SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-046171- -00000-0000

Fecha: 2013-03-07 16:32:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

INDUSTRIA Y COMERCIO

SUPERINTENDENCIA

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. EXPEDIENTE No. _____

54. TITULO HETEROARILOS Y SUS USOS

_____

_____

51. CLASIFICACIÓN INTERNACIONAL _____

71. SOLICITANTE MILLENNIUM PHARMACEUTICALS, INC

DOMICILIO CAMBRIDGE, MA 02139, ESTADOS UNIDOS

74. APODERADO ALVARO CORREA ORDOÑEZ

22. SANTAFE DE BOGOTA, DC. Marzo 6, 2013

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-046171- -00000-0000
Fecha: 2013-03-07 16:32:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

:ación

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: **MILLENNIUM PHARMACEUTICALS, INC.**
Dirección: 40 Landsdowne Street Cambridge, MA 02139 (US)
Nacionalidad o Domicilio: Estados Unidos de América
Lugar de Constitución: Estados Unidos de América
Teléfono: Fax:
E-Mail

IDENTIFICACIÓN
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

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

Nombre: FREEZE, Brian S.; HIROSE, Masaaki; HU, Yongbo; HU, Zhigen; LEE, Hong Myung; SELLS, Todd B.; SHI, Zhan; VYSKOCIL, Stepan; XU, Tianlin;
Dirección: 67 Gates Street, Unit 1 Boston, MA 02127 (US); C/o Takeda Pharmarceutical Company Limited Oncology DDU, C-1 2F 1110 26-1, Muraokahigashi 2-chome, Fujisawa, Kanagawa, 251-0012 (JP); 24 Shepard Court Winchester, MA 01890 (US); 42 Truman Road Newton Center, MA 02459 (US); 321 Harvard Street #309 Cambridge, MA 02139 (US); 32 Ray Avenue Bellingham, MA 02019 (US); 18 Shagbark Road Concord, MA 01742 (US); Stepan; 34 Eustis Street Arlington, MA 02476 (US); 2 Arrowwood Drive Shrewsbury, MA 01545 (US)
Nacionalidad o Domicilio: Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2011/047407 Fecha 11-08-2011
Publicación Internacional No. WO 2012/021696 Fecha 16-02-2012

(6) Título (54) HETEROARILOS Y SUS USOS

(7) Clasificación Internacional (51) A61K 31/33; A61K 31/425

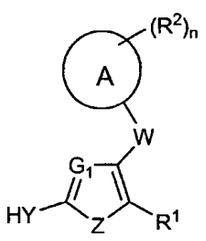
(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	11-08-2010	61/372,594
US	01-02-2011	61/438,375

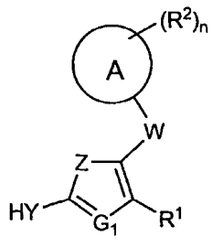
(9) Comprobante de pago No. 13-0015879 **Fecha** 18-02-13

(10) **ANEXOS**

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



(IA-a)



(IB-a)

(11) 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

3

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0015879

Bogotá D.C., Febrero 18 de 2013 - 09:33:08

RECIBIDO DE : BAKER NI 900.532.339

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	197970975	15/02/2013	923623.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	500.000.00	500.000.00
			$500.000.00

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-046171- -00000-0000
Fecha: 2013-03-07 16:32:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-046171- -00000-0000

Fecha: 2013-03-07 16:32:55 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

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, Circulár 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	13-46171-0		
2			
3			
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
10	Otro

Observaciones:

Anexoin CD

Pathy

Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***No.*** (32) ***Fecha*** (33) ***País***
61/372,594 11-08-2010 US
61/438,375 01-02-2011 US

(51) Int Cl: A61K 31/33; A61K 31/425

(71)Solicitante(s) **MILLENNIUM PHARMACEUTICALS, INC**

(72) Inventor(es) FREEZE, Brian S.; HIROSE, Masaaki; HU, Yongbo; HU, Zhigen; LEE, Hong Myung; SELLS, Todd B.; SHI, Zhan; VYSKOCIL, Stepan; XU, Tianlin

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

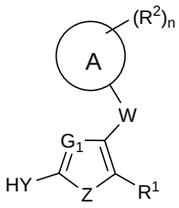
(85) Fecha limite inicio fase nacional: 11-03-2013
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 11-08-2011
No. de solicitud PCT/US2011/047407

(87) Publicación internacional
Fecha: 16-02-2012
N° publicación: WO 2012/021696

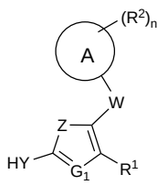
(54) Titulo: HETEROARILOS Y SUS USOS

RESUMEN:

La invención provee compuestos de formula **IA-a** o **IB-a** y sus correspondientes subconjuntos**:**



IA-A



IB-A

donde Z, HY, R^1, R^2, G_1, W, n, y A y sus correspondientes subconjuntos son como se describen en la memoria descriptiva. Los compuestos son inhibidores de P13K y de este modo son útiles para tratar trastornos proliferativos, inflamatorios, o cardiovasculares.

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: A61K 31/33; A61K 31/425

(71)Solicitante(s) **MILLENNIUM PHARMACEUTICALS, INC**

(72) Inventor(es): FREEZE, Brian S.; HIROSE, Masaaki; HU, Yongbo; HU, Zhigen; LEE, Hong Myung; SELLS, Todd B.; SHI, Zhan; VYSKOCIL, Stepan; XU, Tianlin

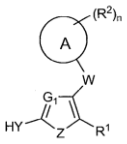
(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad

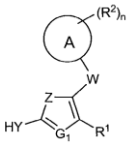
(31) *No. Prioridad*	(32) *Fecha*	(33) *País*
61/372,594	11-08-2010	US
61/438,375	01-02-2011	US

(85) Fecha límite inicio fase nacional: 11-03-2013
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 11-08-2011
No. de solicitud: PCT/US2011/047407

(87) Publicación internacional:
Fecha: 16-02-2012
No. Publicación: WO 2012/021696



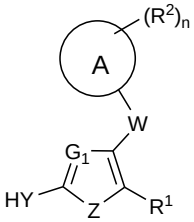
(IA-a)



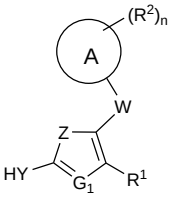
(IB-a)

(54) Titulo: HETEROARILOS Y SUS USOS

(57) Resumen: La invención provee compuestos de formula **IA-a** o **IB-a** y sus correspondientes subconjuntos**:**



IA-A



IB-A

CONTINUA AL RESPALDO ...

donde Z, HY, R^1, R^2, G_1, W, n, y A y sus correspondientes subconjuntos son como se describen en la memoria descriptiva. Los compuestos son inhibidores de P13K y de este modo son útiles para tratar trastornos proliferativos, inflamatorios, o cardiovasculares.

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: A61K 31/33; A61K 31/425

(71)Solicitante(s): **MILLENNIUM PHARMACEUTICALS, INC**

(72) Inventor(es): FREEZE, Brian S.; HIROSE, Masaaki; HU, Yongbo; HU, Zhigen; LEE, Hong Myung; SELLS, Todd B.; SHI, Zhan; VYSKOCIL, Stepan; XU, Tianlin

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/372,594	11-08-2010	*US*
	61/438,375	01-02-2011	*US*

(85) Fecha inicio fase nacional: 11-03-2013

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 11-08-2011
No. de solicitud: PCT/US2011/047407

(87) Publicación internacional
Fecha: 16-02-2012
N° publicación: WO 2012/021696

(54) Titulo: HETEROARILOS Y SUS USOS

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 February 2012 (16.02.2012)

PCT

(10) International Publication Number
WO 2012/021696 A1

(51) International Patent Classification:
A61K 31/33 (2006.01) *A61K 31/425* (2006.01)

(21) International Application Number:
PCT/US2011/047407

(22) International Filing Date:
11 August 2011 (11.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/372,594 11 August 2010 (11.08.2010) US
61/438,375 1 February 2011 (01.02.2011) US

(71) Applicant *(for all designated States except US)*: **MILLENNIUM PHARMACEUTICALS, INC.** [US/US]; 40 Landsdowne Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FREEZE, Brian S.** [US/US]; 67 Gates Street, Unit 1, Boston, MA 02127 (US). **HIROSE, Masaaki** [JP/JP]; C/o Takeda Pharmaceutical Company Limited, Oncology DDU, C-1 2F 1110, 26-1, Muraokahigashi 2-chome, Fujisawa, Kanagawa, 251-0012 (JP). **HU, Yongbo** [US/US]; 24 Shepard Court, Winchester, MA 01890 (US). **HU, Zhigen** [CN/US]; 42 Truman Road, Newton Center, MA 02459 (US). **LEE, Hong Myung** [KR/US]; 321 Harvard Street #309, Cambridge, MA 02139 (US). **SELLS, Todd B.** [US/US]; 32 Ray Avenue, Bellingham, MA 02019 (US). **SHI, Zhan** [US/US]; 18 Shagbark Road, Concord, MA 01742 (US). **VYSKOCIL, Stepan** [CZ/US]; 34 Eustis Street, Arlington, MA 02476 (US). **XU, Tianlin** [US/US]; 2 Arrowwood Drive, Shrewsbury, MA 01545 (US).

(74) Agents: **SHAIR, Karoline K. M.** et al.; Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 (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, QA, 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.

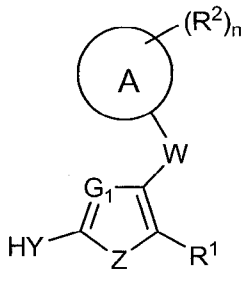
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, 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).

Published:

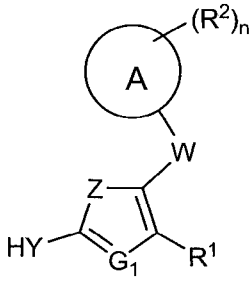
— *with international search report (Art. 21(3))*

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

(54) **Title**: HETEROARYLS AND USES THEREOF



(IA-a)



(IB-a)

(57) **Abstract**: This invention provides compounds of formula (IA-a) or (IB-a) and subsets thereof: wherein Z, HY, R^1, R^2, G_1 W, n, and A and subsets thereof are as described in the specification. The compounds are inhibitors of PI3K and are thus useful for treating proliferative, inflammatory, or cardiovascular disorders.

WO 2012/021696 A1

HETEROARYLS AND USES THEREOF

BACKGROUND OF THE INVENTION

[0001] Phosphatidylinositol 3-kinase (PI3K) is a family of lipid kinases that phosphorylate phosphatidylinositol at the 3' position of the inositol ring. PI3K is comprised of several classes of genes, including Class IA, IB, II and III and some of these classes contain several isoforms (reviewed in Engelman et al., Nature Review Genetics 7:606-619 (2006)). Adding to the complexity of this family is the fact that PI3Ks function as heterodimers, comprising a catalytic domain and a regulatory domain. The PI3K family is structurally related to a larger group of lipid and serine/threonine protein kinases known as the phosphatidylinositol 3-kinase like kinases (PIKKs), which also includes DNA-PK, ATM, ATR, mTOR, TRRAP and SMG1.

[0002] PI3K is activated downstream of various mitogenic signals mediated through receptor tyrosine kinases, and subsequently stimulates a variety of biological outcomes; including increased cell survival, cell cycle progression, cell growth, cell metabolism, cell migration and angiogenesis (reviewed in Cantley, Science 296:1655-57 (2002); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005); Engelman et al., Nature Review Genetics 7:606-619 (2006)). Thus, PI3K hyper-activation is associated with a number of hyper-proliferative, inflammatory, or cardiovascular disorders; including cancer, inflammation, and cardiovascular disease.

[0003] There are a number of genetic aberrations that lead to constitutive PI3K signaling; including activating mutations in PI3K itself (Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005); reviewed in Bader et al., Nature Reviews Cancer 5:921-9 (2005)); RAS (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)) and upstream receptor tyrosine kinases (reviewed in Zwick et al., Trends in Molecular Medicine 8:17-23 (2002)) as well as inactivating mutations in the tumor suppressor PTEN (reviewed in Cully et al., Nature Reviews Cancer 6:184-92 (2006)). Mutations in each of these gene classes have proven to be oncogenic and are commonly found in a variety of cancers.

[0004] The molecules defined within this invention inhibit the activity of PI3K, and therefore may be useful for the treatment of proliferative, inflammatory, or cardiovascular disorders. Cases where PI3K pathway mutations have been linked to proliferative disorders where the molecules defined within this invention may have a therapeutic benefit include benign and malignant tumors and cancers from diverse lineage, including but not limited to those derived from colon (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), liver (reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), intestine (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), stomach (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), esophagus (Phillips et al., International

Journal of Cancer 118:2644-6 (2006)); pancreas (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)); skin (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), prostate (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), lung (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), breast (Samuels et al., Science 304:554 (2004); Isakoff et al., Can Res 65:10992-1000 (2005); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), endometrium (Oda et al., Can Res 65:10669-73 (2005); reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), cervix (reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); ovary (Shayesteh et al., Nature Genetics 21:99-102 (1999); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), testes (Moul et al., Genes Chromosomes Cancer 5:109-18 (1992); Di Vizio et al., Oncogene 24:1882-94 (2005)), hematological cells (reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), pancreas (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)), thyroid (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003); reviewed in Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); brain (Samuels et al., Science 304:554 (2004); reviewed in Karakas et al., British Journal of Cancer 94: 455-59 (2006)), bladder (Lopez-Knowles et al., Cancer Research 66:7401-7404 (2006); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); kidney (reviewed in Downward Nature Reviews Cancer 3:11-22 (2003)) and Head and Neck (reviewed in Engelman et al., Nature Reviews Genetics 7:606-619 (2006)).

[0005] Other classes of disorders with aberrant PI3K pathway signaling where the molecules defined within this invention may have a therapeutic benefit include inflammatory and cardiovascular diseases, including but not limited to allergies/anaphylaxis (reviewed in Rommel et al., Nature Reviews Immunology 7:191-201 (2007)), acute and chronic inflammation (reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006); reviewed in Rommel et al., Nature Reviews Immunology 7:191-201 (2007)), rheumatoid arthritis (reviewed in Rommel et al., Nature Reviews Immunology 7:191-201 (2007)); autoimmunity disorders (reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), thrombosis (Jackson et al., Nature Medicine 11:507-14 (2005); reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), hypertension (reviewed in Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), cardiac hypertrophy (reviewed in Proud et al., Cardiovascular Research 63:403-13 (2004)), and heart failure (reviewed in Mocanu et al., British Journal of Pharmacology 150:833-8 (2007)).

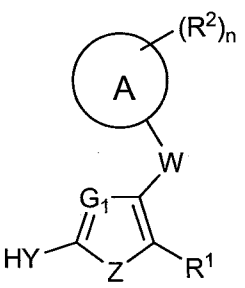
[0006] Vacuolar Protein Sorting 34 (VPS34) is the sole Class III PI3K family member. VPS34 functions in the formation and trafficking of multiple intracellular vesicles, including vacuoles, endosomes, multivessicular bodies, lysosomes and autophagosomes (reviewed in Backer Biochem J

2008; Yan and Backer Biochem J 2007). VPS34 carries out these activities by phosphorylating PtdIns forming PtdIns3P, resulting in the recruitment and localization of a variety of FYVE and PX domain containing effector proteins that facilitate vesicular formation, elongation and movement. At a cellular level, inhibition of VPS34 results in defects in protein sorting and autophagy. Broadly defined, autophagy is a regulated process whereby cells catabolize subcellular components targeted for degradation by enclosing them in double-membrane vesicles which then fuse with lysosomes. Autophagy has been best characterized as occurring during times of nutrient deprivation, but also plays a role in normal cellular and tissue homeostasis and functions, including the development of multiple tissue types, the immune response, clearance of neuronal aggregates and tumor suppression. In addition to functioning in vesicle formation and movement, VPS34 may also participate in several signal transduction pathways (reviewed in Backer Biochem J 2008). Given that VPS34 plays an important role in many critical cellular processes including autophagy, inhibitors of VPS34 may have therapeutic application in a number of diseases, including but not limited to cancer, muscular disorders, neurodegeneration, inflammatory disease, infectious disease and other age related illnesses (reviewed in Shintani and Klionshy Science 2004; Kondo et al Nat Rev Cancer 2005; Delgato et al Immunol Rev 2009).

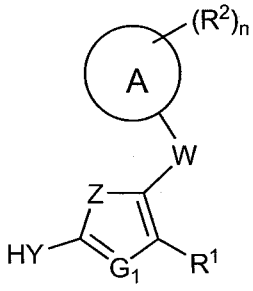
[0007] Clearly, it would be beneficial to provide novel PI3K inhibitors that possess good therapeutic properties, especially for the treatment of proliferative, inflammatory, or cardiovascular disorders.

[0008] *1. General Description of Compounds of the Invention:*

[0009] This invention provides compounds that are inhibitors of PI3K, and accordingly are useful for the treatment of proliferative, inflammatory, or cardiovascular disorders. In one embodiment, the compounds of this invention are represented by formula **IA-a** or **IB-a**:



IA-a

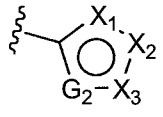


IB-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $–N(R^{3'})$ –, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $–Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-CO_2$-, $-C(O)NR^{4a}$-, $-N(R^{4a})C(O)$-, $-N(R^{4a})CO_2$-, $-S(O)_2NR^{4a}$-, $-N(R^{4a})S(O)_2$-, $-OC(O)N(R^{4a})$-, $-N(R^{4a})C(O)NR^{4a}$-, $-N(R^{4a})S(O)_2N(R^{4a})$-, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $–R^{12a}$, $-T_2\text{-}R^{12d}$, or $–V_2\text{-}T_2\text{-}R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$,

$-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl

having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

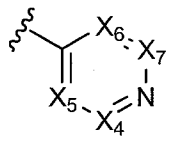
G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -$S(O)$-, $S(O)_2$-, -$C(O)$-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -$OC(O)$-;

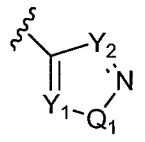
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

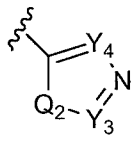
HY is an optionally substituted group selected from:



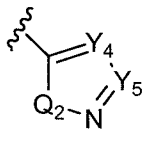
A ,



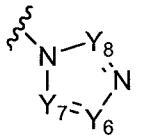
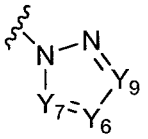
B ,



C ,



D

E , or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$,

$-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

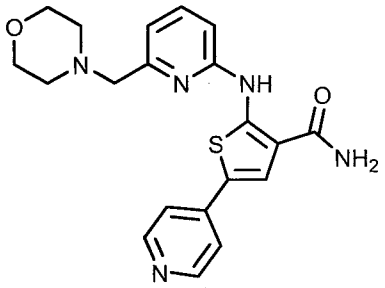
each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

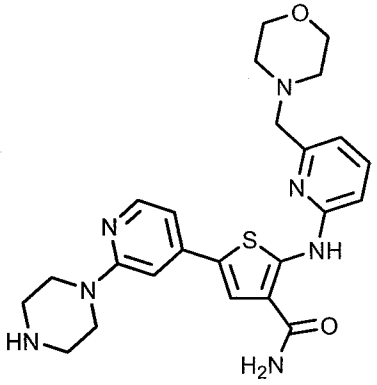
wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

provided that:

a) for compounds of formula IB-a compounds are other than:

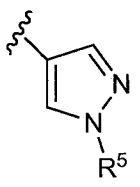


,

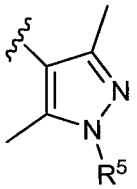


; and

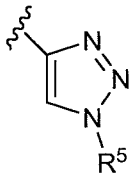
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than



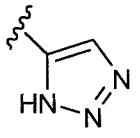
,



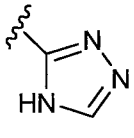
,



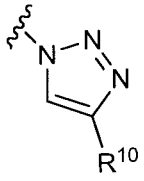
,



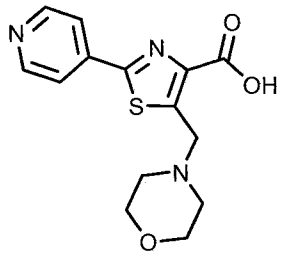
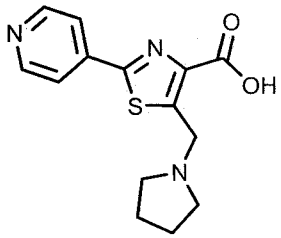
,



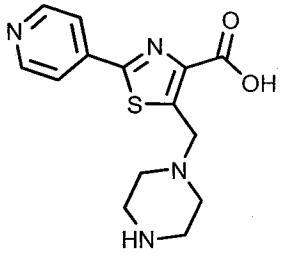
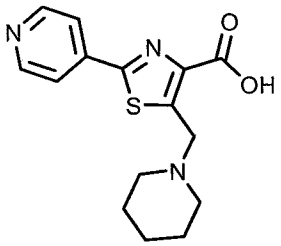
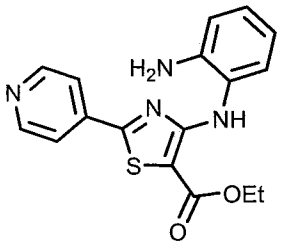
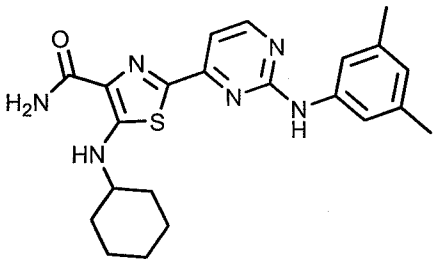
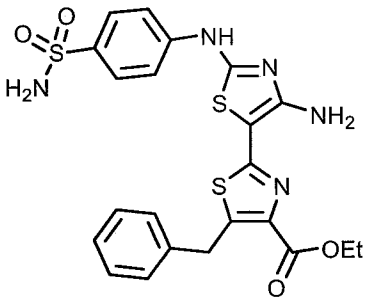
,



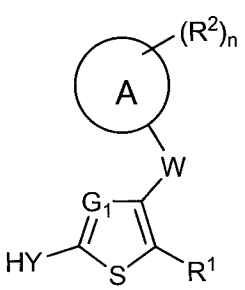
, or ; and

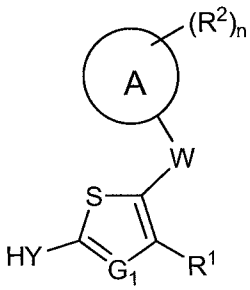
b) the compound is other than:

[0010] In another embodiment, the compounds of this invention are represented by formula **IA** or **IB**:



IA

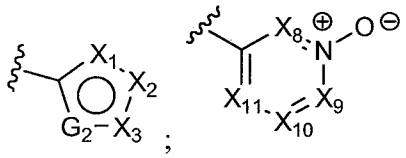


IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is an optionally substituted group selected from:



; ; ; and ;

Q **R** **S** **T**

wherein:

G_2 is –N= , =N–, or $-N(R^{3'})-$, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

X_8, X_9, X_{10}, and X_{11} are each independently N, or CR^4, provided no more than two occurrences of X_8, X_9, X_{10}, and X_{11} are N;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Y_{10} is $-OR^{4'}$ or $-N(R^{4'})_2$;

Y_{11} is O or N-$R^{4'}$;

each occurrence of $R^{4'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{13})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{13})$-, -$S(O)_2N(R^{13})$-, -$OC(O)N(R^{13})$-, -$N(R^{13})C(O)$-, -$N(R^{13})SO_2$-, -$N(R^{13})C(O)O$-, -$N(R^{13})C(O)N(R^{13})$-, -$N(R^{13})S(O)_2N(R^{13})$-, -OC(O)-, or -$C(O)N(R^{13})$-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –$C(R^7)_2$-, –$C(=C(R^7)_2)$-, -$C(R^7)_2O$-, -$C(R^7)_2NR^{7a}$-, –O-, -$N(R^{7b})$-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -$C(O)NR^{7a}$-, or -$N(R^{7a})C(O)$-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

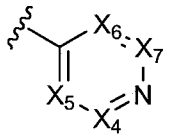
G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

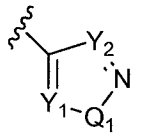
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

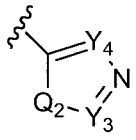
HY is an optionally substituted group selected from:



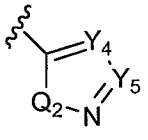
A ,



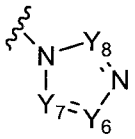
B ,



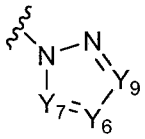
C ,



D



E ,



or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, -CN, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

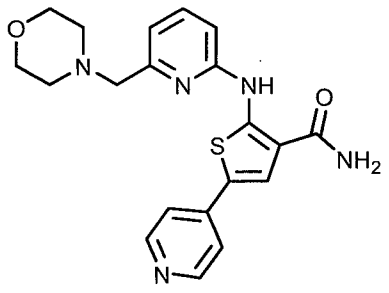
each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

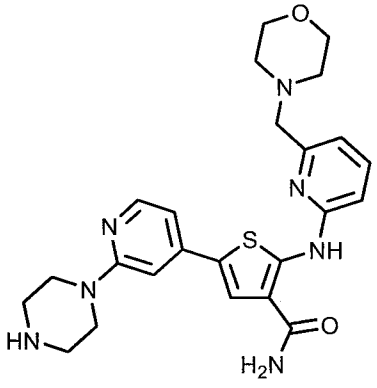
wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

a) for compounds of formula IB compounds are other than:

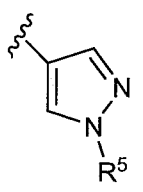
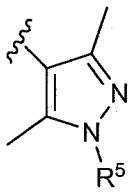
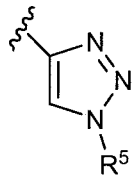


,

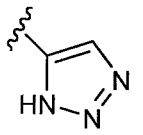
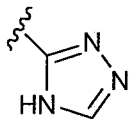
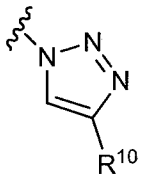


; and

when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than

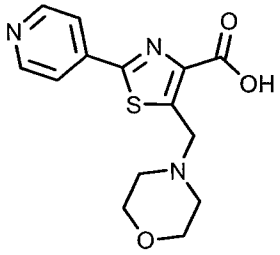
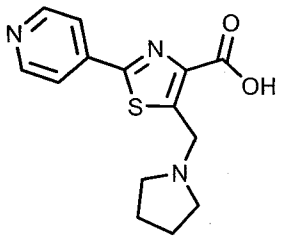
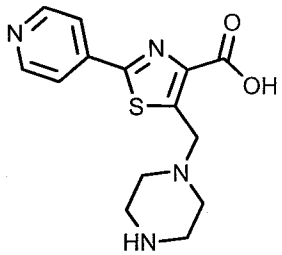
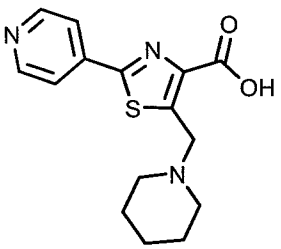




,

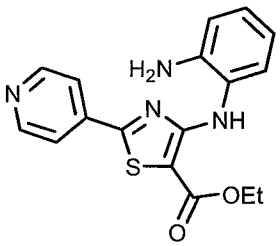
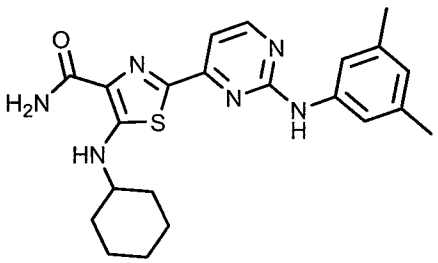




, , or ; and

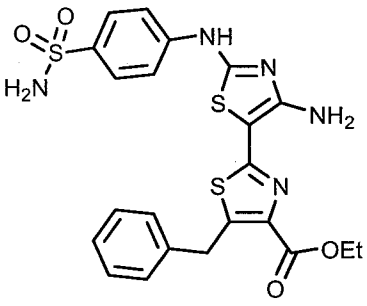
b) the compound is other than:

,

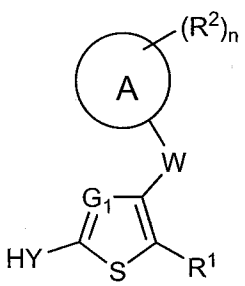



,

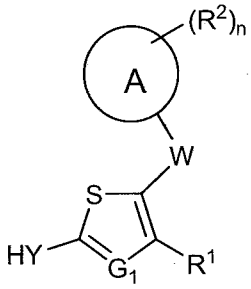


.

[0011] In another aspect, the compounds of this invention are represented by formula **IA** or **IB**:



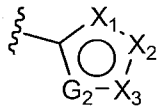
IA



IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $-N(R^{3'})-$, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from

5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted
by -$N(R^{13})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{13})$-, -$S(O)_2N(R^{13})$-, -$OC(O)N(R^{13})$-, -$N(R^{13})C(O)$-, -$N(R^{13})SO_2$-, -$N(R^{13})C(O)O$-, -$N(R^{13})C(O)N(R^{13})$-, -$N(R^{13})S(O)_2N(R^{13})$-, -OC(O)-, or -$C(O)N(R^{13})$-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –$C(R^7)_2$-, –$C(=C(R^7)_2)$-, -$C(R^7)_2O$-, -$C(R^7)_2NR^{7a}$-, –O-, -$N(R^{7b})$-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -$C(O)NR^{7a}$-, or -$N(R^{7a})C(O)$-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -

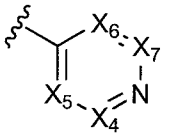
$N(R^{8a})S(O)_2$-,

-$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

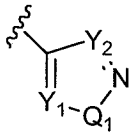
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

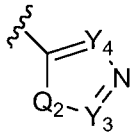
HY is an optionally substituted group selected from:



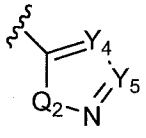
A,



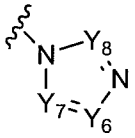
B,



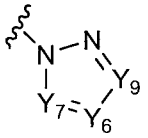
C,



D,



E, or



F;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently -CR^{10} or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, -T_1-R^{10b}, or -V_1-T_1-R^{10b} wherein:

V_1 is $-NR^{11}$-, -NR^{11}-C(O)-, -NR^{11}-C(S)-, -NR^{11}-$C(NR^{11})$-, -$NR^{11}C(O)OR^{10a}$-, -$NR^{11}C(O)NR^{11}$-, -$NR^{11}C(O)SR^{10a}$-, -$NR^{11}C(S)OR^{10a}$-, -$NR^{11}C(S)NR^{11}$-, -$NR^{11}C(S)SR^{10a}$-, -$NR^{11}C(NR^{11})OR^{10a}$-, -$NR^{11}C(NR^{11})NR^{11}$-, -$NR^{11}S(O)_2$-, -$NR^{11}S(O)_2NR^{11}$-, -C(O)-, -$CO_2$-, -$C(O)NR^{11}$-, -$C(O)NR^{11}O$-, -$SO_2$-, or -$SO_2NR^{11}$-;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered

heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5

heteroatoms independently selected from nitrogen, oxygen, or sulfur;

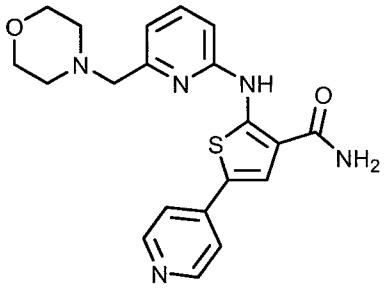
each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

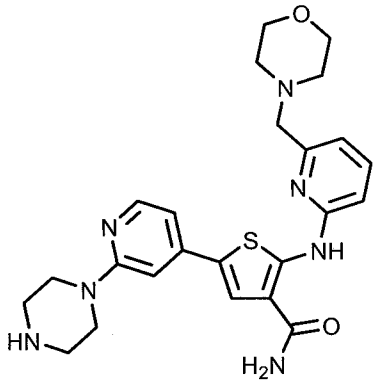
wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

a) for compounds of formula IB compounds are other than:

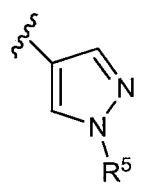
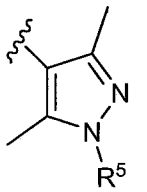
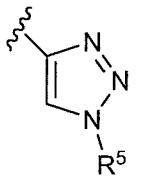


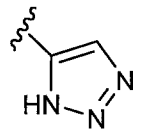
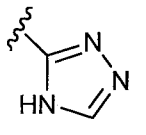
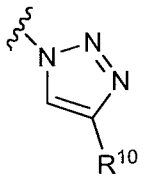
,



; and

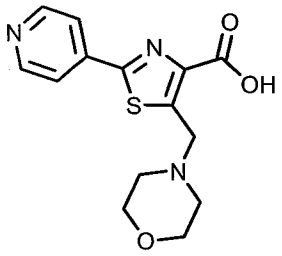
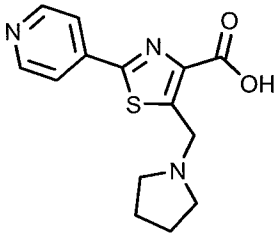
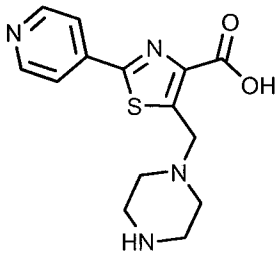
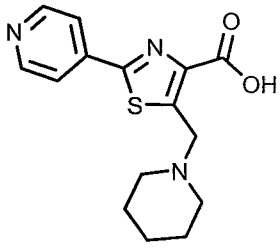
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than

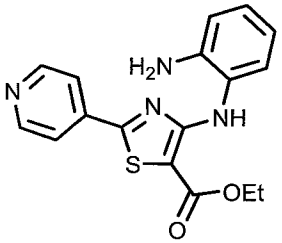
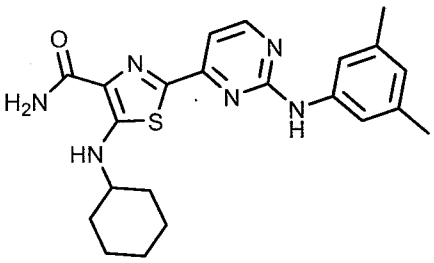
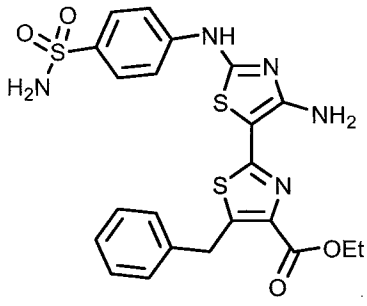

,

,

,

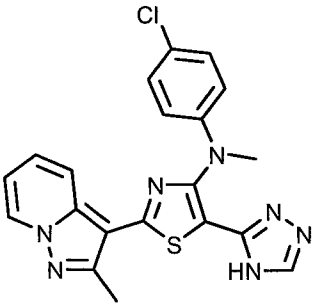

,

,

; and

, or

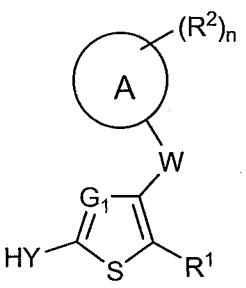
b) the compound is other than:


,

,

,

,

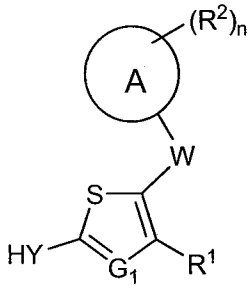

,

,

, or


.

