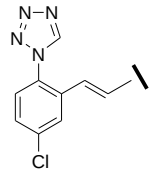
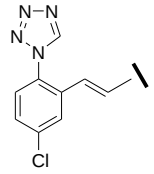
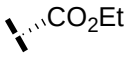
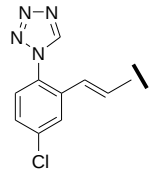
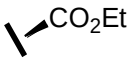
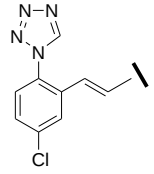
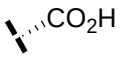
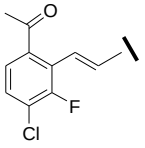
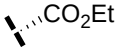
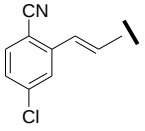
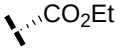
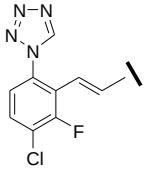
purificación posterior.

II-17F. El Ejemplo II-17 se preparó siguiendo el procedimiento descrito en 1G, sustituyendo 1F por II-17E. EM (IEP) m/z: 647, 645 (M+H)+. 1H NMR (MeOH-d_4, 400 MHz): 9.49 (s, 1H), 8.79 (s, 1H), 8.64 (d, 1H, J = 9), 7.97 (d, 1H, J = 2), 7.77 (d, 1H, J = 9), 7.67 (dd, 1H, J = 9, 2), 7.57 (d, 1H, J = 9), 7.47 (d, 1H, J = 8),7.38 (s, 1H), 7.23 (dd, 1H, J = 9, 2), 7.11 (d, 1H, J = 15), 6.80 (d, 1H, J = 15), 5.15 (m, 1H), 4.00 (m, 3H), 3.75 (s, 3H), 3.31 (m, 1H), 3.08 (d, 1H, J = 9), 2.20 (m, 2H), 1.94 (m, 2H), 1.77 (m, 2H), 1.50 (m, 2H), 1.39 (m, 1H), 1.12 (t, 3H, J = 7), 0.42 (m, 2H).

Tabla II-2: Ejemplos II-12 a II-22

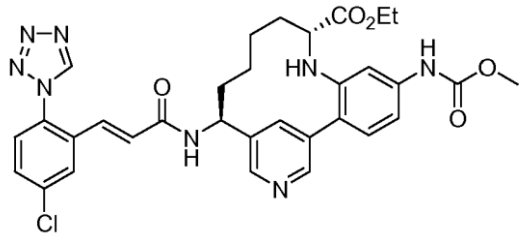


Ej. n°	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
II-12		CF_3 (de II-11F)	641.2	6.9
II-13		CF_3 (de II-11F)	548.4	4.8
II-14		CF_3 (de II-11F)	555.4	4.8

Ej. nº	R	R^3	LCMS $[M+H]^+$	HPLC Tr (min)
II-15		CF_3 (de II-11G)	555.3	3.9
II-16		H	573.3	6.2
II-17			645.4	6.5
II-18			645.4	6.1
II-19			617.4	5.7
II-20			637.5	7.0
II-21			602.5	7.1
II-22			663.4	6.9

Ejemplo II-24.

Éster etílico del ácido (R)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-18-oxo-8,16.17-triaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15-pentaeno-9-carboxílico



II-24A. Éster dimetílico del ácido ((S)-3-*terc*-butoxicarbonilamino-2-oxo-hex-5-enil)-fosfónico: A una solución de metilfosfonato de dimetilo (6.99 ml, 65.4 mmol) en THF (43.6 ml) a -78°C se añadió BuLi (40.9 ml, 65.4 mmol) lentamente. Después de la adición, la reacción se agitó durante 40 min y luego se añadió gota a gota una solución de 2-(*terc*-butoxicarbonilamino)pent-4-enoato de (S)-metilo (3 g, 13.08 mmol) en THF (10 ml). Se continuó agitando durante otros 40 min a -78°C. La reacción se inactivó añadiendo agua, a continuación EtOAc. Se lavó con HCl 1M, $NaHCO_3$ sat. y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró dando un aceite transparente. La purificación por cromatografía en fase normal dio II-24A como un aceite incoloro (4.19 g, 99%). EM (IEP) *m/z*: 344.0 (M+Na)+.

II-24B. Ácido (4-metoxicarbonilamino-2-nitro-fenil)-oxo-acético: A una solución de 4-acetil-3-

nitrofenilcarbamato de metilo (10.5 g, 44.1 mmol) en piridina (44.1 ml) se añadió dióxido de selenio (7.34 g, 66.1 mmol) en porciones. La reacción se agitó bajo argón a 60°C durante la noche. Se evaporó el solvente y se bombeó durante varias horas para eliminar la mayor parte de la piridina, se añadió HCl 1.0N (60 ml) y la mezcla se filtró, se aclaró con HCl 1N. El sólido se colocó un horno de vacío a 45°C durante la noche. Se añadió MeOH (200 ml), se filtró, el filtrado se concentró dando 13.8g de II-24B como una espuma pardusca. EM (IEP) *m/z*: 269.0, 223.0 (M+NH)+.

II-24C. Éster metílico del ácido (4-metoxicarbonilamino-2-nitro-fenil)-oxo-acético: A un aceite rojo de II-24B (5 g, 16.03 mmol) en DCM (57.3 ml) a 0°C se añadió TEA (3.13 ml, 22.45 mmol). La mezcla se sometió a ultrasonidos para disolverse en una solución de color rojo. Se añadió carbonocloridato de metilo (1.739 ml, 22.45 mmol) gota a gota a 0°C. Después de 5 min, la mezcla de reacción se diluyó con CH_2Cl_2 (100 ml), se lavó con HCl 1M, $NaHCO_3$ saturado y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró dando un sólido color rojo. Se trituró con DCM y EtOAc y se filtró. El sólido se lavó con DCM/Hex y se secó en un horno de vacío a 45°C dando 2.79 g (62%)de II-24C como un sólido pardusco claro. EM (IEP) *m/z*: 223.0 (fragmentación).

II-24D. Éster metílico del ácido {4-[6-((S)-1-*terc*-

butoxicarbonilamino-but-3-enil)-3-oxo-2.3-dihidro-piridazin-4-il]-3-nitro-fenil}-carbámico: A una solución transparente de II-24A (911 mg, 2.84 mmol) en EtOH (30 ml) a TA se añadieron carbonato potásico (588 mg, 4.25 mmol). La mezcla de reacción se agitó durante 2 hr. Se eliminó el solvente mediante evaporación rotatoria y bomba de vacío. Se añadió THF (Volumen 30.0 ml), seguido por adición de II-24C. Después de 3 horas se añadió hidrazina (0.356 ml, 11.34 mmol) y la reacción se agitó a ta durante 3 días. La reacción se diluyó con EtOAc, se lavó con HCl 1 N, salmuera, se secó sobre MgSO4, se filtró y se concentró. La purificación por cromatografía en fase normal dio II-24D como una espuma amarilla (380 mg, 29%). EM (IEP) *m/z*: 460.2 (M+NH)+.

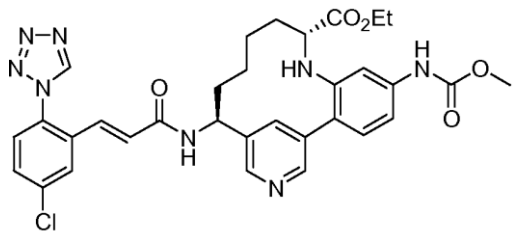
II-24E. Éster metílico del ácido {4-[6-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-3-oxo-2.3-dihidro-piridazin-4-il]-3-amino-fenil}-carbámico: El Ejemplo II-24E se preparó siguiendo los procedimientos descritos en 15B sustituyendo 15A por II-24D.

II-24F. El Ejemplo II-24 se preparó siguiendo los procedimientos descritos en I-67A, sustituyendo 10C por II-24E; seguido por los procedimientos descritos en las etapas II-17B/II-17C; II-17D; II-17E; y II-17F. 1H NMR (500MHz, CD_3OD) d 9.52 (s, 1H), 8.30 (s, 1H), 7.99 (d, *J*=2.2 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 7.36 (d, *J*=1.9 Hz, 1H), 7.18 - 7.01 (m, 1H), 6.80 (d, *J*=15.4 Hz, 1H), 5.03

(dd, *J*=11.4, 5.9 Hz, 1H), 4.14 - 3.92 (m, 2H), 3.83 - 3.72 (m, 2H), 3.51 - 3.39 (m, 1H), 2.21 - 2.01 (m, 1H), 1.63 - 1.40 (m, 2H), 1.15 (t, *J*=7.2 Hz, 2H), 0.96 - 0.81 (m, 1H). EM (IEP) *m/z*: 662.2 (M+H)+. HPLC analítica: Tr = 9.81 min. (Método D).

Ejemplo II-26.

Éster etílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-8.17-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2(7),3,5,15,17-hexaeno-9-carboxílico, diastereómero A, sal 2 TFA



II-26A. (R,E)-N-((5-Bromopiridin-3-il)metileno)-2-metilpropano-2-sulfinamida: El Ejemplo II-26A se preparó siguiendo los procedimientos descritos en 88A, sustituyendo 4-cloropicolinaldehído por 5-bromonicotinaldehído usando (R)-2-metilpropano-2-sulfinamida. EM (IEP) *m/z*: 291.2 (M+H)+.

II-26B. (R)-N-((S)-1-(5-Bromopiridin-3-il)but-3-enil)-2-metilpropano-2-sulfinamida: Referencia: Lin (*Organic Letters*, 10:1259 (2008)). A una solución acuosa saturada de bromuro sódico (600 ml) se añadió II-26A en polvo (8.3 g, 28.7 mmol) e indio (13.18 g, 115 mmol). Se añadió bromuro de alilo (13.66 g, 115 mmol) mediante una bomba de jeringa, y la

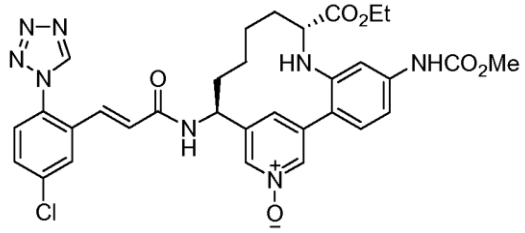
suspensión naranja clara resultante se dejó agitar a TA durante la noche, generando una espuma beige. La reacción se inactivó con $NaHCO_3$ acuoso saturado y se extrajo con EtOAc. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró, se concentró dando un sólido naranja apelusado que pesó 8 g. La purificación por cromatografía en fase normal dio 4.25 g de II-26B como un sólido beige. EM (IEP) *m/z*: 333.0 (M+H)+.

II-26C. El Ejemplo II-26 se preparó siguiendo el procedimiento descrito en 88D, sustituyendo 88C por II-26B; seguido por las etapas que se describen en 88C; 88F; I-67A; 88G; 2G; II-17E; y 1G. 1H NMR (500 MHz, CD_3OD) δ ppm 9.49 (1 H, s), 9.36 (1 H, d, *J*=13.5 Hz), 8.76 (1 H, d, *J*=5.2 Hz), 8.54 (1 H, s ancho), 7.97 (1 H, d, *J*=2.2 Hz), 7.66 (1 H, dd, *J*=8.5, 2.2 Hz), 7.57 (1 H, d, *J*=8.5 Hz), 7.41 (1 H, d, *J*=8.5 Hz), 7.35 (1 H, s), 7.23 (1 H, d, *J*=8.3 Hz), 7.11 (1 H, d, *J*=15.7 Hz), 6.75 (1 H, d, *J*=15.7 Hz), 5.11 - 5.19 (1 H, m), 3.94 - 4.06 (2 H, m), 3.75 (3 H, s), 3.12 (1 H, d, *J*=11.6 Hz), 2.14 - 2.22 (1 H, m), 1.69 - 1.95 (3 H, m), 1.36 - 1.51 (3 H, m), 1.11 (3 H, t, *J*=7.2 Hz), 0.57 (1 H, d, *J*=11.6 Hz) EM (IEP) *m/z*: 645.1 (M+H)+. HPLC analítica: Tr = 6.82 min. (Método D).

Ejemplo II-28.

Éster etílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-17-oxi-8.17-diaza-triciclo[13.3.1.2.7]nonadeca-

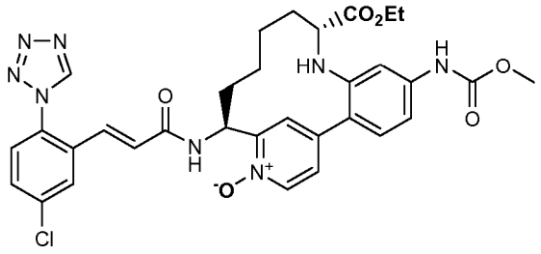
1(19),2,4,6,15,17-hexaeno-9-carboxílico, diastereómero A, sal TFA



II-28A. El Ejemplo II-26 (15 mg, 0.017 mmol) se diluyó con MeOH y se filtró a través de un cartucho de bicarbonato sódico sólido para formar la base libre. El filtrado se concentró y al sólido resultante se añadió DCM (1 ml) y mCPBA (5.78 mg, 0.026 mmol). La solución se agitó a ta durante 1 h. La mezcla de reacción se lavó con sulfito sódico sat., $NaHCO_3$ acuoso saturado y salmuera, a continuación se secó sobre $MgSO_4$. Se filtró y se concentró. La purificación por cromatografía en fase inversa dio II-28 (8.7 mg, 65%) como un sólido amarillo pálido. 1H NMR (500 MHz, CD_3OD) δ ppm 9.49 (1 H, s), 8.53 (1 H, s), 8.37 (1 H, s), 8.18 (1 H, s), 7.98 (1 H, d, *J*=2.2 Hz), 7.66 (1 H, dd, *J*=8.4, 2.3 Hz), 7.56 (1 H, d, *J*=8.5 Hz), 7.27 - 7.39 (2 H, m), 7.05 - 7.22 (2 H, m), 6.73 (1 H, d, *J*=15.4 Hz), 5.01 - 5.12 (1 H, m), 3.88 - 4.07 (2 H, m), 3.74 (3 H, s), 3.18 (1 H, dd, *J*=11.8, 1.4 Hz), 2.05 - 2.19 (1 H, m), 1.79 - 1.94 (1 H, m), 1.67 - 1.79 (2 H, m), 1.35 - 1.53 (3 H, m), 1.10 (3 H, t, *J*=7.0 Hz), 0.56 - 0.72 (1 H, m) EM (IEP) *m/z*: 661.3 (M+H)+. HPLC analítica: Tr = 7.91 min. (Método D).

Ejemplo II-29.

Éster etílico del ácido (9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-metoxicarbonilamino-16-oxi-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-9-carboxílico, sal del ácido trifluoracético



II-29A. Éster etílico del ácido 2-(*terc*-butoxicarbonil-{2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-5-metoxicarbonilamino-fenil}-amino)-pent-4-enoico, sal diclorhidrato: A una solución del Ejemplo II-17A (125 mg, 0.232 mmol) en diclorometano (2.5 ml) se añadió DMAP (28.4 mg, 0.232 mmol) y Boc_2O (0.119 ml, 0.511 mmol) seguido por DIEA (0.101 ml, 0.580 mmol). La mezcla de reacción se agitó a ta durante 1.5h. La mezcla de reacción se concentró a vacío, se disolvió con acetato de etilo y se lavó con salmuera. El producto bruto se purificó entones usando cromatografía en fase normal. EM (IEP) *m/z*: 639.

II-29B. Éster 8-terc-butílico éster 9-etílico del ácido (E)-(S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,11,15,17-heptaeno-8,9-dicarboxílico: Este

compuesto se preparó siguiendo el procedimiento descrito por 88G, sustituyendo 88F por II-29A. El compuesto, como una mezcla de diastereómeros se purificó por cromatografía en fase inversa. EM (IEP) *m/z*: 611.

II-29C. Éster 8-terc-butílico éster 9-etílico del ácido (9R,14S)-14-*terc*-Butoxicarbonilamino-5-metoxicarbonilamino-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-8,9-dicarboxílico: Este Ejemplo se preparó por el procedimiento usado en II-12A, sustituyendo II-11F por II-29B. Los diastereómeros del Ejemplo II-29C se separaron por cromatografía en fase inversa. EM (IEP) *m/z*: 613 para ambos diastereómero 1 (menor tiempo de retención) y diastereómero 2 (mayor tiempo de retención); cada uno es una sal mono-trifluoroacetato.

II-29D. Éster 8-terc-butílico éster 9-etílico del ácido (9R,14S)-14-*terc*-butoxicarbonilamino-5-metoxicarbonilamino-16-oxi-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-8,9-dicarboxílico: A una solución del Ejemplo II-29C, diastereómero 2 (21 mg, 0.034 mmol) en acetato de etilo se añadió una solución saturada de carbonato sódico en agua. Después de mezclar, se separaron las fases y la fase orgánica se secó sobre sulfato de magnesio. La filtración y eliminación del solvente a vacío dio la base libre. Esta se diluyó entonces con DCM (0.5 ml). Se añadió ácido m-

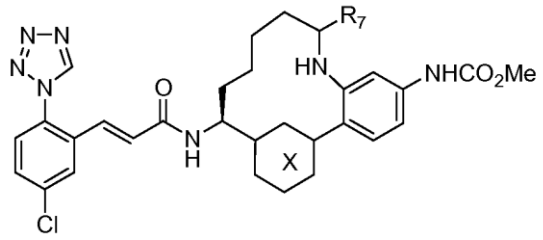
cloroperbenzoico (mCPBA) (11.52 mg, 0.051 mmol). La mezcla de reacción se agitó a TA. La mezcla de reacción se diluyó con acetato de etilo y se lavó con una solución saturada de Na2SO3, solución saturada de $NaHCO_3$, y a continuación salmuera. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a vacío. El producto bruto se usó sin ninguna purificación posterior. EM (IEP) *m/z*: 629.

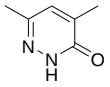
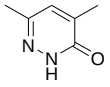
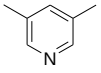
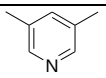
II-29E. Éster etílico del ácido (9R,14S)-14-amino-5-metoxicarbonilamino-16-oxi-8,16-diaza-triciclo[13.3.1.2.7.7]nonadeca-1(19),2,4,6,15,17-hexaeno-9-carboxílico: El Ejemplo II-29D se mezcló con una solución de HCl en dioxano y la mezcla de reacción se agitó a ta durante 1 h. La mezcla de reacción se concentró a vacío y se usó como la sal diclorhidrato para la etapa siguiente sin ninguna purificación adicional. EM (IEP) *m/z*: 429.

Ejemplo II-29. Siguiendo el procedimiento usado para preparar el Ejemplo 1G, se disolvieron 3-(5-cloro-2-(1H-tetrazol-1-il)fenil)acrilato de (E)-2,5-dioxopirrolidin-1-ilo (18 mg, 0.052 mmol) y II-29E (26 mg, 0.052 mmol) en DMF (0.5 ml), y luego se añadió DIPEA (0.090 ml, 0.518 mmol). La mezcla de reacción se agitó a temperatura ambiente bajo argón durante 4h. La mezcla de reacción se diluyó con acetato de etilo (10 ml) y se lavó con solución al 10% de LiCl. El secado sobre Na_2SO_4, filtración y eliminación del solvente a vacío dio el producto bruto, que se purificó por

cromatografía en fase inversa. El solvente se eliminó a vacío por liofilización dando un sólido (peso = 9 mg, 21 % de rendimiento): EM (IEP) *m/z*: 660.4; 1H NMR (500MHz, CD_3CN) δ 9.12 (s, 1H), 8.67 (d, *J* = 6.0 Hz, 1H), 8.41 - 8.23 (m, 2H), 7.96 - 7.80 (m, 2H), 7.64 - 7.44 (m, 3H), 7.32 - 7.21 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 15.4 Hz, 1H), 6.75 (d, *J* = 15.4 Hz, 1H), 5.50 - 5.37 (m, 1H), 4.01 - 3.83 (m, 3H), 3.76 - 3.69 (m, 4H), 2.95 (s, 1H), 2.32 (s ancho, 1H), 1.95 (m, 1H) 1.92 - 1.72 (m, 1H), 1.61 (s ancho, 1H), 1.42 (s ancho, 3H), 1.15 - 0.93 (m, 3H).

Tabla II-3: Ejemplos II-23 a II-29



Ej. n°	x	R^7	LCMS $[M+H]^+$	HPLC Tr (min.)
II-23		CO_2Et (mezcla de diastereómeros)	662.2	9.5
II-24		CO_2Et (mezcla de diastereómeros)	662.2	9.8
II-25			645.1	6.7
II-26			645.1	6.8

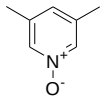
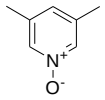
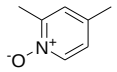
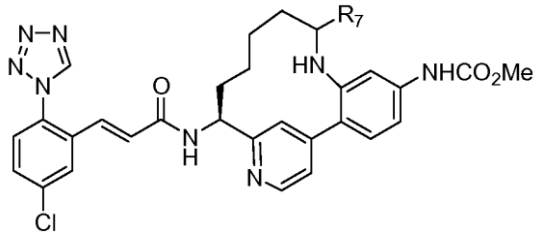
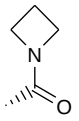
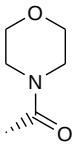
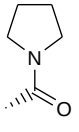
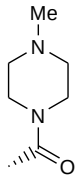
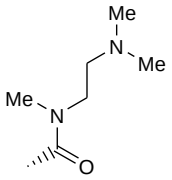
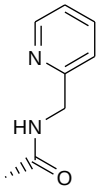
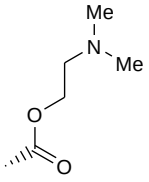
Ej. n°	x	R^7	LCMS $[M+H]^+$	HPLC Tr (min.)
II-27			661.1	8.8
II-28			661.3	7.9
II-29			660.4	7.9

Tabla II-4: Ejemplos II-30 a II-38

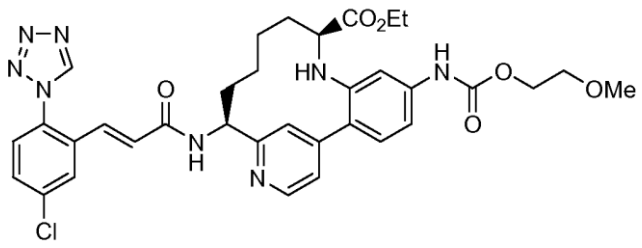


Ej. n°	R^7	LCMS $[M+H]^+$	HPLC TR (min.)
II-30		617.1	6.9
II-31		631.3	7.6
II-32		656.3	7.0
II-33		686.2	6.4
II-34		670.2	6.5

Ej. nº	R^7	LCMS $[M+H]^+$	HPLC TR (min.)
II-35		699.2	6.0
II-36		701.5	5.0
II-37		707.2	5.8
II-38		688.1	9.9

Ejemplo II-39.

Éster etílico del ácido (9S,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-(2-metoxi-etoxicarbonilamino)-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-9-carboxílico, bis-sal del ácido trifluoracético



La síntesis del Ejemplo II-39 siguió los procedimientos generales descritos para II-17. El Ejemplo II-39AE (descrito más adelante) se sustituyó por el compuesto II-17A. Los diastereómeros que corresponden al Ejemplo II-17B, diastereómeros A y B, no se separaron. Estos se sometieron a hidrogenación y luego se separaron por HPLC dando diastereómeros que corresponden al compuesto II-17C y su diastereómero. Los diastereómeros se separaron seguidamente convertidos en los Ejemplos II-39 y II-40 (descritos más adelante). Los siguientes datos se recogieron para el Ejemplo II-39: EM (IEP) *m/z* 689.3, 691.3; 1H NMR (CD_3OD, 400 MHz): δ 9.37 (s, 1H), 8.55 (d, 1H, J = 6), 8.28 (s, 1H), 7.87 (d, 1H, J = 2), 7.55 (dd, 1H, J = 8, 2), 7.46 (d, 1H, J = 8), 7.27 (d, 1H, J = 8), 7.24 (d, 1H, J = 2), 6.99 (d, 1H, J = 16), 6.74 (d, 1H, J = 16), 5.07 (m, 1H), 4.17 (t, 2H, J = 6), 3.94 (m, 2H), 3.55 (t, 2H, J = 6), 3.29 (s, 3H), 3.20 (m, 5H), 3.12 (m, 2H), 2.17 (m, 1H), 1.89 (m, 1H), 1.60 (m, 2H), 1.40 (m, 4H), 1.03 (t, 3H, J = 7), 0.58 (m, 1H).

II-39AA. Éster terc-butílico del ácido ((S)-1-{4-[4-nitro-2-(2,2,2-trifluoro-acetilamino)-fenil]-piridin-2-il}-but-3-enil)-carbámico: A una solución de Ejemplo II-11A (0.40 g, 1.041 mmol) en THF (Volumen 9 ml) a -78°C se añadió Et_3N (0.435 ml, 3.12 mmol), seguido por $(CF_3CO)_2O$ (0.154 ml, 1.093 mmol). La mezcla de reacción se calentó gradualmente

hasta ta y se agitó durante 20.75 h. La mezcla de reacción se concentró a vacío. El residuo se trató con agua (10 ml) y se extrajo tres veces con EtOAc. Los orgánicos reunidos se lavaron una vez con HCl 1N (3 ml), a continuación se secaron sobre $MgSO_4$. La filtración, eliminación del solvente a vacío y purificación del residuo por cromatografía en fase normal proporcionó un aceite (Peso = 239 mg): EM (IEP) *m/z*: 481.2.

II-39AB. Éster terc-butílico del ácido ((S)-1-{4-[4-amino-2-(2,2,2-trifluoro-acetilamino)-fenil]-piridin-2-il}-but-3-enil)-carbámico: A una solución amarilla transparente de II-39AA (0.269 g, 0.560 mmol) en MeOH (5.60 ml) se añadió secuencialmente zinc (0.366 g, 5.60 mmol) y NH4Cl (0.300 g, 5.60 mmol). La suspensión resultante se agitó vigorosamente durante 6.5 h. La mezcla de reacción se filtró a través de un GMF de 0.45 micrómetros eluyendo con metanol dando un filtrado amarillo transparente. La concentración dio un residuo amarillo oscuro. El residuo se repartió tres veces entre EtOAc y HCl 1 M (10 ml) y se separaron las fases. Las fases acuosas combinadas se basificaron con una solución de NaOH 1 N (pH ~ 8 por papel) y luego se extrajeron con EtOAc (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron dando un aceite (Peso = 200 mg): EM (IEP) *m/z* = 451.3.

II-39AC. Éster 2-metoxi-etílico del ácido [4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-3-

(2,2,2-trifluoro-acetilamino)-fenil]-carbámico: Una solución de II-39AB (200 mg, 0.444 mmol) y piridina (0.180 ml, 2.220 mmol) en diclorometano (4 ml) se enfrió hasta 0°C bajo argón con agitación. A continuación, se añadió gota a gota carbonocloridato de 2-metoxietilo (0.103 ml, 0.888 mmol). La mezcla de reacción se agitó durante 50 min a 0°C durante 2 h. Se añadieron 50 µl del reactivo de cloroformiato y se agitó a temperatura ambiente durante 17.75 h. La mezcla de reacción se diluyó con EtOAc y se lavó una vez con 2.2 ml de HCl 1 N, a continuación dos veces con solución saturada de Na_2CO_3. La fase orgánica se secó sobre $MgSO_4$ y se filtró. El solvente se eliminó a vacío dando un aceite amarillo pálido transparente (Peso = 160 mg). EM (IEP) *m/z* = 553.3. 1H NMR (CD_3OD, 500 MHz): δ 11.94 (s, 1H), 10.90 (s, 1H), 9.32 (d, 1H, J = 5), 8.44 (s, 1H), 8.36 (dd, 1H, J = 10, 2), 8.20 (d, 1H, J = 10), 8.17 (s, 1H), 8.01 (m, 1H), 6.55 (m, 1H), 5.87 (d, 1H, J = 17), 5.81 (d, 1H, J = 9), 5.48 (M, 1H), 5.15 (m, 1H), 5.06 (m, 2H), 4.67 (m, 2H), 3.31 (s, 3H), 3.23 (m, 1H).

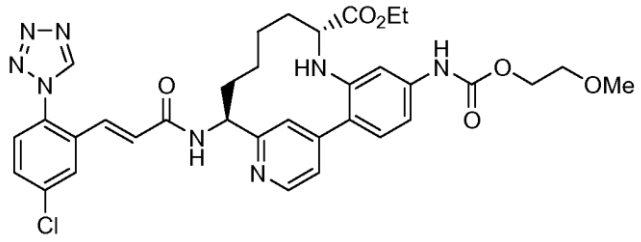
II-39AD. Éster 2-metoxi-etílico del ácido {3-amino-4-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-fenil}-carbámico: Una mezcla del Ejemplo II-39AC (160 mg, 0.290 mmol), una solución 1M de LiOH en agua (0.290 ml, 0.290 mmol) y THF 0.5 ml) se agitó durante ~20 h. Se añadieron 0.2 l de solución 1M de LiOH y se continuó agitando durante 24 h. Se añadió una solución 1 N de HCl (0.5 ml) y la mezcla se

extrajo tres veces con EtOAc. Las fases orgánicas se lavaron con una solución saturada de Na_2CO_3, a continuación se secaron sobre $MgSO_4$ y se filtraron. El solvente se eliminó a vacío. El residuo se purificó por cromatografía en fase normal proporcionando un aceite amarillo (Peso = 103 mg): EM (IEP) *m/z* = 457 (ES+) producto deseado.

II-39AE. Éster etílico del ácido 2-[2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-5-(2-metoxi-etoxicarbonilamino)-fenilamino]-pent-4-enoico: La síntesis del Ejemplo II-39AE siguió el procedimiento general descrito para II-17A donde se sustituyó el Ejemplo II-11C por el Ejemplo II-39AD. El producto bruto se purificó por cromatografía en fase normal proporcionando un aceite amarillo: EM (IEP) *m/z* = 583.4 (ES+) producto deseado.

Ejemplo II-40.

Éster etílico del ácido 9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-(2-metoxi-etoxicarbonilamino)-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-9-carboxílico, bis-sal del ácido trifluoracético



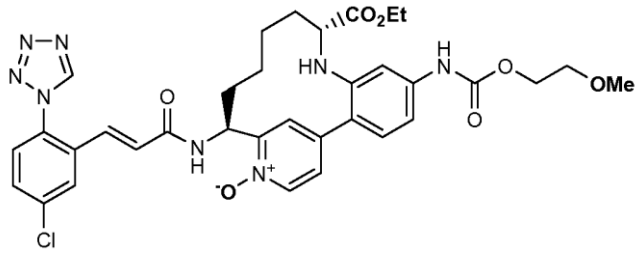
La síntesis del Ejemplo II-40 siguió los

procedimientos generales descritos para II-17. Se sustituyó el Ejemplo II-17A por el Ejemplo II-39AE (descrito antes). Los diastereómeros que corresponden al Ejemplo II-17B, diastereómeros A y B, no se separaron. Estos se sometieron a hidrogenación y luego se separaron por cromatografía en fase normal dando diastereómeros que corresponden al Ejemplo II-17C y su diastereómero. Los diastereómeros se convirtieron entonces por separado en los Ejemplos II-39 y II-40 (descrito más adelante). Se recogieron los siguientes datos para el Ejemplo II-40: EM (IEP) *m/z* 689.3, 691.3; 1H NMR (CD_3OD, 400 MHz): δ 9.49 (s, 1H), 8.71 (s, 1H), 8.64 (d, 1H, J = 6), 7.99 (d, 1H, J = 2), 7.72 (d, 1H, J = 3), 7.67 (dd, 1H, J = 8, 2), 7.57 (d, 1H, J = 9), 7.46 (d, 1H, J = 9), 7.38 (d, 1H, J = 2), 7.22 (dd, 1H, J = 9, 2), 7.11 (d, 1H, J = 16), 6.81 (d, 1H, J = 16), 5.15 (dd, 1H, J = 11, 5), 4.28 (t, 2H, J = 5), 4.00 (m, 2H), 3.66 (t, 2H, J = 4), 3.40 (s, 3H), 3.30 (m, 4H), 3.08 (d, 1H, J = 11), 2.19 (m, 1H), 1.90 (m, 2H), 1.76 (m, 1H), 1.49 (m, 2H), 1.38 (m, 1H), 1.09 (t, 3H, J = 7), 0.37 (m, 1H).

Ejemplo II-41.

Éster etílico del ácido 9R,14S)-14-[(E)-3-(5-cloro-2-tetrazol-1-il-fenil)-acriloilamino]-5-(2-metoxi-etoxicarbonilamino)-16-oxi-8,16-diaza-triciclo[13.3.1.2.7]nonadeca-1(19),2,4,6,15,17-hexaeno-9-

carboxílico, sal del ácido trifluoracético



Este Ejemplo se preparó siguiendo los procedimientos generales descritos para el Ejemplo II-29.

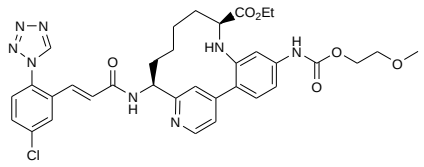
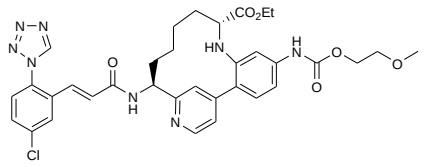
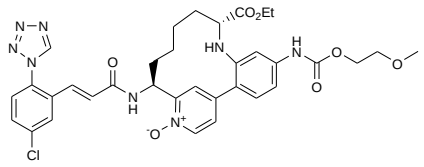
Se sustituyó el Ejemplo II-29A por el Ejemplo II-41A (descrito más adelante). Se recogieron los siguientes datos para el Ejemplo II-41. EM (IEP) *m/z* = 705.3, 707.3. 1H NMR (CD_3CN, 500 MHz): δ 9.02 (s, 1H), 8.38 (d, 1H, J = 8), 8.17 (d, 1H, J = 6), 7.85 (d, 1H, J = 3), 7.75 (s, 1H), 7.51 (dd, 1H, J = 11, 2), 7.41 (d, 1H, J = 8), 7.26 (d, 1H, J = 3), 7.19 (d, 1H, J = 8), 6.92 (d, 1H, J = 16), 6.66 (d, 1H, J = 16), 5.53 (m, 1H), 4.15 (t, 2H, J = 6), 3.86 (m, 2H), 3.49 (t, 2H, J = 6), 3.25 (s, 3H), 2.97 (d, 1H, J = 12), 2.38 (m, 5H), 1.74 (m, 2H), 1.54 (m, 1H), 1.27 (m, 4H), 0.97 (t, 3H, J = 7).

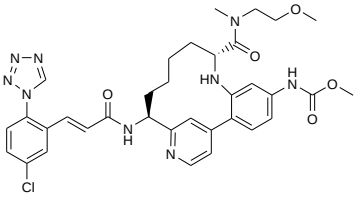
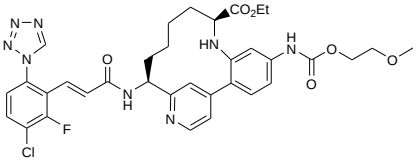
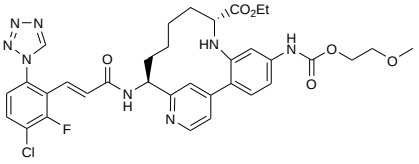
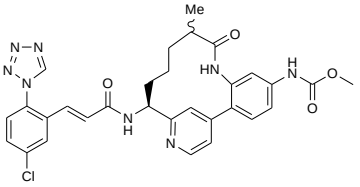
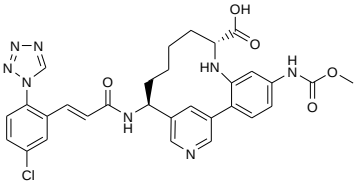
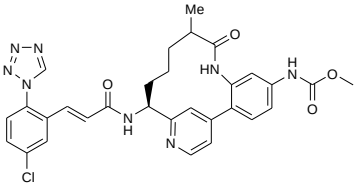
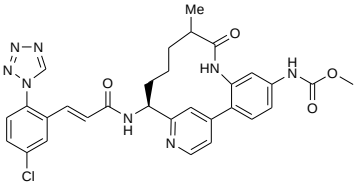
II-41A. Éster etílico del ácido 2-{*terc*-butoxicarbonil-[2-[2-((S)-1-*terc*-butoxicarbonilamino-but-3-enil)-piridin-4-il]-5-(2-metoxi-etoxicarbonilamino)-fenil]-amino}-pent-4-enoico: A una solución del Ejemplo II-39AE (83 mg, 0.142 mmol) en DCM (1.5 ml) se añadió DMAP (17.40 mg, 0.142 mmol) y Boc_2O (68.4 mg, 0.313 mmol) seguido por DIEA (0.062 ml, 0.356 mmol). La mezcla de reacción se agitó a ta

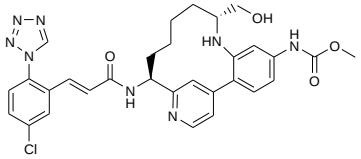
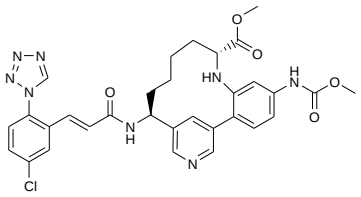
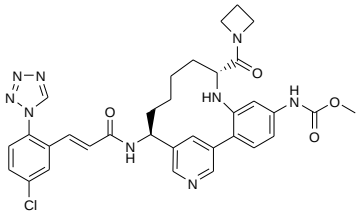
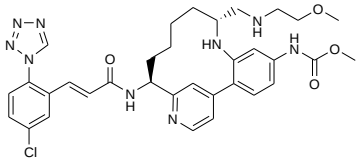
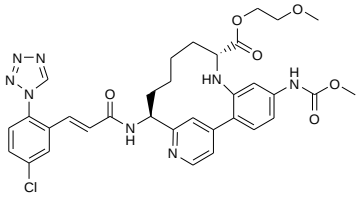
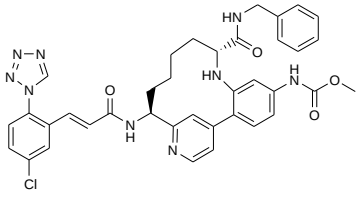
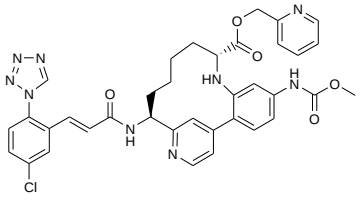
durante 3 h. La mezcla de reacción se concentró a vacío, se disolvió con EtOAc y se lavó con salmuera. El producto bruto se purificó entonces por cromatografía en fase normal dando un aceite (Peso = 98 mg): EM (IEP) *m/z* = 681.3.