[0012] In another aspect, the compounds of this invention are represented by formula **IA** or **IB**:



IA



IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$;

each occurrence of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or $-CN$;

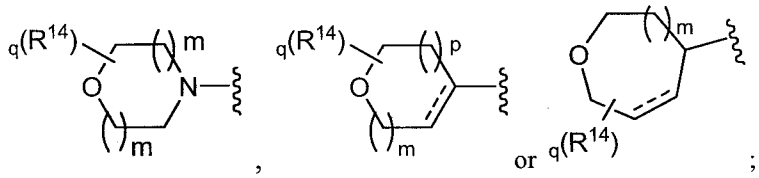
each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N; and

HY is  ;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

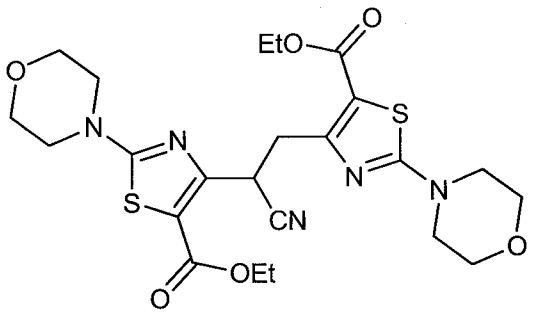
T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

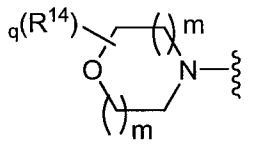
n is 0-6;

m is 1 or 2;

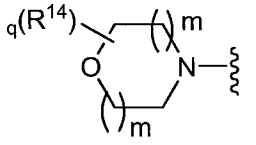
p is 0, 1, or 2;

provided that the compound is other than:



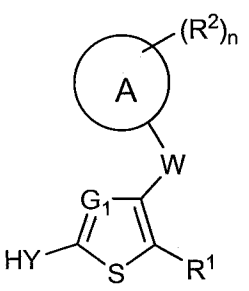


[0013] In some embodiments for compounds described directly above, HY is , wherein both occurrences of m are 1.

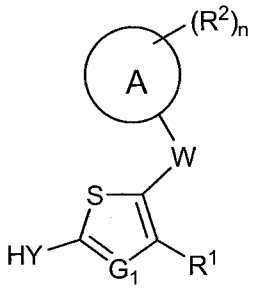


[0014] In other embodiments for compounds described directly above, HY is , wherein both occurrences of m are 1, and R^1 is COOH.

[0015] In yet another aspect, the compounds of this invention are represented by formula **IA** or **IB**:



IA

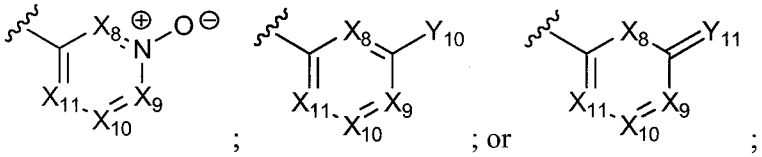


IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, wherein:

CY is an optionally substituted group selected from:



R S T

wherein:

each occurrence of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_8, X_9, X_{10}, and X_{11} are each independently N, or CR^4, provided no more than two occurrences of X_8, X_9, X_{10}, and X_{11} are N;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3-R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Y_{10} is $-OR^{4'}$ or $-N(R^{4'})_2$;

Y_{11} is O or $N-R^{4'}$;

each occurrence of $R^{4'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{13})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{13})$-, -$S(O)_2N(R^{13})$-, -$OC(O)N(R^{13})$-, -$N(R^{13})C(O)$-, -$N(R^{13})SO_2$-, -$N(R^{13})C(O)O$-, -$N(R^{13})C(O)N(R^{13})$-, -$N(R^{13})S(O)_2N(R^{13})$-, -OC(O)-, or -$C(O)N(R^{13})$-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –$C(R^7)_2$-, –$C(=C(R^7)_2)$-, -$C(R^7)_2O$-, -$C(R^7)_2NR^{7a}$-, –O-, -$N(R^{7b})$-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -$C(O)NR^{7a}$-, or -$N(R^{7a})C(O)$-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

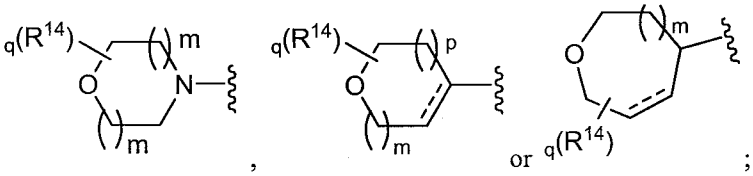
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is 

;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted

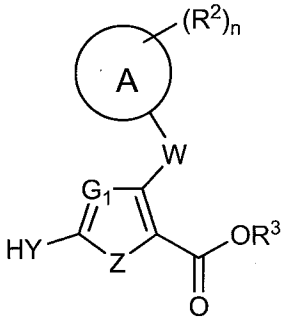
by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

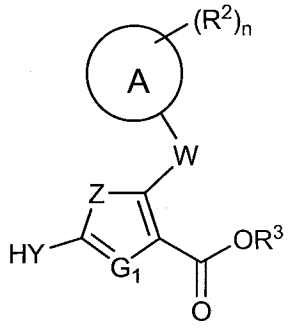
m is 1 or 2; and

p is 0, 1, or 2.

[0016] In still another embodiment of the invention, compounds of this invention are represented by formula **IA-i-a** or **IB-i-a**:



IA-i-a



IB-i-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, -OC(O)-, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, -O-, $-N(R^{7b})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7c}, -SR^{7a}, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

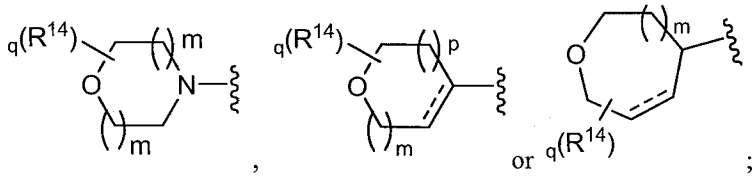
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or -CR^8, wherein R^8 is H, –CN, halogen, –Z_2-R^9, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, -$N(R^{8a})$-, -S-, -S(O)-, $S(O)_2$-, -C(O)-, -CO_2-, -$C(O)NR^{8a}$-, -$N(R^{8a})C(O)$-, -$N(R^{8a})CO_2$-, -$S(O)_2NR^{8a}$-, -$N(R^{8a})S(O)_2$-, -$OC(O)N(R^{8a})$-, -$N(R^{8a})C(O)NR^{8a}$-, -$N(R^{8a})S(O)_2N(R^{8a})$-, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is  ;

$\overset{\text{------}}{}$ represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{14a})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{14a})$-, -$S(O)_2N(R^{14a})$-, -$OC(O)N(R^{14a})$-, -$N(R^{14a})C(O)$-, -$N(R^{14a})SO_2$-, -$N(R^{14a})C(O)O$-, -$NR^{14a}C(O)N(R^{14a})$-,

$-N(R^{14a})S(O)_2N(R^{14a})-$, -OC(O)-, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

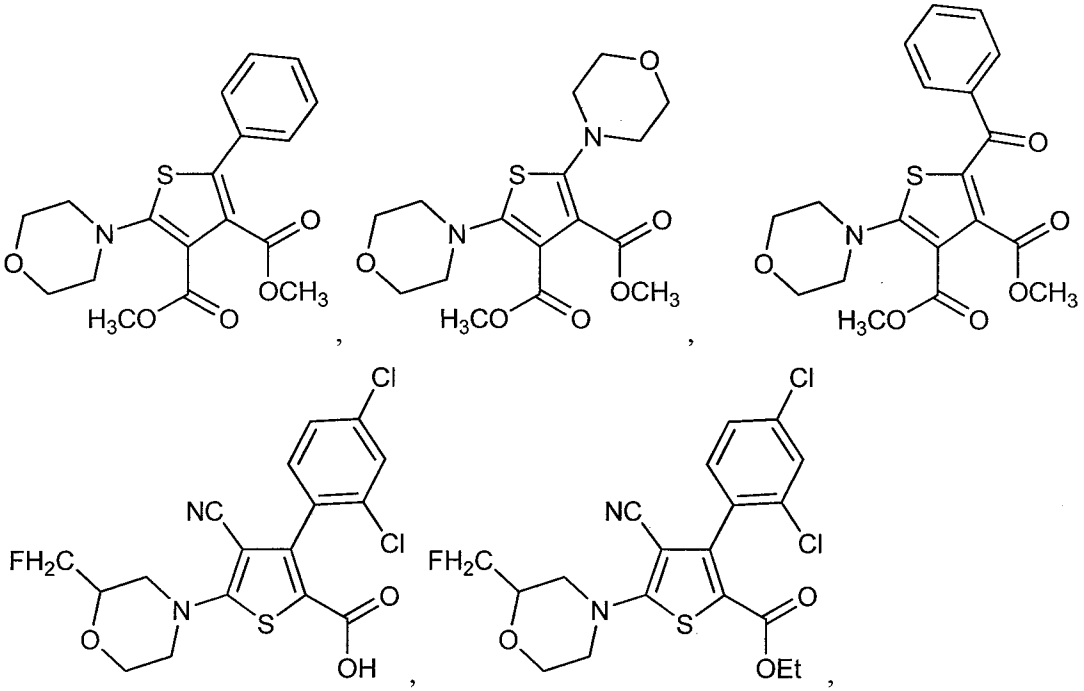
p is 0, 1, or 2;

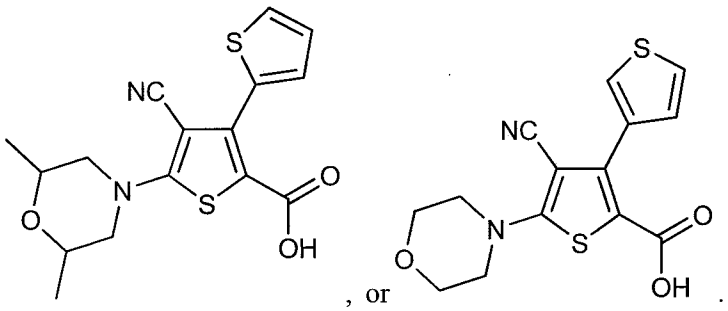
provided that:

a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

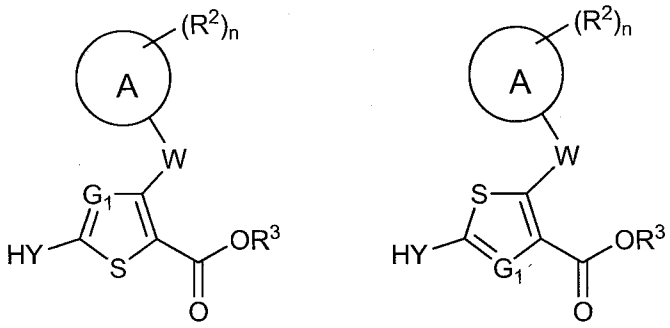
c) the compound is other than:





, or .

[0017] In yet another embodiment of the invention, compounds of this invention are represented by formula **IA-i** or **IB-i**:



IA-i **IB-i**

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having

1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

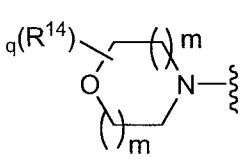
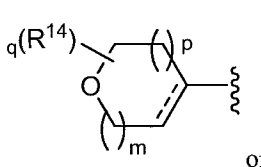
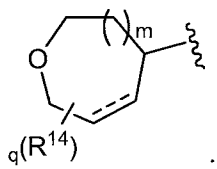
G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2$-, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$,

$-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is  ,  , or  ;

====== represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or -T_1-R^{14d}, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, -NO_2, -R^{14c}, -$N(R^{14b})_2$, -OR^{14b}, -SR^{14c}, -$S(O)_2R^{14c}$, -$C(O)R^{14b}$, -$C(O)OR^{14b}$, -$C(O)N(R^{14b})_2$, -$S(O)_2N(R^{14b})_2$, -$OC(O)N(R^{14b})_2$, -$N(R^{14e})C(O)R^{14b}$, -$N(R^{14e})SO_2R^{14c}$, -$N(R^{14e})C(O)OR^{14b}$, -$N(R^{14e})C(O)N(R^{14b})_2$, or –$N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{14a})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{14a})$-, -$S(O)_2N(R^{14a})$-, -$OC(O)N(R^{14a})$-, -$N(R^{14a})C(O)$-, -$N(R^{14a})SO_2$-, -$N(R^{14a})C(O)O$-, -$NR^{14a}C(O)N(R^{14a})$-, -$N(R^{14a})S(O)_2N(R^{14a})$-, -OC(O)-, or -$C(O)N(R^{14a})$-O- or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

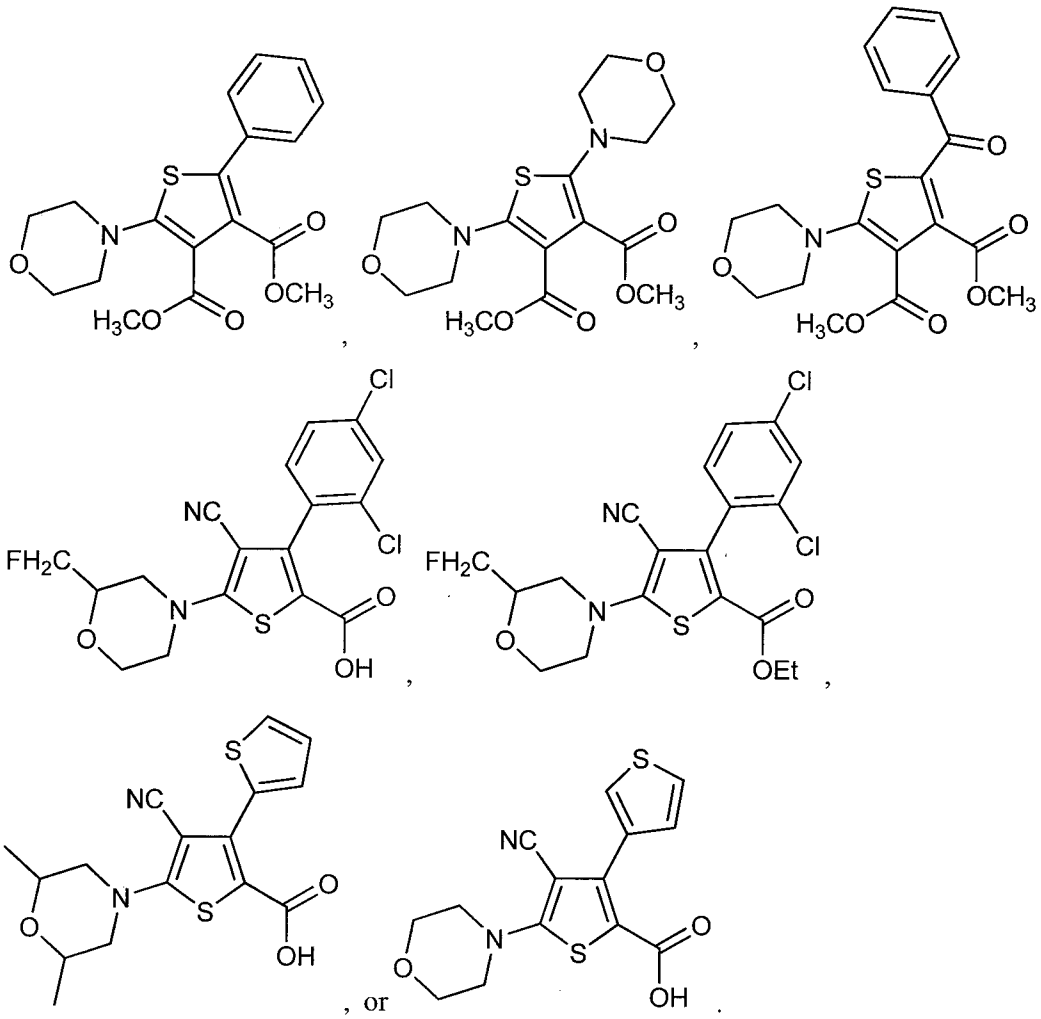
p is 0, 1, or 2;

provided that:

a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

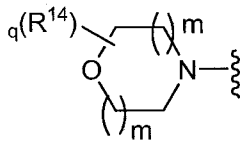
c) the compound is other than:



, or .

[0018] In some embodiments for compounds described directly above, G_1 is N.

[0019] In some embodiments for compounds described directly above, G_1 is $C(R^8)$, wherein R^8 is –CN or C_{2-4} alkynyl.

[0020] In some embodiments for compounds described directly above, HY is  , wherein both occurrences of m are 1.

[0021] In some embodiments for compounds described directly above, R^3 is H.

DETAILED DESCRIPTION OF THE INVENTION

[0022] *2. Compounds and Definitions:*

[0023] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. It will be appreciated that preferred subsets described for each variable herein can be used for any of the structural subsets as well. As used herein, the following definitions shall apply unless otherwise indicated.

[0024] As described herein, compounds of the invention may be optionally substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. The term "substitutable", when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which hydrogen atom can be replaced with the radical of a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

[0025] A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature from about –80°C to about +40°, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a patient.

[0026] The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[0027] As used herein, the term "independently selected" means that the same or different values may be selected for multiple instances of a given variable in a single compound.

[0028] As used herein, "a 3-7-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10-membered partially unsaturated, or aromatic bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur" includes cycloaliphatic, heterocyclic, aryl and heteroaryl rings.

[0029] As used herein, the term "aromatic" includes aryl and heteroaryl groups as described generally below and herein.

[0030] The term "aliphatic" or "aliphatic group", as used herein, means an optionally substituted straight-chain or branched C_{1-12} hydrocarbon, or a cyclic C_{1-12} hydrocarbon which is completely saturated or which contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle", "cycloaliphatic", "cycloalkyl", or "cycloalkenyl"). For example, suitable aliphatic groups include optionally substituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, or (cycloalkyl)alkenyl. Unless otherwise specified, in various embodiments, aliphatic groups have 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, or 1-2 carbon atoms.

[0031] The term "alkyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, or 1-2 carbon atoms.

[0032] The term "alkenyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one double bond and having 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms.

[0033] The term "alkynyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms.

[0034] The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, refer to an optionally substituted saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 ring carbon atoms. In some embodiments, the cycloaliphatic group is an optionally substituted monocyclic hydrocarbon having 3-8 or 3-6 ring carbon atoms. Cycloaliphatic groups include, without limitation, optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, or cyclooctadienyl. The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo",

or "carbocyclic" also include optionally substituted bridged or fused bicyclic rings having 6-12, 6-10, or 6-8 ring carbon atoms, wherein any individual ring in the bicyclic system has 3-8 ring carbon atoms.

[0035] The term "cycloalkyl" refers to an optionally substituted saturated ring system of about 3 to about 10 ring carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0036] The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentyl, cyclohexenyl, and cycloheptenyl.

[0037] The terms "haloaliphatic", "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, which is substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. The term "fluoroaliphatic" refers to a haloaliphatic wherein the halogen is fluoro, including perfluorinated aliphatic groups. Examples of fluoroaliphatic groups include, without limitation, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, and pentafluoroethyl.

[0038] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0039] The terms "aryl" and "ar-", used alone or as part of a larger moiety, e.g., "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to an optionally substituted C_{6-14}aromatic hydrocarbon moiety comprising one to three aromatic rings. Preferably, the aryl group is a C_{6-10}aryl group. Aryl groups include, without limitation, optionally substituted phenyl, naphthyl, or anthracenyl. The terms "aryl" and "ar-", as used herein, also include groups in which an aryl ring is fused to one or more cycloaliphatic rings to form an optionally substituted cyclic structure such as a tetrahydronaphthyl, indenyl, or indanyl ring. The term "aryl" may be used interchangeably with the terms "aryl group", "aryl ring", and "aromatic ring".

[0040] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C_{6-10} arylC_{1-6}alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0041] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably

mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. For example, a nitrogen atom of a heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. When a heteroaryl is substituted by a hydroxy group, it also includes its corresponding tautomer. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocycloaliphatic rings. Nonlimiting examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0042] As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 8-membered monocyclic or 7–10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR^+ (as in N-substituted pyrrolidinyl).

[0043] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and thiamorpholinyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. Additionally, a heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl rings.

[0044] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (e.g., aryl or heteroaryl) moieties, as herein defined.

[0045] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. An optionally substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is optionally replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group and also include those described in the specification herein. It will be appreciated that two substituents of the alkylene group may be taken together to form a ring system. In certain embodiments, two substituents can be taken together to form a 3-7-membered ring. The substituents can be on the same or different atoms.

[0046] An alkylene chain also can be optionally interrupted by a functional group. An alkylene chain is "interrupted" by a functional group when an internal methylene unit is interrupted by the functional group. Examples of suitable "interrupting functional groups" are described in the specification and claims herein.

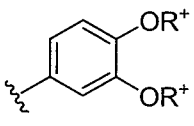
[0047] For purposes of clarity, all bivalent groups described herein, including, e.g., the alkylene chain linkers described above, are intended to be read from left to right, with a corresponding left-to-right reading of the formula or structure in which the variable appears.

[0048] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". In addition to the substituents defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group also include and are generally selected from -halo, $-NO_2$, -CN, $-R^+$, $-C(R^+)=C(R^+)_2$, $-C\equiv C-R^+$, $-OR^+$, $-SR^\circ$, $-S(O)R^\circ$, $-SO_2R^\circ$, $-SO_3R^+$, $-SO_2N(R^+)_2$, $-N(R^+)_2$, $-NR^+C(O)R^+$, $-NR^+C(S)R^+$, $-NR^+C(O)N(R^+)_2$, $-NR^+C(S)N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-R^\circ$, $-NR^+CO_2R^+$, $-NR^+SO_2R^\circ$, $-NR^+SO_2N(R^+)_2$, $-O-C(O)R^+$, $-O-CO_2R^+$, $-OC(O)N(R^+)_2$, $-C(O)R^+$, $-C(S)R^\circ$, $-CO_2R^+$, $-C(O)-C(O)R^+$, $-C(O)N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(O)N(R^+)-OR^+$, $-C(O)N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)-C(O)R^+$, $-C(=NR^+)-N(R^+)_2$, $-C(=NR^+)-OR^+$, $-N(R^+)-N(R^+)_2$, $-C(=NR^+)-N(R^+)-OR^+$, $-C(R^\circ)=N-OR^+$, $-P(O)(R^+)_2$, $-P(O)(OR^+)_2$, $-O-P(O)-OR^+$, and $-P(O)(NR^+)-N(R^+)_2$, wherein R^+, independently, is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group, or two independent occurrences of R^+ are taken together with their intervening atom(s) to form an optionally substituted 5-7-membered aryl, heteroaryl, cycloaliphatic, or heterocyclyl ring. Each R° is an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group.

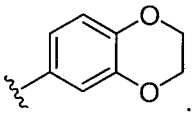
[0049] An aliphatic or heteroaliphatic group, or a non-aromatic carbycyclic or heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic carbocyclic or heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=C(R^*)_2$, $=N-N(R^*)_2$, =N-OR*, =N-NHC(O)R*, $=N-NHCO_2R^\circ$ $=N-NHSO_2R^\circ$ or =N-R* where R° is defined above, and each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

[0050] In addition to the substituents defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring also include and are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-C(O)OR^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-S(O)_2R^+$, $-S(O)_2N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-N(R^+)S(O)_2R^+$; wherein each R^+ is defined above. A ring nitrogen atom of a heteroaryl or non-aromatic heterocyclic ring also may be oxidized to form the corresponding N-hydroxy or N-oxide compound. A nonlimiting example of such a heteroaryl having an oxidized ring nitrogen atom is N-oxidopyridyl.

[0051] As detailed above, in some embodiments, two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) to form a monocyclic or bicyclic ring selected from 3–13-membered cycloaliphatic, 3–12-membered heterocyclyl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6–10-membered aryl, or 5–10-membered heteroaryl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0052] Exemplary rings that are formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) include, but are not limited to the following: a) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^+)_2$, where both occurrences of R^+ are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^+ 

, these two occurrences of R^+ are taken together with the oxygen atoms to which they are bound to form a fused 6-

membered oxygen containing ring:  . It will be appreciated that a variety of other rings (e.g., spiro and bridged rings) can be formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein) are taken together with their intervening atom(s) and that the examples detailed above are not intended to be limiting.

[0053] Exemplary rings that are formed when two independent occurrences of $R^{3'}$ or R^4 are taken together with their intervening atom(s) include, but are not limited to the following: indolizinyl, imidazopyridyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, 4H-furo[3,2-b]pyrrolyl, pyrazolopyrimidinyl, purinyl, and pyrrolizinyl.

[0054] Exemplary rings that are formed when two independent occurrences of R^7, R^{7a}, or R^{7b} are taken together with their intervening atom(s) include, but are not limited to the following: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, oxazolidinyl, piperazinyl, dioxanyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, and thiomorpholinyl.

[0055] Exemplary rings that are formed when two independent occurrences of R^{7a} and R^2, or R^{7b} and R^2 are taken together with their intervening atom(s) include, but are not limited to the following: isoindolyl, indazolyl, benzothienyl, dihydrobenzothienyl, isobenzofuranyl, benzoisoxazolyl, dihydroisobenzofuranyl, pyrazolopyrimidinyl, pyrazolopyridinyl, isoquinolyl, tetrahydroisoquinolinyl, phthalazinyl, isochromanyl, isothiochromanyl, isoindolinyl, and benzoisothiazolyl.

[0056] Exemplary rings that are formed when two independent occurrences of X_4 and X_5, or X_6 and X_7; are taken together with their intervening atom(s) include, but are not limited to the following: pyrazolopyrimidinyl, purinyl, quinolyl, tetrahydroquinolinyl, quinazolinyl, naphthyridinyl, pyridopyrimidinyl, pyrazolopyridinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, imidazopyridinyl, 1H-pyrrolo[2,3-b]pyridinyl-2(3H)-one, 3,4-dihydro-1,8-naphthyridinyl-2(1H)-one, 1,8-naphthyridinyl-2(1H)-one, 1H-pyridyl[2,3-d][1,3]oxazin-2(4H)-one, 1H-imidazo[4,5-b]pyridyl-2(3H)-one, oxazolo[4,5-b]pyridyl-2(3H)-one, 1,2-dihydropyridyl[2,3-b]pyrazin-3(4H)-one, 2H-pyridyl[3,2-b][1,4]oxazin-3(4H)-one, 3,4-dihydropyridyl[2,3-d]pyrimidin-2(1H)-one, imidazopyridinyl, and tetrahydroquinazolinyl.

[0057] Exemplary rings that are formed when two independent occurrences of Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 are taken together with their intervening atom(s) include, but are not limited to the following: indolyl, indazolyl, 4H-furo[3,2-b]pyrrolyl, 4H-thieno[3,2-b]pyrrolyl, 5H-furo[2,3-b]pyrrolyl, 5H-thieno[2,3-b]pyrrolyl, pyrrolo[3,4-b]pyrrolyl, pyrrolo[3,2-b]pyrrolyl, pyrrolo[2,3-b]pyrrolyl,

dihydropyrrolo[3,2-b]pyrrolyl, dihydropyrrolo[2,3-b]pyrrolyl, 5H-pyrrolo[3,2-d]oxazole, 5H-pyrrolo[3,2-d]thiazole, pyrrolopyrimidinyl, pyrrolopyridinyl, pyrazolopyrimidinyl and pyrazolopyridinyl.

[0058] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures where there is a replacement of hydrogen by deuterium or tritium, or a replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, as a nonlimiting example, as analytical tools or probes in biological assays.

[0059] It is to be understood that, when a disclosed compound has at least one chiral center, the present invention encompasses one enantiomer of inhibitor free from the corresponding optical isomer, racemic mixture of the inhibitor and mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a mixture is enriched in one enantiomer relative to its optical isomers, the mixture contains, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95% 99% or 99.5%.

[0060] The enantiomers of the present invention may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

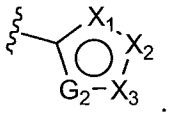
[0061] When a disclosed compound has at least two chiral centers, the present invention encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diasteromeric pairs, mixtures of diasteromers, mixtures of diasteromeric pairs, mixtures of diasteromers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diasteromeric

pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s). When a mixture is enriched in one diastereomer or diastereomeric pair(s) relative to the other diastereomers or diastereomeric pair(s), the mixture is enriched with the depicted or referenced diastereomer or diastereomeric pair(s) relative to other diastereomers or diastereomeric pair(s) for the compound, for example, by a molar excess of at least 50%, 75%, 90%, 95%, 99% or 99.5%.

[0062] The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Specific procedures for chromatographically separating diastereomeric pairs of precursors used in the preparation of compounds disclosed herein are provided the examples herein.

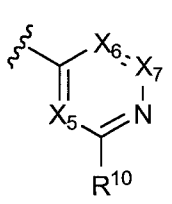
[0063] *3. Description of Exemplary Compounds:*

[0064] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**, CY is:

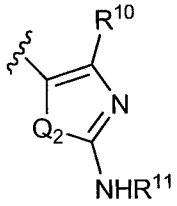


[0065] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, X_1 is N, G_2 is -N($R^{3'}$)-, and X_2 and X_3 are CH. In certain other embodiments, X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH. In certain other embodiments, X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH. In certain other embodiments, X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

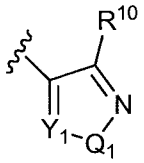
[0066] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, HY is selected from:



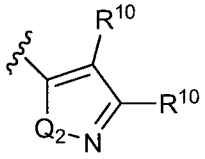
H,



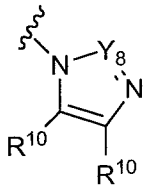
J,



K,



L, or



M;

wherein each occurrence of X_5, X_6, and X_7 is independently –CR^{10} or N, provided no more than

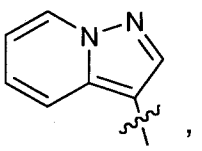
two occurrences of X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

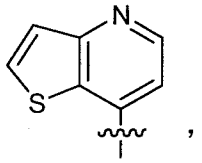
each occurrence of Y_1 and Y_7 is independently $-CR^{10}$ or N;

or wherein two adjacent occurrences of X_6 and X_7, or Y_1 and Q_1, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

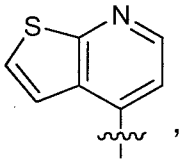
[0067] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, HY is selected from:



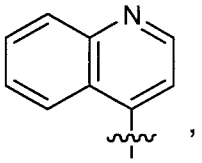
i



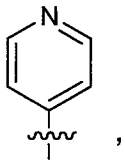
ii



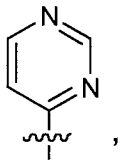
iii



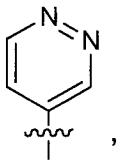
iv



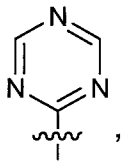
v



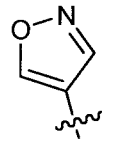
vi



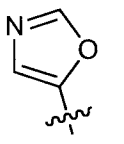
vii



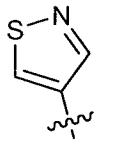
viii



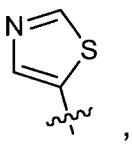
ix



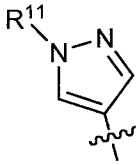
x



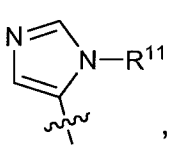
xi



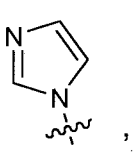
xii



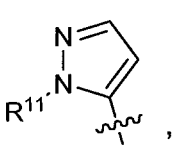
xiii



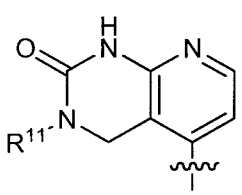
xiv

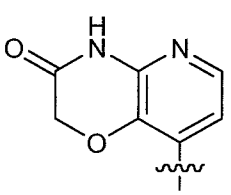


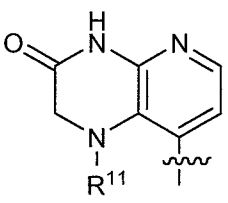
xv

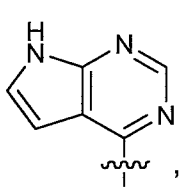


xvi

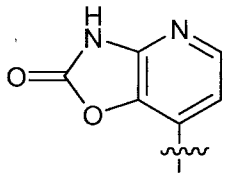
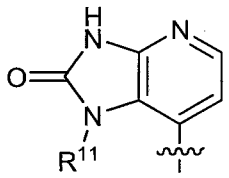
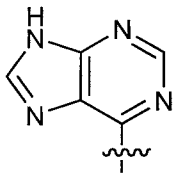
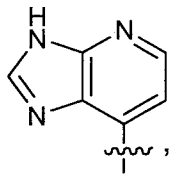




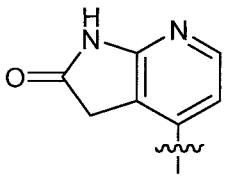
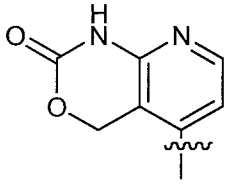
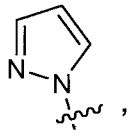




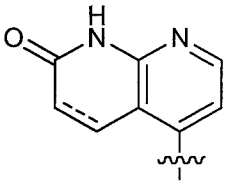
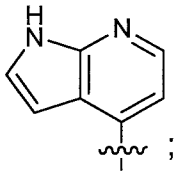
xvii xviii xix xx


,

,

,

,

xxi xxii xxiii xxiv


,

,

,

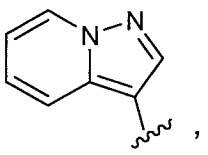
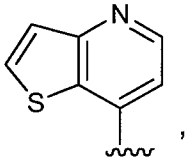
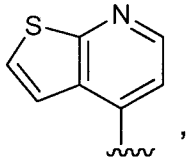
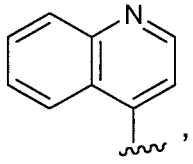
xxv xxvi xxvii


, or

;

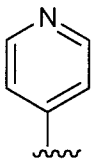
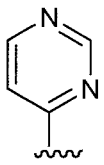
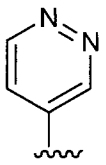
xxviii xxix

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

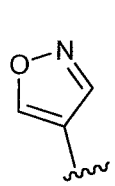
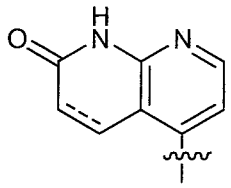
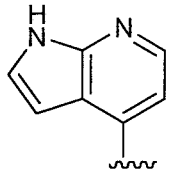
[0068] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a,**, HY is selected from:


,

,

,

,

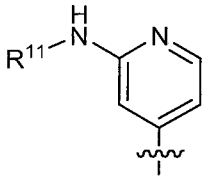
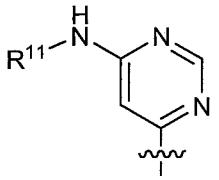
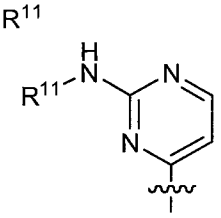
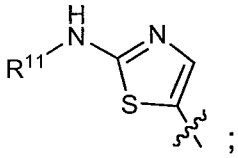
i ii iii iv


,

,

,

v vi vii

ix **xxviii** **xxix;**

xxx **xxxi** **xxxii** **xxxiii**

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

[0069] In yet other embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, G_1 is $C(R^8)$. In other embodiments, G_1 is CH.