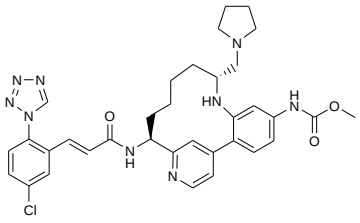
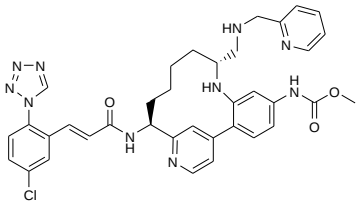
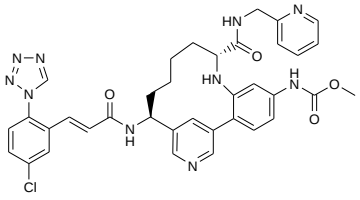
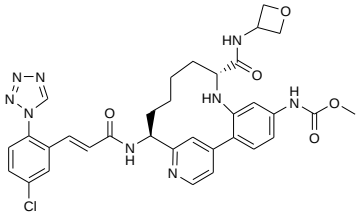
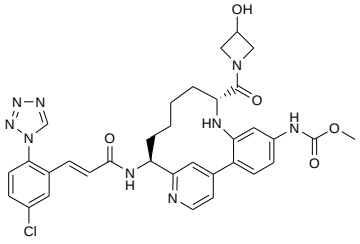
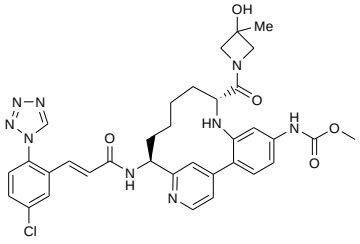
Los Compuestos II-47 (diastereómero A) y II-48 (diastereómero B) se prepararon siguiendo los procedimientos descritos en la etapa de acoplamiento de amida 88E, sustituyendo 88D por II-11C y sustituyendo ácido pent-4-enoico por ácido 2-metilbut-3-enoico; seguido por la etapa de metátesis de cierre del anillo 88G; etapa de hidrogenación 2G en donde los diastereómeros se separaron por HLC prep quiral [Chiralcel OD, eluyendo con isopropanol al 80%/heptano] dando diastereómero A y diastereómero B; etapa de desprotección Boc 3C; y 1G.

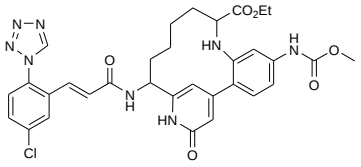
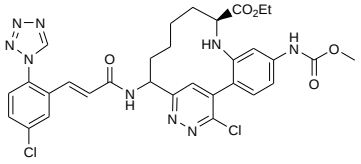
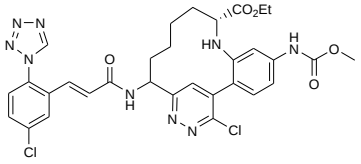
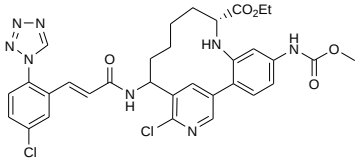
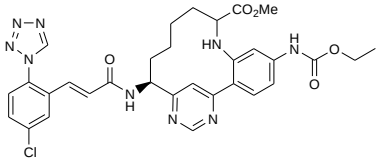
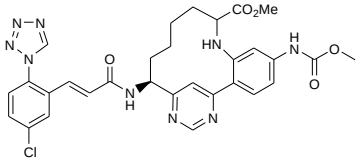
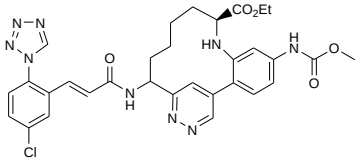
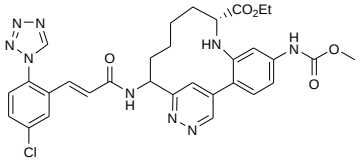
Tabla II-5: Ejemplos II-39 a I-72

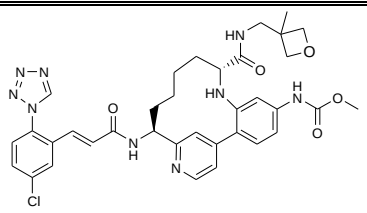
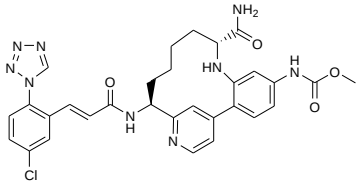
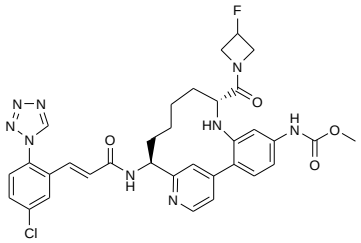
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.)
II-39		689.3	6.1
II-40		689.3	6.5
II-41		705.3	7.7

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.)
II-42		688.2	10.9
II-43		707.1	5.7
II-44		707.1	6.2
II-45		601.4	4.6/4.7
II-46		617.1	5.8
II-47 (Diastereómero A)		601.0	5.4
II-48 (Diastereómero B)		601.0	5.4

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.)
II-49		603.0	5.6
II-50		631.1	5.95
II-51		656.1	5.40
II-52		660.2	5.02
II-53		675.1	7.1
II-54		706.1	7.3
II-55		708.1	6.0

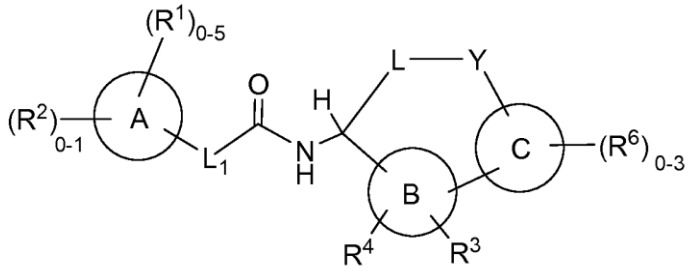
Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.)
II-56		656.1	5.16
II-57		693.1	5.22
II-58		707.0	4.44
II-59		672.1	5.4
II-60		672.1	5.2
II-61		686.1	5.3

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.)
II-62		661.2	7.41
II-63		680.2	10.21
II-64		680.3	10.56
II-65		679.0	9.46 9.72
II-66		646.0	8.78
II-67		632.0	8.24
II-68		646.0	8.37
II-69		646.0	9.04

Ej. n°		LCMS $[M+H]^+$	HPLC Tr (min.)
II-70		700.0	5.61
II-71		616.1	5.60
II-72		674.0	6.09

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



(I)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato o un profármaco del mismo, caracterizados porque:

el anillo A es independientemente un carbociclo C_{3-10} o un carbociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, NH, N(alquilo C_{1-4}), O y S(O)p;

el anillo B es independientemente un anillo de benceno o un heteroarilo de 5 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, O y S(O)p;

el anillo C es independientemente un anillo de benceno o un heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados del N, NH, N(alquilo C_{1-4}), O y $S(O)_p$;

L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CHR^5-$, $-CHR^5CHR^5-$, $-CR^5=CR^5-$,

-C≡C-, $-OCH_2-$, $-CHR_5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CN_2NH-$ y $-CR^5R^5-$;

L se selecciona independientemente del grupo constituido por: alquileno C_{3-8}, alquenileno C_{3-8} y alquinileno C_{4-8}, en donde alquileno, alquenileno y alquinileno están sustituidos con 0-2 R^7 y opcionalmente uno o varios de los átomos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, S, NH, N(alquilo C_{1-4}), CO, CONH, NHCO, OCONH, $NHCO_2$, -NHCONH-, SO_2NH, $NHSO_2$, CON(alquilo C_{1-4}) o N(alquilo C_{1-4})CO;

Y se selecciona independientemente del grupo constituido por: CH_2, CH(alquilo C_{1-4}), C(alquilo C_{1-4})$_2$, CO, O, S, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4}), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, $-CONHCH_2-$, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -OCON(alquilo C_{1-4})-, -NHCONH-, $-SO_2NH-$, $-NHCO_2-$ y $-NHSO_2-$;

alternativamente, L-Y es alquileno C_{3-6}-CH=N-;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, haloalquilo C_{1-4}, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, $-CO_2$(alquilo C_{1-4}), -CO(alquilo C_{1-4}), $-CH_2NH_2$, $-CONH_2$, -CONH(alquilo C_{1-4}), $-OCH_2CO_2H$, -NHCO(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-C(=NH)NH_2$ y fenilo sustituido con 0-2 R^a;

R^2 es independientemente un heterociclo de 5 a 7 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados del N, NH, N(alquilo C_{1-4}), O, y $S(O)_p$, en el heterociclo está sustituido con 0-2 R^{2a};

R^{2a}, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, $-CH_2OH$, alcoxi C_{1-4}, OH, CF_3, OCF_3, CN, NH_2, CO_2H, CO_2(alquilo C_{1-4}), COalquilo C_{1-4}, $-CONH_2$, -CONH(alquilo C_{1-4}), -CON(alquilo $C_{1-4})_2$, $-SO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-SO_2$NH(alquilo C_{1-4}) y $-SO_2$N(alquilo $C_{1-4})_2$;

R^3 se selecciona independientemente del grupo constituido por: H, =O, halógeno, OH, NH_2, CN, alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, $-CH_2OH$, CO_2H, CO_2(alquilo C_{1-4}), $-C(O)NH_2$, -C(O)NH(alquilo C_{1-4}), -C(O)N(alquilo $C_{1-4})_2$, $-CH_2CO_2H$ y cicloalquilo C_{3-6};

R^4 se selecciona independientemente del grupo constituido por: H y alquilo C_{1-4};

R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H, halógeno, OH y alquilo C_{1-4};

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), $-(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), $-NHCOCF^3$, $-NHCO_2$(alquilo C_{1-4}),

$-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHC(O)NH$(alquilo C_{1-4}), $-NHC(O)N$(alquilo C_{1-4})$_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH_2$, $-SO_2NH$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $-CONH_2$, $-CONH$(alquilo C_{1-4}), $-CON$(alquilo C_{1-4})$_2$, $-CH_2CONH_2$ y $-NHCO_2(CH_2)_{0-2}R^9$;

R^7, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, NH_2, CH_2NH_2, haloalquilo C_{1-4}, OCH_2F, $OCHF_2$, OCF_3, $-NH$(alquilo C_{1-4}), $-N$(alquilo C_{1-4})$_2$, alcoxi C_1-$_4$, CH_2OH, CH_2O(alquilo C_{1-4}), $CH_2O(CH_2)_{1-4}O$(alquilo C_{1-4}), CO_2H, CO_2(alquilo C_{1-4}), $CO_2(CH_2)_2O$(alquilo C_{1-4}), CO_2(haloalquilo C_{1-4}), $CO_2(CH_2)_2SO_2$(alquilo C_{1-4}), CH_2CO_2H, CH_2CO_2(alquilo C_{1-4}), $CONH_2$, $CONH$(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, $-OCO$(alquilo C_{1-4}), $-CH_2NH_2(CH_2)_2O$(alquilo C_{1-4}), $-CONH$(alcoxi C_{1-4}), $-CO_2(CH_2)_2O$(alquilo C_{1-4}), $-CO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-CONH(CH_2)_2O$(alquilo C_{1-4}), $-CONH(CH_2)_2N$(alquilo C_{1-4})$_2$, $-CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}), $-CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo C_{1-4})$_2$, alquilo C_1-$_4$, $-CONHBn$, $-CONH(OBn)$, $-(CO)_{0-1}(CH_2)_{0-3}$-carbociclo C_{3-6} y $-(CH_2)_{0-1}-(CO)_{0-1}-(W)_{0-1}-(CH_2)_{0-2}$-(heterociclo de 4 a 6 miembros que comprende átomos de carbonos y 1-4 hetoroátomos seleccionados de entre N, NH, N(alquilo C_{1-4}), O y $S(O)_p$); donde los carbociclo y

heterociclo están sustituidos con 0-2 R^8;

R^8, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CHF_2, CF_3, alcoxi C_{1-4}, CH_2OH, CO_2H, CO_2(alquilo C_{1-4}), $CONH_2$ y alquilo C_{1-4};

R^9 es un heterociclo de 4 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de N, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4})), O y $S(O)_p$;

R^a, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CF_3, alcoxi C_{1-4} y alquilo C_{1-4};

W se selecciona independientemente del grupo constituido por: O, NH y N(alquilo C_{1-4}); y

p, en cada aparición, se selecciona independientemente del grupo constituido por: 0, 1 y 2.

2. Compuesto de conformidad con la reivindicación 1, caracterizado porque:

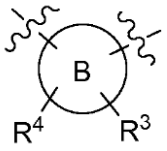
el anillo A es independientemente un carbociclo de 6 miembros, un carbociclo de 9 a 10 miembros o un heterociclo de 5 a 10 miembros que comprende: átomos de carbono y 1-3 heteroátomos seleccionados de N, NH, N(alquilo C_{1-4}), O y $S(O)_p$;

el anillo B se selecciona independientemente del grupo constituido por: imidazol, oxazol, oxadiazol, triazol, piridina, piridazina, pirimidina y benceno y

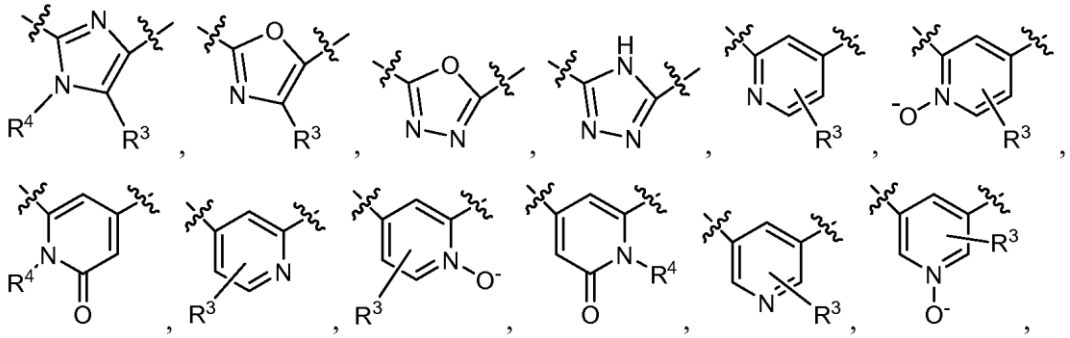
el anillo C se selecciona independientemente del grupo constituido por: benceno, piridina, indazol, indol, bencimidazol, quinolina, isoquinolina, tetrahidroquinolina, tetrahidroisoquinilina y quinazolina.

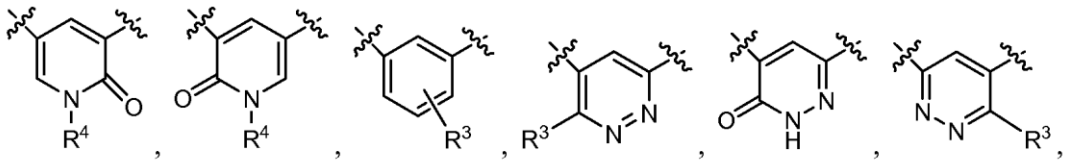
3. El compuesto de conformidad con la reivindicación 2, caracterizado porque:

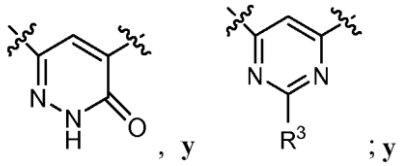
el anillo A se selecciona independientemente del grupo constituido por: benceno, ciclohexano, indano, tetrahidronaftaleno, naftaleno, isoxazolina, isoxazol, pirazol, imidazol, triazol, piperidina, piridina, indazol, indol, bencimidazol, quinolina, isoquinolina, tetrahidroquinolina y tetrahidroisoquinolina;

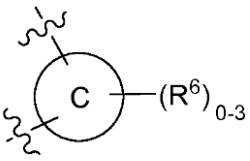


se selecciona independientemente del grupo constituido por:

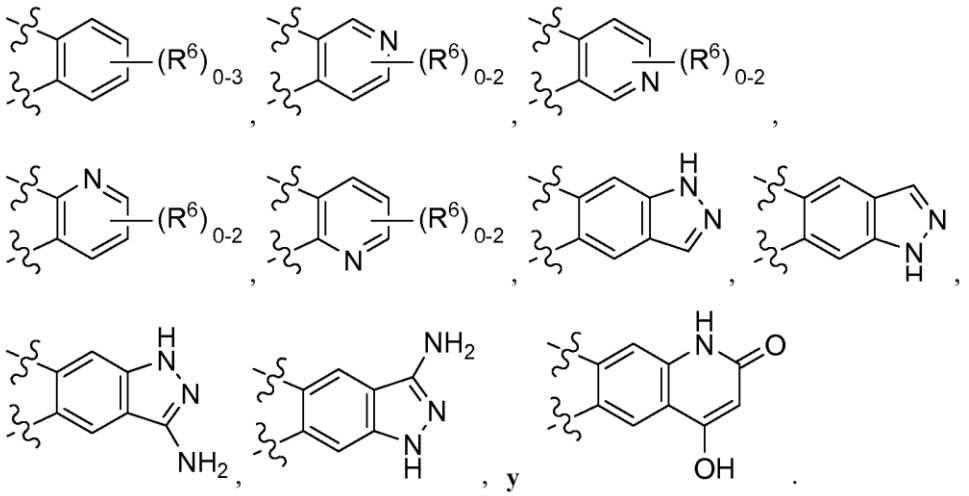




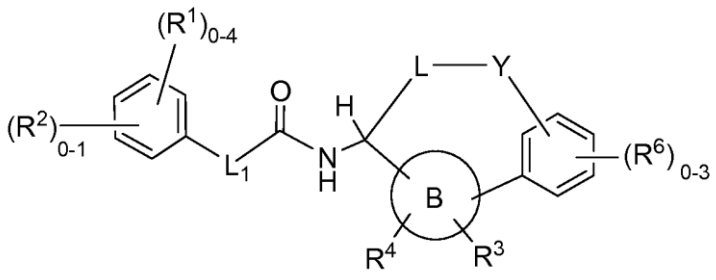




se selecciona independientemente del grupo constituido por:



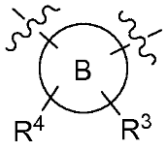
4. Un compuesto de Fórmula:



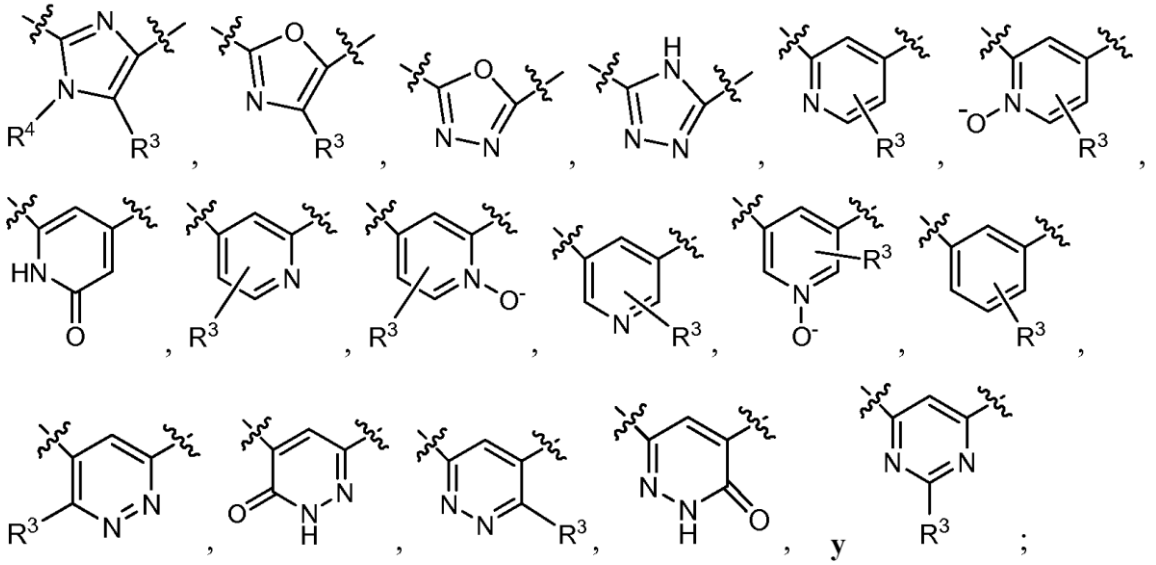
(II)

o un estereoisómero, un tautómero, una sal

farmacéuticamente aceptable, un solvato o un profármaco del mismo, caracterizados porque:



se selecciona independientemente del grupo constituido por:



L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CHR^5CHR^5-$, $-CR^5=CHR^5-$, $-C\equiv C-$, $-OCH_2-$, $-CHR^5NH-$, $-CH_2O-$, $-SCH_2-$, $-SO_2CH_2-$, $-CN_2NH-$ y $-CR^5R^5-$;

L se selecciona independientemente del grupo constituido por: alquileno C_{3-8} y alquenileno C_{3-8}; en el alquileno y alquenileno están sustituidos con 0-2 R^7 y opcionalmente uno o dos de los átomos de carbono del alquileno y alquenileno pueden estar reemplazados por O, CO, S, NH, N(alquilo C_{1-4}), CONH-, NHCO, OCONH, SO_2NH o CON(alquilo C_{1-4});

Y se selecciona independientemente del grupo constituido por: CH_2, CO ,CH(alquilo C_{1-4}), C(alquilo C_{1-4})$_2$, O, S, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4}), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -OCON(alquilo C_{1-4})-, -NHCONH- y -SO_2NH-;

alternativamente, L-Y es –alquileno C_{3-6}-CH=N-;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-6}, alcoxi C_{1-4}, alquiltio C_{1-4}, haloalquilo C_{1-4}, OH, OCH_2F, $OCHF_2$, OCF_3, CN, NH_2, NH(alquilo C_{1-4})$_2$, N(alquilo C_{1-4})$_2$, CO_2(alquilo C_{1-4}), CO(alquilo C_{1-4}), -OCH_2CO_2H, -CH_2NH_2, -$CONH_2$, -CONH(alquilo C_{1-4}), -SO_2NH_2 y -C(=NH)NH_2;

R^2 es independientemente un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y S(O)$_p$, en los que el heterocilo está sustituido con 0-2 R^{2a};

R^{2a}, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, -CH_2OH, alcoxi C_{1-4}, OH, CF_3, CN, NH_2, CO_2H, CO_2(alquilo C_{1-4}), COalquilo C_{1-4}, -$CONH_2$, -CONH(alquilo C_{1-4}) y -CON(alquilo C_{1-4})$_2$;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, OH, NH_2, CN, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, -CH_2OH, CO_2H, CO_2(alquilo C_{1-4}), -C(O)NH_2, -

C(O)NH(alquilo C_{1-4}), $-C(O)N(\text{alquilo } C_{1-4})_2$, $-CH_2CO_2H$ y cicloalquilo C_{3-6};

R^4 se selecciona independientemente del grupo constituido por: H y alquilo C_{1-4};

R^5, en cada aparición, se selecciona independientemente del grupo constituido por: H, halógeno, OH y alquilo C_{1-4};

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, $CO_2(\text{alquilo } C_{1-4})$, $-CH_2CO_2H$, $-(CH_2)_2CO_2H$, $-CH_2CO_2(\text{alquilo } C_{1-4})$, $-(CH_2)_2CO_2(\text{alquilo } C_{1-4})$, NH_2, $-CH_2NH_2$, $-NHCO(\text{alquilo } C_{1-4})$, $-NHCO_2(\text{alquilo } C_{1-4})$, $-NHCO_2(CH_2)_2O(\text{alquilo } C_{1-4})$, $-NHCO_2(CH_2)_3O(\text{alquilo } C_{1-4})$, $-NHCO_2CH_2CH(\text{alquilo } C_{1-4})O(\text{alquilo } C_{1-4})$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2(\text{alquilo } C_{1-4})$, $-NHC(O)NH(\text{alquilo } C_{1-4})$, $-NHC(O)N(\text{alquilo } C_{1-4})_2$, $-NHSO_2(\text{alquilo } C_{1-4})$, $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O(\text{alquilo } C_{1-4})$, $-CONH(CH_2)_2O(\text{alquilo } C_{1-4})$, $CONH_2$, $CONH(\text{alquilo } C_{1-4})$, $CON(\text{alquilo } C_{1-4})_2$, $-CH_2CONH_2$ $-NHCO_2(CH_2)_2N(\text{alquilo } C_{1-4})_2$, $-NHCOCF_3$ y $-NHCO_2(CH_2)_{0-1}R^9$;

R^7, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, haloalquilo C_{1-4}, OH, alcoxi C_{1-4}, CH_2OH, $CH_2O(\text{alcoxi } C_{1-4})$, CO_2H, $CO_2(\text{alquilo } C_{1-4})$, $CO_2(CH_2)_2O(\text{alquilo } C_{1-4}))$, $CO_2CH_2CF_3$, $CO_2(CH_2)_2SO_2(\text{alquilo } C_{1-4})$, CH_2CO_2H, $CH_2CO_2(\text{alquilo } C_{1-4})$, $CONH_2$,

$CONH(alquilo\ C_{1-4})$, $CON(alquilo\ C_{1-4})_2$, $-OCO(alquilo\ C_{1-4})$, $-CH_2NH(CH_2)_2O(alquilo\ C_{1-4})$, $-CO_2(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CONH(CH_2)_2O(alquilo\ C_{1-4})$, $-CONH(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CON(alquilo\ C_{1-4})(CH_2)_2O(alquilo\ C_{1-4})$, $-CONH(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CON(alquilo\ C_{1-4})(CH_2)_2N(alquilo\ C_{1-4})_2$, $-CONH(alcoxi\ C_{1-4})$, -CONHBn, -CONH(OBn), $-(CH_2)_{1-3}Ph$, alquilo C1-$_4$ y $-(CH_2)_{0-1}-(CO)_{0-1}-(W)_{0-1}-(CH_2)_{0-2}-$(heterociclo de 4 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de entre N, NH, $N(alquilo\ C_{1-4})$, O y $S(O)_p$); en los que el heterociclo está sustituido con 0-2 R^8;

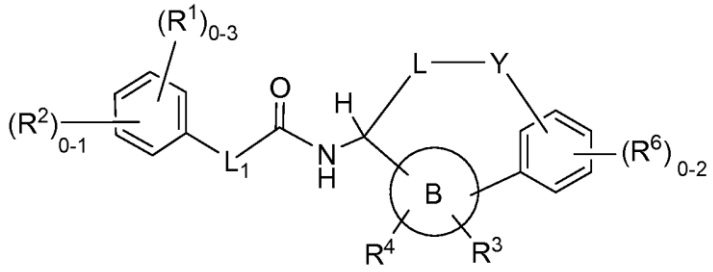
R^8, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, OH, CHF_2, CF_3, alcoxi C_{1-4} y alquilo C_{1-4};

R^9 es un heterociclo de 4 a 6 miembros que comprende: átomos de carbono y 1-4 heteroátomos seleccionados de entre N, NH, $N(alquilo\ C_{1-4})$, $N(CO_2(alquilo\ C_{1-4}))$, O y $S(O)_p$;

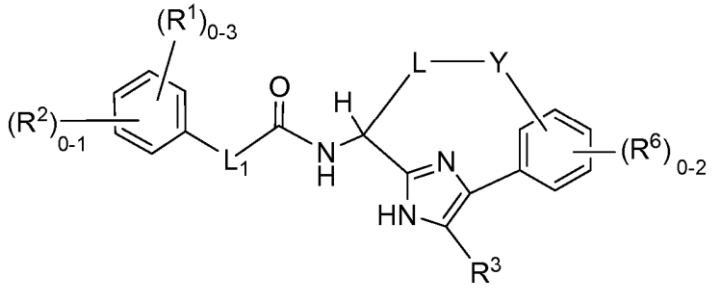
W se selecciona independientemente del grupo constituido por: O y NH; y

p, en cada aparición, se selecciona independientemente del grupo constituido por: 0, 1 y 2.

5. Un compuesto de conformidad con la reivindicación 4, caracterizado porque tiene la fórmula (IIa) o fórmula (IIb):



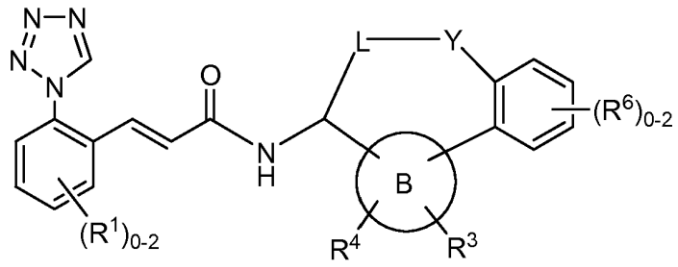
(IIa)



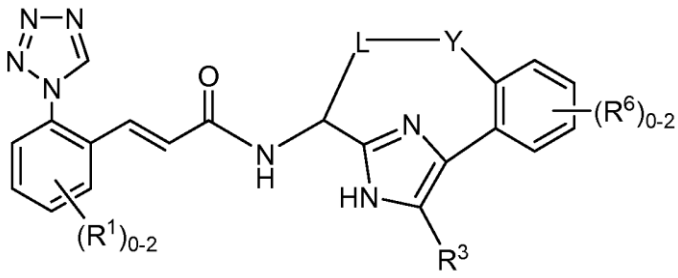
(IIb)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, o un solvato de los mismos.

6. Compuesto de conformidad con la reivindicación 4, caracterizado porque tiene la Fórmula (IIc) o Fórmula (IId):



(IIc)

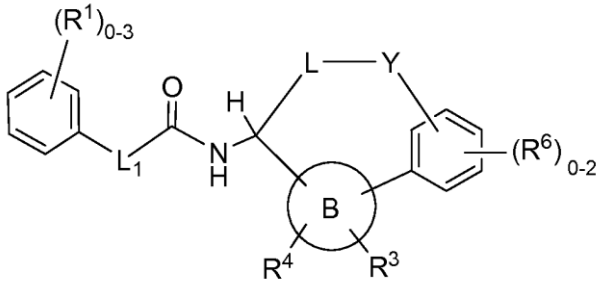


(IId)

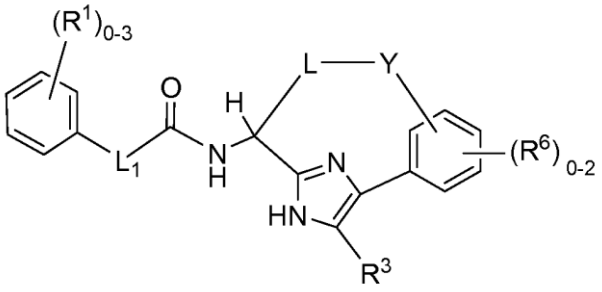
o un estereoisómero, un tautómero, una sal

farmacéuticamente aceptable, o un solvato de los mismos.

7. Compuesto de conformidad con la reivindicación 4, caracterizado porque tiene la Fórmula (IIe) o Fórmula (IIf):



(IIe)



(IIf)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, o un solvato de los mismos.

8. Compuesto de conformidad con cualquiera de las reivndicaciones 1-7, caracterizado porque:

L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CH_2CH_2-$, CH=CH-, -C(Me)=CH-, -C≡C- y $-CN_2NH-$ en la fórmula (I), (II), (IIa), (IIb), (IIe) o (IIf);

L se selecciona independientemente del grupo constituido por: alquileno C_{3-7} y alquenileno C_{3-7}, en donde los alquileno y alquenileno están sustituido con 0-2 R^7 y

opcionalmente uno o dos de los átomos de carbono de los alquileno y alquenileno pueden estar reemplazados por O, CO, NH, N(alquilo C_{1-4}), CONH, NHCO o CON(alquilo C_{1-4});

Y se selecciona independientemente del grupo constituido por: CH_2, CO, CH(alquilo C_{1-4}), C(alquilo C_{1-4})$_2$, O, S, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4}), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, $CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -NHCONH- y -SO_2NH-;

alternativamente, L-Y es -$(CH_2)_{4-6}$-CH=N-;

R^1, en cada aparición, se selecciona independientemente de entre: halógeno, CN, OH, OCH_2F, $OCHF_2$, OCF_3, haloalquilo C_{1-4}, alquilo C_{1-4}, alcoxi C_{1-4}, CO(alquilo C_{1-4}), NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, -C(=NH)NH_2, -C(O)NH_2, $-CH_2NH_2$ y -SO_2NH_2;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, OH, NH_2, CN, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, $-CH_2OH$, CO_2H, CO_2(alquilo C_{1-4}), -C(O)NH_2, -C(O)NH(alquilo C_{1-4}), -C(O)N(alquilo C_{1-4})$_2$ y $-CH_2CO_2H$ y cicloalquilo C_{3-6}; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, -$(CH_2)_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), -$(CH_2)_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, -NHCO(alquilo C_{1-4}), -$NHCO_2$(alquilo C_{1-4}), -

$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2(CH_2)_3O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2NH_2$, $-NHCO_2CH_2CO_2H$, $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHC(O)NH$(alquilo C_{1-4}), $-NHC(O)N$(alquilo $C_{1-4})_2$, $-NHSO_2$(alquilo C_{1-4}), $-SO_2NH(CH_2)_2OH$, $-SO_2NH(CH_2)_2O$(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo $C_{1-4})_2$, $-NHCO_2(CH_2)_2N$(alquilo $C_{1-4})_2$, $-NHCOCF_3$ y $-NHCO_2(CH_2)_{0-1}R^9$.

9. Compuesto de conformidad con cualquiera de las reivindicaciones 1-7, caracterizado porque:

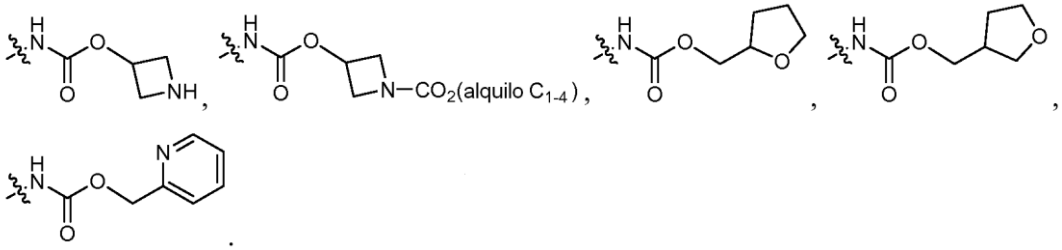
L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CH_2CH_2-$ y $-CH=CH-$ en la fórmula (I), (II), (IIa), (IIb), (IIe) o (IIf);

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CN, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, OCF_3, CO(alquilo C_{1-4}), NH_2, NH(alquilo $C_{1-4})_2$, N(alquilo $C_{1-4})_2$, $-CH_2NH_2$ y $-C(=NH)NH_2$;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, CN, CF_3, CO_2H, CO_2(alquilo C_{1-4}), alquilo C_{1-4},$CONH_2$, CON(alquilo $C_{1-4})_2$ y cicloalquilo C_{3-6}; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, CN, OH, CF_3, CO_2H, CO_2(alquilo C_{1-4}), $-CH_2CO_2H$, $-CH_2CO_2$(alquilo C_{1-4}), NH_2, $-CH_2NH_2$, $-NHCO$(alquilo C_{1-4}), $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-CONH_2$,

CONH(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -$NHCO_2CH_2CO_2H$, -$NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), -$NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, -$NHCOCF_3$,



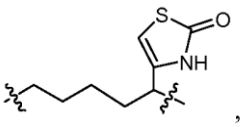
.

10. Compuesto de conformidad con cualquiera de las reivindicaciones 1-7, caracterizado porque:

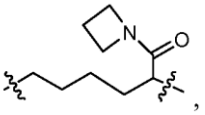
L_1 se selecciona independientemente del grupo constituido por: un enlace y -CH=CH- en la fórmula (I), (II), (IIa), (IIb), (IIe) o (IIf);

L se selecciona independientemente del grupo constituido por: -$(CH_2)_{3-6}$-, -$(CH_2)_{2-4}$CH(alquilo C_{1-4})$(CH_2)_{0-2}$-, -$(CH_2)_{1-2}$-CH=CH-$(CH_2)_{0-3}$-, -CH_2-CH=C(alquilo C_{1-4})-$(CH_2)_{1-2}$-, -CH_2-C(alquilo C_{1-4})=CH-$(CH_2)_{1-2}$-, -CH_2-CH=CH-CH_2CH(alquilo C_{1-4})-, -CH_2-CH=CH-CH(alquilo C_{1-4})-$(CH_2)_{0-2}$-, -CH_2-CH=CH-CH_2C(halo)$_2$-, -CH_2-CH=CH-$(CH_2)_{1-2}$CH(CF_3)-, -CH_2-CH=CH-CH(OH)CH_2-, -$(CH_2)_3$CH(halo)-, -$(CH_2)_{3-4}$C(halo)$_2$-, -$(CH_2)_4$CH(CH_2OH)-, -$(CH_2)_{3-4}$CH(alcoxi C_{1-4})-, -$(CH_2)_4$CH(CH_2(alcoxi C_{1-4}))-, -$(CH_2)_4$CH(CO_2H)-, -$(CH_2)_4$CH(CH_2CO_2H)-, -$(CH_2)_{4-5}$CH(CO_2(alquilo C_{1-4}))-, -$(CH_2)_4$CH(CH_2CO_2(alquilo C_{1-4}))-, -$(CH_2)_4$CH($CO_2CH_2CF_3$)-, -$(CH_2)_4$CH($CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))-, -$(CH_2)_4$C(alquilo C_{1-4})(CO_2(alquilo C_{1-4}))-, -$(CH_2)_4$C(CF_3)(CO_2(alquilo C_{1-4}))-, -

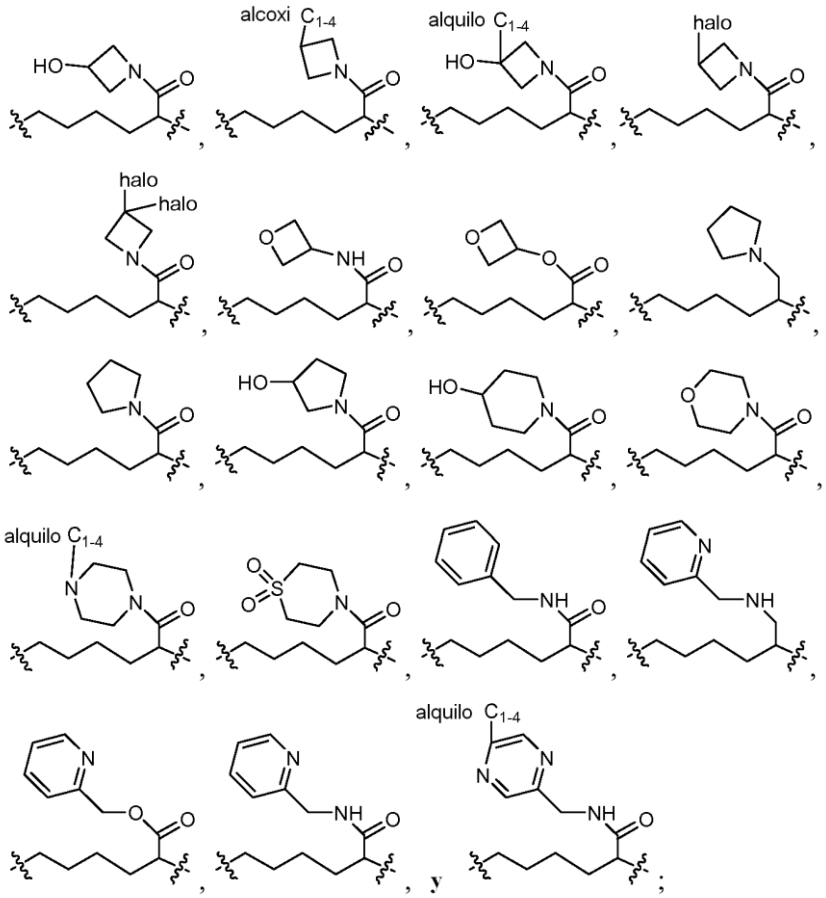
$(CH_2)_4CH(CONH_2))$-, -$(CH_2)_4CH(CONH$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CON$(alquilo $C_{1-4})_2$)-, -$(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)$-, -$(CH_2)_4CH(CO_2(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CH_2NH(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CONH$(alcoxi C_{1-4}))-, -$(CH_2)_4CH(CONH(OBn))$-, -$(CH_2)_4CH((CH_2)_3Ph)$-, -$(CH_2)_4CH(CO_2(CH_2)_2N$(alquilo $C_{1-4})_2$)-, -$(CH_2)_4CH(CONH(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CONH(CH_2)_2N$(alquilo $C_{1-4})_2$)-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo $C_{1-4})_2$)-, -$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_{4-5}CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-, -$(CH_2)_{1-3}CH(OH)(CH_2)_{1-2}$-, -$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO$(alquilo C_{1-4}))CH_2-, -$(CH_2)_3C(O)CH_2$-, -$CH_2O(CH_2)_{2-4}$-, -$CH_2NH(CH_2)_{2-4}$-, -$(CH_2)_{2-3}NH(CH_2)_{1-2}$-, -$(CH_2)_{2-4}N$(alquilo C_{1-4})$(CH_2)_{0-2}$-, -$CH_2CONH(CH_2)_{2-4}$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_{2-4}$-, -$CH_2NHCOC(halo)_2CH_2$-, -$(CH_2)_4CH$(3-alquilo C_{1-4}-oxetan-3-il)-, -$(CH_2)_4CH$(tiazol-4-il)-, -$(CH_2)_4CH$(4-alquilo C_{1-4}-tiazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-imidazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-3-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-5-il)-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)-; -$(CH_2)_4CH$(1-alquilo C_{1-4}-4-halo-pirazol-3-i



,



,

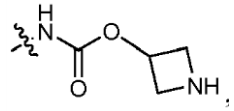
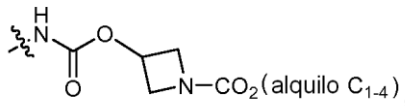
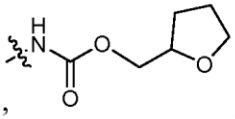
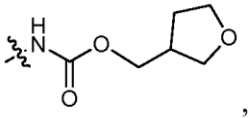
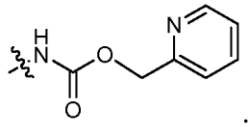


Y se selecciona independientemente del grupo constituido por: CH_2, CO, O, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4})), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -NHCONH- y -SO_2NH-; y

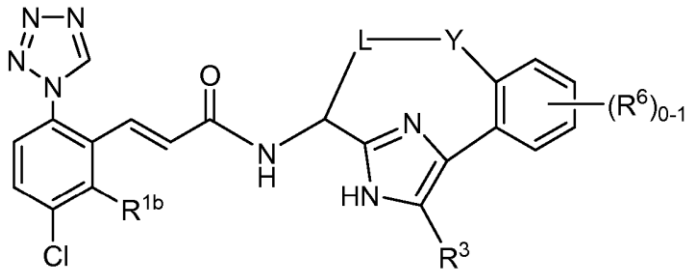
alternativamente, L-Y es -$(CH_2)_{3-6}$-CH=N-;

R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CO(alquilo C_{1-4}), CN, CH_2F, CHF_2, $OCHF_2$, CF_3, NH_2, N(alquilo C_{1-4})$_2$, -CH_2NH_2 y -C(=NH)NH_2;

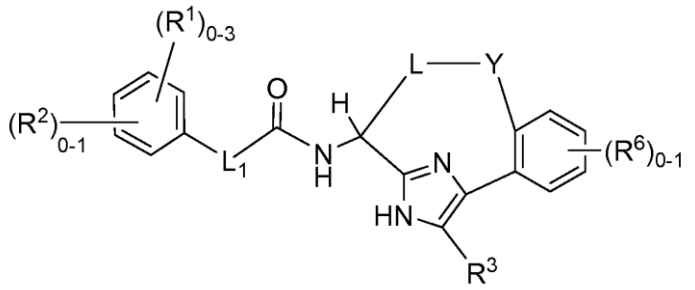
R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6}; y

R^6, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, CO_2(alquilo C_{1-4}), $CONH_2$, CONH(alquilo C_{1-4}), CON(alquilo C_{1-4})$_2$, $NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHCO_2CH_2CO_2H$, $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), $-NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, $-NHCOCF_3$,  ,  ,  ,  , y  .

11. Un compuesto de Fórmula (III) o Fórmula (IIIa):



(III)



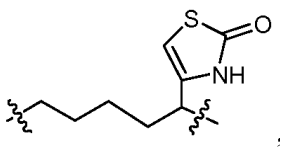
(IIIa)

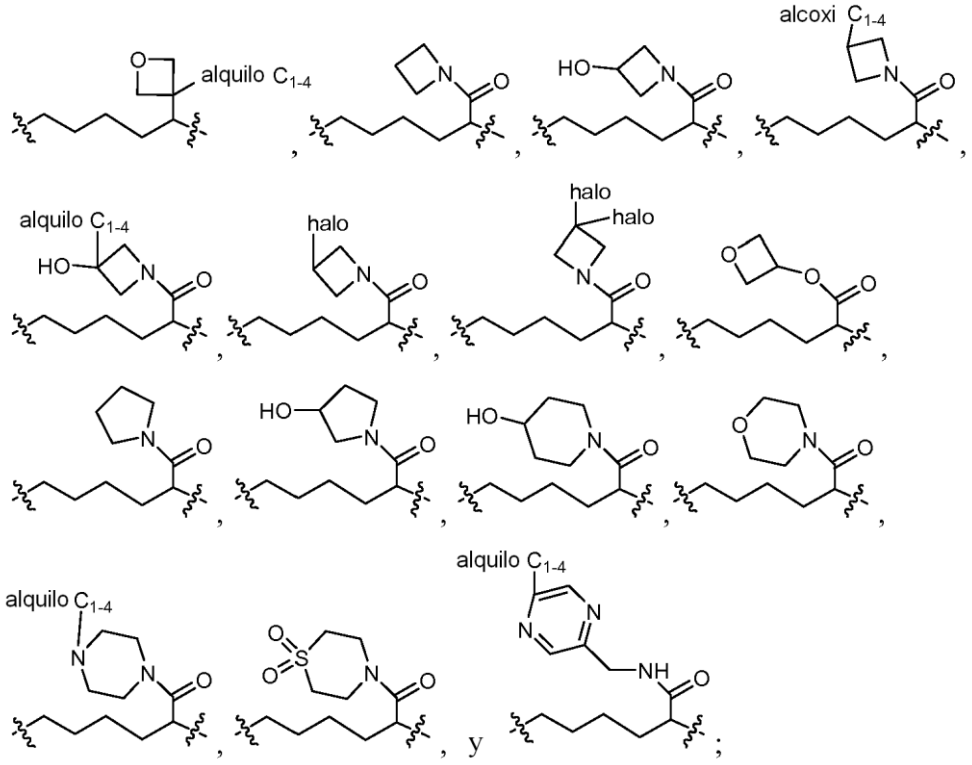
o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, un solvato, o un profármaco de los mismos, caracterizados porque:

L_1 se selecciona independientemente del grupo constituido por: un enlace y -CH=CH- en la fórmula (IIIa);

L se selecciona independientemente del grupo constituido por: $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_3CH$(alquilo C_{1-4})-, $-(CH_2)_4CH$(alquilo C_{1-4})-, $-(CH_2)_2CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_2CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_4CH$(alquilo C_{1-4})CH_2-, $-(CH_2)_4CH$(alquilo C_{1-4})$(CH_2)_2-$, $-(CH_2)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH_2)_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=C$(alquilo C_{1-4})$-(CH_2)_2-$, $-CH_2-CH=CH-CH_2CH$(alquilo C_{1-4})-, $-CH_2-CH=CH-CH$(alquilo C_{1-4})CH_2-, $-CH_2-CH=CH-CH_2C(halo)_2-$, $-CH_2-CH=CH-CH2CH(CF_3)-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)-$, $-CH_2-CH=CH-CH(OH)CH_2-$, $-(CH_2)_3CH(halo)-$, $-(CH_2)_3C(halo)_2-$, $-(CH_2)_4C(halo)_2-$, $-(CH_2)_4CH(CH_2OH)-$, $-(CH_2)_3CH$(alcoxi C_{1-4})-, $-(CH_2)_4CH(CH_2$(alcoxi C_{1-4})$)-$, $-(CH_2)_4CH(CO_2H)-$, $-(CH_2)_4CH(CH_2CO_2H)-$, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4})$)-$, $-(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4})$)-$, $-(CH_2)_4CH(CO_2CH_2CF_3)-$,

-$(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))-, -$(CH_2)_5CH(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4C$(alquilo C_{1-4})$(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4C(CF_3)(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CONH_2)$-, -$(CH_2)_4CH(CONH$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CON$(alquilo $C_{1-4})_2$)-, -$(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)$-, -$(CH_2)_4CH(CONH$(alcoxi C_{1-4}))-, -$(CH_2)_4CH(CONH(OBn))$-, -$(CH_2)_4CH((CH_2)_3Ph)$-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo $C_{1-4})_2$)-, -$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-, -$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-, -$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO$(alquilo C_{1-4}))CH_2-, -$(CH_2)_3C(O)CH_2$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-, -$(CH_2)_2N$(alquilo C_{1-4})CH_2-, -$(CH_2)_2N$(alquilo C_{1-4})$(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-, -$CH_2CONH(CH_2)_3$-, -$CH_2CONH(CH_2)_4$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_2$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_3$-, -$(CH_2)_4CH$(tiazol-4-il)-, -$(CH_2)_4CH$(4-alquilo C_{1-4}-tiazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-imidazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-3-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-5-il)-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-4-halo-pirazol-3-il)-,





Y se selecciona independientemente del grupo constituido por: CH_2, CO, O, NH, N(alquilo C_{1-4}), N(CO_2(alquilo C_{1-4})), -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -CONH-, -NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -OCONH-, -NHCONH- y -SO_2NH-;

alternativamente, L-Y es -$(CH_2)_4$-CH=N-;

L_1 se selecciona independientemente del grupo constituido por: un enlace y -CH=CH-;

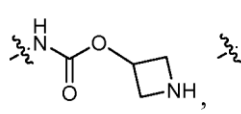
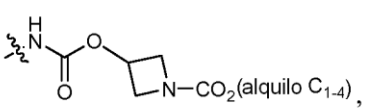
R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, alquilo C_{1-4}, OH, alcoxi C_{1-4}, CO(alquilo C_{1-4}), CN, CH_2F, CHF_2, CF_3, $OCHF_2$, NH_2, N(alquilo $C_{1-4})_2$, $-CH_2NH_2$ y -C(=NH)NH_2 en la fórmula (IIIa);

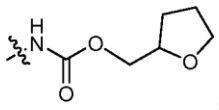
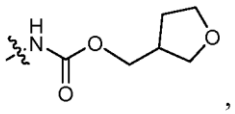
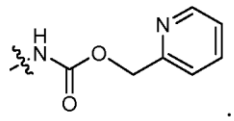
R^{1b} se selecciona independientemente del grupo constituido por: H y halógeno en la fórmula (IIIa);

R^2 es independientemente un heteroarilo de 5 miembros seleccionado de entre: triazolilo y tetrazolilo en la fórmula (IIIa);

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6}; y

R^6 se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, CO_2(alquilo C_{1-4}), -$NHCO_2$(alquilo C_{1-4}), -$NHCO_2(CH_2)_2OH$, $NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -$NHCO_2CH_2CO_2H$, $NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}) -$NHCO_2(CH_2)_2N$(alquilo C_{1-4})$_2$, -$NHCOCF_3$,

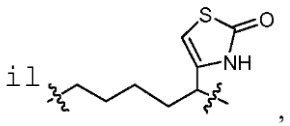




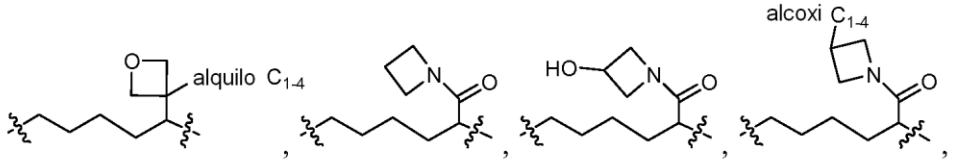
12. Compuesto de conformidad con la reivindicación 11, caracterizado porque:

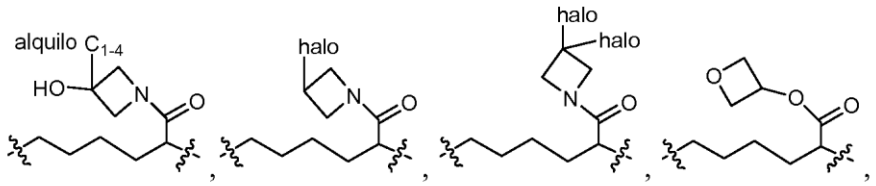
L se selecciona independientemente del grupo constituido por: -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$(CH_2)_3$CH(alquilo C_{1-4})-, -$(CH_2)_4$CH(alquilo C_{1-4})-, -$(CH_2)_2$CH(alquilo C_{1-4})CH_2-, -$(CH_2)_3$CH(alquilo C_{1-4})CH_2-, -

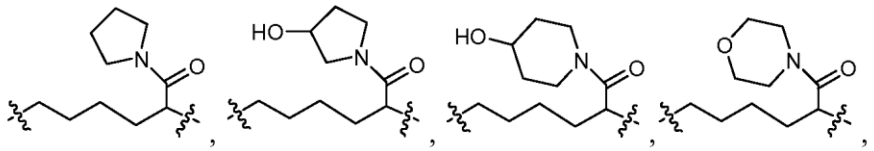
$(CH_2)_2CH$(alquilo C_{1-4})$(CH_2)_2$-, -$(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2$-, -$(CH_2)_4CH$(alquilo C_{1-4})CH_2-, -$(CH_2)_4CH$(alquilo C_{1-4})$(CH_2)_2$-, -$(CH_2)_2$-CH=CH-, -CH_2-CH=CH-CH_2-, -CH_2-CH=CH-$(CH_2)_2$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=C(alquilo C_{1-4})-$(CH_2)_2$-, -CH_2-CH=CH-CH_2CH(alquilo C_{1-4})-, -CH_2-CH=CH-CH(alquilo C_{1-4})CH_2-, -CH_2-CH=CH-$CH_2CH(halo)_2$-, -CH_2-CH=CH-$CH_2CH(CF_3)$-, -CH_2-CH=CH-$(CH_2)_2CH(CF_3)$-, -CH_2-CH=CH-CH(OH)CH_2-, -$(CH_2)_3CH$(halo)-, -$(CH_2)_3C(halo)_2$-, -$(CH_2)_4C(halo)_2$-, -$(CH_2)_4CH(CH_2OH)$-, -$(CH_2)_4CH(CH_2$(alcoxi C_{1-4}))-, -$(CH_2)_3CH$(alcoxi C_{1-4})-, -$(CH_2)_4CH$(alcoxi C_{1-4})-, -$(CH_2)_4CH(CO_2H)$-, -$(CH_2)_4CH(CH_2CO_2H)$-, -$(CH_2)_4CH(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CO_2CH_2CF_3)$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))-, -$(CH_2)_5CH(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4C$(alquilo C_{1-4})$(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4C(CF_3)(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4CH(CONH_2)$-, -$(CH_2)_4CH$(CONH(alquilo C_{1-4}))-, -$(CH_2)_4CH$(CON(alquilo $C_{1-4})_2$)-, -$(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)$-, -$(CH_2)_4CH$(CONH(alcoxi C_{1-4}))-, -$(CH_2)_4CH$(CONH(OBn))-, -$(CH_2)_4CH$(CON(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))-, -$(CH_2)_4CH$(CON(alquilo C_{1-4})$(CH_2)_2N$(alquilo $C_{1-4})_2$)-, -$(CH_2)_4CH(CH(halo)_2)$-, -$(CH_2)_4CH(CF_3)$-, -$(CH_2)_5CH(CF_3)$-, -$(CH_2)_3C(halo)_2CH_2$-, -$CH_2CH(OH)(CH_2)_2$-, -$(CH_2)_2CH(OH)CH_2$-, -$(CH_2)_3CH(OH)CH_2$-, -$CH_2CH(OH)CH(OH)CH_2$-, -$(CH_2)_3CH(OCO$(alquilo C_{1-4}))CH_2-, -$(CH_2)_3C(O)CH_2$-, -$CH_2O(CH_2)_3$-, -$CH_2O(CH_2)_4$-, -$CH_2NH(CH_2)_2$-, -$CH_2NH(CH_2)_3$-, -$CH_2NH(CH_2)_4$-, -$(CH_2)_2N$(alquilo C_{1-4})CH_2-, -$(CH_2)_2N$(alquilo C_{1-4})$(CH_2)_2$-, -$CH_2CONH(CH_2)_2$-, -$CH_2CONH(CH_2)_3$-,

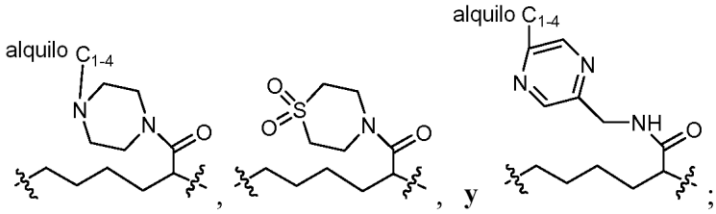
-$CH_2CONH(CH_2)_4$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_2$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_3$-, -$(CH_2)_4CH$(tiazol-4-il)-, -$(CH_2)_4CH$(4-alquilo C_{1-4}-tiazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-imidazol-2-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-3-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-5-il)-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-4-halo-pirazol-3-











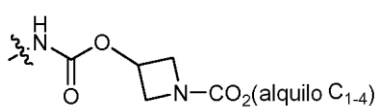
y

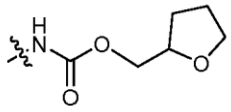
Y se selecciona independientemente del grupo constituido por: CH2, O, NH, -CONH-, NHCO-, -$CONHCH_2$-, -CON(alquilo C_{1-4})CH_2-, -N(alquilo C_{1-4})CH_2-, -N(CO_2(alquilo C_{1-4}))CH_2-, -N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -OCONH-, -NHCONH- y -

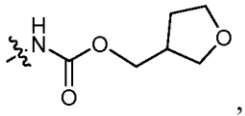
SO_2NH-;

alternativamente, L-Y es -(CH_2)4-CH=N-; y

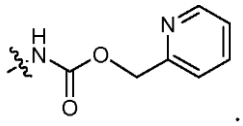
R^{6a} se selecciona independiente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, -$NHCO_2$(alquilo C_{1-4}), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -$NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), -$NHCO_2CH_2CO_2H$,



,


,


,



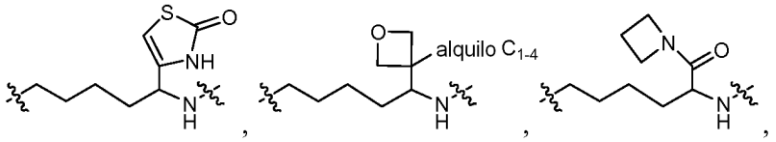
.