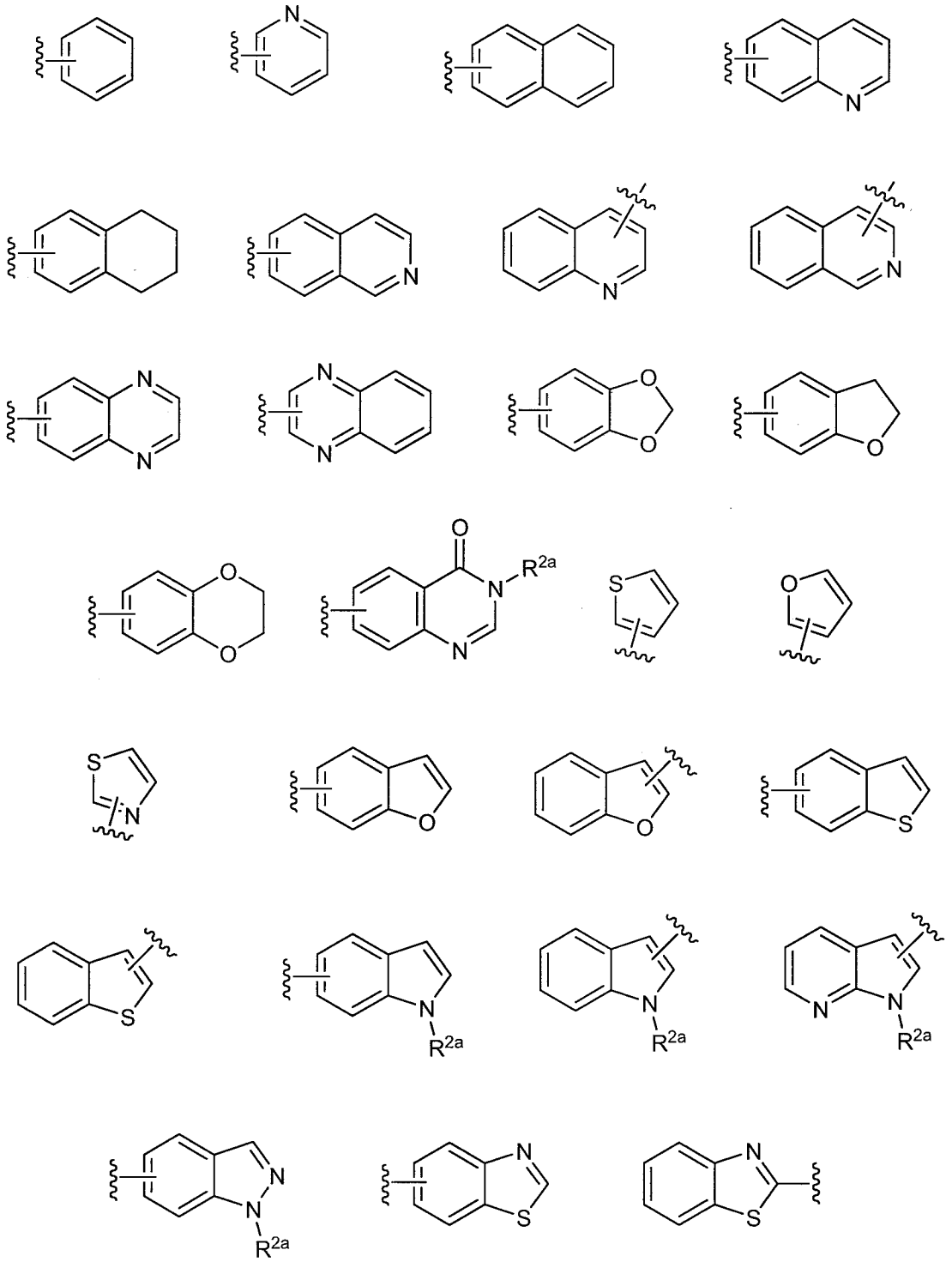
[0070] In still other embodiments, G_1 is N.

[0071] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,W is -$C(R^7)_2$-, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN; and wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, -$C(O)R^{7a}$, or -$S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring.

[0072] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, W is –$C(H)(N(R^{7b})_2)$-, -CH_2-, -$C(H)(OR^{7a})$-, -NR^{7b}-, or –$N(R^{7a})C(O)$-, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0073] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

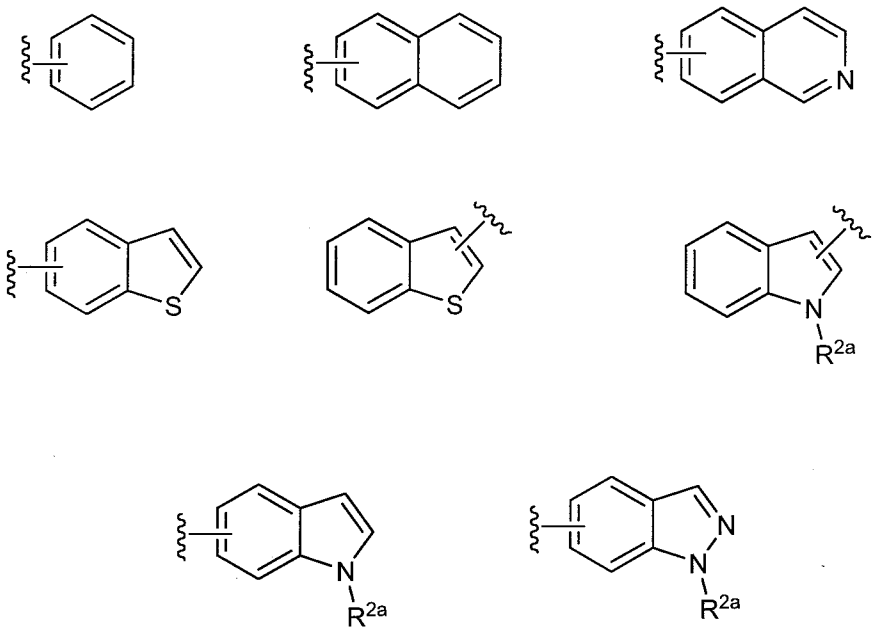
[0074] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0075] In certain other embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0076] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

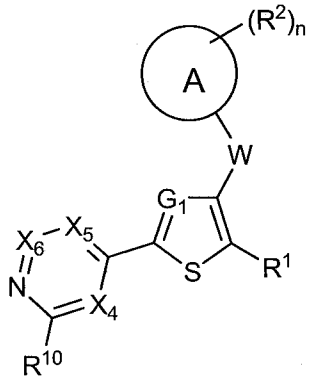
[0077] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0078] In certain embodiments, for compounds of general formula **IA, IA-a, IB** or **IB-a**,, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3}

alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[0079] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0080] In still other embodiments, a compound having the structure of formula **II** is provided:



II

wherein:

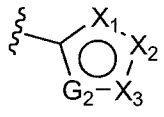
X_4, X_5 and X_6 are each independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5 and X_6 are N;

or two adjacent groups selected from R^{10}, X_4, X_5, and X_6, taken together, form an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0081] In some embodiments, for compounds of formula **II**, one of X^4, X^5, or X^6 is N.

[0082] In still other embodiments, for compounds of formula **II**, all of X^4, X^5, or X^6 are CR^{10}.

[0083] In other embodiments, for compounds of formula **II**, each occurrence of R^{10} is independently selected from –CN, $-OR^{10a}$, $-N(R^{11})_2$, halogen, C_{1-4}alkyl, $-N(R^{11})COR^{10a}$, or wherein two occurrences of R^{10}, taken together with the atoms to which they are bound form an optionally substituted group selected from a fused 5- or 6-membered cycloaliphatic, 4-10-membered heterocyclyl, 6-10-membered aryl or 5-10-membered heteroaryl ring, wherein the heterocyclyl and heteroaryl rings have 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0084] In some other embodiments, for compounds of formula **II**, CY is 

.

[0085] In some other embodiments, for compounds of formula **II**, X_1 is N, G_2 is $-N(R^{3'})-$, and X_2 and X_3 are CH.

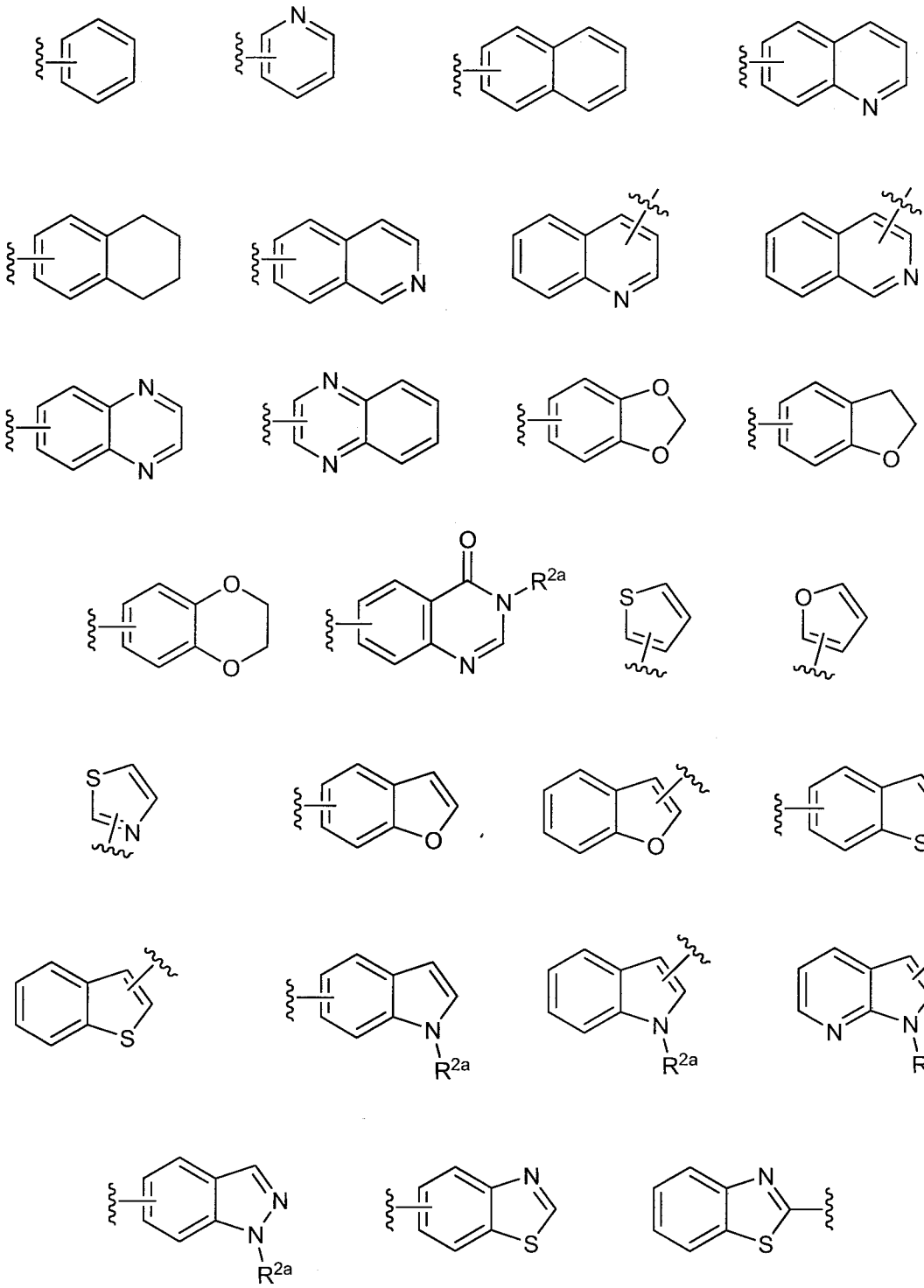
[0086] In some other embodiments, for compounds of formula **II**, X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH.

[0087] In some other embodiments, for compounds of formula **II**, X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH.

[0088] In some other embodiments, for compounds of formula **II**, X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

[0089] In some other embodiments, for compounds of formula **II**, Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

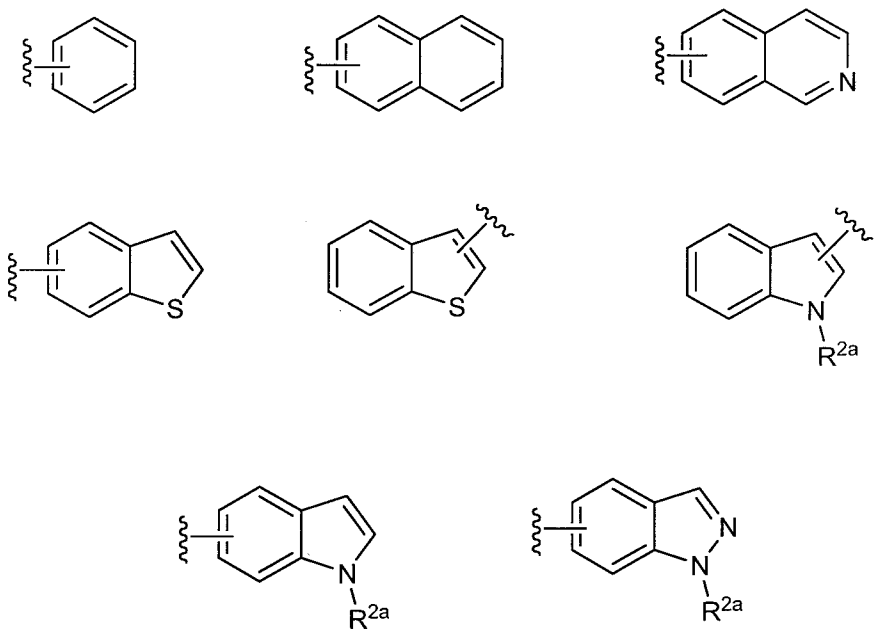
[0090] In other embodiments, for compounds of formula **II**, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0091] In certain other embodiments, for compounds of general formula **II**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0092] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -NHS(O)$_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[0093] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0094] In some other embodiments, for compounds of formula **II**, Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl,

-OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, $NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[0095] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[0096] In some other embodiments, for compounds of formula **II**, W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or –CN; and

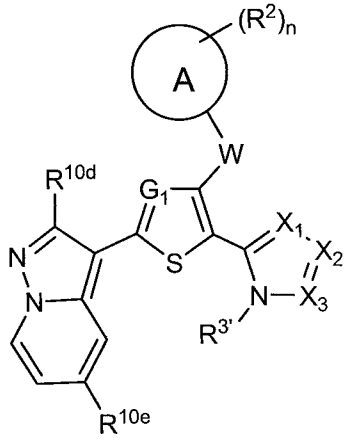
wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0097] In some other embodiments, for compounds of formula **II**, W is $–C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $–N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0098] In still other embodiments, a compound having the structure of formula **III** is provided:



III

wherein R^{10d} is hydrogen or optionally substituted C_{1-4}alkyl, and R^{10e} is R^{10}.

[0099] In some other embodiments, for compounds of formula **III**, R^{10e} is $-T_1-R^{10b}$, or hydrogen.

[00100] In still other embodiments, for compounds of formula **III**, R^{10e} is hydrogen, $-CH_2N(R^{11})_2$, or $-CH_2N(R^{11})C(=NR^{11})N(R^{11})_2$, wherein R^{11} is $-C(O)R^{11a}$, an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00101] In some other embodiments, for compounds of formula **III**, R^{11} is an optionally substituted C_{1-6} aliphatic group, the C_{1-6} aliphatic group is further defined as $-(CH_2)_xR^{11b}$ or $-(CH_2)_xN(R^{11b})_2$, $-(CH_2)_xN(R^{11b})C(O)R^{11b}$, or $-(CH_2)_xN(R^{11b})C(O)OR^{11b}$, wherein R^{11b} is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and x is 1 to 3.

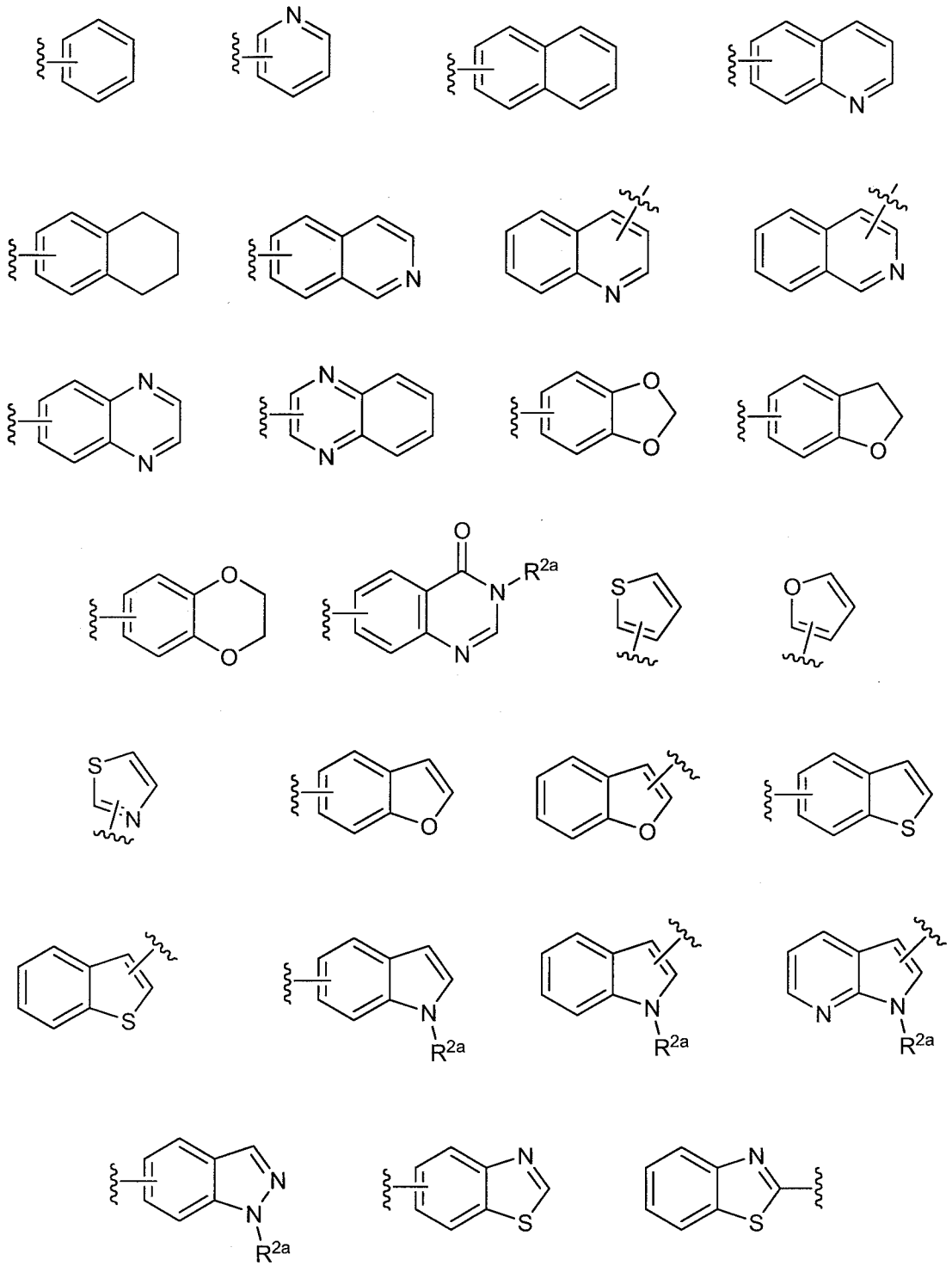
[00102] In some other embodiments, for compounds of formula **III**, X_1 is N, and X_2 and X_3 are CH.

[00103] In some other embodiments, for compounds of formula **III**, X_1 and X_2 are N, and X_3 is CH.

[00104] In some other embodiments, for compounds of formula **III**, X_3 is N, and X_1 and X_2 are CH.

[00105] In some other embodiments, for compounds of formula **III**, Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

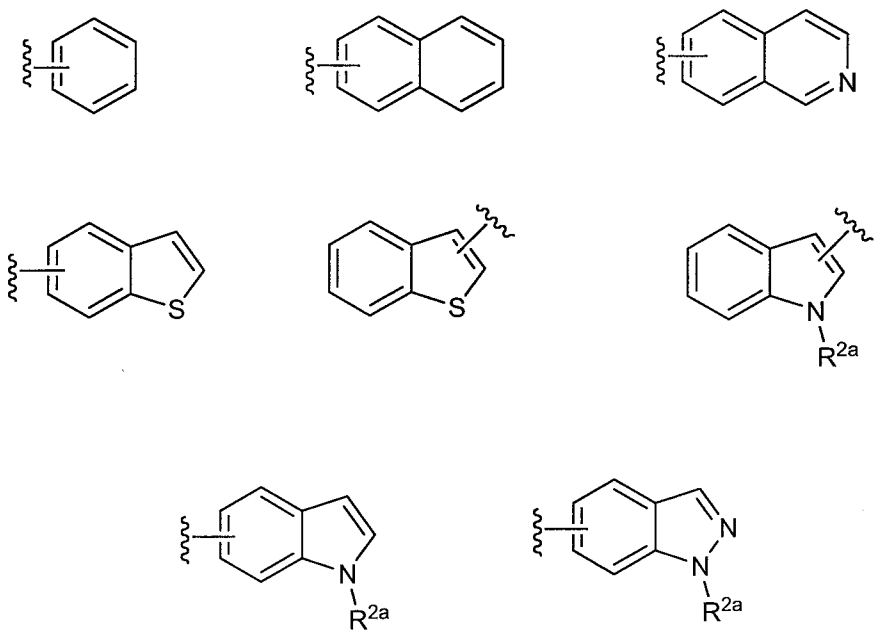
[00106] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00107] In certain other embodiments, for compounds of general formula **III**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00108] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00109] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00110] In some other embodiments, for compounds of formula **III**, Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl, -OC_{1-3}

alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00111] In some other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00112] In some other embodiments, for compounds of formula **III**, W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or -CN; and

wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

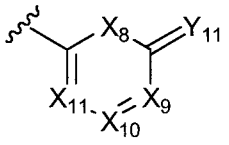
each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

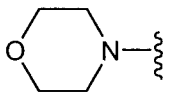
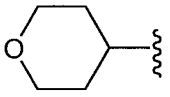
[00113] In some other embodiments, for compounds of formula **III**, W is $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00114] In certain embodiments, for compounds of general formula **IA-a**, **IB-a, IA, IB, II or III**, CY is:



[00115] In certain embodiments, for compounds of general formula IA-a, IB-a, IA, IB, II or III, X_8 and X_{11} are N, X_9 and X_{10} are CR^4, and Y_{11} is O.

[00116] In certain embodiments, for compounds of general formula **IA-a**, **IB-a, IA, IB, II or III**, HY is selected from:


and

,

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{14}.

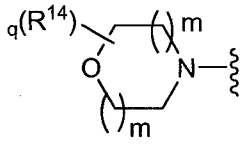
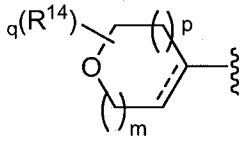
[00117] In yet other embodiments, for compounds of general formula **IA-a, IB-a, IA, IB, II or III**, G_1 is N.

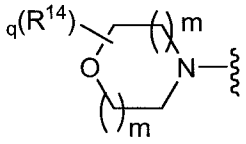
[00118] In still other embodiments, for compounds of general formula **IA-a, IB-a, IA, IB, II or III**, R^1 is -C(O)OH.

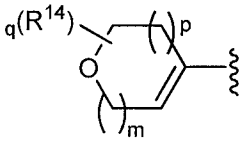
[00119] In certain other embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,** R^3 is H. In certain other embodiments, R^3 is C_{1-6} aliphatic. In certain embodiments, R^3 is C_{1-4} alkyl. In certain embodiments, R^3 is methyl or ethyl.

[00120] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,** G_1 is N. In certain other embodiments, G_1 is $C(R^8)$. In certain embodiments, G_1 is $C(R^8)$ and R^8 is –CN, halogen, or C_{1-6} aliphatic. In certain embodiments, R^8 is C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl. In certain embodiments, R^8 is –CN or C_{2-4} alkynyl.

[00121] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** HY is selected from:


or

.

[00122] In certain embodiments, HY is  wherein each occurrence of m is 1 and q is 0 or 1. In certain embodiments, q is 0.

[00123] In certain embodiments, HY is  wherein m and p are 1 and q is 0 or 1. In certain embodiments, q is 0.

[00124] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and each occurrence of R^{7b} is independently hydrogen,

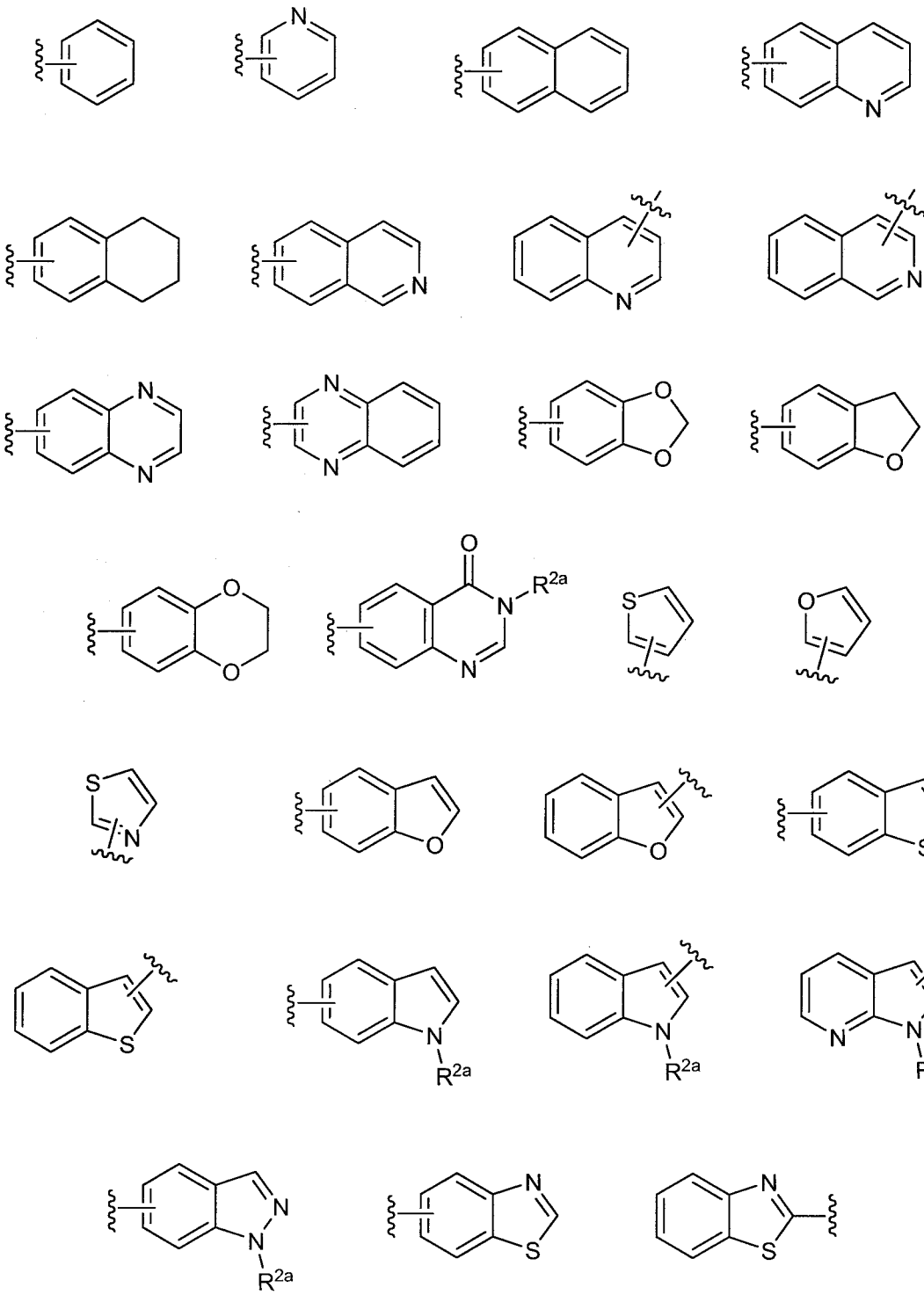
optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00125] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00126] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** W is a covalent bond.

[00127] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

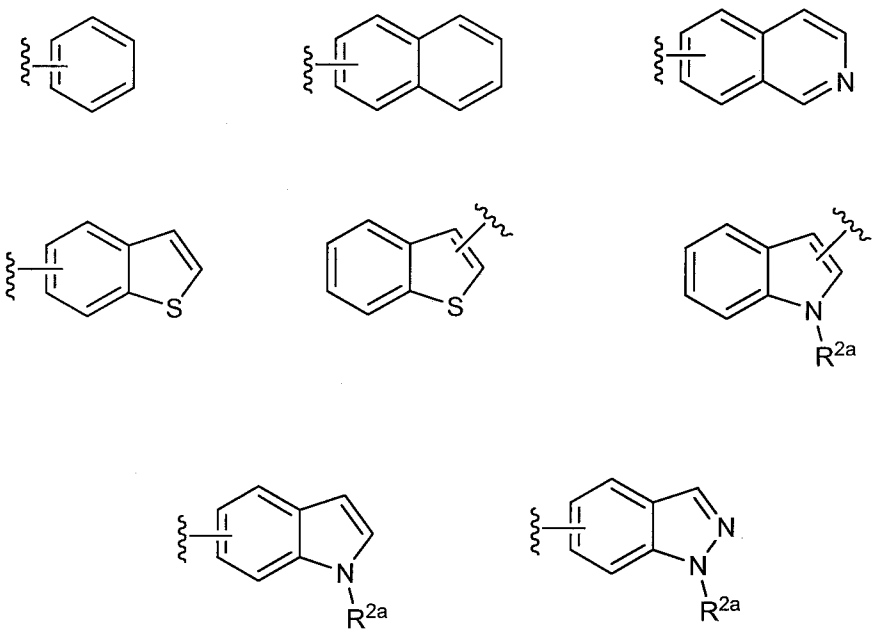
[00128] In other embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,** ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00129] In certain other embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00130] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00131] In yet other embodiments, ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00132] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00133] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

[00134] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00135] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

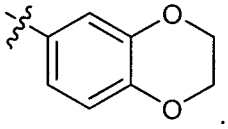
[00136] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00137] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00138] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

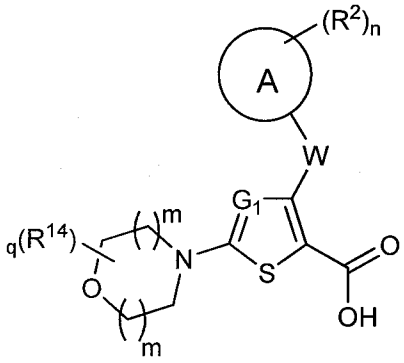
[00139] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

[00140] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00141] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,,** Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is  .