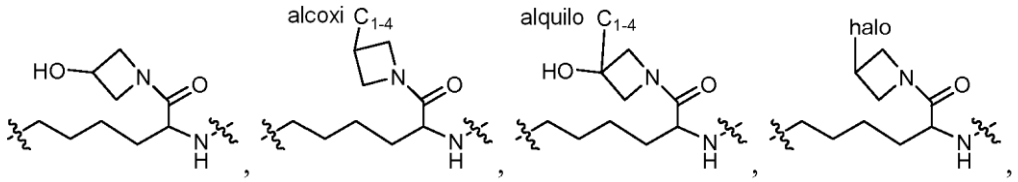
13. Compuesto de conformidad con la reivindicación 11, caracterizado porque tiene la Fórmula (III), en donde:

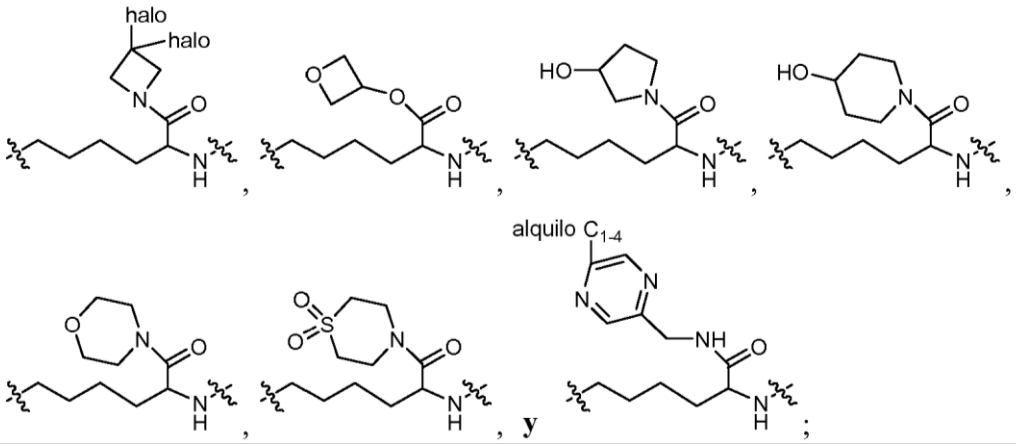
L-Y se selecciona independientemente del grupo constituido por: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2$(alquilo C_{1-4}))CH_2-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONH$(alquilo C_{1-4}))CH_2-, -$(CH_2)_4CH(CON$(alquilo $C_{1-4})_2)CH_2$-, -$(CH_2)_4CF_2CO$-, -CH_2-CH=CH-$(CH_2)_3$-, -CH_2-CH=CH-$(CH_2)_4$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_3$-, -CH_2CON(alquilo C_{1-4})$(CH_2)_4$-, -$(CH_2)_4N$(alquilo C_{1-4})CH_2-, -$(CH_2)_4N(CO_2$(alquilo C_{1-4}))CH_2-, -$(CH_2)_4N(CH_2CO_2$(alquilo C_{1-4}))CH_2-, -$(CH_2)_5O$-, -$(CH_2)_6O$-, -$(CH_2)_3CH$(alquilo C_{1-4})$(CH_2)_2O$-, -$(CH_2)_4CH$(alquilo C_{1-4})CH_2O-, -$CH_2CONH(CH_2)_2O$-, -$CH_2NH(CH_2)_4O$-, -CH_2-CH=CH-$(CH_2)_2O$-, -CH_2-CH=CH-$(CH_2)_3O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_3CH$(alquilo C_{1-4})CH_2NH-, -$(CH_2)_4CH$(alquilo C_{1-4})NH-, -$(CH_2)_4CH$(alquilo

C_{1-4})CH_2NH-, -$(CH_2)_4CH(CH_2OH)NH$-, -$(CH_2)_4CH(CH_2$(alcoxi C_{1-4}))NH-, -$(CH_2)_4CH(CO_2H)NH$-, -$(CH_2)_4CH((CH_2)_3Ph)NH$-, -$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4}))NH-, -$(CH_2)_4CH(CO_2$(alquilo C_{1-4}))NH-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))NH-, -$(CH_2)_5CH(CO_2$(alquilo C_{1-4}))NH-, -$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH$(alquilo C_{1-4}))NH-, -$(CH_2)_4CH(CON$(alquilo $C_{1-4})_2)NH$-, -$(CH_2)_4C$(alquilo C_{1-4})$(CO_2$(alquilo C_{1-4}))NH-, -$(CH_2)_4C(CF_3)(CO_2$(alquilo C_{1-4}))NH-, -$(CH_2)_3CH$(alquilo C_{1-4})$CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH$(alcoxi C_{1-4}))NH-, -$(CH_2)_4CH(CONH(OBn))NH$-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$ (alquilo C_{1-4}))NH-, -$(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo $C_{1-4})_2)NH$-, -CH_2-CH=CH-$(CH_2)_2NH$-, -CH_2-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-, -$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_5CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-, -CH_2-CH=CH-$CH_2CH(CF_3)NH$-, -CH_2-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-, -$CH_2NHCOCF_2CH_2NH$-, -$CH_2CONH(CH_2)_4NH$-, -$(CH_2)_4CH$(CO-pirrolidin-1-il)NH-, -$(CH_2)_4CH$(tiazol-4-il)NH-, -$(CH_2)_4CH$(4-alquilo C_{1-4}-tiazol-2-il)NH-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-imidazol-2-il)NH-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-3-il)NH-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4CH$(1-alquilo C_{1-4}-4-halo-pirazol-3-il)NH-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_6N$(alquilo C_{1-4})-, -$(CH_2)_5N(CO_2$(alquilo C_{1-4}))-, -$(CH_2)_4CONH$-, -$(CH_2)_5CONH$-, -$(CH_2)_6CONH$-, -$(CH_2)_3CH$(alquilo C_{1-4})$CONH$-, -$(CH_2)_4CH$(alquilo

C_{1-4})CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH_2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-CH=CH-CH_2CH(alquilo C_{1-4})CONH-, -CH_2-CH=CH-CH(alquilo C_{1-4})CH_2CONH-, -CH_2-CH=C(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH_2CONH-, -$(CH_2)_3$CH(alcoxi C_{1-4})CONH-, -$(CH_2)_3$CH(OCO(alquilo C_{1-4}))CH_2CONH-, -$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-, -$CH_2NH(CH_2)_2$CONH-, -$CH_2NH(CH_2)_3$CONH-, -$(CH_2)_2$N(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$N(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-, -$(CH_2)_3$OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2OCONH-, -CH_2-CH=CH-CH_2NHCONH-, -$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,



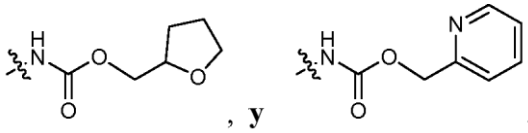




R^{1b} se selecciona independientemente del grupo constituido por: H y halógeno;

R^{3} se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y cicloalquilo C_{3-6};

R^{6} se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, -$NHCO_2$(alquilo C_{1-4}), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}),

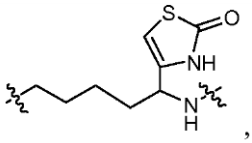


14. Compuesto de conformidad con la reivindicación 11, caracterizado porque tiene la Fórmula (III), en donde:

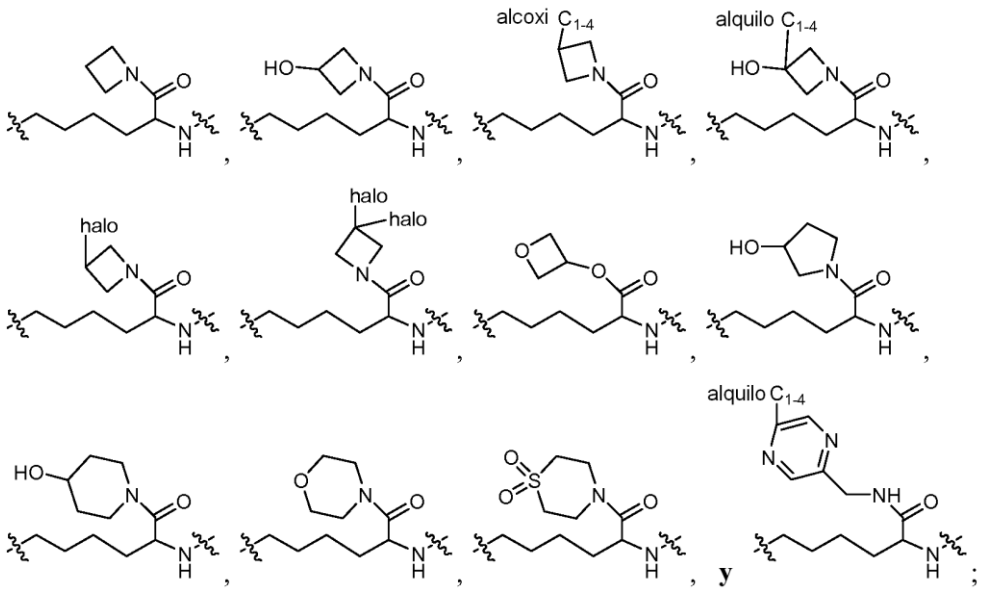
L-Y se selecciona independientemente del grupo constituido por: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2$(alquilo C_{1-4}))CH_2-, -$(CH_2)_4CH(CONH_2)CH_2$-, -

$(CH_2)_4CH(CONH(alquilo\ C_{1-4}))CH_2-$, $-(CH_2)_4CH(CON(alquilo\ C_{1-4})_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_3-$, $-CH_2-CH=CH-(CH_2)_4-$, $-CH_2CON(alquilo\ C_{1-4})(CH_2)_3-$, $-(CH_2)_5O-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(alquilo\ C_{1-4})(CH_2)_2O-$, $-(CH_2)_4CH(alquilo\ C_{1-4})CH_2O-$, $-CH_2NH(CH_2)_4O-$, $-CH_2-CH=CH-(CH_2)_3O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_3CH(alquilo\ C_{1-4})CH_2NH-$, $-(CH_2)_4CH(alquilo\ C_{1-4})NH-$, $-(CH_2)_4CH(alquilo\ C_{1-4})CH_2NH-$, $-(CH_2)_4CH(CH_2OH)NH-$, $-(CH_2)_4CH(CH_2(alcoxi\ C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2H)NH-$, $-(CH_2)_4CH(CH_2CO_2(alquilo\ C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2(alquilo\ C_{1-4}))NH-$, $-(CH_2)_4CH(CO_2CH_2CF_3)NH-$, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2(alquilo\ C_{1-4}))NH-$, $-(CH_2)_5CH(CO_2(alquilo\ C_{1-4}))NH-$, $-(CH_2)_4CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(alquilo\ C_{1-4}))NH-$, $-(CH_2)_4CH(CON(alquilo\ C_{1-4})_2)NH-$, $-(CH_2)_4C(alquilo\ C_{1-4})(CO_2(alquilo\ C_{1-4}))NH-$, $-(CH_2)_4C(CF_3)(CO_2(alquilo\ C_{1-4}))NH-$, $-(CH_2)_3CH(alquilo\ C_{1-4})CH(CONH_2)NH-$, $-(CH_2)_4CH(CONH(alcoxi\ C_{1-4}))NH-$, $-(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(alquilo\ C_{1-4})(CH_2)_2O(alquilo\ C_{1-4}))NH-$, $-(CH_2)_4CH(CON(alquilo\ C_{1-4})(CH_2)_2N(alquilo\ C_{1-4})_2)NH-$, $-CH_2-CH=CH-(CH_2)_2NH-$, $-CH_2-CH=CH-(CH_2)_3NH-$, $-(CH_2)_4CH(CHF_2)NH-$, $-(CH_2)_4CH(CF_3)NH-$, $-(CH_2)_5CH(CF_3)NH-$, $-(CH_2)_3CF_2CH_2NH-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH-$, $-CH_2CONH(CH_2)_2NH-$, $-CH_2CONH(CH_2)_3NH-$, $-(CH_2)_4CH(3\text{-alquilo}\ C_{1-4}\text{-oxetan-3-il})NH-$, $-(CH_2)_4CH(CO\text{-pirrolidin-1-il})NH-$, $-(CH_2)_4CH(tiazol\text{-}4\text{-}il)NH-$, $-(CH_2)_4CH(4\text{-alquilo}\ C_{1-4}\text{-tiazol-2-il})NH-$, $-(CH_2)_4CH(1\text{-alquilo}\ C_{1-4}\text{-imidazol-2-il})NH-$, $-(CH_2)4CH(1\text{-alquilo}\ C_{1-4}\ \text{-pirazol-3-il})NH-$, $-(CH_2)_4CH(1\text{-alquilo}$

C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$CH(1-alquilo C_{1-4}-4-halo-pirazol-3-il)NH-, -CH_2-CH=CH-CH_2CH(1-alquilo C_{1-4}-pirazol-5-il)NH-, -$(CH_2)_4$N(CO_2(alquilo C_{1-4}))CH_2-, -$(CH_2)_4$N(CH_2CO_2(alquilo C_{1-4}))CH_2-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-, -$(CH_2)_6$CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_4$CH(alquilo C_{1-4})CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$CH(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-CH=CH-CH_2CH(alquilo C_{1-4})CONH-, -CH_2-CH=CH-CH(alquilo C_{1-4})CH_2CONH-, -CH_2-CH=C(alquilo C_{1-4})-$(CH_2)_2$CONH-, -$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH_2CONH-, -$(CH_2)_3$CH(alcoxi C_{1-4})CONH-, -$(CH_2)_3$CH(OCO(alquilo C_{1-4}))CH_2CONH-, -$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-, -$CH_2NH(CH_2)_2$CONH-, -$CH_2NH(CH_2)_3$CONH-, -$(CH_2)_2$N(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$N(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-, -CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-, -$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-,

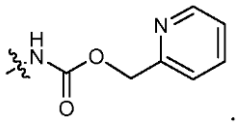
-$(CH_2)_4$-CH=N-, 

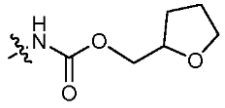
,



R^{1b} se selecciona independientemente del grupo constituido por: H y halógeno;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y ciclopropilo; y

R^6 se selecciona independientemente del grupo constituido por: halógeno, NH_2, CO_2H, $CONH_2$, $-NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2OH$, $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), $-NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), y  .

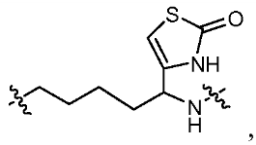
y 

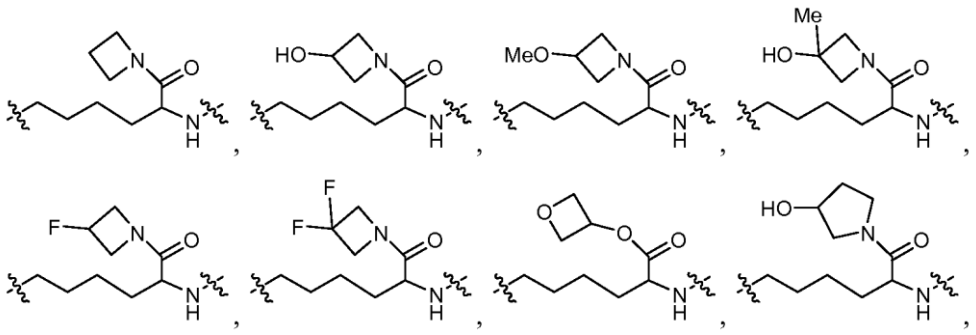
15. Compuesto de conformidad con la reivindicación 11, caracterizado porque tiene la Fórmula (III), en donde:

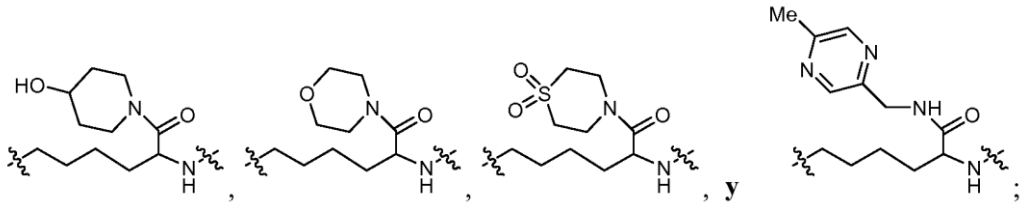
L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, -