[00142] In certain embodiments, for compounds of general formula **IA-i-a, IB-i-a, IA-i, or IB-i,,** Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00143] In still other embodiments, a compound having the structure of formula **II-i** is provided:



II-i

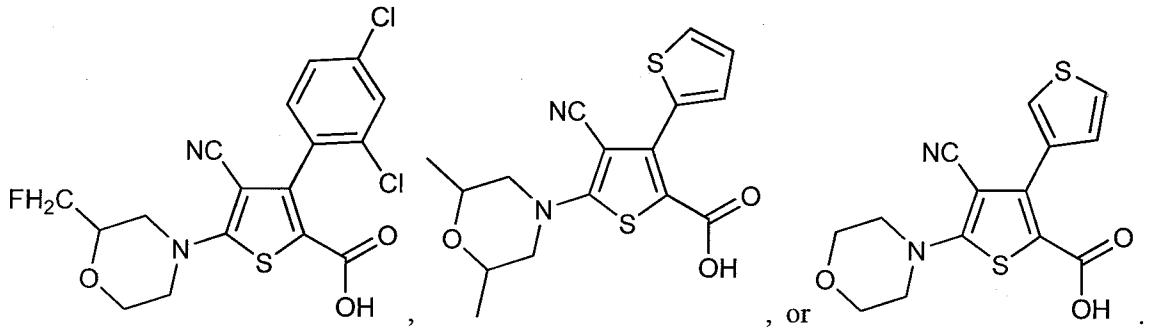
wherein Ring A, G_1, W, R^2, n, m, q, and R^{14} are as defined for the compounds described generally above and in subsets herein.

[00144] In certain embodiments, for compounds of general formula **II-i**:

a) when G_1 is C-CN, HY is unsubstituted morpholine, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:



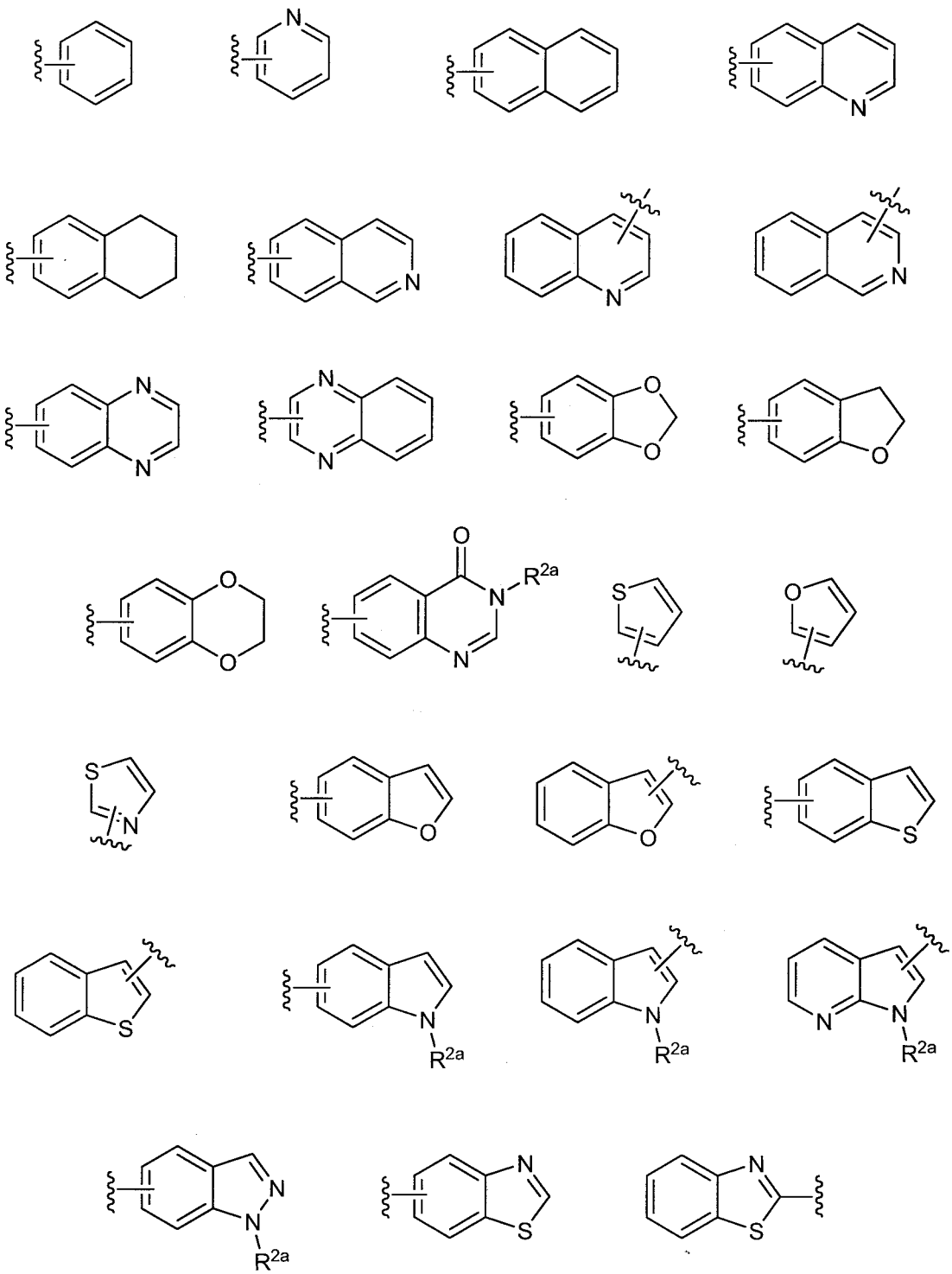
[00145] In certain embodiments, for compounds of general formula **II-i**, W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00146] In certain embodiments, for compounds of general formula **II-i**, W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00147] In certain embodiments, for compounds of general formula **II-i**, W is a covalent bond.

[00148] In certain embodiments, for compounds of general formula **II-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

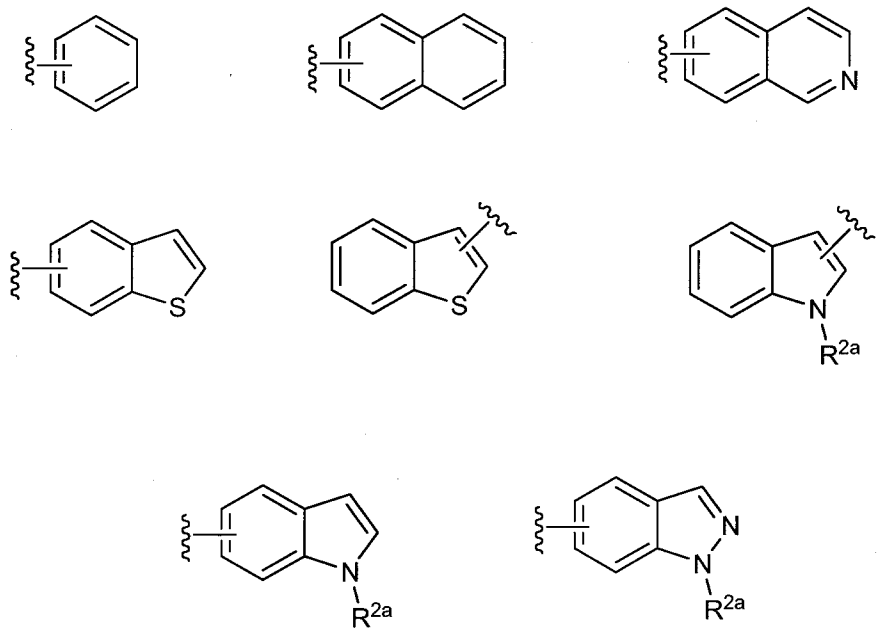
[00149] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00150] In certain other embodiments, for compounds of general formula **II-i**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00151] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00152] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00153] In certain embodiments, for compounds of general formula **II-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen,

or sulfur; n is 0 to 3, and W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

[00154] In certain embodiments, for compounds of general formula **II-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl,

$-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00155] In certain embodiments, for compounds of general formula **II-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

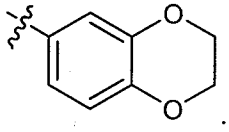
[00156] In certain embodiments, for compounds of general formula **II-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00157] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00158] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

[00159] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

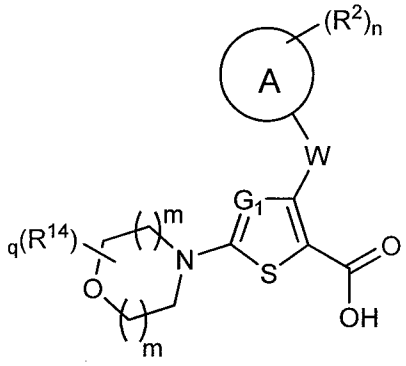
[00160] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00161] In certain embodiments, for compounds of general formula **II-i**, Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is  .

[00162] In certain embodiments, for compounds of general formula **II-i**, Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00163] In certain embodiments, for compounds of general formula **II-i**, each occurrence of m is 1 and q is 0.

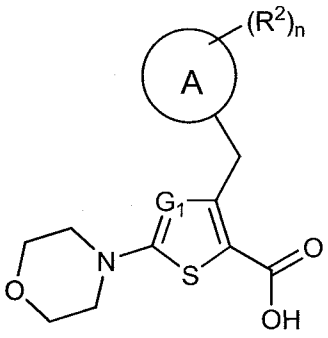
[00164] In still other embodiments, a compound having the structure of formula **II-i** is provided:



II-i

[00165] wherein G_1 is N or $-CR^8$, and R^8 is –CN; ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3; and W is $-C(R^7)_2-$, or >=O, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-OR^{7a}$, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00166] In still other embodiments, a compound having the structure of formula **III-i** is provided:

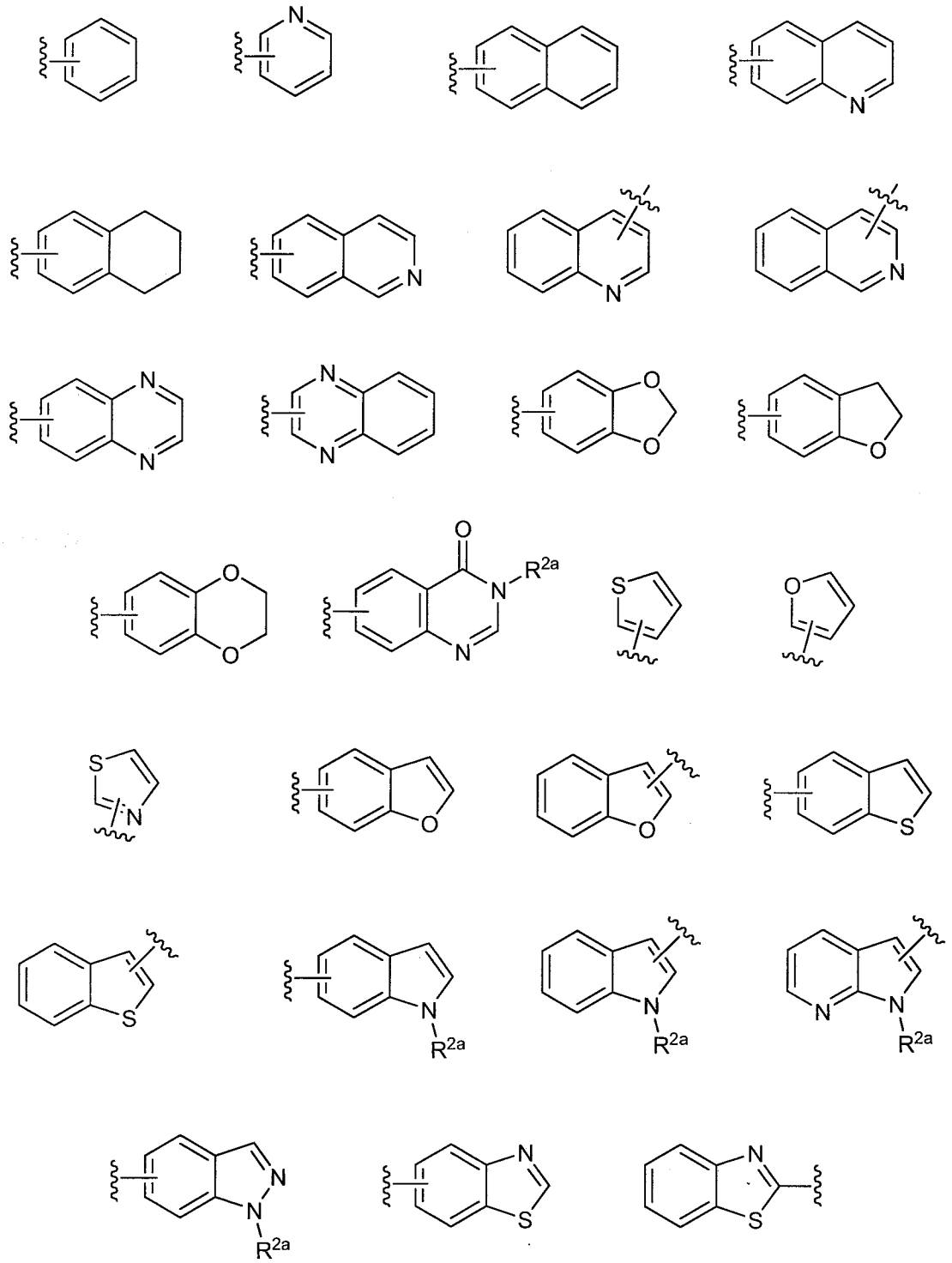


III

wherein G_1 is N or $-CR^8$, and R^8 is –CN; and wherein Ring A, n and R^2 are as defined for the compounds described generally and in subsets herein.

[00167] In certain embodiments, for compounds of general formula **III-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

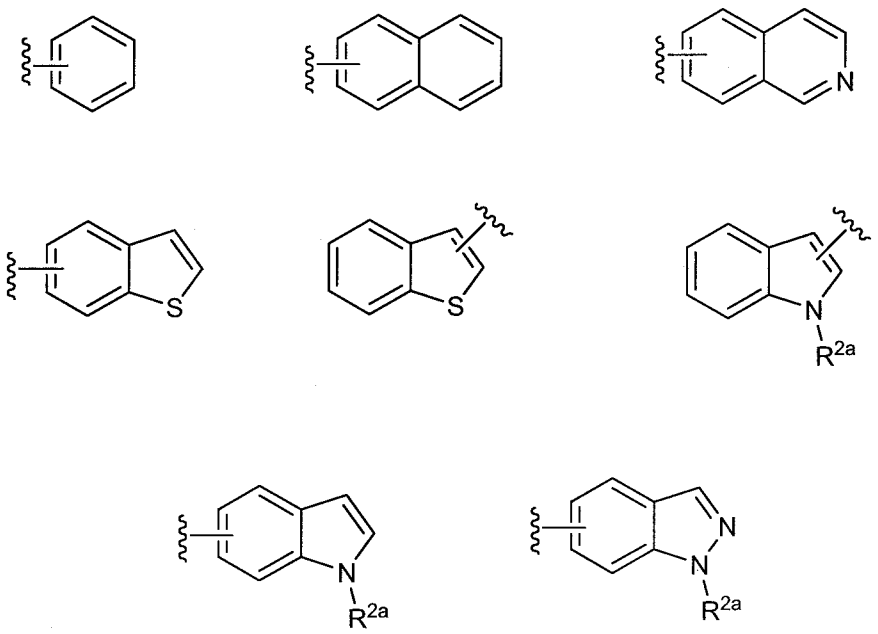
[00168] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00169] In certain other embodiments, for compounds of general formula **III-i**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00170] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00171] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00172] In certain embodiments, for compounds of general formula **III-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl,

$-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00173] In certain embodiments, for compounds of general formula **III-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

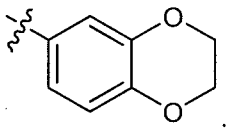
[00174] In certain embodiments, for compounds of general formula **III-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00175] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00176] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

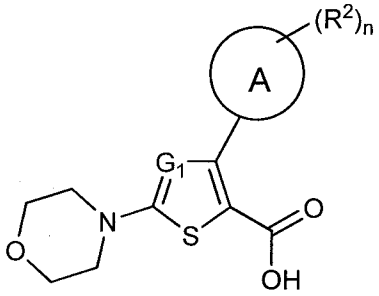
[00177] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

[00178] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00179] In certain embodiments, for compounds of general formula **III-i**, Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is  .

[00180] In certain embodiments, for compounds of general formula **III-i**, Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00181] In yet other embodiments, a compound having the structure of formula **IV-i** is provided:



IV-i

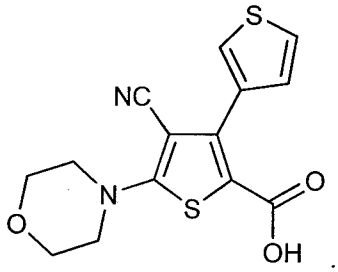
wherein Ring A, G_1, n and R^2 are as defined for compounds described generally above in subsets herein.

[00182] In certain embodiments, for compounds of general formula **IV-i**:

a) when G_1 is C-CN, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

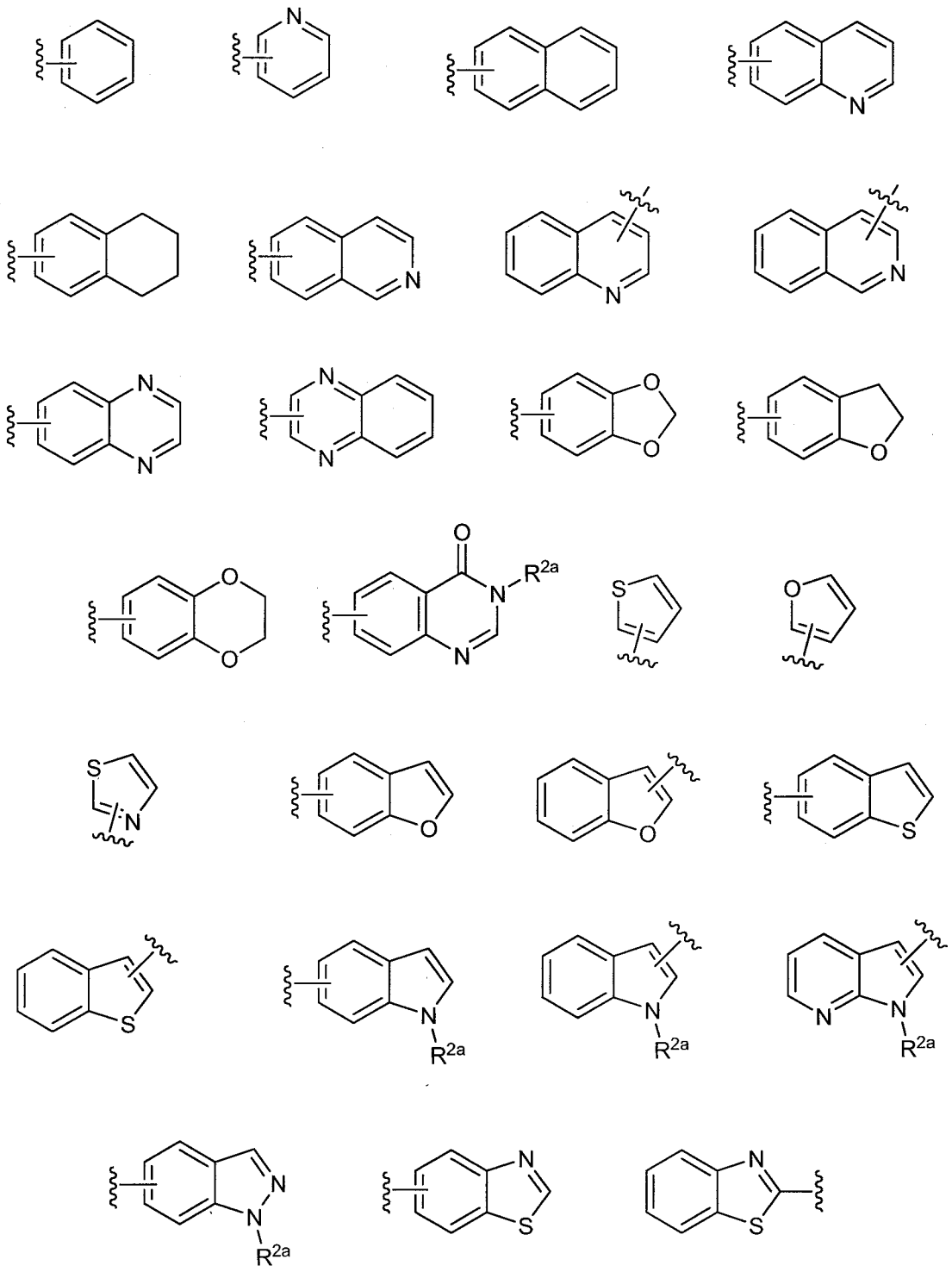
b) when G_1 is N, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:



[00183] In certain embodiments, for compounds of general formula **IV-i**, Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

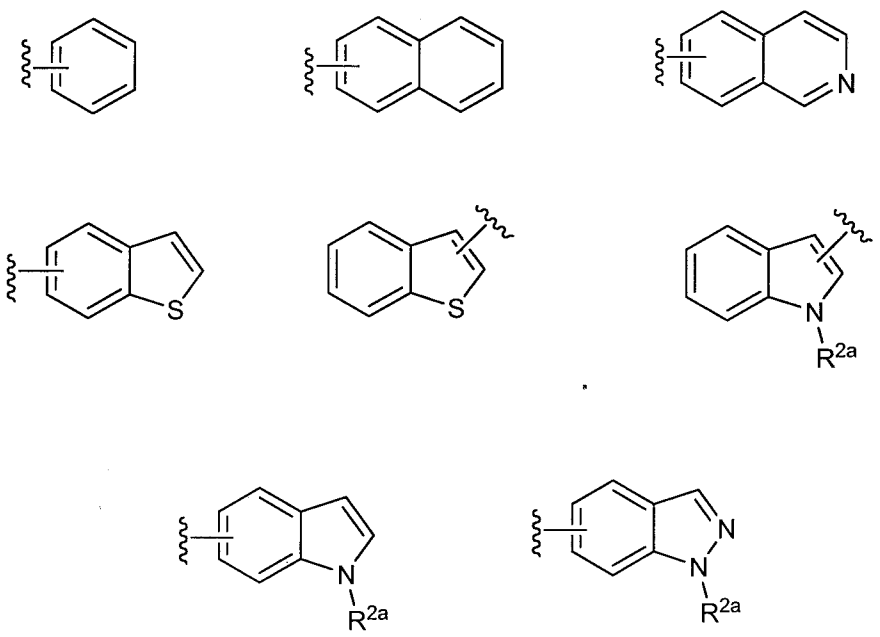
[00184] In other embodiments, ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00185] In certain other embodiments, for compounds of general formula **VI-i**, Ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00186] In still other embodiments, ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00187] In still other embodiments,ring A is a naphthyl group, R^2 is halogen and n is 1 to 2. In yet other embodiments, ring A is a naphthyl group and n is 0. In yet other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00188] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl,

$-OC_{1-3}$ haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -NHS$(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

[00189] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, -NHC(O)C_{1-3} alkyl, or $-T_2-R^{12d}$, T_2 is an optionally substituted C_{1-6} alkylene chain, R^{12d} is $-N(R^{7b})_2$, and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

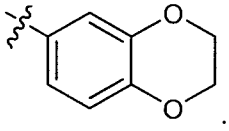
[00190] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3. In certain embodiments, Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

[00191] In still other embodiments, Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

[00192] In still other embodiments, Ring A is a phenyl group, R^2 is halogen or $-(CH_2)N(R^{7b})_2$ and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic, or any two occurrences of R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 2.

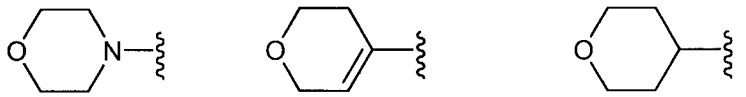
[00193] In certain embodiments, Ring A is a phenyl group, n is 1, and R^2 is in the para position. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions. In certain other embodiments, Ring A is a phenyl group, n is 2, and the two R^2 groups are in the ortho and meta positions, and para with respect to each other.

[00194] In certain embodiments, Ring A is 2-chloro-5(dimethylaminomethyl)phenyl. In certain other embodiments, Ring A is 2-chloro-5(pyrrolidin-1-ylmethyl)phenyl.

[00195] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a 2-naphthyl group. In certain other embodiments, Ring A is  .

[00196] In certain embodiments, for compounds of general formula **IV-i**, Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, Ring A is substituted with one or more C_{1-3} alkyl groups.

[00197] In certain embodiments, for compounds of general formula **IA-i** or **IB-i**, HY is selected from:



, , and ,

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{14}.

[00198] In yet other embodiments, for compounds of general formula **IA-i** or **IB-i**, G_1 is N.

[00199] *4. Uses, Formulation and Administration*

[00200] As discussed above, the present invention provides compounds that are useful as inhibitors of PI3K enzymes, and thus the present compounds are useful for treating proliferative, inflammatory, or cardiovascular disorders such as tumor and/or cancerous cell growth mediated by PI3K. In particular, the compounds are useful in the treatment of cancers in a subject, including, but not limited to, lung and bronchus, prostate, breast, pancreas, colon and recum, thyroid, liver and intrahepatic bile duct, hepatocellular, gastric, glioma/glioblastoma, endometrial, melanoma, kidney, and renal pelvis, urinary bladder, utering corpus, uterine cervix, ovary, multiple myeloma, esophagus, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, myeloid leukemia, brain, oral cavity, and pharynx, small intestine, non-Hodgkin lymphoma, and villous colon adenoma.

[00201] In some embodiments, compounds of the invention are suitable for the treatment of breast cancer, bladder cancer, colon cancer, glioma, glioblastoma, lung cancer, hepatocellular cancer, gastric cancer, melanoma, thyroid cancer, endometrial cancer, renal cancer, cervical cancer, pancreatic cancer, esophageal cancer, prostate cancer, brain cancer, or ovarian cancer.

[00202] In other embodiments, compounds of the invention are suitable for the treatment of inflammatory and cardiovascular disorders including, but not limited to, allergies/anaphylaxis, acute and chronic inflammation, rheumatoid arthritis; autoimmunity disorders, thrombosis, hypertension, cardiac hypertrophy, and heart failure.

[00203] Accordingly, in another aspect of the present invention, pharmaceutical compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00204] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00205] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of PI3K.

[00206] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically

acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00207] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00208] In yet another aspect, a method for treating a proliferative, inflammatory, or cardiovascular disorder is provided comprising administering an effective amount of a compound, or a pharmaceutical composition to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutical composition is that amount effective for treating a

proliferative, inflammatory, or cardiovascular disorder, or is that amount effective for treating cancer. In other embodiments, an "effective amount" of a compound is an amount which inhibits binding of PI3K and thereby blocks the resulting signaling cascades that lead to the abnormal activity of growth factors, receptor tyrosine kinases, protein serine/threonine kinases, G protein coupled receptors and phospholipid kinases and phosphatases.

[00209] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating the disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disease being treated and the severity of the disease; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00210] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00211] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and

sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00212] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00213] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00214] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00215] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00216] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a)

fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00217] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00218] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00219] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are

also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00220] While one or more of the inventive compounds may be used in an application of monotherapy to treat a disorder, disease or symptom, they also may be used in combination therapy, in which the use of an inventive compound or composition (therapeutic agent) is combined with the use of one or more other therapeutic agents for treating the same and/or other types of disorders, symptoms and diseases. Combination therapy includes administration of the therapeutic agents concurrently or sequentially. Alternatively, the therapeutic agents can be combined into one composition which is administered to the patient.

[00221] In one embodiment, the compounds of this invention are used in combination with other therapeutic agents, such as other inhibitors of PI3K or other inhibitors such as mTor. In some embodiments, a compound of the invention is administered in conjunction with a therapeutic agent selected from the group consisting of cytotoxic agents, radiotherapy, and immunotherapy. It is understood that other combinations may be undertaken while remaining within the scope of the invention.

[00222] Another aspect of the invention relates to inhibiting PI3K, activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, generally includes in vivo, in vitro, and ex vivo materials, and also includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00223] Still another aspect of this invention is to provide a kit comprising separate containers in a single package, wherein the inventive pharmaceutical compounds, compositions and/or salts thereof are used in combination with pharmaceutically acceptable carriers to treat disorders, symptoms and diseases where PI3K kinase plays a role.

EXPERIMENTAL PROCEDURES

[00224] **I-A. PREPARATION OF CERTAIN EXEMPLARY COMPOUNDS:** Compounds 1 through 92 (Shown in Table 1 below) were prepared using the general methods and specific examples described directly below.

[00225] 1. General Synthetic Methods and Intermediates:

[00226] The compounds of the present invention can be prepared by methods known to one of ordinary skill in the art and / or by reference to the schemes shown below and the synthetic examples that follow. Exemplary synthetic routes are set forth in Schemes 1-52 below, and in the Examples.

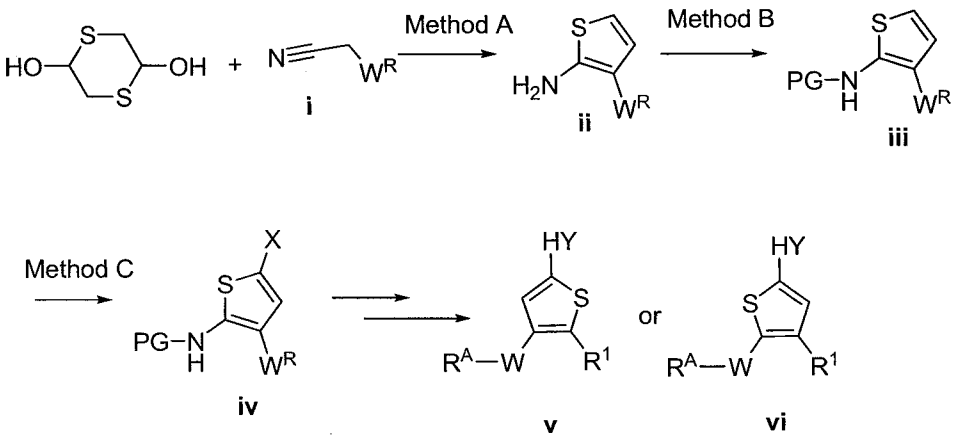
[00227] In methods defined below X represents halogen (Br, I or Cl), P is HY itself or a substituent convertible to HY by applying a generally known method, R^A represents Ring A, W^R is W-R^A itself, or a substituent convertible to W-R^A by applying a generally known method, W^L is R^A itself, or a part of W linker connected to R^A and Q is R^1 itself or a substituent convertible to R^1 by applying a generally known method.

[00228] Examples of the solvent for the below-mentioned reactions include, but are not limited to halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, aromatic hydrocarbons such as benzene, toluene, xylene and the like, alcohols such as methanol, ethanol, isopropanol, tert-butanol, phenol and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, DME and the like, acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like.

[00229] One of ordinary skill in the art will recognise that numerous variations in reaction conditions including variations in solvent, reagents, catalysts, reaction temperatures and times are possible for each of the reactions described. Variation of order of synthetic steps and alternative synthetic routes are also possible.

[00230] In many cases, synthesis can be started from commercially available thiophene / thiazole analogs to prepare target compounds. In some cases, specially functionalized thiophene / thiazole analogs can be prepared by the procedures described in Schemes 1-4.

[00231] **Scheme 1: General method for the synthesis of 2-aminothiophenes**

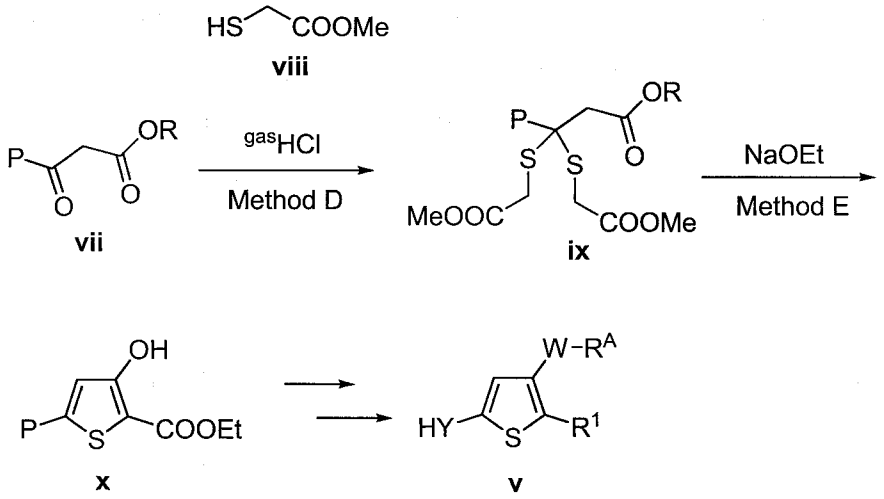


[00232] Scheme 1 shows a procedure to prepare compounds of formula **v**.

Condensation of nitriles **i** with 2,5-dihydroxy-1,4-dithiane can be accomplished using reported procedure (C. E. Stephens et al. Bioorg. Med. Chem., 2001, 9, 1123-1132, Method A). Aminothiophenes **ii** may then be protected with an appropriate protecting group, for example Boc using standard conditions, such as Boc anhydride, DMAP, dioxane (Method B). Halogenation of protected thiophenes **iii** may be achieved using a suitable reagent, for example NBS in DCM to afford halides of formula **iv** (Method C), that can be converted into compounds of formula **v** by a combination of generally known functional group conversion reactions described below.

[00233] Alternatively, reverse type of thiophene analogs **vi** can also be prepared using functional group transformations described below.

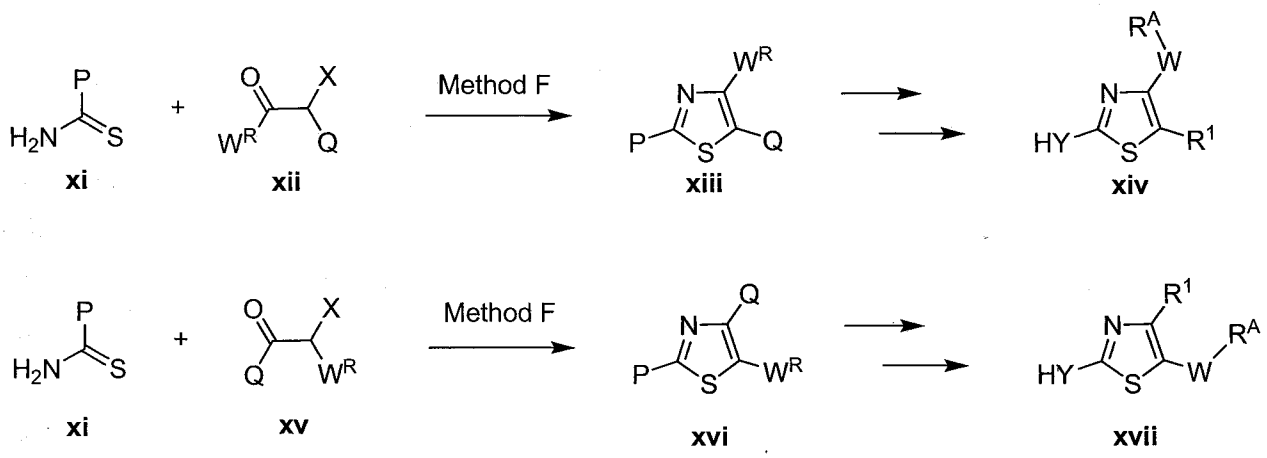
[00234] **Scheme 2: General method for the synthesis of 4-hydroxyl thiophenes**



[00235] Suitably functionalized 4-hydroxyl thiophenes can be prepared according to the published procedure such as M. D. Mullican, et al., J. Med. Chem., 1991, 34, 2186—2194.

For example, scheme 2 describes a general procedure for preparing 4-hydroxythiophenes of formula **x**. Beta-ketoesters **vii** may be treated with thiols, such as methyl thioglycolate **viii** in the presence of suitable acid, such as HCl in ethanol (Method D), to afford dithio-ketal **ix**, which may then be treated with an appropriate base, like sodium ethoxide in a suitable solvent, for example, ethanol, to give 4-hydroxythiophenes of formula **x** (Method E). These 4-hydroxythiophenes can be converted to target compounds **v** according to the procedures described below.

[00236] **Scheme 3: General method for the synthesis of substituted thiazoles**

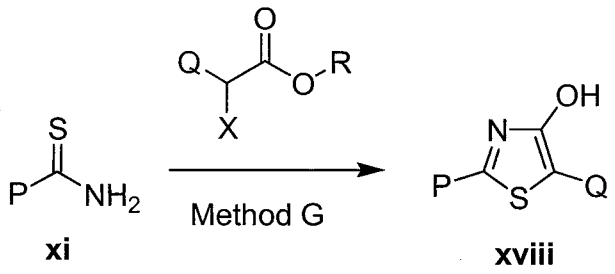


xi xii xiii xiv

xi xv xvi xvii

[00237] Scheme 3 shows a general route for the synthesis of compounds of formula **xiii** and **xvi**. Thioamides **xi** or thioureas (When P = NHR) may be treated with alpha-halogenated carbonyl compounds **xii** in a suitable solvent, such as isopropanol at elevated temprerature to give thiazoles **xiii**. (Method F). When P = NH_2, 2-aminothiazoles **xiii** that are obtained can be then subjected to Sandmeyer reaction to afford 2-halothiazoles **xxxi** (P = X), which can be used for further functional transformations described below. A conversion reaction from **xiii** to compounds **xiv** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.
If an alpha-halogenated carbonyl compound is suitably selected, i.e. **xv**, reverse type thiazole analogs **xvi** and **xvii** can be also prepared using well known organic functional group transformation reactions described below.

[00238] **Scheme 4: General method for the preparation of 4-hydroxythiazoles**



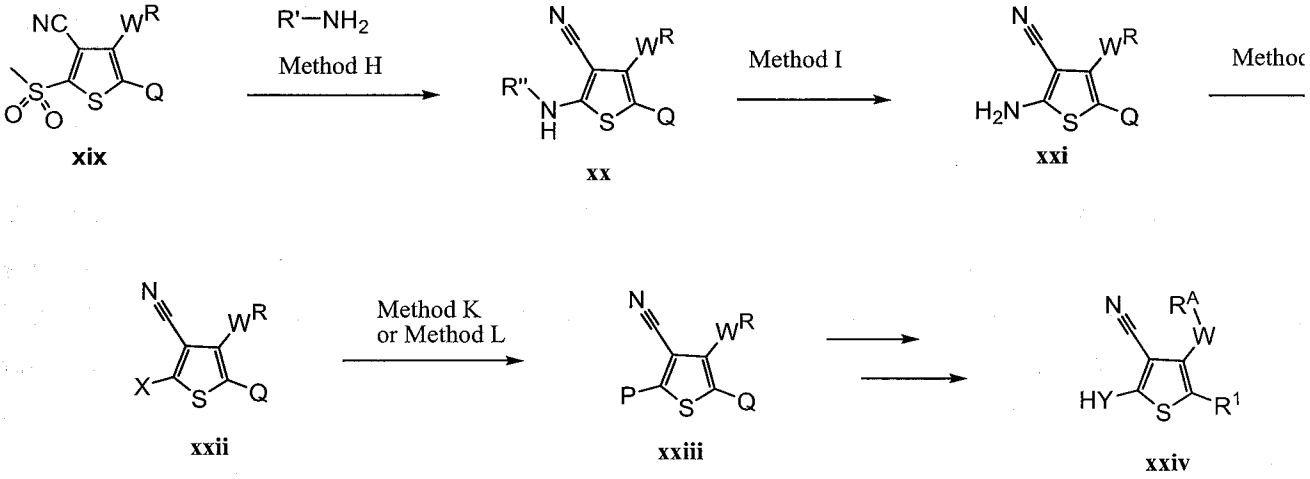
xi xviii

As shown in scheme 4, thioamides **xi** can be condensed with alpha-halogenated esters in a similar manner as reported by Rzasa, R.M. et al, Bioorg. Med. Chem. **2007,** *15*, 6574 to obtain 4- hydroxythiazole derivatives **xviii**. The reaction can be carried out in a suitable solvent, such as ethanol, in the presence of an appropriate base, *i.e.*, pyridine, under elevated temperature (Method G).

[00239] Schemes 5-19 describe procedures for basic functional group transformations on thiophene / thiazole central core scaffolds.

[00240] In the schemes 5-8, general functional group transformation procedures for introduction of the HY group are described.

[00241] Scheme 5: Introduction of HY to 3-cyanothiophenes



[00242] Scheme 5 describes the procedure for the introduction of HY to 3-cyanothiophene analogs by a known functional group transformation reaction.

As shown in Scheme 5, sulfones of formula **xix** (synthetic examples given in Mansanet et al, WO 2005070916) may be treated with amines R'-NH_2, such as 2,4-dimethoxybenzylamine, in a suitable solvent, *e.g.*, THF, at elevated temperature (Method H) to give **xx**.

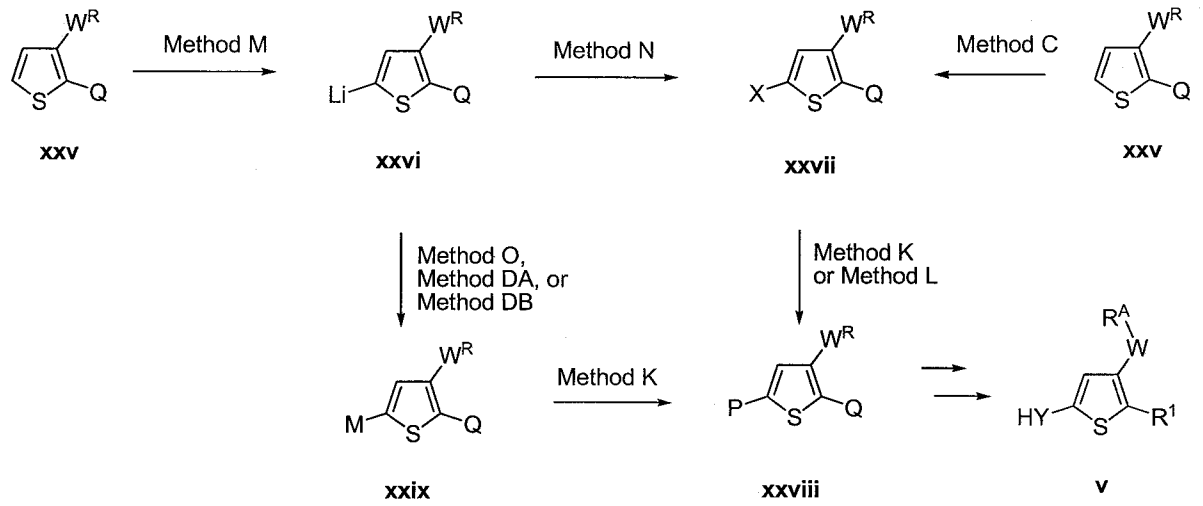
Deprotection of R'' group may be carried out using a standard procedure, in the case of dimethoxybenzyl group with an acid, such as TFA in DCM, to afford amines **xxi** (Method I).

Amines **xxi** can then be subjected to Sandmeyer reaction using appropriate reagents, such as methylene iodide and amyl nitrite in ACN (Method J).

The resulting halogenated thiophenes **xxii** can be coupled with aryl stannanes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in a suitable solvent, such as dioxane, at elevated temperature to give compounds of formula **xxiii** (Method K). Alternatively, boronic acids or esters can be used for such coupling reactions, for example $Pd(PPh_3)_4$, Na_2CO_3, DME/water, elevated temperature or microwave irradiation (Method L).

A conversion reaction from **xxiii** to compounds **xxiv** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.

[00243] Scheme 6: General method for the introduction of HY to 2-unsubstituted thiophenes.



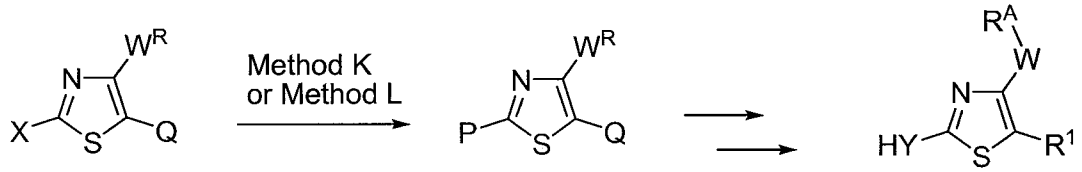
[00244] Scheme 6 shows a general route for introducing HY to unsubstituted 2-position of thiophene core.

2-unsubstituted thiophenes **xxv** can be treated with suitable base, such as n-BuLi in THF at low temperature, to produce lithiated thiophene intermediates **xxvi** (Method M). The intermediate organolithium species can be quenched with halogen molecule, for example iodine in a suitable solvent, such as THF, to afford halogenated compounds of formula **xxvii** (Method N). Alternatively, thiophenes **xxv** can be directly halogenated using suitable conditions, for example NBS in DCM to afford halogenated compounds of formula **xxvii** (Method C). Halides **xxvii** can be coupled with aryl stannanes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in a suitable solvent, such as dioxane at elevated temperature to give compounds of formula **xxviii** (Method K), or boronic acids or esters. with an appropriate catalyst, for example $Pd(PPh_3)_4$, in the presence of a suitable base, such as sodium carbonate, in DME-water mixture at elevated temperature (Method L) to afford compounds of formula **xxviii**. Alternatively, lithium intermediates **xxvi** can be transformed to organometallic reagents, such as stannanes by quenching with suitable tin halide, such as tributyltin chloride (Method O), or boronic esters, such as alkoxy-tetramethyl-1,3,2-dioxaborolane (method DA), or trifluoroborates by the subsequent treatment of boronic esters with a suitable fluorine source, such as KHF_2 (Method DB). Stannanes **xxix** may then be coupled with aryl halides, triflates, or mesylates using appropriate conditions, such as $Pd(PPh_3)_4$, CuI, LiCl in a suitable solvent, such as dioxane, at elevated temperature to give compounds of formula **xxviii** (Method K). Boronic acids, esters or trifluoroborates can be then coupled with aryl halides, triflates, or mesylates with an appropriate catalyst, for example $Pd(PPh_3)_4$, in the presence of a suitable base, such as sodium carbonate in DME-water mixture at elevated temperature

(Method L) to afford compounds of formula **xxviii**.

A conversion reaction from **xxviii** to compounds **v** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.

[00245] Scheme 7: General method for introduction of HY to 2-position of thiazole core.

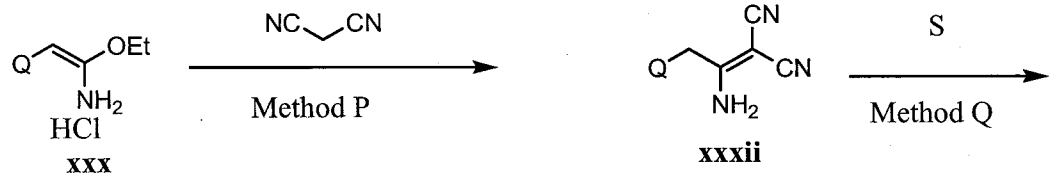


xxxi **xiii** **xiv**

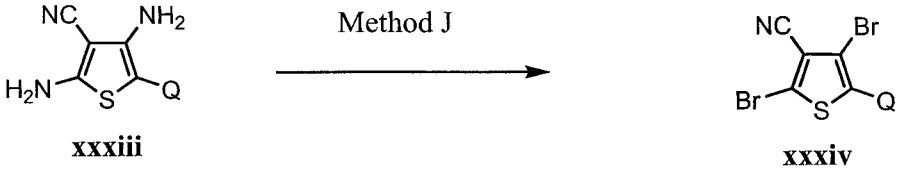
[00246] Scheme 7 shows a general route for introducing HY to 2-position of thiazole core scaffold. Halogenated thiazoles **xxxi**, which may be available as described in scheme 3, can coupled with suitable partners, such as boronic acids, stannanes, etc under standard Suzuki conditions, such as $Pd(PPh_3)_4$, Na_2CO_3, DME/water, elevated temperature or microwave irradiation (Method L), or standard Stille conditions, such as $Pd(PPh_3)_4$, CuI, LiCl, dioxane at elevated temperature (Method K) to afford compounds of formula **xiii**.

A conversion reaction from **xiii** to compounds **xiv** can be performed, for example, by a combination of generally known functional group conversion reactions shown below.

[00247] Scheme 8: General method for the synthesis of 3-cyanothiophenes



xxx **xxxii**

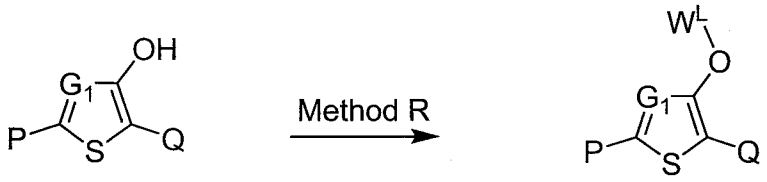


xxxiii **xxxiv**

[00248] Scheme 8 describes the procedure for the synthesis of 3-cyanothiophenes **xxxiv**. Substituted alkoxyethenamine **xxx** may be treated with malononitrile in the presence of a suitable base, such as TEA, in a suitable solvent, like chloroform, at elevated temperature to afford substituted aminoethylene malononitriles **xxxii** (Method P), that are treated with sulfur under suitable conditions, such as DMF and elevated temperature, to give diaminocyanothiophenes **xxxiii** (Method Q). Diamines **xxxiii** may then be subjected to a Sandmeyer reaction using appropriate reagents, such as copper(II)bromide, amyl nitrite in ACN at elevated temperature (Method J) to afford compounds of formula **xxxiv**.

[00249] Schemes 9—21 describe methods for the introduction of R^1 and W-R^A groups.

[00250] **Scheme 9: General method for the synthesis of preparation of 4-alkoxy thiophene / thiazole derivatives.**

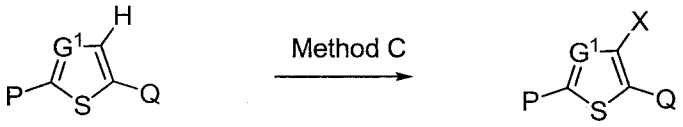


xviii **xxxv**

4-Alkoxy thiophenes/ thiazoles can be obtained by the conventional alkylation method of 4-hydroxythiazole derivatives obtained in scheme 4.

As shown in scheme 9, 4-hydroxy thiophenes / thiazoles **xviii** can be treated with alkyl halides using a suitable base, such as potassium carbonate, in a suitable solvent, for example DMF, at elevated temperature to afford compounds of formula **xxxv** (Method R).

[00251] **Scheme 10: General method for halogenation of thiophenes / thiazoles**



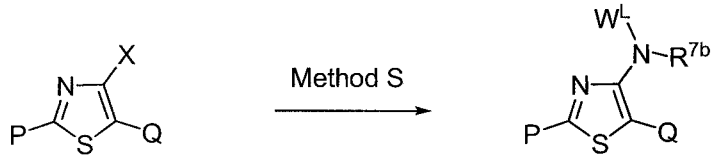
xxxvi **xxxvii**

[00252] Scheme 10 shows a general route for introducing halogen functionality at the 4-unsubstituted position of thiophene / thiazole core.

Halogenation of thiophene / thiazoles can be achieved in a similar manner as reported in the literature (Takami et al, Tetrahedron **2004**, *60*, 6155). For example, **xxxvi** is treated with a generally known halogenating reagent, such as bromine or N-bromosuccinimide, in a suitable solvent, such as DCM, at elevated temperature to afford compounds of formula **xxxvii** (Method C).

The halogenated thiazole **xxxvii** can be used for further functional group transformation shown below.

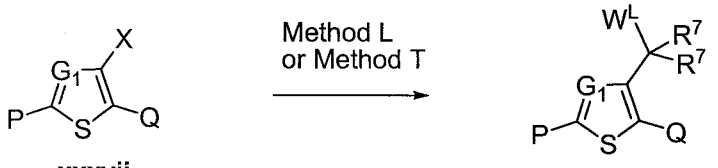
[00253] **Scheme 11: General method for the preparation of 4-aminothiazoles**



xxxviii **xxxix**

[00254] Scheme 11 shows general methods for the synthesis of 4-aminothiazole derivatives **xxxix** from 4-halogenated thiazoles **xxxviii**, which can be prepared by the procedure described in scheme 10. Displacement of a halogen group with an amine can be achieved in a similar manner as reported in the literature (J. Med. Chem **2006**, *49*, 5769). Treatment of **xxxviii** with an amine at elevated temperature in a suitable solvent, such as DMF, can lead to amines **xxxix** (Method S). If necessary a base, such as sodium carbonate, can be added.

[00255] Scheme 12: General method for introducing carbon functionality to 4-halogenated thiophenes / thiazoles.

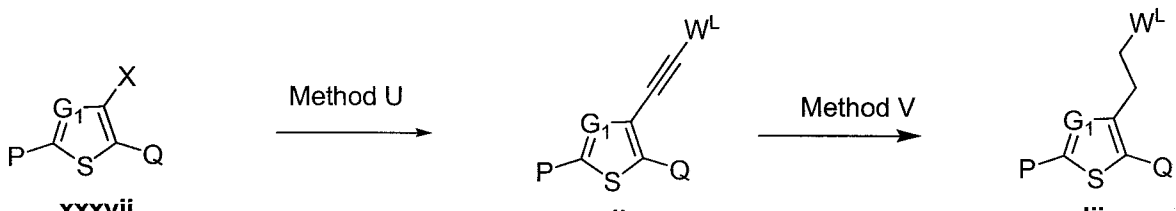


xxxvii **xv**

[00256] As shown in Scheme 12, carbon functionality can be introduced by the well known cross-coupling technique from the 4-halogenated thiophenes / thiazoles **xxxvii** which can be prepared by the procedure described in scheme 10.

For example, **xv** can be obtained from 4-halogenated thiophenes / thiazoles **xxxvii** by reaction with an organic boronic acid reagent, or an organic zinc reagent in a presence of palladium catalyst. Suzuki couplings with alkyl, alkenyl boronic acids or esters can be performed using $Pd(PPh_3)_4$, or a similar palladium catalyst, a suitable base, such as sodium carbonate in an appropriate solvent, such as DME/water, at elevated temperature (Method L), while $Pd(tBu_3P)_2$ can be used for Negishi coupling reactions, together with in a suitable solvent, such as THF, at elevated temperature (Method T).

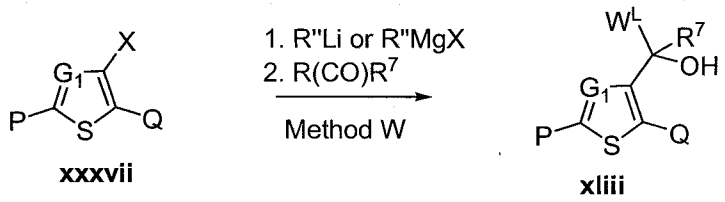
[00257] Scheme 13: General method for introducing carbon functionality to 4-halogenated thiophenes / thiazoles.



xxxvii **xli** **xlii**

[00258] Scheme 13 shows a general method for the synthesis carbon substituted thiophenes/thiazoles. 4-halogenated thiophenes/thiazoles **xxxvii** can be treated with an alkyne in the presence of a suitable catalyst, for example $Pd(PPh_3)_4$, CuI, base, such as TEA in a suitable solvent, like DCM, to afford alkynes **xli** (Method U). Compounds **xli** can be then reduced to alkyl substituted thiophenes/thiazoles **xlii**, for example using hydrogenation with Pd/C in a suitable solvent, such as ethanol (Method V)

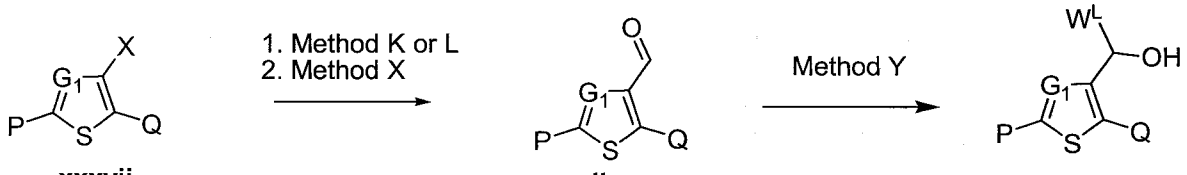
[00259] **Scheme 14: General method for introducing carbon functionality to halogenated thiophenes.**



xxxvii **xliii**

[00260] Scheme 14 shows a general method for the synthesis of carbon substituted thiophenes. Halogenated thiophenes **xxxvii** can be treated with alkyllithium, arryllithium or alkylmagnesium reagents, such as of *n*-BuLi at low temperature to generate intermediate metallated thiophenes that are subsequently treated with aldehydes or ketones to afford carbinols **xliii** (Method W).

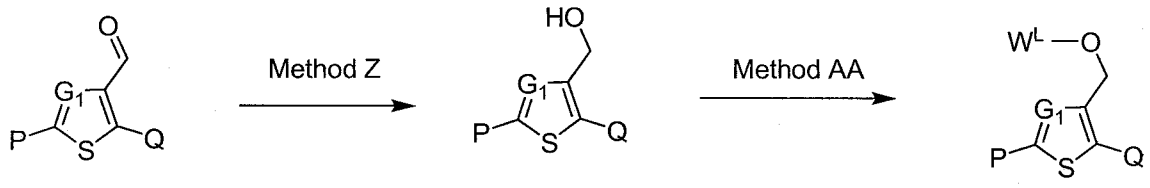
[00261] **Scheme 15: General method for introducing carbon functionality to 4-halogenated thiophenes / thiazoles.**



xxxvii **xliv** **xlv**

[00262] Scheme 15 shows a general method for the synthesis carbon substituted thiophenes/thiazoles. Halogenated thiophenes/thiazoles **xxxvii** can be treated with vinylorganometallic reagents, for example vinyltributylstannane under Stille conditions (Method K), or vinyltrifluoroborate under Suzuki conditions (Method L) to afford vinyl thiophenes/thiazoles, that can be oxidized to aldehydes **xliv** using a suitable method, for example OsO_4, sodium periodate in water-dioxane mixture (Method X). Aldehydes **xliv** can be then treated with organometallic reagents, such as Grignard or alkyl/aryllithium compounds in a suitable solvent, such as THF, at low temperature to afford carbinols of formula **xlv** (Method Y).

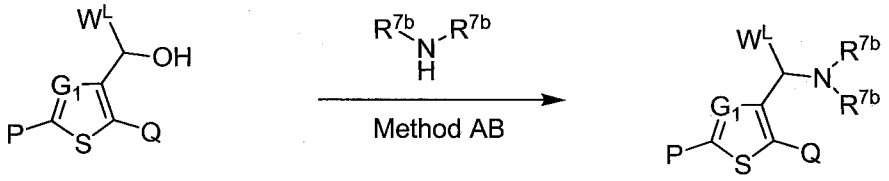
[00263] **Scheme 16: General method for the synthesis of ethers**



xliv xlvi xlvii

[00264] Scheme 16 shows a general method for the synthesis of alcohols **xlvi** and ethers **xlvii**. Aldehydes prepared as described in Scheme 15 above can be treated with a suitable reducing agent, such as $NaBH_4$ in an appropriate solvent, for example THF, to afford alcohols of formula **xlvi** (Method Z). Alcohols **xlvi** can be then alkylated using standard conditions, for example with alkyl halides in the presence of base, such as K_2CO_3, in THF to afford ethers **xlvii** (Method AA).

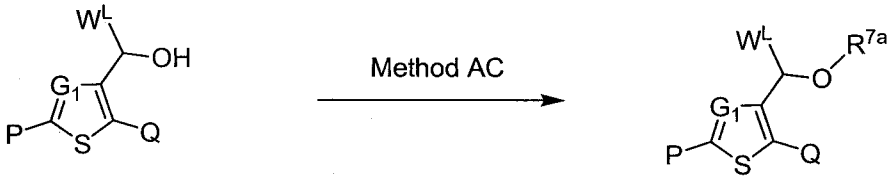
[00265] **Scheme 17: General method for the synthesis of amines**



xlv xlviii

[00266] Scheme 17 shows a general method for the synthesis of amines **xlviii**. As shown is Scheme 17, alcohols can be activated via sulfonyl esters, for example by reaction with methanesulfonic chloride and a base, such as pyridine in a suitable solvent, for example DCM. Sulfonyl esters are then treated with amines at elevated temperature to provide target amines **xlviii** (Method AB).

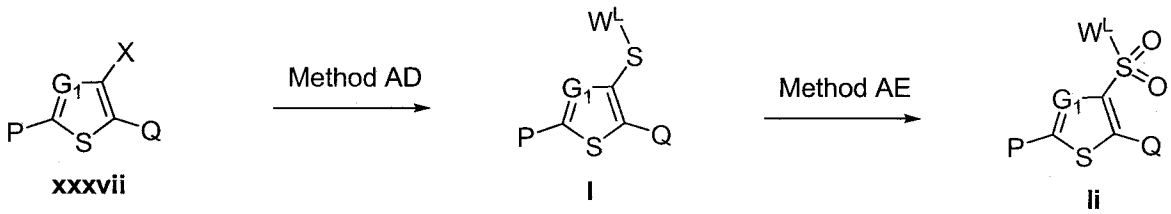
[00267] **Scheme 18: General method for the synthesis of ethers**



xlv il

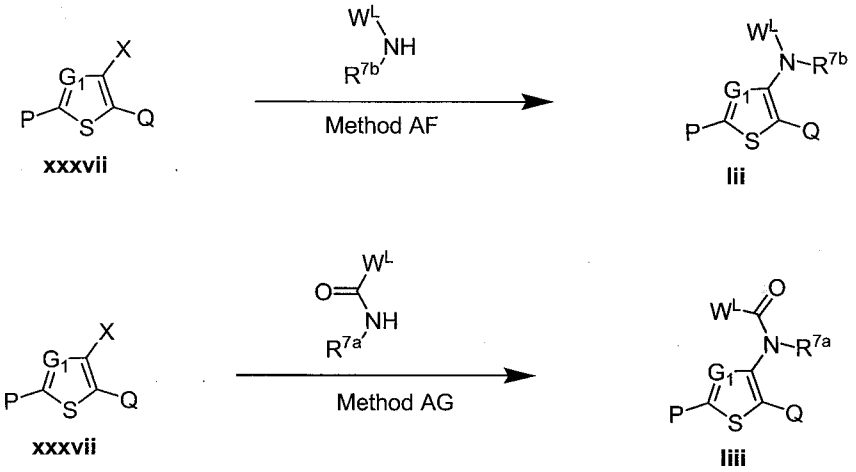
[00268] Scheme 18 shows a general method for the synthesis of ethers **il** when W^L is an aromatic or heteroaromatic group. As shown is Scheme 18, alcohols **xlv** are treated with an excess of alcohol, such as methanol, in the presence of an acid, like aqueous HCl with an optional co-solvent, for example dioxane at ambient temperature to afford ethers of formula **il**.

[00269] **Scheme 19: General method for introducing sulfur functionality**



[00270] As shown in Scheme 19, sulfur functionality can be introduced to the 4- halogenated thiazoles/thiophenes **xxxvii** by a similar manner as described by Rossignol et al, US2009036467. Treatment of **xxxvii** with thiols in the presence of a copper catalyst, like CuI in a suitable solvent, such as DMF, with an appropriate base, for example sodium hydroxide, at elevated temperature gives thioethers of formula **I** (Method AD). Thioethers **I** can subsequently be oxidized to sulfones **Ii** using a suitable oxidating agent, for example mCPBA in DCM (Method AE).

[00271] **Scheme 20: General method for Pd-catalyzed amination /amidation of 4-halogenated thiophenes / thiazoles**

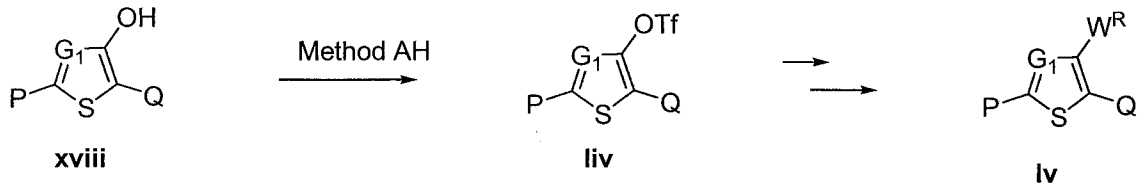


[00272] As shown in Scheme 20, amine or amide functionality can be introduced by the well known palladium catalyzed amination / amidation reaction, so called Buchwald coupling, to the 4-halogenated thiophenes / thiazoles **xxxvii**.

For example, halides **xxxvii** can be treated with amines using an appropriate Pd catalyst, such as Pd_2dba_3/BINAP, with a suitable solvent/base combination, for example NaOtBu in toluene at elevated temperature or using microwave irradiation to afford amines of formula **Iii** (Method AF).

Coupling with amides also can be carried out using a suitable Pd catalyst, for example Pd_2dba_3/XantPhos, with a suitable solvent/base combination, like Cs_2CO_3 in dioxane at elevated temperature or using microwave irradiation to give amides of formula **Iiii** (Method AG).

[00273] **Scheme 21: General method for the functionalization of 4-hydroxyl group of thiophene / thiazole derivatives**

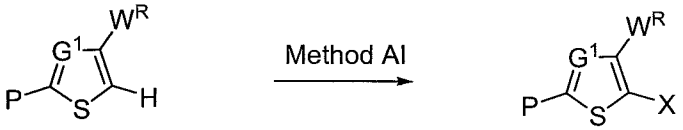


xviii liv lv

[00274] As shown in Scheme 21, 4-hydroxythiazoles or thiophenes **xviii** can be transformed to various functionalized thiazole / thiophene derivatives via triflate **liv**.

For example, compounds **xviii** can be transformed into triflates **liv**, using, *e.g.*, triflic anhydride, with pyridine as base in DCM (Method U). Triflates **liv** can be then subjected to coupling reactions with amines, boronic esters, stannanes, or thiols under similar conditions as described for analogous halides in Schemes 11 – 14 (analogous literature examples include Rzasa, R. et al, Bioorg. Med. Chem. **2007**, *15*, 6574; Langille, N.F., Org. Lett. **2002**, *4*, 2485.) to afford compounds of formula **lv**.

[00275] **Scheme 22: General method for halogenation of 3-posittion onto thiophene / thiazoles.**



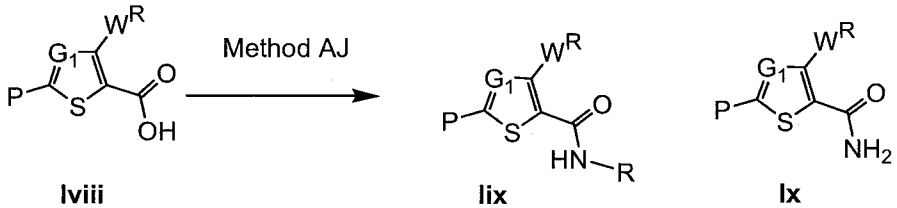
lvi lvii

[00276] Scheme 22 shows a general route for introducing halogen functionality onto unsubstituted 5-position of thiophene / thiazole core scaffold.

Halogenation of 5-unsubstituted thiazoles / thiophenes can be achieved in a similar manner as reported in the literature (Haelmmerle et al, Synlett **2007**, 2975). For example, **lvi** is treated with a generally known halogenating reagent such as bromine or N-bromosuccinimide in a suitable solvent, such as DCM to afford compounds of formula **lvii** (Method AI).

The resulting halogenated thiophenes / thiazoles **lvii** can be used for the further functional group transformation reaction such as described in scheme 11—15.

[00277] **Scheme 23: General route for the synthesis of carboxamides**



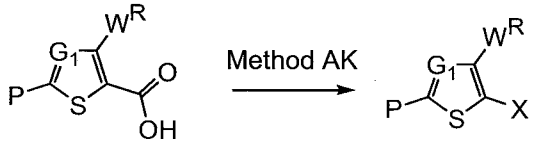
lviii lix lx

[00278] Scheme 23 shows a general route for preparing amide compounds of formula **lix**.