$(CH_2)_4CH(CO_2Me)CH_2$-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONHMe)CH_2$-, -$(CH_2)_4CH(CON(Me)_2)CH_2$-, -$CH_2$-CH=CH-$(CH_2)_3$-, -$CH_2$-CH=CH-$(CH_2)_4$-, -$CH_2CON(CH_3)(CH_2)_3$-, -$(CH_2)_4N(CO_2Me)CH_2$-, -$(CH_2)_4N(CH_2CO_2Et)CH_2$-, -$(CH_2)_5O$-, -$(CH_2)_6O$-, -$(CH_2)_3CH(Me)(CH_2)_2O$-, -$(CH_2)_4CH(Me)CH_2O$-, -$CH_2NH(CH_2)_4O$-, -$CH_2$-CH=CH-$(CH_2)_3O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_3CH(Me)CH_2NH$-, -$(CH_2)_4CH(Me)NH$-, -$(CH_2)_4CH(Me)CH_2NH$-, -$(CH_2)_4CH(CH_2OH)NH$-, -$(CH_2)_4CH(CH_2OMe)NH$-, -$(CH_2)_4CH(CO_2H)NH$-, -$(CH_2)_4CH(CO_2Me)NH$-, -$(CH_2)_4CH(CO_2Et)NH$-, -$CH_2CONH(CH_2)_4NH$-, -$(CH_2)_4CH(CO_2(i\text{-}Pr))NH$-, -$(CH_2)_4CH(CO_2(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH$-, -$(CH_2)_5CH(CO_2Me)NH$-, -$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2Me)NH$-, -$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(Me))NH$-, -$(CH_2)_4CH(CONH(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CON(Me)_2)NH$-, -$(CH_2)_4CH(CONH(OMe))NH$-, -$(CH_2)_4CH(CONH(OBn))NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH$-, -$(CH_2)_4C(Me)(CO_2Me)NH$-, -$(CH_2)_4C(CF_3)(CO_2Me)NH$-, -$(CH_2)_3CH(Me)CH(CONH_2)NH$-, -$(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH$-, -CH2-CH=CH-$(CH_2)_2NH$-, -$CH_2$-CH=CH-$(CH_2)_3NH$-, -$(CH_2)_4CH(CHF_2)NH$-, -$(CH_2)_4CH(CF_3)NH$-, -$(CH_2)_5CH(CF_3)NH$-, -$(CH_2)_3CF_2CH_2NH$-, -$CH_2$-CH=CH-$(CH_2)_2CH(CF_3)NH$-, -$CH_2CONH(CH_2)_2NH$-, -$CH_2CONH(CH_2)_3NH$-, -$(CH_2)_4CH$(3-Me-oxetan-3-il)NH-, -$(CH_2)_4CH$(CO-pirrolidin-1-il)NH-, -$(CH_2)_4CH$(tiazol-4-il)NH-, -$(CH_2)_4CH$(4-Me-tiazol-2-il)NH-, -$(CH_2)_4CH$(1-Me-imidazol-2-il)NH-, -$(CH_2)_4CH$(1-Me-pirazol-3-il)NH-, -$(CH_2)_4CH$(1-(n-Pr)-pirazol-3-il)NH-, -$(CH_2)_4CH$(1-Me-pirazol-5-il)NH-, -$(CH_2)_4CH$(1,3-di-Me-pirazol-

5-il)NH-, -$(CH_2)_4$CH(1-Me-4-Cl-pirazol-3-il)NH-, -CH_2-CH=CH-CH_2CH(1-Me-pirazol-5-il)NH-, -$(CH_2)_4$CONH-, -$(CH_2)_5$CONH-, -$(CH_2)_6$CONH-, -$(CH_2)_3$CH(Me)CONH-, -$(CH_2)_4$CH(Me)CONH-, -$(CH_2)_2$CH(Me)CH_2CONH-, -$(CH_2)_3$CH(Me)CH_2CONH-, -$(CH_2)_2$CH(Me)$(CH_2)_2$CONH-, -$(CH_2)_2$-CH=CH-CONH-, -CH2-CH=CH-CH_2CONH-, -CH_2-CH=CH-$(CH_2)_2$CONH-, -CH_2-CH=CH-$(CH_2)_3$CONH-, -CH_2-CH=CH-CH_2CH(Me)CONH-, -CH_2-CH=CHCH(Me)CH_2CONH-, -CH_2-CH=CHCH(Et)CH_2CONH-, -CH_2-CH=C(Me)-$(CH_2)_2$CONH-, -$(CH_2)_3$CH(Et)CONH-, -$(CH_2)_3$CH(i-Pr)CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OMe)CONH-, -$(CH_2)_3$CH(OCOMe)CH_2CONH-, -$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-, -CH_2NH$(CH_2)_2$CONH-, -CH_2NH$(CH_2)_3$CONH-, -$(CH_2)_2$N(Me)CH_2CONH-, -$(CH_2)_2$N(Me)$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-, -CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-, -$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,



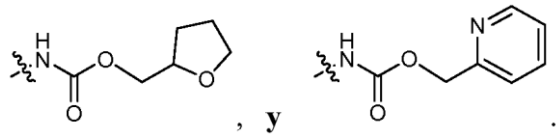




R^{1b} se selecciona independientemente del grupo constituido por: H y F;

R^3 se selecciona independientemente del grupo constituido por: H, F, Cl, Br, CH_3, CN, CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$ y ciclopropilo; y

R^6 se selecciona independiente del grupo constituido por: F, NH_2, CO_2H, $CONH_2$, $-NHCO_2Me$, $-NHCO_2(CH_2)2OH$, $-NHCO_2(CH_2)_2OMe$, $-NHCO_2(CH_2)_2OEt$, $-NHCO_2CH_2CH(Et)OMe$,

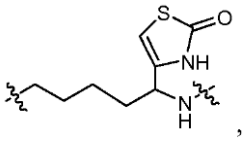


16. Compuesto de conformidad con la reivindicación 11, caracterizado porque tiene la Fórmula (III), en donde:

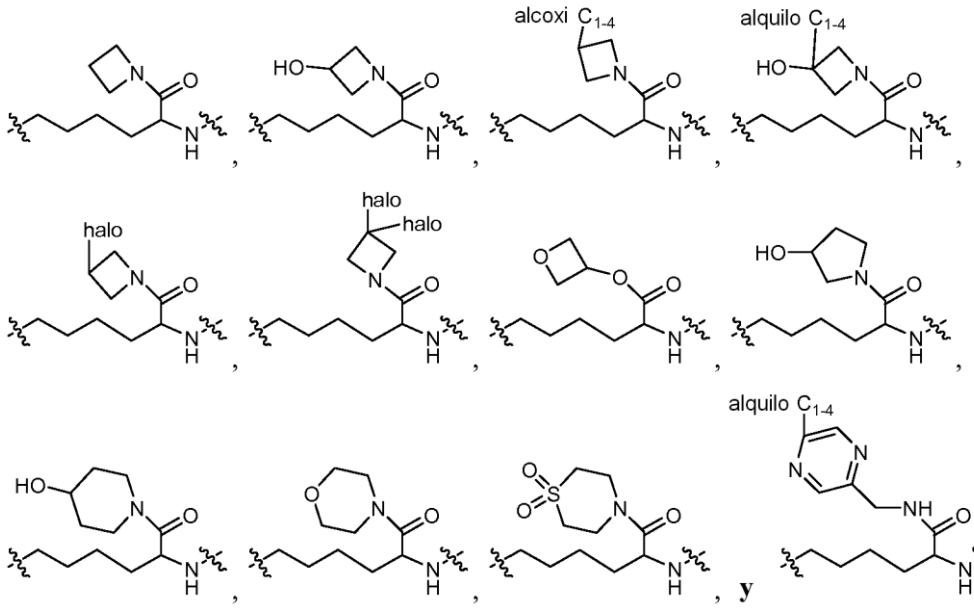
L-Y se selecciona independientemente del grupo constituido por: $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_4CH(CO_2H)CH_2-$, $-(CH_2)_4CH(CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4CH(CONH_2)CH_2-$, $-(CH_2)_4CH(CONH(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_4CH(CON(\text{alquilo } C_{1-4})_2)CH_2-$, $-CH_2-CH=CH-(CH_2)_4-$, $-(CH_2)_4N(CO_2(\text{alquilo } C_{1-4}))CH_2-$, $-(CH_2)_6O-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})(CH_2)_2O-$, $-CH_2NH(CH_2)_4O-$, $-(CH_2)_5NH-$, $-(CH_2)_6NH-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})NH-$, $-(CH_2)_3CH(\text{alquilo } C_{1-4})CH_2NH-$, $-(CH_2)_4CH(\text{alquilo } C_{1-4})CH_2NH-$, -

$(CH_2)_4CH(CH_2OH)NH$-, $-(CH_2)_4CH(CH_2$(alcoxi C_{1-4}))NH-, $-(CH_2)_4CH(CO_2H)NH$-, $-(CH_2)_4CH(CH_2CO_2H)NH$-, $-(CH_2)_4CH(CH_2CO_2$(alquilo C_{1-4}))NH-, $-(CH_2)_4CH(CO_2$(alquilo C_{1-4}))NH-, $-(CH_2)_4CH(CO_2CH_2CF_3)NH$-, $-(CH_2)_4CH(CO_2(CH_2)_2SO_2$(alquilo C_{1-4}))NH-, $-(CH_2)_5CH(CO_2$(alquilo C_{1-4}))NH-, $-(CH_2)_4CH(CONH_2)NH$-, $-(CH_2)_4CH(CONH$(alquilo C_{1-4}))NH-, $-(CH_2)_4CH(CON$(alquilo $C_{1-4})_2$)NH-, $-(CH_2)_4CH(CONH$(alcoxi C_{1-4}))NH-, $-(CH_2)_4CH(CONH(OBn))NH$-, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2O$(alquilo C_{1-4}))NH-, $-(CH_2)_4CH(CON$(alquilo C_{1-4})$(CH_2)_2N$(alquilo $C_{1-4})_2$)NH-, $-CH_2-CH=CH-(CH_2)_2NH$-, $-CH_2-CH=CH-(CH_2)_3NH$-, $-(CH_2)_4CH(CHF_2)NH$-, $-(CH_2)_4CH(CF_3)NH$-, $-(CH_2)_3CF_2CH_2NH$-, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH$-, $-(CH_2)_4CH(3$-alquilo C_{1-4}-oxetan-3-il)NH-, $-(CH_2)_4CH(CO$-pirrolidin-1-il)NH-, $-(CH_2)_4CH(tiazol-4-il)NH$-, $-(CH_2)_4CH(4$-alquilo C_{1-4}-tiazol-2-il)NH-, $-(CH_2)_4CH(1$-alquilo C_{1-4}-imidazol-2-il)NH-, $-(CH_2)_4CH(1$-alquilo C_{1-4}-pirazol-3-il)NH-, $-(CH_2)_4CH(1$-alquilo C_{1-4}-pirazol-5-il)NH-, $-(CH_2)_4CH(1$-alquilo C_{1-4}-3-alquilo C_{1-4}-pirazol-5-il)NH-, $-(CH_2)_4CH(1$-alquilo C_{1-4}-4-halo-pirazol-3-il)NH-, $-(CH_2)_4CONH$-, $-(CH_2)_5CONH$-, $-(CH_2)_6CONH$-, $-(CH_2)_3CH$(alquilo C_{1-4})CONH-, $-(CH_2)_4CH$(alquilo C_{1-4})CONH-, $-(CH_2)_2CH$(alquilo C_{1-4})CH_2CONH-, $-(CH_2)_3CH$(alquilo C_{1-4})CH_2CONH-, $-(CH_2)_2CH$(alquilo C_{1-4})$(CH_2)_2CONH$-, $-(CH_2)_2-CH=CH-CONH$-, $-CH_2-CH=CH-CH_2CONH$-, $-CH_2-CH=CH-(CH_2)_2CONH$-, $-CH_2-CH=CH-(CH_2)_3CONH$-, $-CH_2-CH=CH-CH_2CH$(alquilo C_{1-4})CONH-, $-CH_2-CH=CH-CH$(alquilo C_{1-4})CH_2CONH-, $-CH_2-CH=C$(alquilo C_{1-4})$-(CH_2)_2CONH$-,

-$(CH_2)_3$CH(alquilo C_{1-4})CONH-, -$(CH_2)_3$CHFCONH-, -$(CH_2)_3CF_2$CONH-, -$(CH_2)_4CF_2$CONH-, -CH_2-CH=CH-CH_2CF_2CONH-, -$(CH_2)_3$CH(CF_3)CONH-, -CH_2CH(OH)$(CH_2)_2$CONH-, -$(CH_2)_2$CH(OH)CH_2CONH-, -$(CH_2)_3$CH(OH)CH_2CONH-, -CH_2CH(OH)CH(OH)CH_2CONH-, -CH_2-CH=CH-CH(OH)CH2CONH-, -$(CH_2)_3$CH(alcoxi C_{1-4})CONH-, -$(CH_2)_3$CH(OCO(alquilo C_{1-4}))CH_2CONH-, -$(CH_2)_3$C(O)CH_2CONH-, -$CH_2O(CH_2)_3$CONH-, -$CH_2O(CH_2)_4$CONH-, -$CH_2NH(CH_2)_2$CONH-, -$CH_2NH(CH_2)_3$CONH-, -$(CH_2)_2$N(alquilo C_{1-4})CH_2CONH-, -$(CH_2)_2$N(alquilo C_{1-4})$(CH_2)_2$CONH-, -$(CH_2)_5$NHCO-, -CH_2-CH=CH-$(CH_2)_2$NHCO-, -CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-, -



$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,

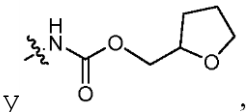
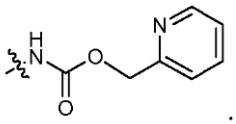


y

R^{1b} se selecciona independientemente del grupo

constituido por: H y halógeno;

R^3 se selecciona independientemente del grupo constituido por: H, halógeno, alquilo C_{1-4}, CN, CO_2(alquilo C_{1-4}), $CONH_2$, CON(alquilo C_{1-4})$_2$ y ciclopropilo;

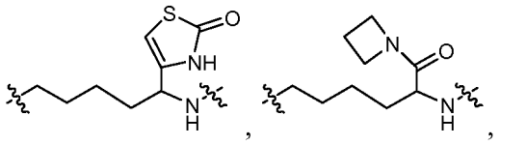
R^6 se selecciona independientemente del grupo constituido por: F, NH_2, CO_2H, -$NHCO_2$(alquilo C_{1-4}), -$NHCO_2(CH_2)_2OH$, -$NHCO_2(CH_2)_2O$(alquilo C_{1-4}), -$NHCO_2CH_2CH$(alquilo C_{1-4})O(alquilo C_{1-4}), y  , y  .

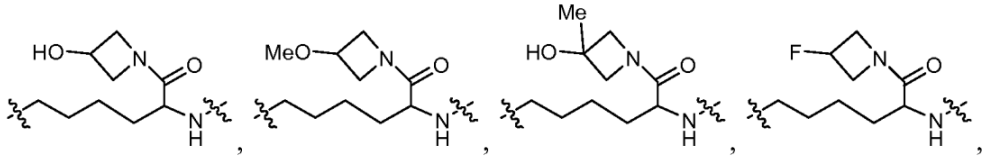
17. Compuesto de conformidad con la reivindicación 11, caracterizado porque tiene la Fórmula (III), en donde:

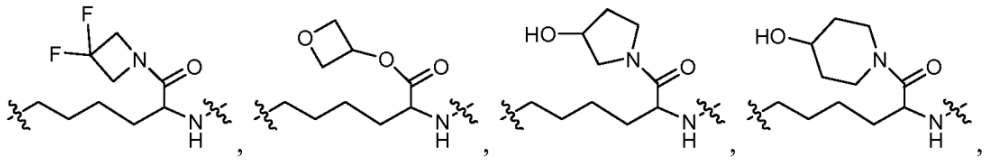
L-Y se selecciona independientemente del grupo constituido por: -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_4CH(CO_2H)CH_2$-, -$(CH_2)_4CH(CO_2Me)CH_2$-, -$(CH_2)_4CH(CONH_2)CH_2$-, -$(CH_2)_4CH(CONHMe)CH_2$-, -$(CH_2)_4CH(CON(Me)_2)CH_2$-, -$CH_2$-CH=CH-$(CH_2)_4$-, -$(CH_2)_4N(CO_2Me)CH_2$-, -$(CH_2)_6O$-, -$(CH_2)_3CH(Me)(CH_2)_2O$-, -$CH_2NH(CH_2)_4O$-, -$(CH_2)_5NH$-, -$(CH_2)_6NH$-, -$(CH_2)_4CH(Me)NH$-, -$(CH_2)_3CH(Me)CH_2NH$-, -$(CH_2)_4CH(Me)CH_2NH$-, -$(CH_2)_4CH(CH_2OH)NH$-, -$(CH_2)_4CH(CH_2OMe)NH$-, -$(CH_2)_4CH(CO_2H)NH$-, -$(CH_2)_4CH(CO_2Me)NH$-, -$(CH_2)_4CH(CO_2Et)NH$-, -$(CH_2)_4CH(CO_2(i\text{-}Pr))NH$-, -$(CH_2)_4CH(CO_2(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CO_2CH_2CF_3)NH$-, -$(CH_2)_4CH(CO_2(CH_2)_2SO_2Me)NH$-, -$(CH_2)_5CH(CO_2Me)NH$-, -$(CH_2)_4CH(CH_2CO_2H)NH$-, -$(CH_2)_4CH(CH_2CO_2Me)NH$-, -$(CH_2)_4CH(CONH_2)NH$-, -$(CH_2)_4CH(CONH(Me))NH$-, -$(CH_2)_4CH(CONH(t\text{-}Bu))NH$-, -$(CH_2)_4CH(CON(Me)_2)NH$-, -$(CH_2)_4CH(CONH(OMe))NH$-, -

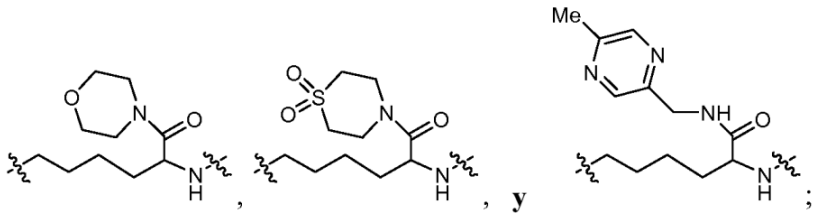
$(CH_2)_4CH(CONH(OBn))NH-$, $-(CH_2)_4CH(CON(Me)(CH_2)_2OMe)NH-$, $-(CH_2)_4CH(CON(Me)(CH_2)_2N(Me)_2)NH-$, $-CH_2-CH=CH-(CH_2)_2NH-$, $-CH_2-CH=CH-(CH_2)_3NH-$, $-(CH_2)_4CH(CHF_2)NH-$, $-(CH_2)_4CH(CF_3)NH-$, $-(CH_2)_3CF_2CH_2NH-$, $-CH_2-CH=CH-(CH_2)_2CH(CF_3)NH-$, $-(CH_2)_4CH$(3-Me-oxetan-3-il)NH-, $-(CH_2)_4CH$(CO-pirrolidin-1-il)NH-, $-(CH_2)_4CH$(tiazol-4-il)NH-, $-(CH_2)_4CH$(4-Me-tiazol-2-il)NH-, $-(CH_2)_4CH$(1-Me-imidazol-2-il)NH-, $-(CH_2)_4CH$(1-Me-pirazol-3-il)NH-, $-(CH_2)_4CH$(1-(n-Pr)-pirazol-3-il)NH-, $-(CH_2)_4CH$(1-Me-pirazol-5-il)NH-, $-(CH_2)_4CH$(1,3-di-Me-pirazol-5-il)NH-, $(CH_2)_4CH$(1-Me-4-Cl-pirazol-3-il)NH-, $-(CH2)_4N(CO_2Me)CH_2-$, $-(CH_2)_4CONH-$, $-(CH_2)_5CONH-$, $-(CH_2)_6CONH-$, $-(CH_2)_3CH(Me)CONH-$, $-(CH_2)_4CH(Me)CONH-$, $-(CH_2)_2CH(Me)CH_2CONH-$, $-(CH_2)_3CH(Me)CH_2CONH-$, $-(CH_2)_2CH(Me)(CH_2)_2CONH-$, $-(CH_2)_2-CH=CH-CONH-$, $-CH_2-CH=CH-CH_2CONH-$, $-CH_2-CH=CH-(CH_2)_2CONH-$, $-CH_2-CH=CH-(CH_2)_3CONH-$, $-CH_2-CH=CH-CH_2CH(Me)CONH-$, $-CH_2-CH=CH-CH(Me)CH_2CONH-$, $-CH_2-CH=CHCH(Et)CH_2CONH-$, $-CH_2-CH=C(Me)-(CH_2)_2CONH-$, $-(CH_2)_3CH(Me)CONH-$, $-(CH_2)_3CH(Et)CONH-$, $-(CH_2)_3CH(i-Pr)CONH-$, $-(CH_2)_3CHFCONH-$, $-(CH_2)_3CF_2CONH-$, $-(CH_2)_4CF_2CONH-$, $-CH_2-CH=CH-CH_2CF_2CONH-$, $-(CH_2)_3CH(CF_3)CONH-$, $-CH_2CH(OH)(CH_2)_2CONH-$, $-(CH_2)_2CH(OH)CH_2CONH-$, $-(CH_2)_3CH(OH)CH_2CONH-$, $-CH_2CH(OH)CH(OH)CH_2CONH-$, $-CH_2-CH=CH-CH(OH)CH_2CONH-$, $-(CH_2)_3CH(OMe)CONH-$, $-(CH_2)_3CH(OCOMe)CH_2CONH-$, $-(CH_2)_3C(O)CH_2CONH-$, $-CH_2O(CH_2)_3CONH-$, $-CH_2O(CH_2)_4CONH-$, $-CH_2NH(CH_2)_2CONH-$, $-CH_2NH(CH_2)_3CONH-$, $-(CH_2)_2N(Me)CH_2CONH-$, $-(CH_2)2N(Me)(CH_2)_2CONH-$, $-(CH_2)_5NHCO-$, $-CH_2-CH=CH-(CH_2)_2NHCO-$, -