As shown in Scheme 23, acids **lviii** may be treated with amines using standard coupling conditions, such as EDCI and HOBt in DCM to afford amides **lix** (Method AJ).

When ammonia is used as an amine source, primary amide derivatives **lx** may be obtained, which can be used as intermediates for the construction of azoles as described in Schemes 25, 26, 28 and 37.

[00279] Scheme 24: General route for the synthesis of 5-halogenated thiophenes / thiazoles by Hunsdiecker reaction

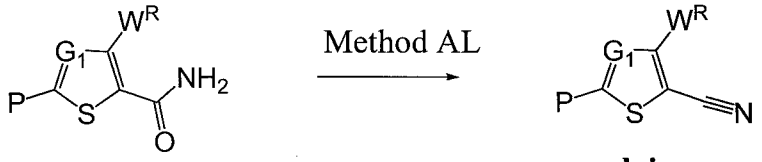


lviii **lvii**

[00280] As shown Scheme 24, 5-halogenated thiophenes / thiazoles **lvii** can be prepared by the Hunsdiecker reaction from thiophene /thiazole carboxylic acid analogs **lviii**.

As shown in Scheme 24, acids **xlviii** may be treated with sliver hydroxide to form a silver salt, which is subsequently treated with halogen, for example bromine, in a suitable solvent, such as CCl_4 at elevated temperature to form **lvii** (Method AK).

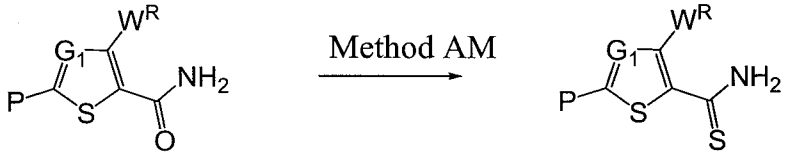
[00281] Scheme 25: General route for the synthesis of 5-cyano thiophenes / thiazoles



lx **lxiv**

[00282] As shown in scheme 25, amides **lx**, which can be prepared by the procedure described in scheme 23, are treated with phosphoryl chloride, or similar reagents to form 5-cyano thiophenes / thiazoles of formula **lxiv** (Method AL).

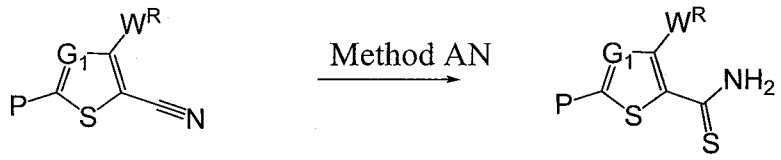
[00283] Scheme 26: General route for the synthesis of thioamides



lx **lxv**

[00284] As shown in scheme 26, amides **lx**, which can be prepared by the procedure described in scheme 23, are treated with a suitable reagent, for example Lawesson's reagent, or P_2S_5 in a suitable solvent, such as toluene at elevated temperature to afford thioamides of formula **lxv** (Method AM).

[00285] Scheme 27: Alternative route for the synthesis of thioamides



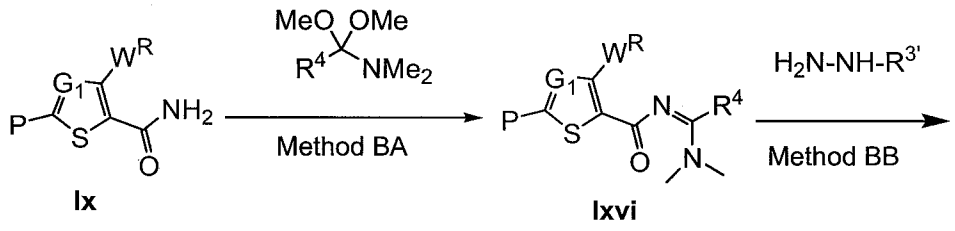
lxiv lxv

[00286] As shown in scheme 27, 5-cyano thiazoles / thiophenes **lxiv**, which can be prepared by the procedure described in scheme 25, are treated with a suitable reagent, for example ammonium sulfide in a suitable solvent, such as methanol to afford thioamides of formula **lxv** (method AN).

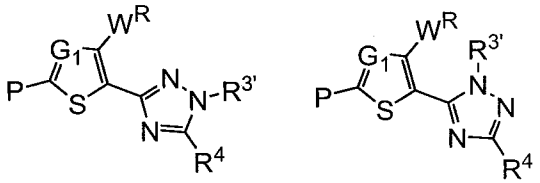
[00287] In the schemes 28—46, general procedures for the construction of the representative azoles as R^1 are described.

Schemes 28 -30 describe the formation of 1,2,4-triazolyl group as R^1.

[00288] **Scheme 28: General route for the construction of 1,2,4- triazolyl**



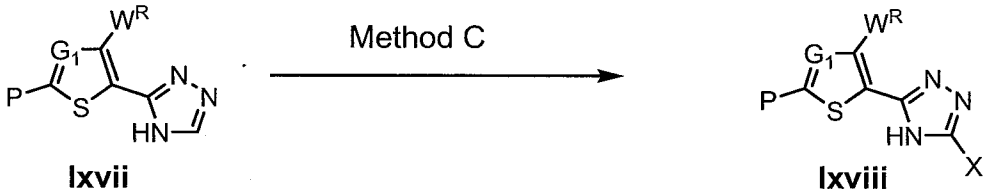
lx lxvi



lxvii' lxvii"

[00289] As shown in Scheme 28, amides **lx**, which can be prepared by the procedure described in scheme 23, can be treated with DMF-DMA at elevated temperature or under microwave irradiation (Method BA) to give intermediate amidines **lxvi** that are transformed to 1,2,4-triazoles **lxvii'** and **lxvii"** using hydrazine or substituted hydrazines in acetic acid at elevated temperature or under microwave irradiation (Method BB).

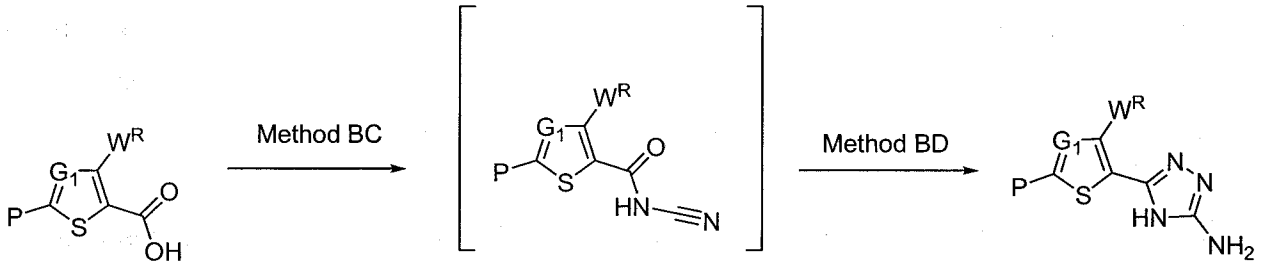
[00290] **Scheme 29: General route for the construction of 5-halogenated 1,2,4-triazolyl**



lxvii lxviii

[00291] As shown in Scheme 29, 1,2,4-triazoles **lxvii**, which can be prepared by the procedure described in scheme 28, are treated with a suitable halogenating agent, like NBS, in a suitable solvent, for example tetrachloromethane, to afford compounds of formula **lxviii** (Method C).

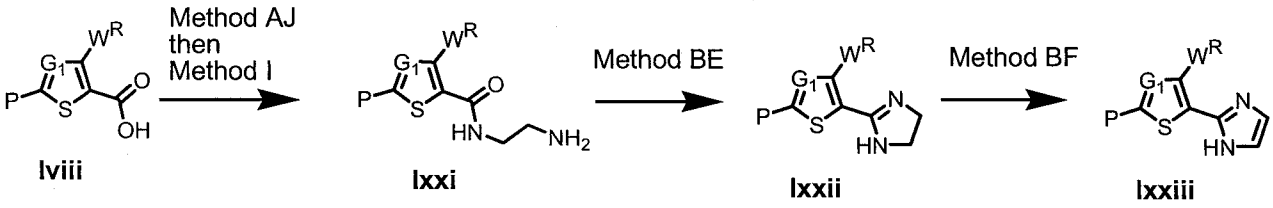
[00292] **Scheme 30: General route for the construction of 5-amino-1,2,4-triazolyl**



[00293] As shown in Scheme 30, acids **lviii** may be coupled with cyanamide, for example via an intermediate acid halide in a suitable solvent, such as DCM to acylcyanamides **lxix** (Method BC), that are in turn treated with hydrazine using appropriate conditions, for example acetic acid at elevated temperature to give compounds of formula **lxx** (Method BD).

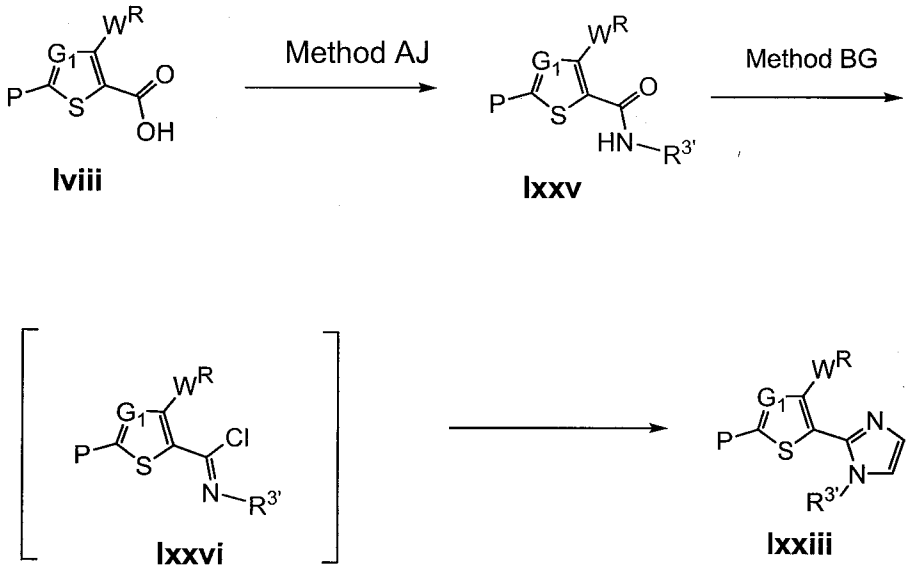
[00294] Scheme 31—39 describes the formation of 2-imidazolyl group as R^1.

[00295] **Scheme 31: General route for the construction of 2-imidazolyl**



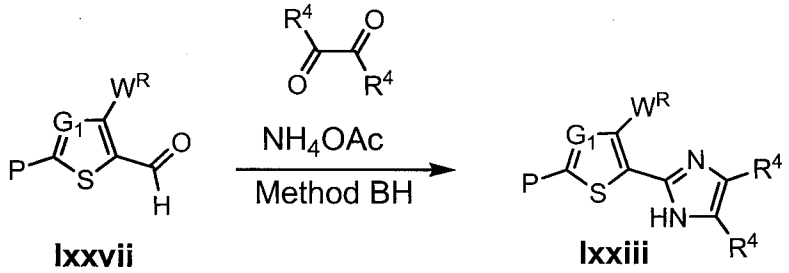
[00296] As shown in Scheme 31, acids **lviii** are treated with Boc protected ethylenediamine using standard coupling conditions, such as EDCI and HOBt in DCM (Method AJ). Protective group is removed using an appropriate acid, for example TFA in DCM to give amide **lxxi** (Method I). Cyclization of **lxxi** is achieved using suitable conditions, for example $POCl_3$ (Method BE) to form dihydroimidazoles **lxxii**. Dihydroimidazoles **lxxii** can be oxidized to imidazoles **lxxiii** using a suitable oxidative method, for example heating with Magtrieve (Method BF).

[00297] **Scheme 32: Alternative route for the construction of 2-imidazolyl**



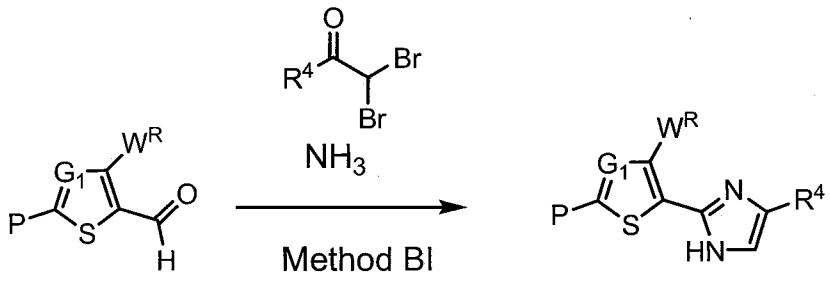
[00298] Scheme 32 above shows an alternative route for preparing imidazoles of formula **lxxiii**. As shown in Scheme 32, acids **lviii** are treated with amines using standard coupling conditions, such as EDCI and HOBt in DCM to afford amides **lxxv** (Method AJ). Cyclization to imidazoles may be achieved through a 3-step one pot process that involves treatment with phosphorus pentachloride and HCl in dioxane to afford carbimidoyl chloride intermediates **lxxvi**, that can be then treated with aminoacetaldehyde dimethylacetal followed by HCl in dioxane at elevated temperature to give **lxxiii** (Method BG). When $R^{3'}$ = allyl, benzyl or substituted benzyl, it can also serve as a protecting group.

[00299] **Scheme 33: Alternative route for the synthesis of 2-imidazolyl**



[00300] As shown in scheme 33, aldehydes **lxxvii** may be condensed with dicarbonyl compounds, such as diketones, ketoaldehydes, or glyoxal with an appropriate ammonia source, such as ammonium acetate, with suitable acid, such as acetic acid in solvent such as methanol to form imidazoles **lxxiii** (Method BH).

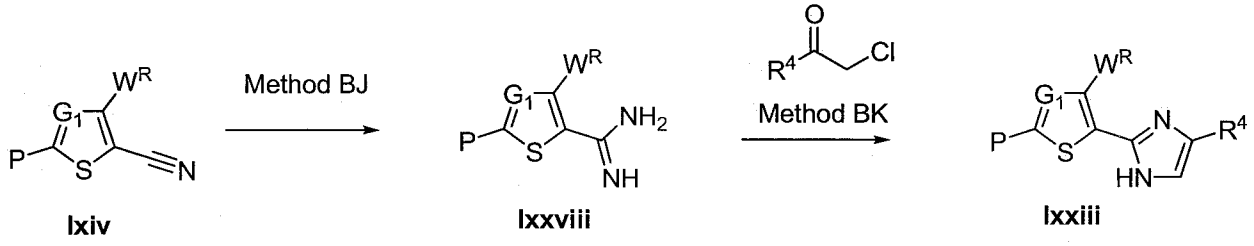
[00301] **Scheme 34: Alternative method for the construction of substituted 2-imidazolyl.**



lxxvii **lxxiii**

[00302] As shown in scheme 34, aldehydes of formula **lxxvii** can be treated with alpha, alpha-dihalo-ketones under suitable conditions, such as ammonium hydroxide, sodium acetate in an appropriate solvent, for example methanol and water to afford imidazoles of formula **lxxiii** (Method BI).

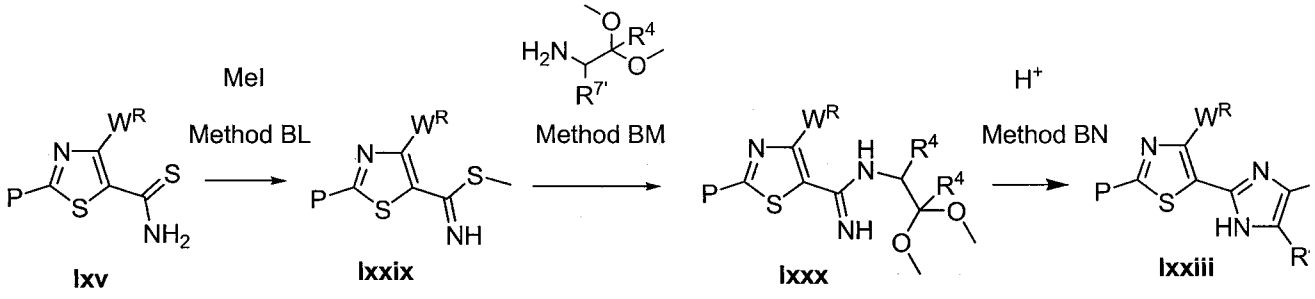
[00303] **Scheme 35: Alternative method for the construction of substituted 2-imidazolyl.**



lxiv **lxxviii** **lxxiii**

[00304] As shown in scheme 35, treatment of nitriles **lxiv**, which can be prepared by the procedure described in scheme 25, with LiHMDS in a suitable solvent mixture, such as THF/ether/hexane gives amidines of formula **lxxviii** (Method BJ) that can be treated with haloketones in the presence of a suitable base, such as potassium carbonate in an appropriate solvent, such as DCM under elevated temperature to give imidazoles of general formula **lxxiii** (Method BK).

[00305] **Scheme 36: Alternative method for the construction of substituted 2-imidazolyl.**

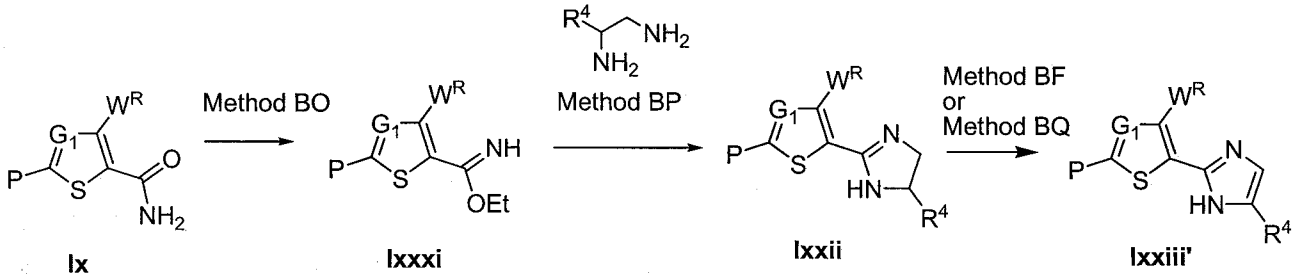


lxv **lxxix** **lxxx** **lxxiii**

[00306] As shown in scheme 36, treatment of thioamides **lxv**, which can be prepared by the procedure described in scheme 26 or 27, with methyl iodide affords imidothioate intermediates **lxxix** (Method BL), which may then be treated with optionally substituted aminoacetaldehyde dimethyl acetal in a suitable solvent, like acetic acid, at elevated temperature to afford intermediate amidines **lxxx** (Method BM).

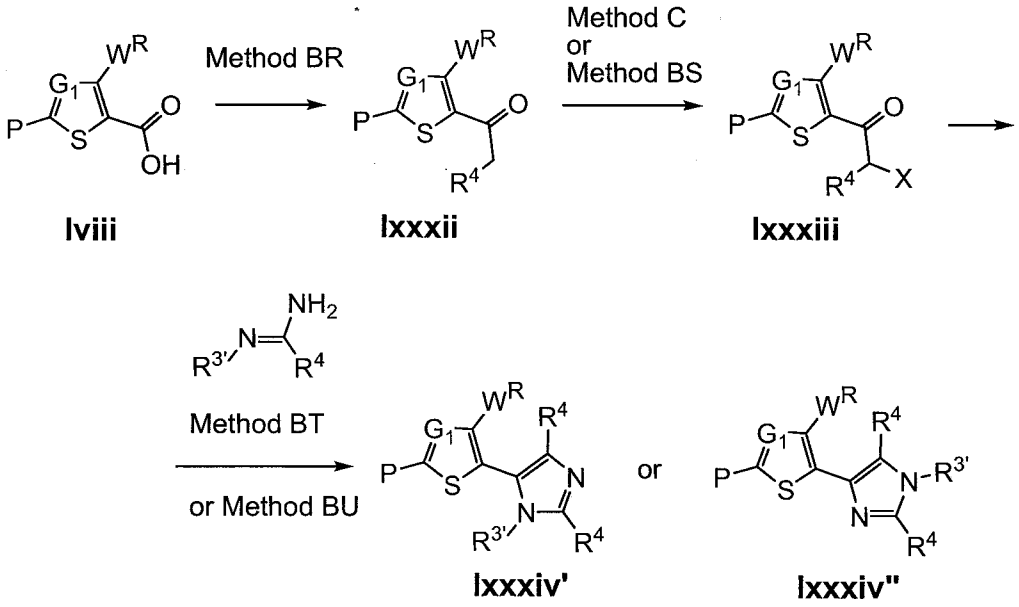
Amidines **lxxx** can then be treated with an acid, such as aqueous HCl and a suitable co-solvent, like ethanol, at elevated temperature to give imidazoles of formula **lxxiii** (Method BN).

[00307] Scheme 37: Alternative method for the construction of substituted 2-imidazolyl.



[00308] As shown in scheme 37, treatment of amides **lx**, which can be prepared by the procedure described in scheme 23, with an alkylating agent, such as Meerwein's reagent, in DCM (Method BO) gives iminoesters **lxxxi**, which can be then treated with diamines using appropriate conditions, for example ethanol at elevated temperature (Method BP) to forme dihydroimidazoles **lxxii**, which can be then oxidized in a same manner as in Method BF described in Scheme 31, or when R^4 is an appropriate leaving group, elimination can be carried out using a base, such as DBU in DCM (Method BQ).

[00309] Scheme 38: General route for the construction of substituted 4 (5)-imidazolyl.

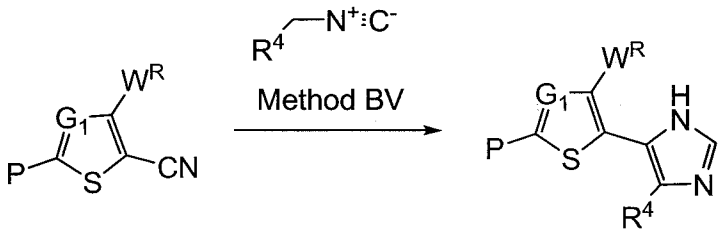


[00310] As shown in Scheme 38, acids **lviii** may be transformed to ketones **lxxxii** using a suitable synthetic sequence, for example through a coupling with *N,O*-dimethylhydroxylamine and subsequent treatment of the resulting Weinreb amides with alkyllithium or Grignard reagents in a suitable solvent, like THF (Method BR).

Ketones **lxxxii** are then halogenated with a suitable reagent, such as bromine or NBS in an appropriate solvent, like DCM (Method C) to form alpha-halogenated ketones **lxxxiii** (X = halogen). Alternatively, treatment of ketones **lxxxii** with a suitable oxidative sulfonylating agent, like hydroxy(tosyloxy)iodobenzene using suitable conditions, for example heating in acetonitrile (Method AS) affords sulfonyl esters of formula **lxxxiii** (X = OSO_2R).

Treatment of **lxxxiii** with amidine reagents in the presence of a suitable base, like potassium carbonate in a suitable solvent, such as THF-water mixture at elevated temperature or microwave irradiation affords the final imidazoles **lxxxiv'** and **lxxxiv"** (Method BT). Alternatively, compounds **lxxxiii** can be treated with large excess of amides, such as formamide using microwave irradiation to afford imidazoles **lxxxiv'**and **lxxxiv"** (Method BU).

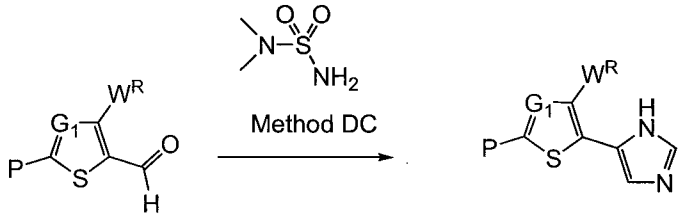
[00311] Scheme 39: Alternative method for the construction of substituted 4 (5)-imidazolyl.



lxiv **lxxxiv'"**

[00312] As shown in scheme 39, treatment of nitriles **lxiv**, which can be prepared by the procedure described in scheme 25, with isocyanates in the presence of a suitable base, such as tOBuK, in a suitable solvent, for example THF gives imidazoles of formula **lxxxiv'"**. (Method BV).

[00313] Scheme 40: Alternative method for the construction of 4-imidazolyl.

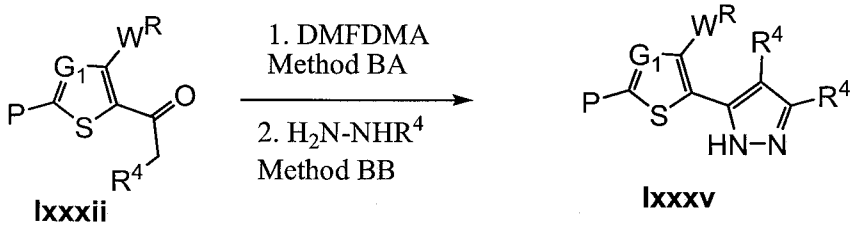


lxxvii **lxxxiv**

[00314] As shown in scheme 40, treatment of aldehydes **lxxvii** with N,N-dimethylsulfonamide at elevated temperature in a suitable solvent, for example toluene, to allow azeotropic removal of water can afford intermediate imines, that are treated with TOSMIC, a suitable base, like potassium carbonate in a suitable solvent, such as DME at elevated temperature to afford intermediate imidazole sulfonamides, that can be hydrolyzed to imidazoles **lxxxiv** with an acid, for example aqueous HBr at elevated temperature (Method DC).

[00315] Schemes 41 and 42 describe the procedures for introducing a pyrazolyl group.

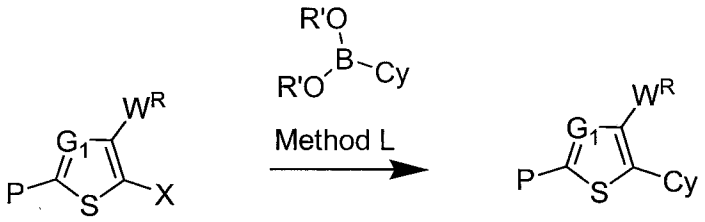
[00316] **Scheme 41: General route for the construction of 3 (5)-pyrazolyl.**



lxxxii **lxxxv**

[00317] As shown in Scheme 41, ketones **lxxxii**, which can be prepared by the procedure described in scheme 38, are treated with DMF-DMA to afford an intermediate enamines (Method BA) followed by reaction with substituted hydrazine, or hydrazine hydrate in a suitable solvent, for example acetic acid, to give pyrazoles **lxxxv** (Method BB).

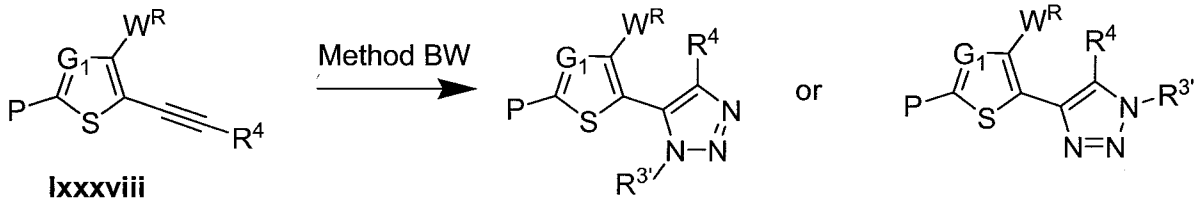
[00318] **Scvheme 42: General route for the introduction of heteroaromatic group.**



lvii **lxxxvi**

[00319] As shown in Scheme 42, halides **lvii**, which can be prepared by the procedure described in scheme 24, are treated with heteroaryl boronic acids or esters, in the presence of a suitable catalyst, for example $Pd(PPh_3)_4$, using a base, such as cesium carbonate in a suitable solvent, like dioxane-water mixture at elevated temperature to afford compounds of formula **lxxxvi** (Method L).

[00320] **Scheme 43: General route for the construction of 1,2,3-triazolyl.**

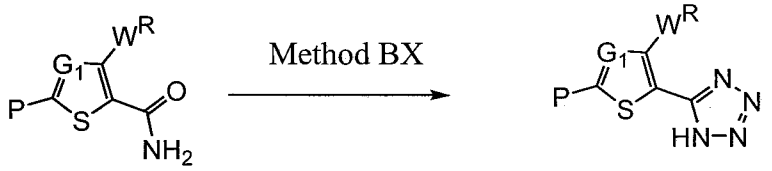


lxxxviii **lxxxix** **lxxxix'**

[00321] As shown in Scheme 43, alkynes **lxxxviii**, which can be prepared by the known Stille- or Sonogashira-coupling reaction in which a halide **lvii**, which can be prepared by the procedure described in scheme 24, and an appropriate alkyne derivative may be treated with azides, inorganic or organic a

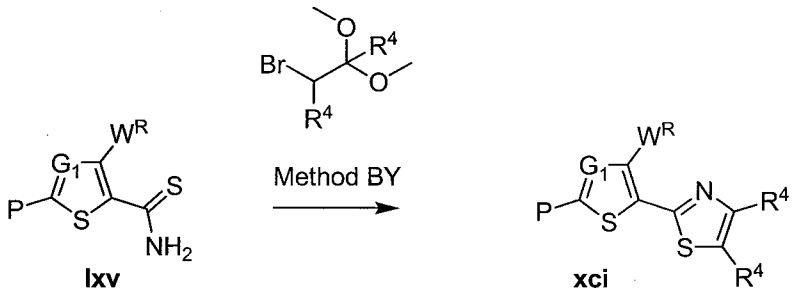
suitable solvent, such as dioxane, at elevated temperature to afford triazoles of formula **lxxxix** and **lxxxix'** (Method BW).

[00322] Scheme 44: General route for the construction of tetrazolyl.



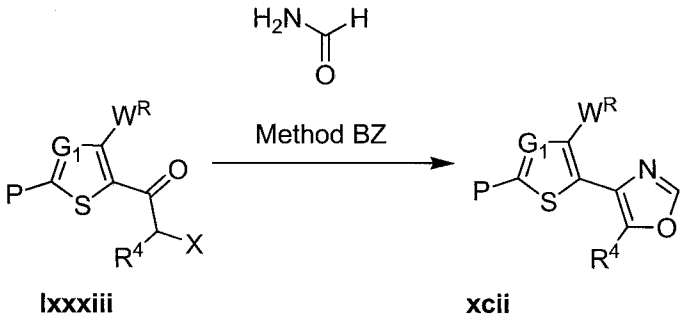
[00323] As shown in Scheme 44, amides **lx**, which can be prepared by the procedure described in scheme 23, may be treated with an azide source, for example sodium azide using a suitable Lewis acid, for example silicon tetrachloride in an appropriate solvent, such as acetonitrile to give tetrazoles **xc** (Method BX).

[00324] Scheme 45: General route for the construction of 2-thiazolyl.



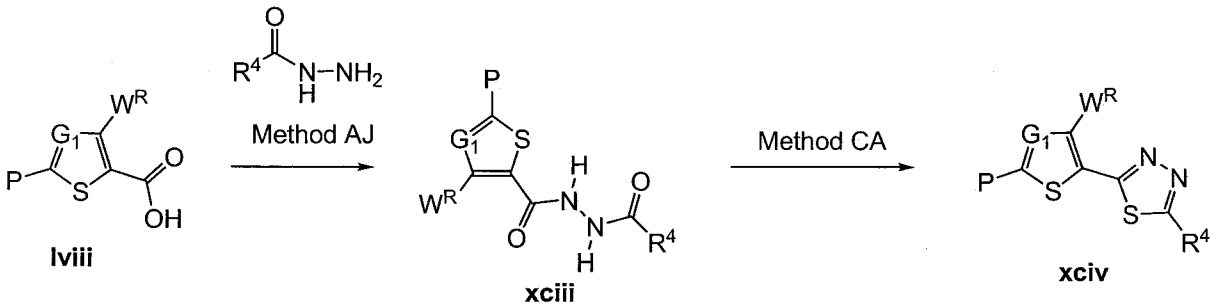
[00325] As shown in scheme 45, thioamides **lxv**, which can be prepared by the procedure described in scheme 26 or 27, are treated with substituted bromoacetaldehyde dimethyl acetals to afford thiazoles of formula **xci** (Method BY).

[00326] Scheme 46: General route for the construction of 4-oxazolyl



[00327] As shown in scheme 46, alpha-halogenated ketones **lxxxiii**, which can be prepared by the procedure described in scheme 38, may be treated with formamide under elevated temperature or microwave irradiation to afford the final 4-oxazoles **xcii** (Method BZ).

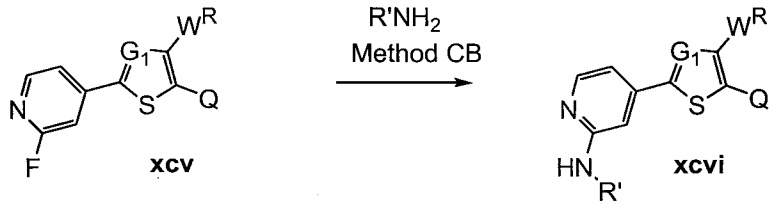
[00328] Scheme 47: General route for the construction of 1,3,4-thiadiazolyl



[00329] As shown in scheme 47, acids **lviii** are coupled with acylhydrazines using standard coupling conditions, such as EDCI, HOBt, DMF at elevated temperature to afford intermediates **xciii** (Method AJ), that are treated with Lawesson's reagent using suitable conditions, for example in toluene under reflux to afford thiadiazoles **xciv** (Method CA).

[00330] Scheme 48—51 describe general procedure for the functional group transformation on HY.

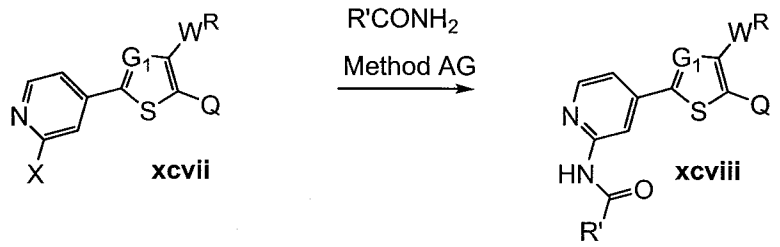
[00331] Scheme 48: General method for the introduction of amino group to 2-fluoropyridyl



[00332] Scheme 48 shows a general route for the transformation of 2-fluoropyridyl to 2-substituted aminopyridyl to give the compounds of formula **xcvi**.

As shown in Scheme 48, compounds **xcv** can be treated with amines at elevated temperature or under microwave irradiation to give 2-aminopyridines **xcvi** (Method CB).

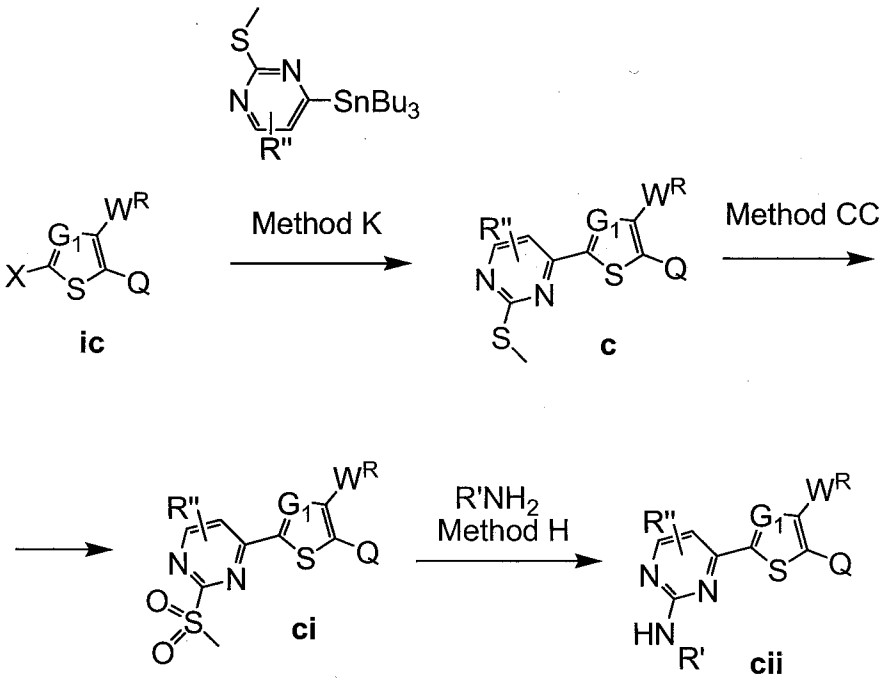
[00333] Scheme 49: General method for the introduction of 2-acylaminopyridines by Buchwald reaction



[00334] Scheme 49 shows a general route for the transformation of 2-halopyridyl to 2-acylaminopyridyl by Buchwald reaction to give the compounds formula **xcviii**.

As shown in Scheme 49, compounds **xcvii** can be treated with amides or carboxamides in the presence of a suitable catalyst, such as Pd_2dba_3, XantPhos, base like cesium carbonate in an appropriate solvent, for example dioxane at elevated temperature or under microwave irradiation to give acylaminopyridines **xcviii** (Method AG).

[00335] Scheme 50: General method for the synthesis of 2-aminopyrimidyl thiophene / thiazole

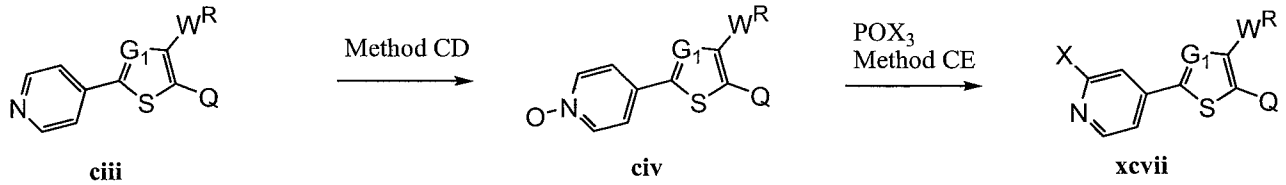


[00336] As shown in Scheme 50, compounds **ic** can be coupled with stannanes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in dioxane at elevated temperature to give compounds **c** (Method K).

Oxidation of thioethers **c** to sulfones **ci** can be achieved using a suitable oxidant, for example mCPBA in DCM (Method CC).

Methanesulfonyl group of sulfones **ci** can be displaced by treatment with amines in a suitable solvent, for example THF to afford 2-aminopyrimidines **cii** (method H).

[00337] Scheme 51: General method for the introduction of 2-halo substituent on 4-pyridyl group

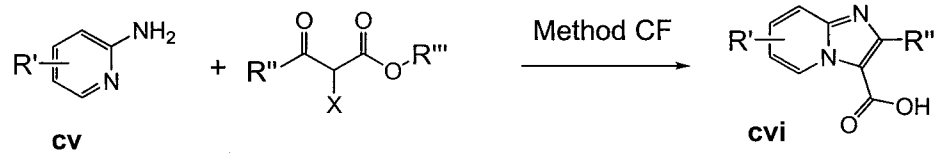


[00338] Scheme 51 shows a general route for the transformation of 4-pyridyl to 2-halo-4-pyridyl compounds formula **xcvii**.

As shown in Scheme 51, compounds **ciii** can be treated with an oxidant, for example mCPBA in a suitable solvent, such as DCM to afford intermediate N-oxides **civ** (Method CD), which may be halogenated in 2-position using phosphoryl halides, for example phosphoryl chloride, under elevated temperature to afford compounds of formula **xcvii** (Method CE).

[00339] Schemes 52—58 describe the procedures for the synthesis of building blocks for HY.

[00340] **Scheme 52: General method for the synthesis of imidazo[1,2-a]pyridine building blocks.**

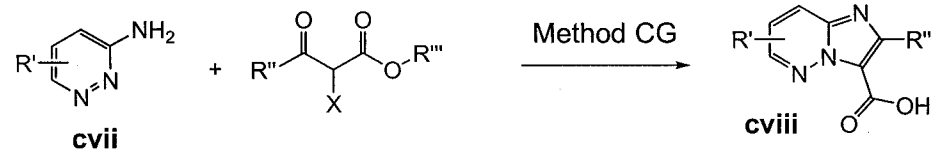


cv **cvi**

[00341] Scheme 52 shows a general method for the synthesis of imidazo[1,2-a]pyridines **cvi**.

As shown in Scheme 52, 2-aminopyridines **cv** may be condensed with alpha-halogenated beta-ketoesters in a suitable solvent, for example ethanol, at elevated temperature to afford intermediate esters, that are hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cvi** (Method CF).

[00342] **Scheme 53: General method for the synthesis of imidazo[1,2-b]pyridazine building blocks**

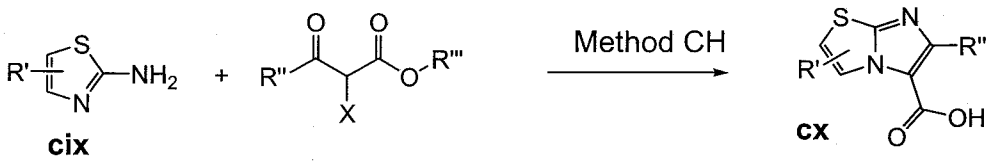


cvii **cviii**

[00343] Scheme 53 shows a general method for the synthesis of imidazo[1,2-b]pyridazines **cviii**.

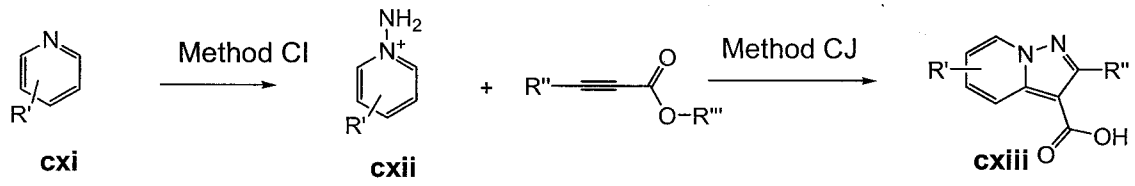
As shown in Scheme 53, 2-aminopyridazines **cvii** may be condensed with α-halogenated beta-ketoesters in a suitable solvent, for example ethanol at elevated temperature to afford intermediate esters, that are hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cviii** (Method CG).

[00344] **Scheme 54: General method for the synthesis of imidazo[2,1-b][1,3]thiazole building blocks**



[00345] Scheme 54 shows a general method for the synthesis of imidazo[2,1-b][1,3]thiazoles **cx**. As shown in Scheme 54, 2-aminothiazoles **cix** may be condensed with α-halogenated β-ketoesters in a suitable solvent, for example ethanol, at elevated temperature to afford intermediate esters, which may be hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cx** (Method CH).

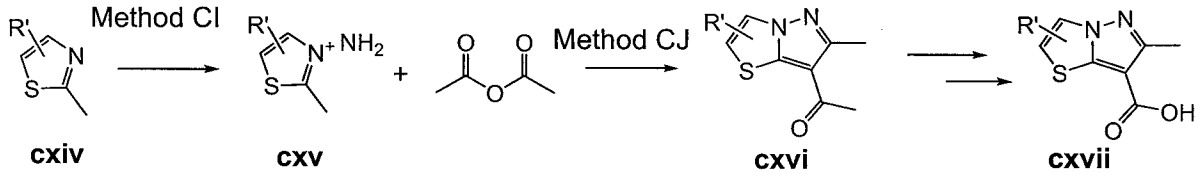
[00346] **Scheme 55: General method for the synthesis of pyrazolo[1,5-a]pyridine building blocks**



[00347] Scheme 55 shows a general method for the synthesis of pyrazolo[1,5-a]pyridines **cxiii**. As shown in Scheme 55, pyridines **cxi** may be *N*-aminated with a suitable agent, such as *O*-(mesitylsulfonyl)hydroxylamine using appropriate conditions, for example toluene or ethyl acetate as solvent (Method CI).

Resulting *N*-aminopyridinium salts **cxii** may then be condensed with alkynylcarboxylic acid esters with a suitable base, such as potassium carbonate in a suitable solvent, for example DMF to afford intermediate esters, which may be hydrolyzed using standard conditions, such as aqueous sodium hydroxide in THF followed by acidic workup to give acids **cxiii** (Method CJ).

[00348] **Scheme 56: General method for the synthesis of pyrazolo[5,1-b][1,3]thiazole building blocks**

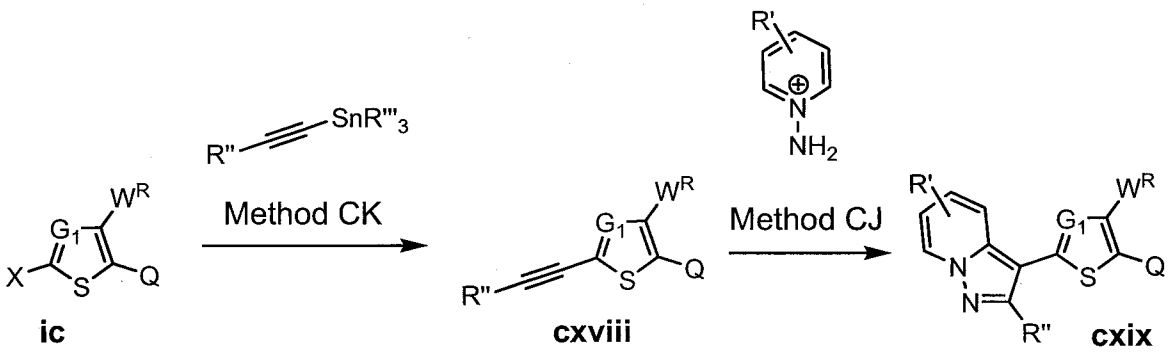


[00349] Scheme 56 shows a general method for the synthesis of pyrazolo[5,1-b][1,3]thiazoles **cxvii**. As shown in Scheme 56, 2-methylthiazoles **cxiv** may be *N*-aminated with a suitable agent, such as *O*-(mesitylsulfonyl)hydroxylamine using appropriate conditions, for example toluene or ethyl acetate as solvent (Method CI).

Resulting *N*-aminothiazolium salts **cxv** can then be condensed with acetic anhydride and potassium

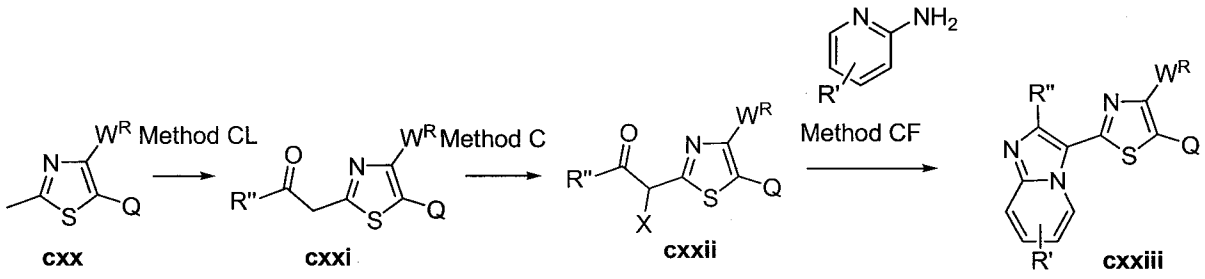
acetate at elevated temperature to afford methyl ketone intermediate **cxvi** (Method CJ), which can be converted to carboxylic acid **cxvii** moiety by well known functional transformation of methyl ketone to carboxylic acid.

[00350] Scheme 57: Alternative method for the synthesis of pyrazolo[5,1-b][1,3]thiazole derivatives



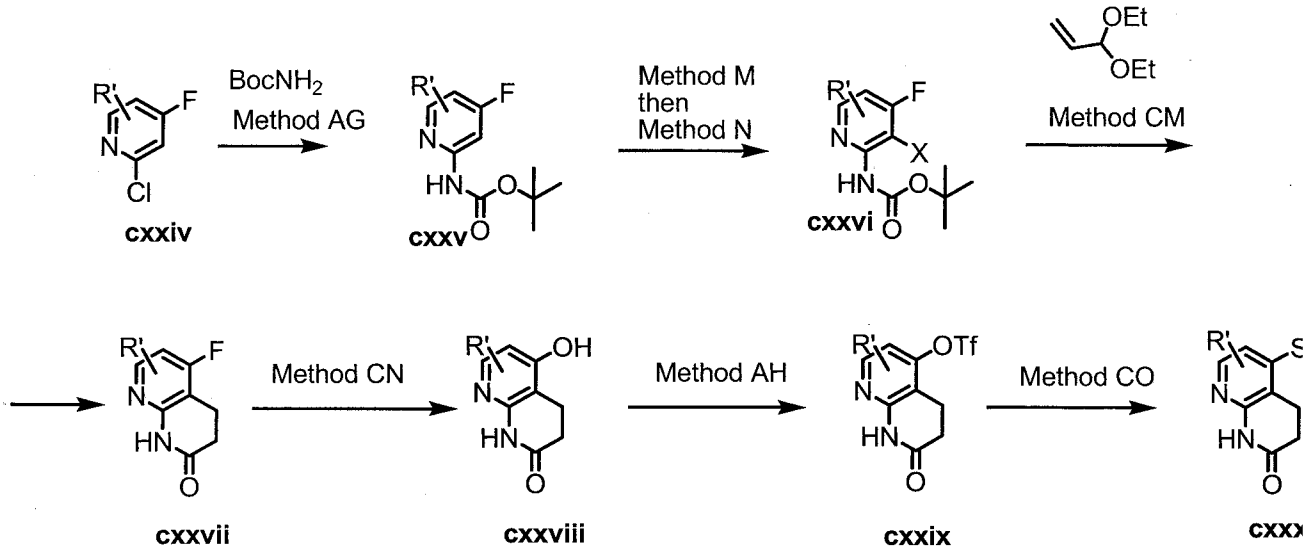
[00351] Scheme 57 shows an alternative method for the synthesis of pyrazolopyridines **cxix**. As shown in Scheme 57, halides **ic** are treated with alkynyl stannanes in the presence of a suitable catalysts, such as $Pd(PPh_3)_4$, CuI, with LiCl in an appropriate solvent, like dioxane at elevated temperature to give alkynes of formula **cxviii** (Method CK). Alkynes **cxviii** are then coupled with *N*-aminopyridinium salts with a base, like potassium carbonate in a suitable solvent, for example DMF to afford compounds of formula **cxix** (Method CJ).

[00352] Scheme 58: Alternative method for the synthesis of imidazo[1,2-a]pyridine building blocks.



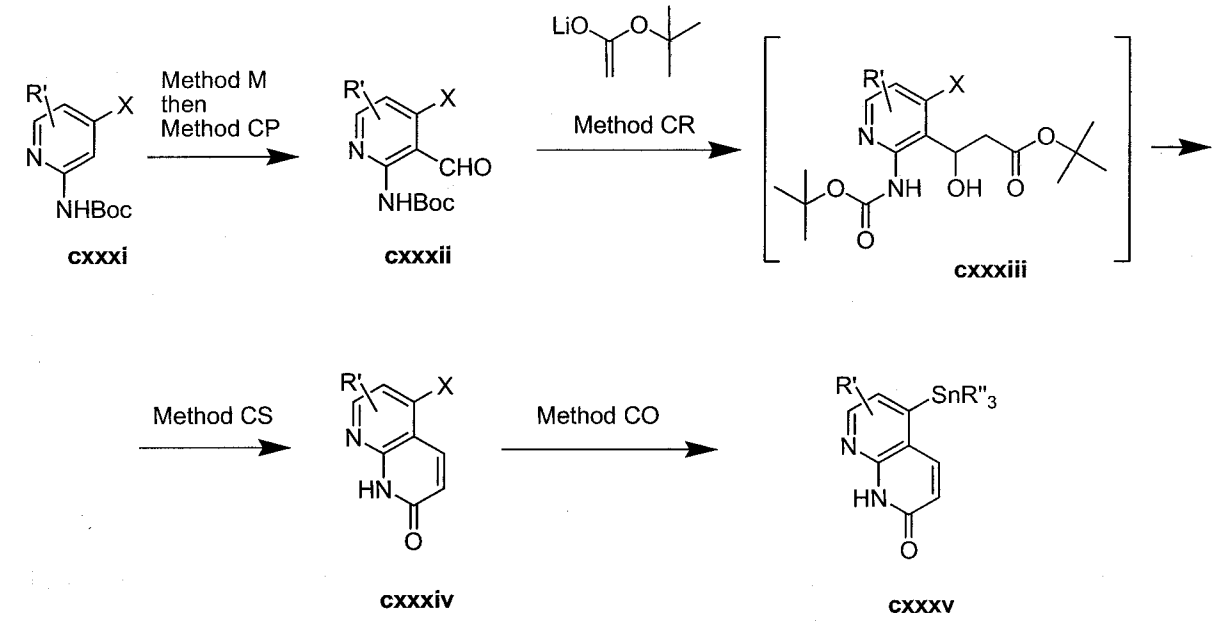
[00353] Scheme 58 shows an alternative method for the synthesis of imidazolopyridines **cxxiii**. As shown in Scheme 58, 2-methylthiazoles **cxx** may be deprotonated with a suitable reagent, such as *n*-BuLi and subsequently treated with Weinreb amides in a suitable solvent, such as THF to give ketones **cxxi** (Method CL). Halogenation of ketones can be achieved using standard conditions, for example NBS in DCM (Method C) and the resulting haloketones **cxxii** are then treated with aminopyridines in a suitable solvent, for example ethanol at elevated temperature to give compounds of formula **cxxiii** (Method CF).

[00354] Scheme 59: General method for the synthesis of bicyclic lactam building blocks



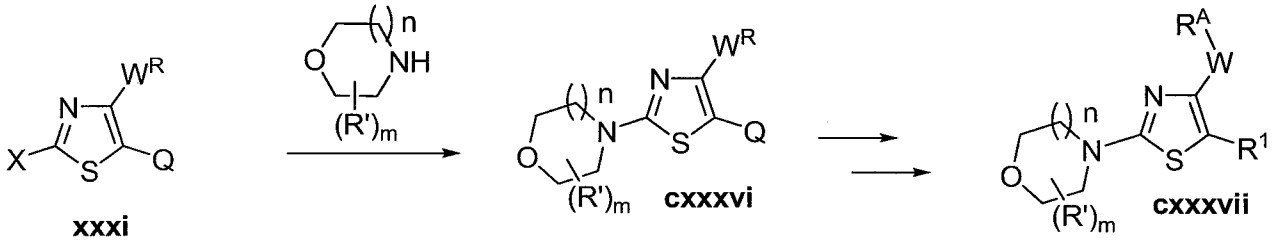
[00355] Scheme 59 shows a general method for the synthesis of bicyclic lactam building blocks **cxxix** and **cxxx**. As shown in Scheme 59, substituted 2-chloro-4-fluoropyridines can be amidated, for example with $BocNH_2$, Pd_2dba_3 and a suitable ligand, such as X-Phos in the presence of a base, for example cesium carbonate in an appropriate solvent, like dioxane to afford Boc-protected 2-aminopyridines **cxxv** (Method AG). Compounds **cxxv** can be deprotonated, for example using *n*-BuLi/TMEDA in THF at low temperature (Method M) and then quenched with a molecule of halogen, such as iodine in THF (Method N) to give halogenated compounds **cxxvi**. Compounds **cxxvi** can be coupled with diethoxypropene using a suitable Pd catalyst, such as Di-mu-chlorobis[5-hydroxy-2-[1-(hydroxyimino-kappaN)ethyl]phenyl-kappaC]palladium(II) dimer with an appropriate base, like *N,N*-diisopropylethylamine in a suitable solvent, for example DMF-water mixture (Method CM) to afford lactams of formula **cxxvii**. Transformation of fluoro **cxxvii** into hydroxyl analogs **cxxviii** can be carried out using a standard procedure, for example treatment with benzyl alcohol in the presence of a base, such as sodium hydride at elevated temperature and subsequent debenzylation, such as using hydrogenation with Pd/C catalyst in a suitable solvent, such as ethanol (Method CN). Triflates **cxxix** can be formed by treatment of **cxxviii** with a suitable reagent, for example triflic anhydride using appropriate conditions, such as pyridine as a base in DCM (Method AH). Triflates **cxxix** can be coupled with stannanes **xxix**, obtained in Scheme 6 using standard Stille conditions (Method K). Alternatively, triflates **cxxix** can be transformed into stannanes **cxxx** using a suitable method, such as heating with hexamethyldistannane, $Pd(PPh_3)_4$ in a suitable solvent, like THF (Method CO). Stannanes **cxxx** can be then coupled with thiophene/thiazole halides **ic**, which can be prepared by the procedures described in schemes 3, 5, 6 using standard Stille conditions (Method K).

[00356] Scheme 60: Alternative method for the synthesis of bicyclic lactam building blocks



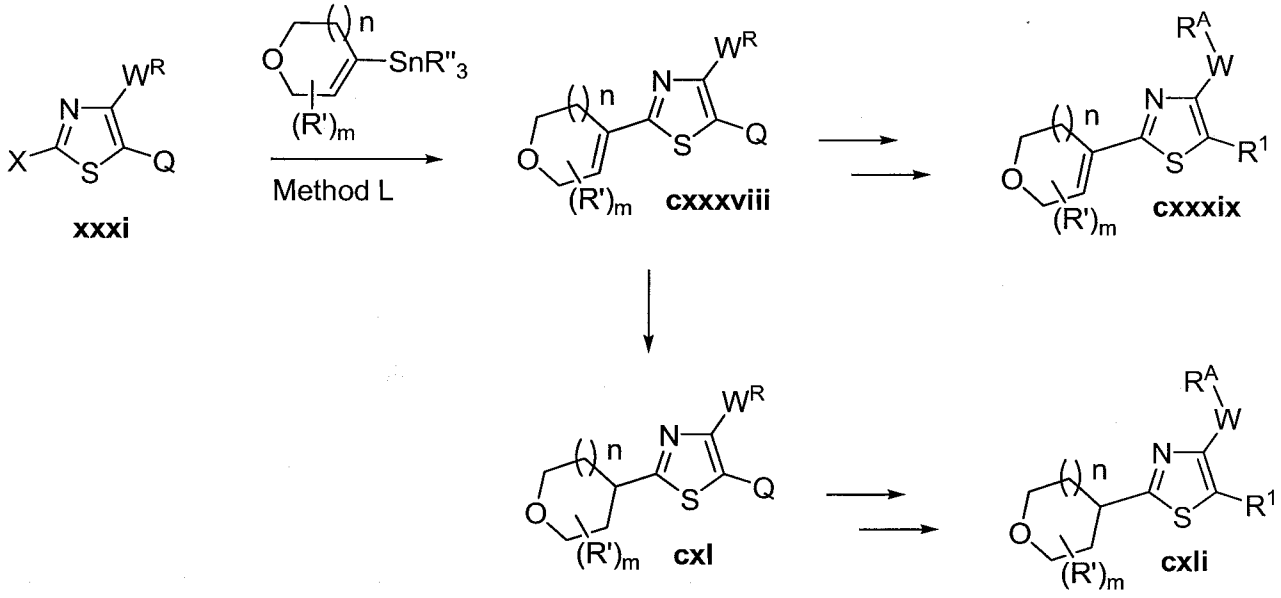
[00357] Scheme 60 shows an alternative method for the synthesis of bicyclic lactam building blocks **cxxxv**. As shown in Scheme 60, compounds **cxxxi** can be deprotonated with a suitable reagent, such as *n*-BuLi in THF at low temperature (Method M) and then treated with DMF to produce carbaldehydes **cxxxii** (Method CP). Aldehyde group in **cxxxii** can be then treated with enolate generated from *t*-Butylacetate and LDA in a suitable solvent, such as THF at low temperature (Method CR) to form intermediate β-hydroxyesters **cxxxiii** that can be cyclized to lactams **cxxxiv** using an acid, such as HCl, in water at elevated temperature (Method CS). Halides **cxxxiv** can be coupled with stannanes **xxix**, obtained in Scheme 6 using standard Stille conditions (Method K). Alternatively, transformation of aryl halides **cxxxiv** to stannanes **cxxxv** can be carried out using hexamethyldistannane, $Pd(PPh_3)_4$ in a suitable solvent, like THF (Method CO). Stannanes **cxxxv** can be then coupled with thiophene/thiazole halides **ic**, which can be prepared by the procedures described in schemes 3, 5, 6 using standard Stille conditions (Method K).

[00358] **Scheme 61: General method for the preparation of 2-aminothiazoles**



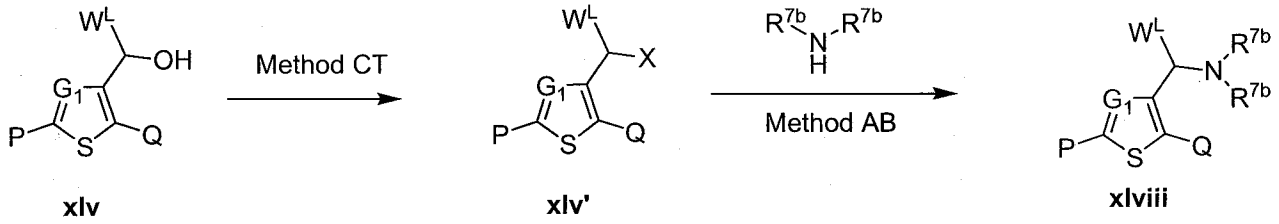
[00359] Scheme 61 shows a general method for preparation of compounds of formula **cxxxvii**. As shown in scheme 61, 2-halothiazoles are treated with amines at elevated temperature, either neat, or in a suitable solvent, such as NMP with an appropriate base, for example K_2CO_3 (Method H) to afford 2-aminothiazoles **cxxxvi**, that can be further transformed to compounds **cxxxvii** using generally known methods.

[00360] **Scheme 62: General method for coupling of halothiazoles with vinylstannanes**



[00361] Scheme 62 shows a general method for preparation of compounds of formula **cxxxix** and **cxli**. As shown in Scheme 62, compounds **xxxi** can be coupled with vinylstananes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in dioxane under elevated temperature to give alkenes cxxxviii (Method K), that can be further transformed to compounds **cxxxix** by generally known methods. Alternatively, hydrogenation of **cxxxviii**, for example using Pd/C as catalyst in a suitable solvent, such as ethanol (Method V) can afford compounds **cxl**, that can be further transformed to **cxli** by generally known methods.

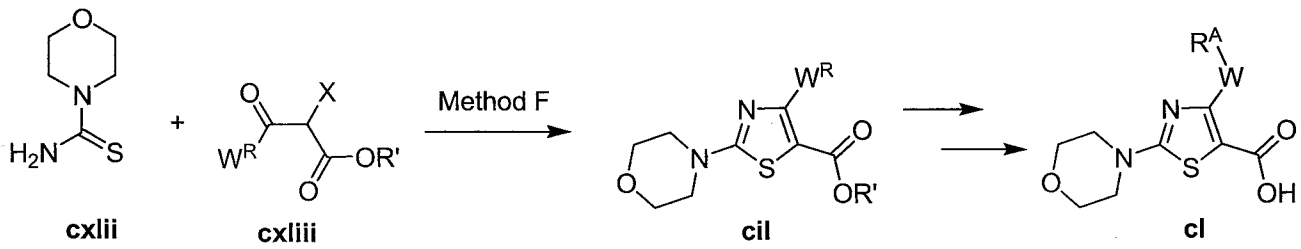
[00362] **Scheme 71: General method for the synthesis of amines**



xlv xlv' xlviii

[00363] Scheme 71 shows a general method for the synthesis of amines **xlviii**. As shown is Scheme 71, alcohols **xlv** can be transformed to halides **xlv'** using treatment with a suitable reagent, such as PCl_5 in a suitable solvent, such as DCM. Halides **xlv'** are then treated with amines at elevated temperature to provide target amines **xlviii** (Method AB).

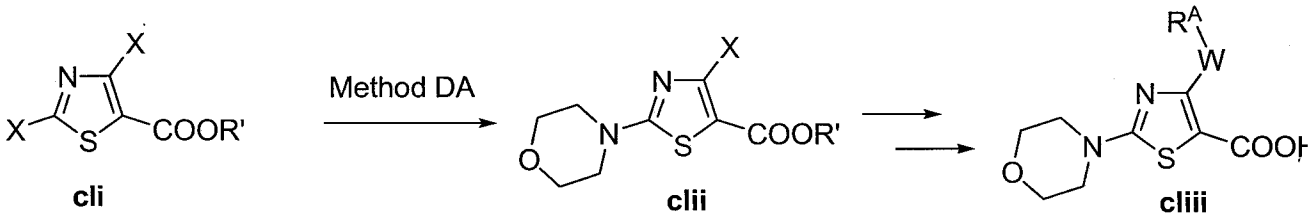
[00364] **Scheme 63: General method for the synthesis of substituted thiazoles**



cxlii cxliii cil cl

[00365] Scheme 63 shows a general route for the synthesis of compounds of formula **cl**. Thioamide **cxlii** can be treated with alpha-halogenated carbonyl compounds **cxliii** in a suitable solvent, such as isopropanol at elevated temprerature to give thiazoles **cil**. (Method F). A conversion reaction from **cil** to compounds **cl** can be performed by a combination of generally known functional group conversion reactions.

[00366] **Scheme 64: General method for introduction of morpholine to 2-position of thiazole core.**

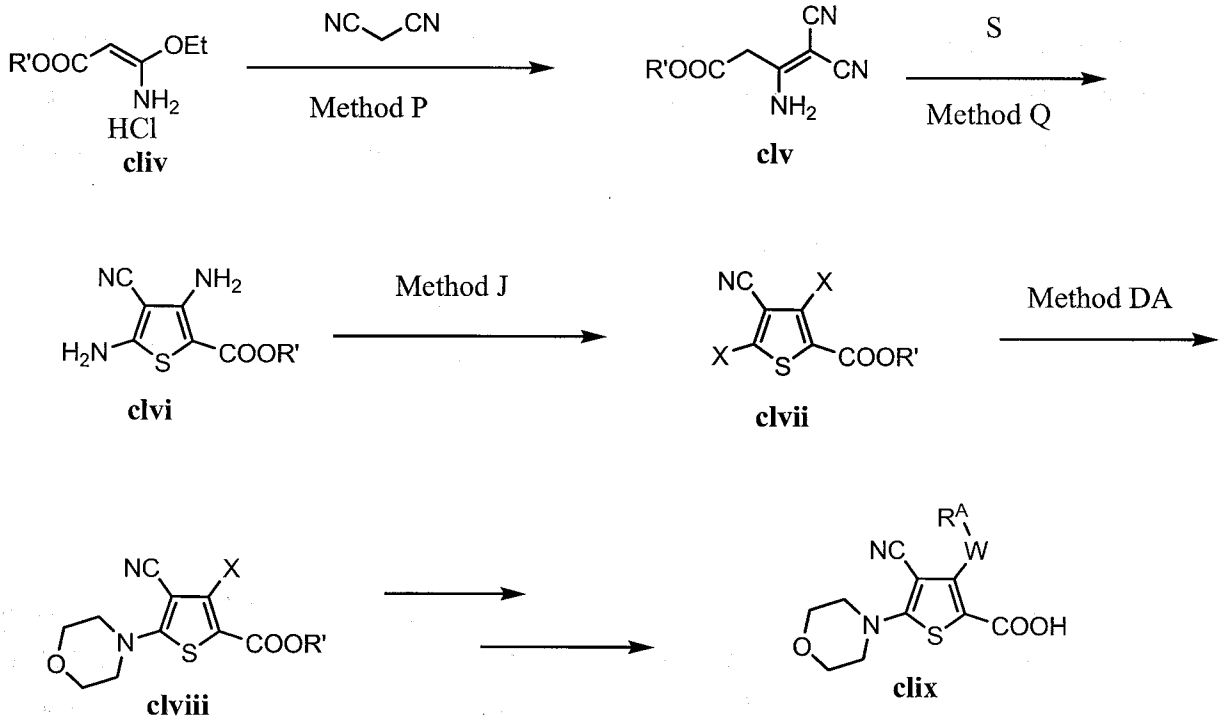


cli clii cliii

[00367] Scheme 64 shows a general route for introducing morpholine to the 2-position of thiazole core scaffold. Dihalothiazole esters, such as Methyl 2,4-dibromo-5-thiazolecarboxylate can be treated with morpholine at elevated temperature, with a suitable base, such as cesium carbonate in THF or other

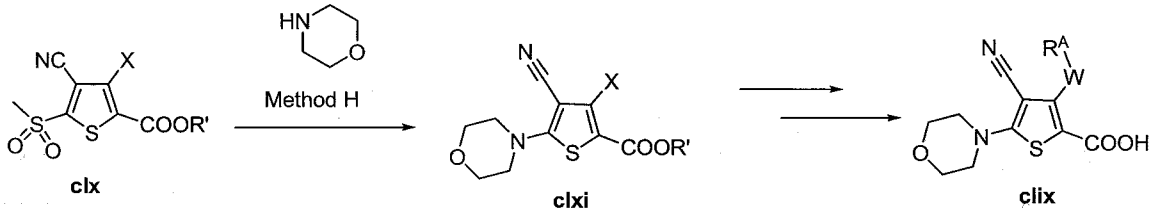
appropriate solvent (Method DA) to afford compounds of formula **clii**. Compounds **clii** can be then transformed into compounds **cliii** using generally known functional group conversion reactions.