CH_2-CH=CH-CH_2OCONH-, -$(CH_2)_4$OCONH-, -CH_2-CH=CH-CH_2NHCONH-, -$(CH_2)_4SO_2$NH-, -CH_2-CH=CH-CH_2SO_2NH-, -$(CH_2)_4$-CH=N-,

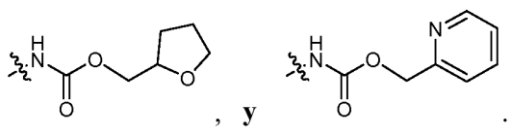








y



15 R^{1b} se selecciona independientemente del grupo constituido por: H y F;

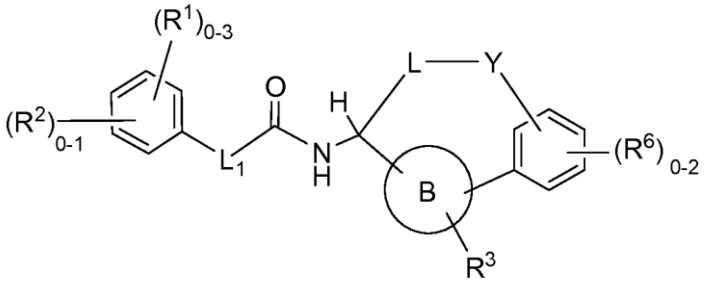
R^3 se selecciona independientemente del grupo constituido por: H, F, Cl, Br, CH_3, CN CO_2Me, CO_2Et, $CONH_2$, $CONMe_2$ y ciclopropilo;

20 R^6 se selecciona independientemente del grupo constituido por: F, NH_2, CO_2H, $NHCO_2$Me, -$NHCO_2(CH_2)_2$OH, -$NHCO_2(CH_2)_2$OMe, -$NHCO_2(CH_2)_2$OEt, $NHCO_2CH_2$CH(Et)OMe y

y

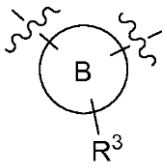
25

18. Un compuesto de conformidad con cualquiera de las reivindicaciones 1-7, caracterizado porque tiene la Fórmula (IV):

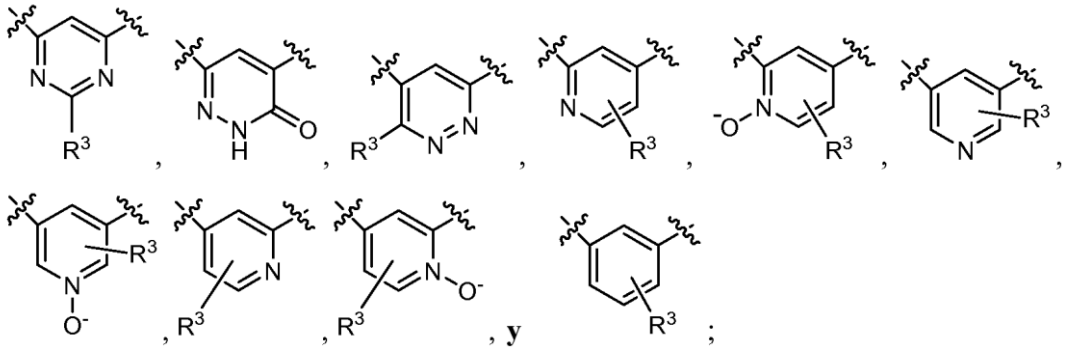


(IV)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, o un solvato del mismo, en donde:



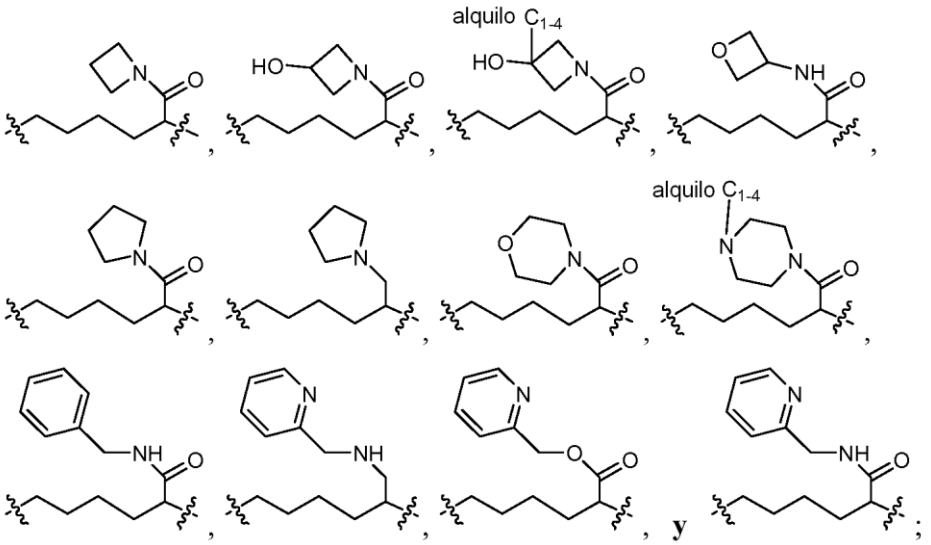
se selecciona independientemente del grupo constituido por:



L_1 se selecciona independientemente del grupo constituido por: un enlace, $-CH_2CH_2-$ y $-CH=CH-$;

L se selecciona independientemente del grupo constituido por: $-CH_2-CH=CH-CH_2-$, $-CH_2-CH=CH-(CH2)_2-$, $-(CH_2)_4-$,

-$(CH_2)_5$-, -$(CH_2)_3$CH(alquilo C_{1-4})-, -CH_2-CH=CH-CH_2CH(CF_3)-, -$(CH_2)_4$CH(CF_3)-, -$(CH_2)_4$CH(CH_2OH)-, -$(CH_2)_4$CH(CO_2H)-, -$(CH_2)_4$CH(CO_2(alquilo C_{1-4}))-, -CH_2CONH$(CH_2)_2$-, -$(CH_2)_4$CH($CO_2(CH_2)_2$O(alquilo C_{1-4}))-, -$(CH_2)_4$CH(CH_2NH$(CH_2)_2$O(alquilo C_{1-4}))-, -$(CH_2)_4$CH($CO_2(CH_2)_2$N(alquilo $C_{1-4})_2$)-, -$(CH_2)_4$CH(CON(alquilo C_{1-4})$(CH_2)_2$O(alquilo C_{1-4}))-, -$(CH_2)_4$CH(CON(alquilo C_{1-4})$(CH_2)_2$N(alquilo $C_{1-4})_2$)-,



Y es independientemente -CONH-, O o NH;

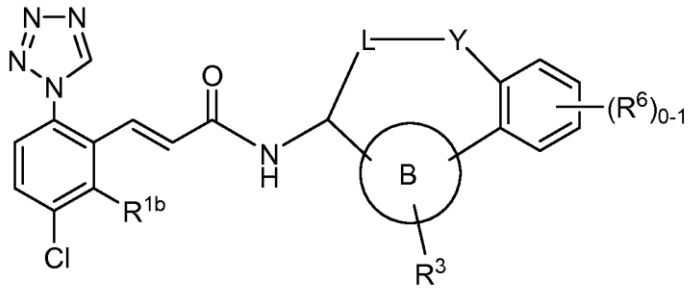
R^1, en cada aparición, se selecciona independientemente del grupo constituido por: halógeno, CN, OCF_3, CHF_2, CF_3, alquilo C_{1-4}, alcoxi C_{1-4}, CO(alquilo C_{1-4}), NH_2, -C(=NH)NH_2, -C(O)NH_2 y -CH_2NH_2;

R^2 es independientemente un heterociclo de 5 miembros seleccionado de entre: pirazolilo, imidazolilo, triazolilo y tetrazolilo;

R^3 se selecciona independientemente del grupo constituido por: H y halógeno y alquilo C_{1-4}; y

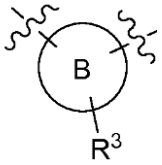
R_6 se selecciona independientemente del grupo constituido por: H, halógeno, CN, $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}), CO_2H y $CONH_2$.

19. Compuesto de conformidad con la reivindicación 18, caracterizado porque tiene la fórmula (IVa):

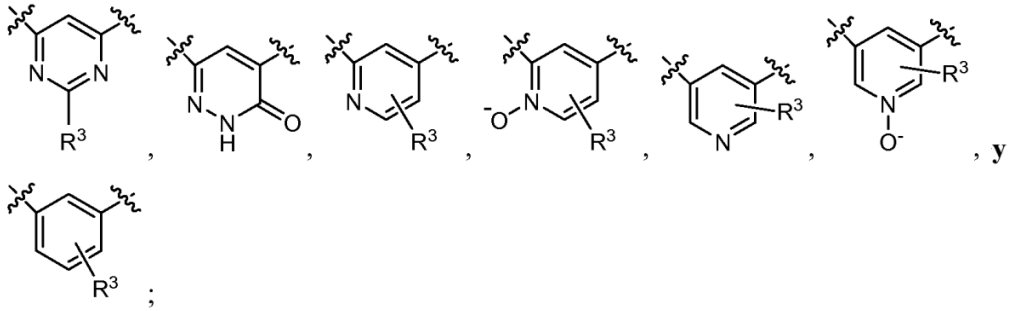


(IVa)

o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable, o un solvato del mismo, en donde:



se selecciona independientemente del grupo constituido por:



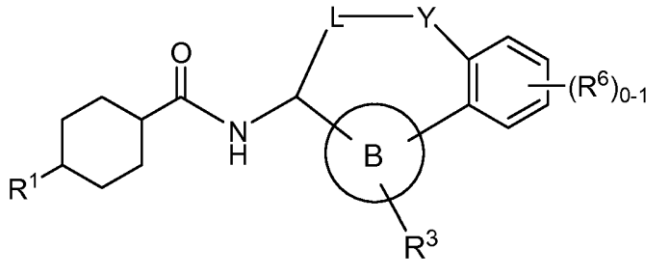
;

Y es independientemente -CONH- o NH;

R^3 se selecciona independientemente del grupo constituido por: H, F, Cl y alquilo C_{1-4}; y

R^6 se selecciona independientemente del grupo constituido por: F, $-NHCO_2$(alquilo C_{1-4}), $-CH_2NHCO_2$(alquilo C_{1-4}), CO_2H, $CONH_2$ y $-NHCO_2(CH_2)_2O$(alquilo C_{1-4}).

20. Compuesto de conformidad con cualquiera de las reivindicaciones 1-3, caracterizado porque tiene la Fórmula (V):



(V)

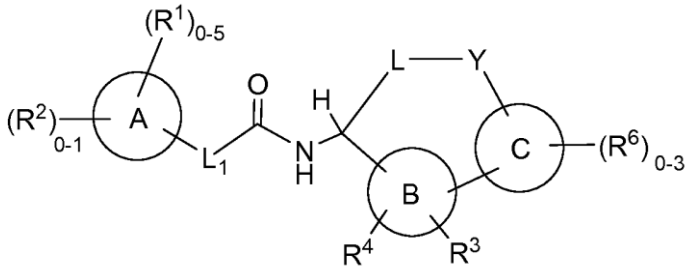
o un estereoisómero, un tautómero, una sal farmacéuticamente aceptable o un solvato del mismo, en donde:

el anillo B se selecciona independientemente del grupo constituido por: imidazol y piridina; y

R^1 se selecciona independientemente del grupo constituido por: alquilo C_{1-4} y CH_2NH_2.

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos de fórmula (I):



(I)

o un estereoisómero o un tautómero o una sal farmacéuticamente aceptable del mismo, en donde todas las variables son como se han definido en el presente documento. Estos compuestos son inhibidores selectivos del Factor XIa o inhibidores duales de fXIa y calicreína de plasma. La presente invención también se refiere a composiciones farmacéuticas que comprenden estos compuestos y métodos para tratar trastornos tromboembólicos y/o inflamatorios usando las mismas.

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

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***No.*** 32) ***Fecha*** (33) ***País***
61/303,423 11-02-2010 *US*
61/405,338 21-10-2010 US

(51) Int Cl: C07D 487/08*;* C07D 498/08

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

(72) Inventor(es) CORTE, James, R.; FANG, Tianan; DECICCO, Carl, P.; PINTO, Donald, J., P.; ROSSI, Karen, A.; HU, Zilun; JEON, Yoon; QUAN, Mimi, L.; SMALLHEER, Joanne, M.; WANG, Yufeng; YANG, Wu

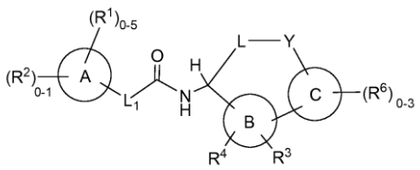
(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(85) Fecha limite inicio fase nacional: 11-09-2012
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 10-02-2011
No. de solicitud PCT/US2011/024305

(87) Publicación internacional
Fecha: 18-08-2011
N° publicación: WO 2011/100401

(54) Titulo: **MACROCICLOS COMO INHIBIDORES DEL FACTOR DE COAGULACION (FXIA)**

Resumen: La presente invención se refiere a compuestos de fórmula (I):



(I)

o un estereoisómero o un tautómero o una sal farmacéuticamente aceptable del mismo, en donde todas las variables son como se han definido en el presente documento. Estos compuestos son inhibidores selectivos del Factor XIa o inhibidores duales de fXIa y calicreína de plasma. La presente invención también se refiere a composiciones farmacéuticas que comprenden estos compuestos y métodos para tratar trastornos tromboembólicos y/o inflamatorios usando las mismas.

Industria y Comercio
SUPERINTENDENCIA

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

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

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

(51) Clasificación Internacional: C07D 487/08; C07D 498/08

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

(72) Inventor(es): CORTE, James, R.; FANG, Tianan; DECICCO, Carl, P.; PINTO, Donald, J., P.; ROSSI, Karen, A.; HU, Zilun; JEON, Yoon; QUAN, Mimi, L.; SMALLHEER, Joanne, M.; WANG, Yufeng; YANG, Wu

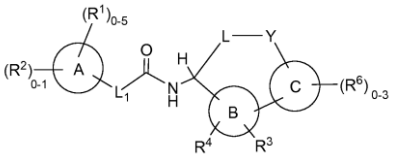
(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/303,423	11-02-2010	*US*
	61/405,338	21-10-2010	US

(85) Fecha límite inicio fase nacional: 11-09-2012

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 10-02-2011
No. de solicitud: PCT/US2011/024305

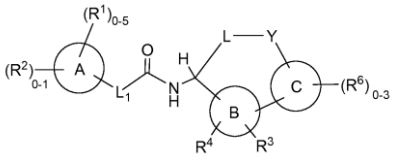
(87) Publicación internacional:
Fecha: 18-08-2011
No. Publicación: WO 2011/100401



(I)

(54)Titulo: **MACROCICLOS COMO INHIBIDORES DEL FACTOR DE COAGULACION (FXIA)**

(57) Resumen: La presente invención se refiere a compuestos de fórmula (I):



(I)

CONTINUA AL RESPALDO ...

o un estereoisómero o un tautómero o una sal farmacéuticamente aceptable del mismo, en donde todas las variables son como se han definido en el presente documento. Estos compuestos son inhibidores selectivos del Factor XIa o inhibidores duales de fXIa y calicreína de plasma. La presente invención también se refiere a composiciones farmacéuticas que comprenden estos compuestos y métodos para tratar trastornos tromboembólicos y/o inflamatorios usando las mismas.

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 487/08; C07D 498/08

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

(72) Inventor(es): CORTE, James, R.; FANG, Tianan; DECICCO, Carl, P.; PINTO, Donald, J., P.; ROSSI, Karen, A.; HU, Zilun; JEON, Yoon; QUAN, Mimi, L.; SMALLHEER, Joanne, M.; WANG, Yufeng; YANG, Wu

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) ***No. Prioridad***	(32) ***Fecha***	(33) ***País***
	61/303,423	11-02-2010	US
	61/405,338	21-10-2010	US

(85) Fecha inicio fase nacional: 11-09-2012

(87) Publicación internacional
Fecha: 18-08-2011
N° publicación WO 2011/100401

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 10-02-2011 No. de solicitud PCT/US2011/024305

(54) Titulo: **MACROCICLOS COMO INHIBIDORES DEL FACTOR DE COAGULACION (FXIA)**

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from CORTE, James R. to BRISTOL-MYERS SQUIBB COMPANY, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from FANG, Tianan to BRISTOL-MYERS SQUIBB COMPANY, dated 13 September 2010 (13.09.2010)
VIII-2-1(iv)		an assignment from DECICCO, Carl P. to BRISTOL-MYERS SQUIBB COMPANY, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from PINTO, Donald J.P. to BRISTOL-MYERS SQUIBB COMPANY, dated 13 September 2010 (13.09.2010)
VIII-2-1(iv)		an assignment from ROSSI, Karen A. to BRISTOL-MYERS SQUIBB COMPANY, dated 31 August 2010 (31.08.2010)
VIII-2-1(iv)		an assignment from HU, Zilun to BRISTOL-MYERS SQUIBB COMPANY, dated 02 September 2010 (02.09.2010)
VIII-2-1(iv)		an assignment from JEON, Yoon to BRISTOL-MYERS SQUIBB COMPANY, dated 15 September 2010 (15.09.2010)
VIII-2-1(iv)		an assignment from SMALLHEER, Joanne M. to BRISTOL-MYERS SQUIBB COMPANY, dated 13 September 2010 (13.09.2010)
VIII-2-1(iv)		an assignment from WANG, Yufeng to BRISTOL-MYERS SQUIBB COMPANY, dated 13 September 2010 (13.09.2010)
VIII-2-1(iv)		an assignment from YANG, Wu to BRISTOL-MYERS SQUIBB COMPANY, dated 02 September 2010 (02.09.2010)
VIII-2-1(iv)		an assignment from QUAN, Mimi L. to BRISTOL-MYERS SQUIBB COMPANY, dated 07 September 2010 (07.09.2010)

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

1

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

2

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

BAKER & MCKENZIE

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

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

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

BAKER & MCKENZIE

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

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

5