[00368] Scheme 65: General method for the synthesis of 3-cyanothiophenes



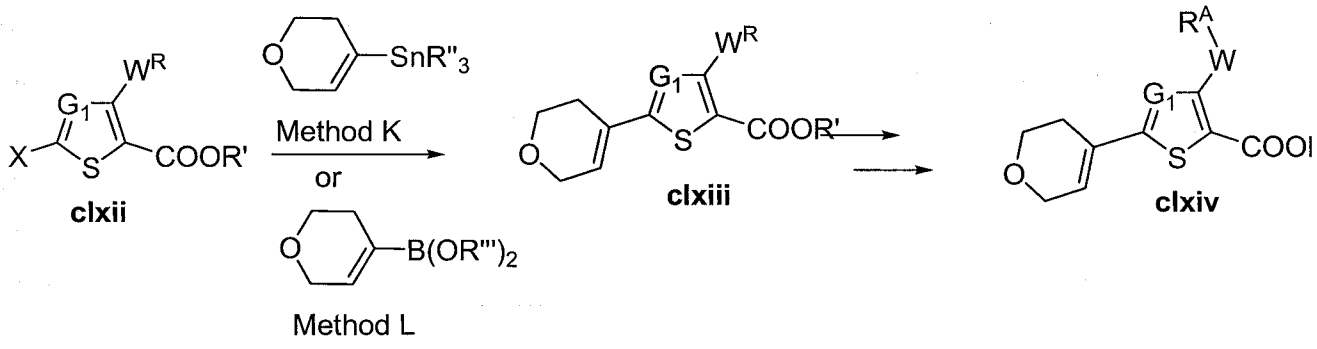
[00369] Scheme 65 describes the procedure for the synthesis of 3-cyanothiophenes **clix**. Substituted alkoxyethenamine **cliv** can be treated with malononitrile in the presence of a suitable base, such as TEA, in a suitable solvent, like chloroform, at elevated temperature to afford substituted aminoethylene malononitriles **clv** (Method P), that are treated with sulfur under suitable conditions, such as DMF and elevated temperature, to give diaminocyanothiophenes **xclvi** (Method Q). Diamines **clvi** may then be subjected to a Sandmeyer reaction using appropriate reagents, such as copper(II)bromide, amyl nitrite in ACN at elevated temperature (Method J) to afford compounds of formula **clvii**. Dihalocyanothiophenes can be then treated with morpholine at elevated temperature, with a suitable base, such as cesium carbonate in THF or other appropriate solvent (Method DA) to afford compounds of formula **clviii**. Compounds **clviii** can be then transformed into compounds **clvix** using generally known functional group conversion reactions.

[00370] Scheme 66: Alternative method for the synthesis of cyanothiophenes



[00371] Scheme 66 describes a procedure for the introduction of morpholine to 3-cyanothiophene analogs. As shown in Scheme 66, sulfones of formula **clx** (synthetic examples given in Mansanet et al, WO 2005070916) can be treated with morpholine in a suitable solvent, *e.g.*, THF, at elevated temperature (Method H) to give **clxi**. Conversion reactions from **clxi** to compounds **clix** can be performed, for example, by a combination of generally known functional group conversion reactions.

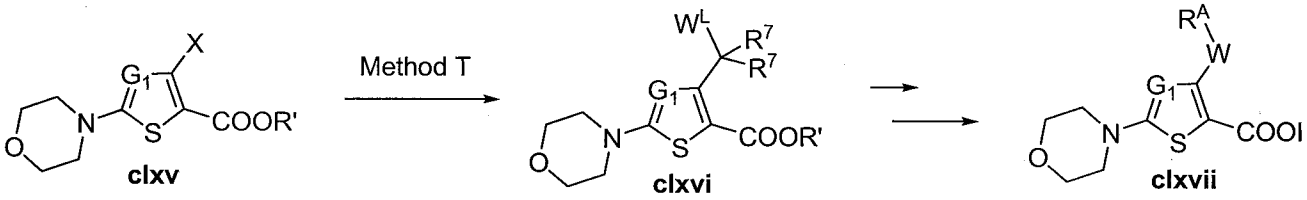
[00372] Scheme 67: General method for coupling of halothiophenes/ thiazoles with vinylstannanes / boronic esters



[00373] Scheme 67 shows a general method for preparation of compounds of formula **clxiv**. As shown in Scheme 67, compounds **clxii** can be coupled with vinylstananes under suitable conditions, for example $Pd(PPh_3)_4$, CuI, LiCl in dioxane under elevated temperature to give alkenes **clxiii** (Method K). Alternatively, Suzuki conditions, such as $Pd(PPh_3)_4$, $CsCO_3$, dioxane at elevated temperature (Method L)

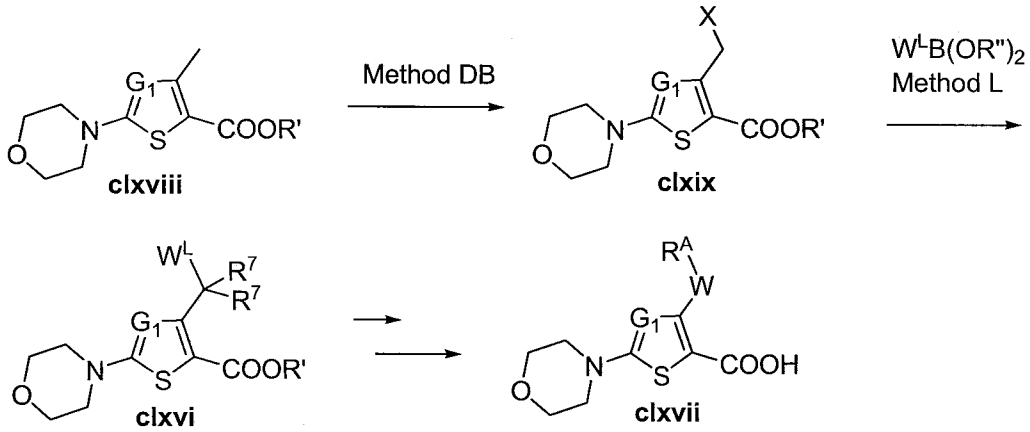
can be used. Compounds **clxiii** can be then further transformed to compounds **clxiv** by generally known methods.

[00374] Scheme 68: General method for introducing carbon functionality to halogenated thiophenes / thiazoles.



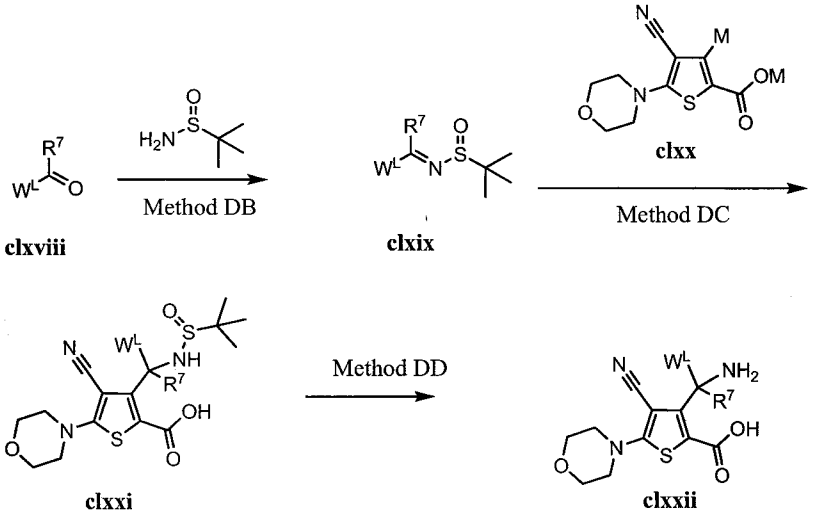
[00375] As shown in Scheme 68 carbon functionality can be introduced by the well known Negishi cross-coupling technique. Halogenated thiophenes / thiazoles **clxv** can be treated with alkyl zinc halides using Pd catalyst, such as $Pd(tBu_3P)_2$ under standard Negishi coupling conditions, such as THF at elevated temperature (Method T) to afford compounds **clxvi**, that can be further transformed to compounds **clxvii** using generally known methods.

[00376] Scheme 69: Alternative method for introducing carbon functionality to thiophenes / thiazoles.



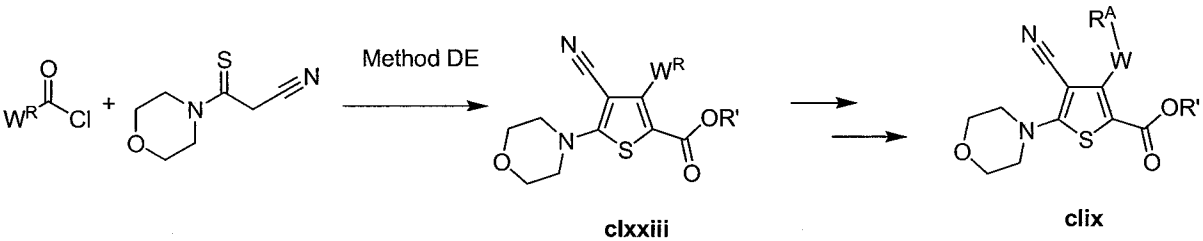
[00377] As shown in Scheme 69, methyl substituent of thiophenes/thiazoles **clxviii** can be halogenated using a suitable reagent, for example NBS with a radical source, such as AIBN in an appropriate solvent, like DCM (Method DB) to afford halides **clxix**. Halides **clxix** can be then coupled with boronic acids or esters using the well known Suzuki cross-coupling technique, for example $Pd(PPh_3)_4$, Cs_2CO_3, dioxane-water at elevated temperature (Method L) to afford compounds **clxvi**, that can be further transformed to compounds **clxvii** using generally known methods.

[00378] Scheme 70: General method for the synthesis of amino acids



[00379] As shown in Scheme 70, aldehydes or ketones **clxx** can be treated with 2-Methyl-2-propanesulfinamide in the presence of a suitable Lewis acid, such as $Ti(OiPr)_4$ in anhydrous THF, or other suitable solvent to afford sulfinamides **clxixi** (Method DC), that can be subsequently treated with thiophene metal compounds **clxxii** (Method DD), obtained from corresponding thiophene halides through halogen-metal exchange, for example from thiophene bromide using an excess of phenyllithium at low temperature. Formed sulfinyl amines **clxxiii** can be then treated with an acid, such as HCl in dioxane with an optional co-solvent, for example DCM (Method DE) to afford amino acids **clxxiv**.

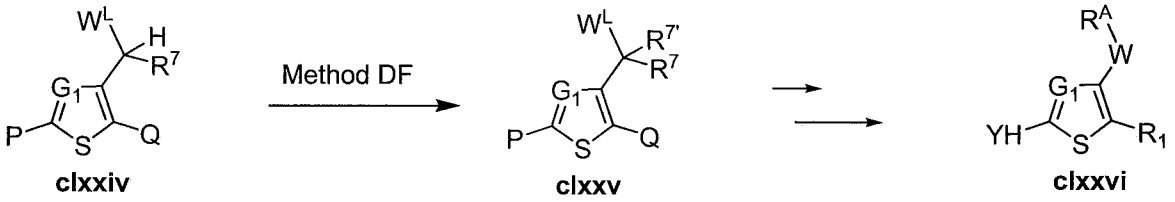
[00380] Scheme 72: Alternative method for the synthesis of cyanothiophenes



[00381] As shown in Scheme 72, acyl halides can be coupled with thiomorpholine and alkylhaloacetate in the presence of a suitable base, such as diisopropylamine in an appropriate solvent, for example MeCN at elevated temperature to afford cyanothiophenes **clxxiii** (Method DE). A conversion

reaction from **clxxiii** to compounds **clix** can be performed by a combination of generally known functional group manipulations.

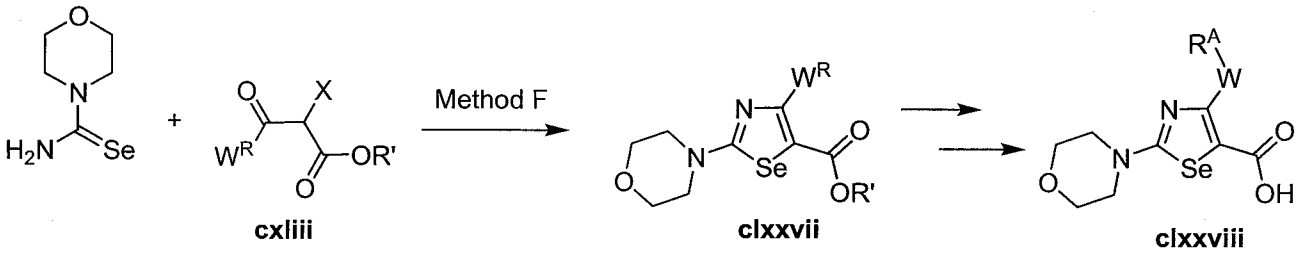
[00382] Scheme 73: General method for benzylic alkylation



[00383] As shown in Scheme 73, compounds **clxxiv** (where W^L is an aromatic or heteroaromatic group) can be deprotonated using a suitable base, such as KO*t*Bu in an appropriate solvent, for example THF and subsequently alkylated using an alkyl halide $R^{7'}$-X (Method DF) to afford products of benzylic alkylations **clxxv**. Compounds **clxxv** can be further transformed to compounds **clxxvi** using generally known methods.

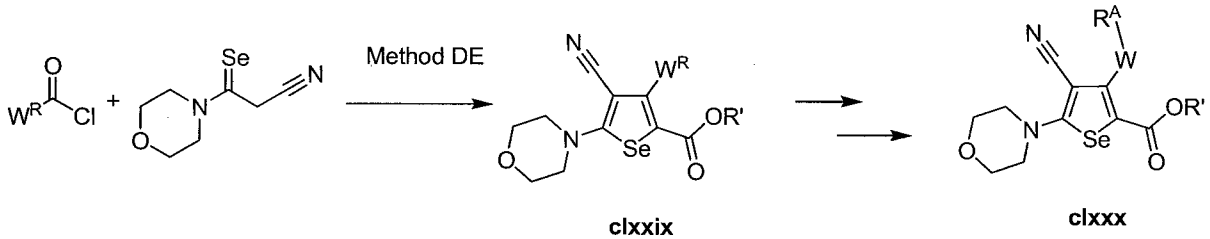
[00384]

[00385] Scheme 74: General method for the synthesis of substituted selenazoles



[00386] Scheme 74 shows a general route for the synthesis of compounds of formula **clxxvii**. Selenoamide can be treated with alpha-halogenated carbonyl compounds **cxliii** in a suitable solvent, such as isopropanol at elevated temprerature to give selenazoles **clxxvii**. (Method F). A conversion reaction from **clxxvii** to compounds **clxxviii** can be performed by a combination of generally known functional group manipulations.

[00387] Scheme 75: General method for the synthesis of selenophenes



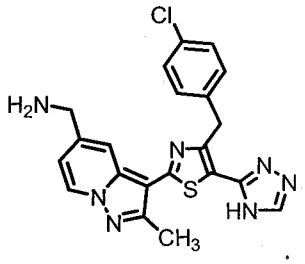
[00388] As shown in Scheme 75, acyl halides can be coupled with selenomorpholine building block and alkylhaloacetate in the presence of a suitable base, such as diisopropylamine in an appropriate

solvent, for example MeCN at elevated temperature to afford selenophenes **clxxix** (Method DE). A conversion reaction from **clxxix** to compounds **clxxx** can be performed by a combination of generally known functional group manipulations.

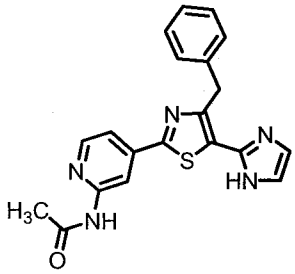
[00389] EXAMPLES

[00390] Table 1 below depicts certain compounds represented by compounds of general formula **IA** and **IB**.

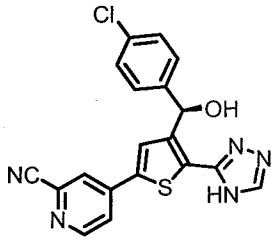
[00391] Table 1



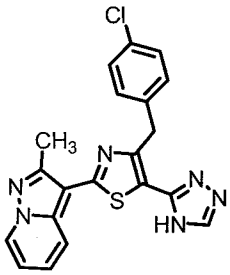
1



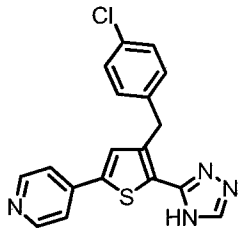
2



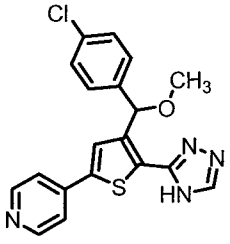
3



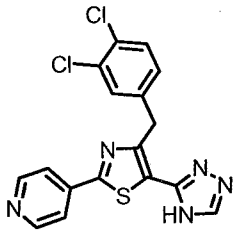
4



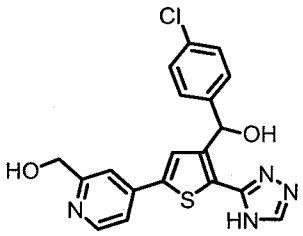
5



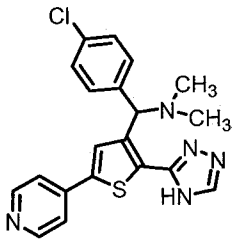
6



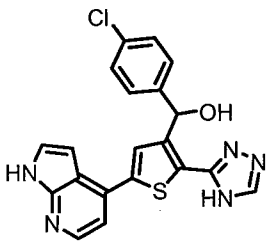
7



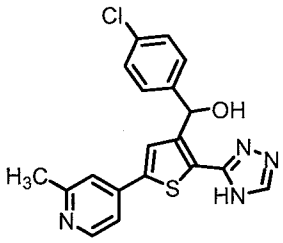
8



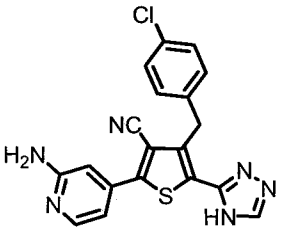
9



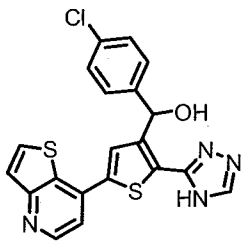
10



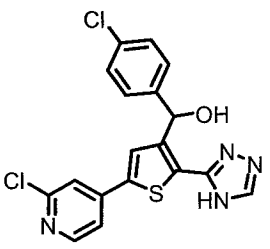
11



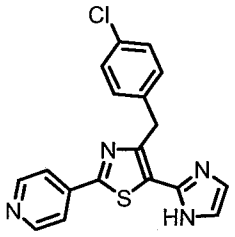
12



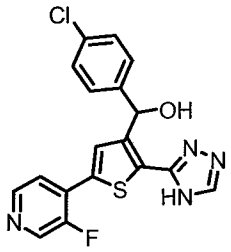
13



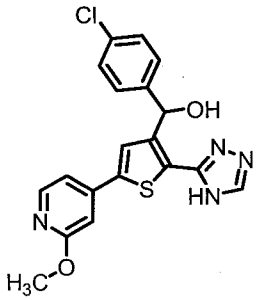
14



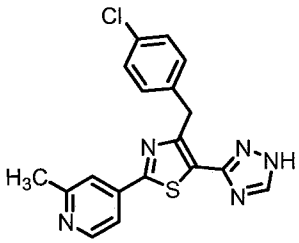
15



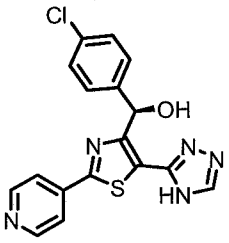
16



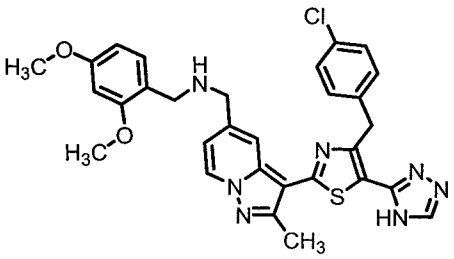
17



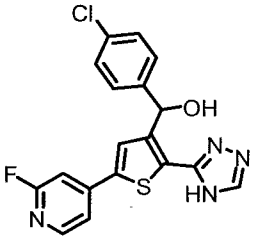
18

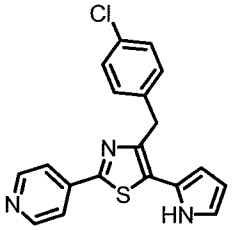


19

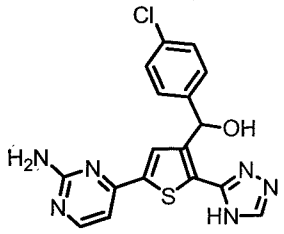


20

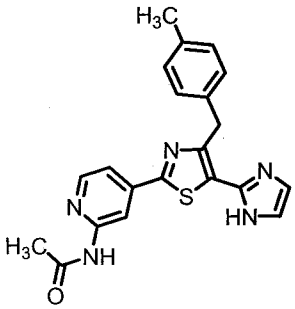




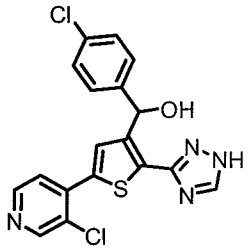
21



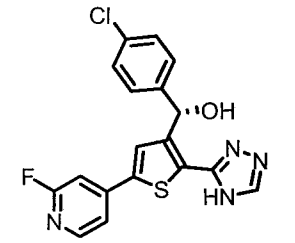
22



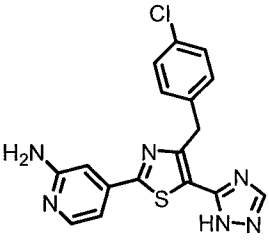
23



24



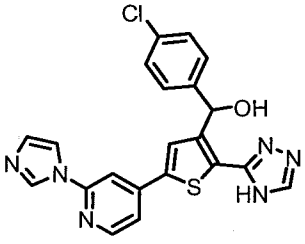
25

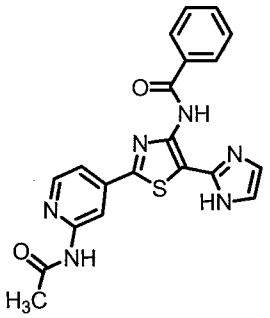


26

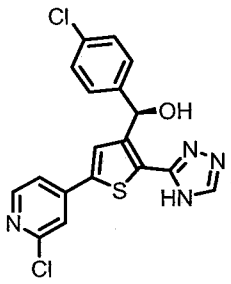
27

28

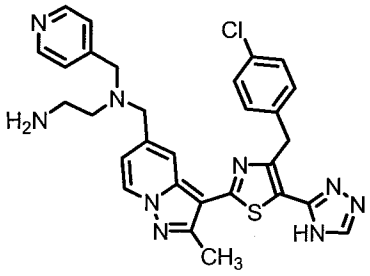




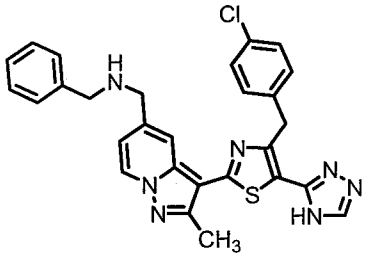
29



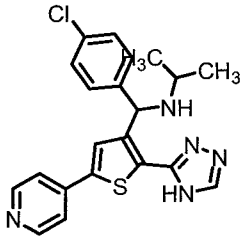
30



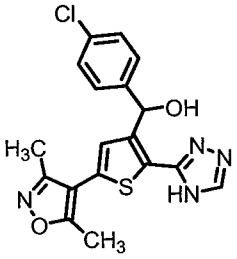
31



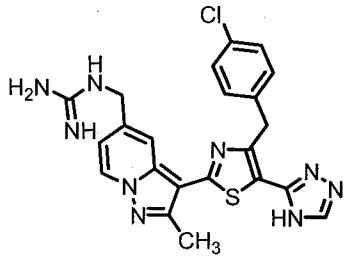
32



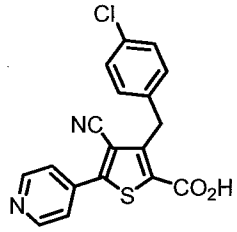
33



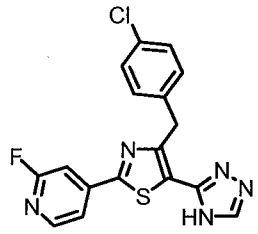
34



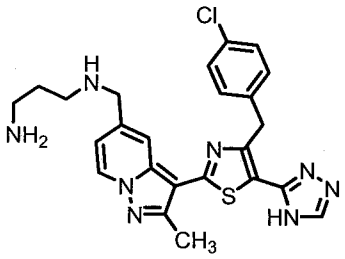
35



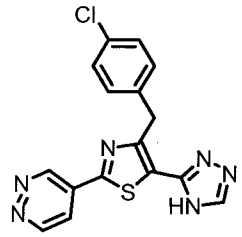
36



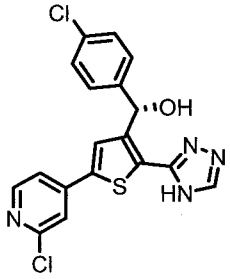
37



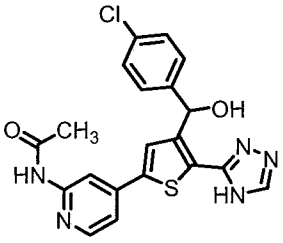
38



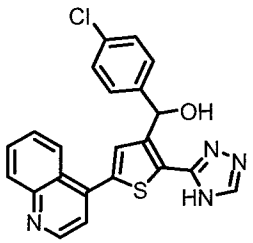
39



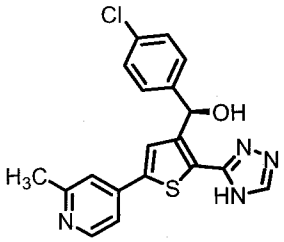
40



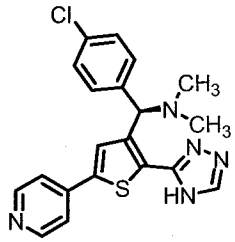
41



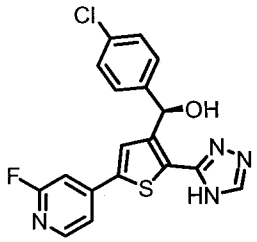
42



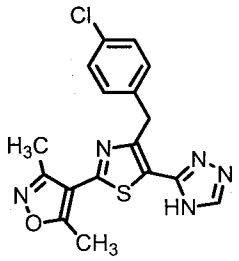
43



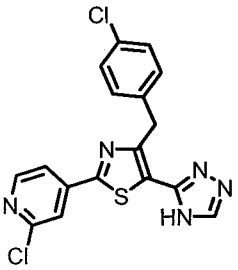
44



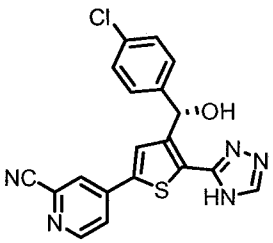
45



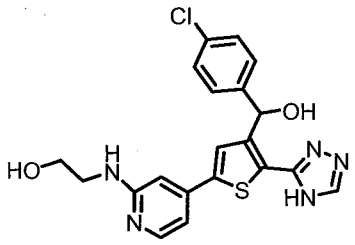
46



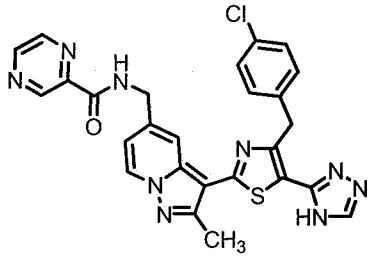
47



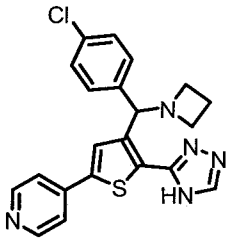
48



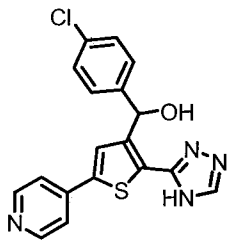
49



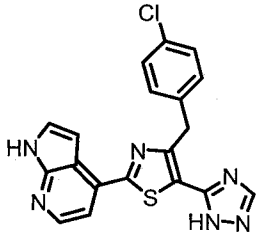
50



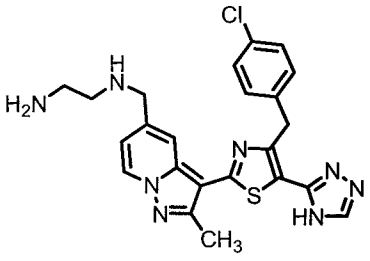
51



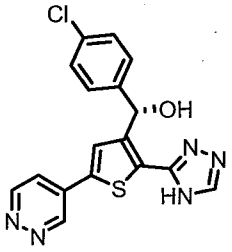
52



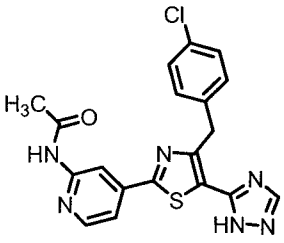
53



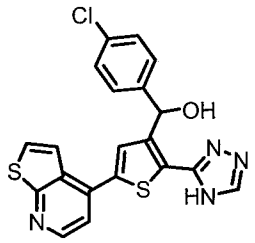
54



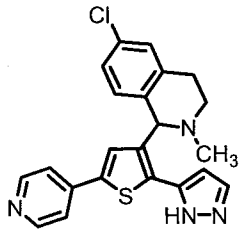
55



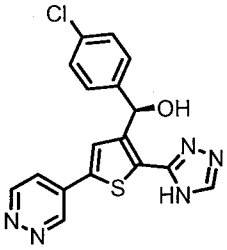
56



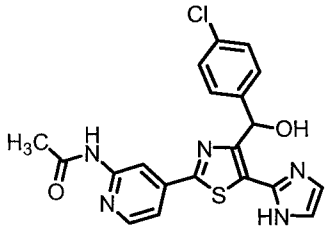
57



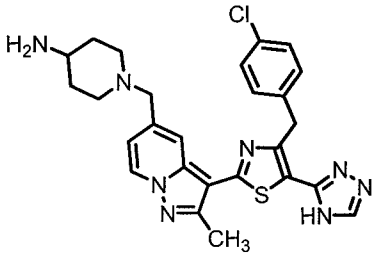
58



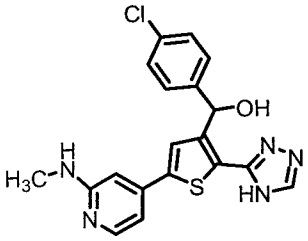
59



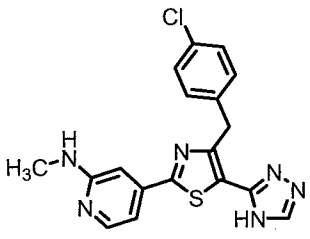
60



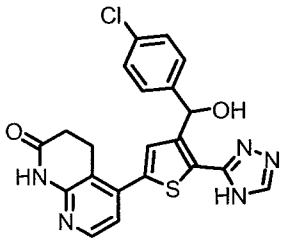
61



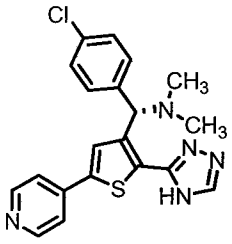
62



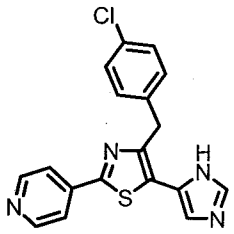
63



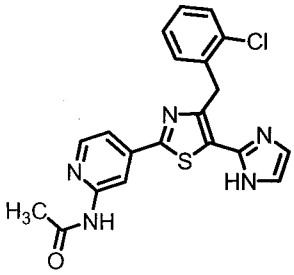
64



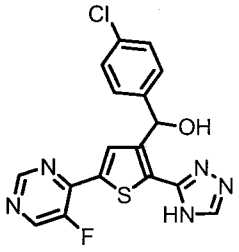
65



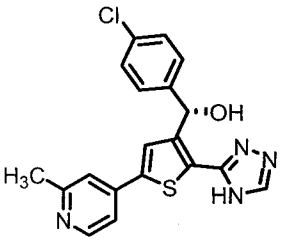
66



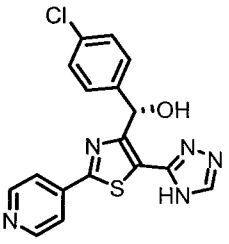
67



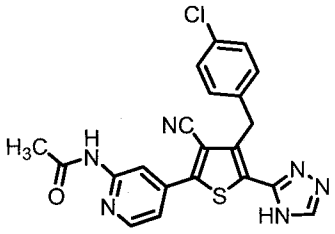
68



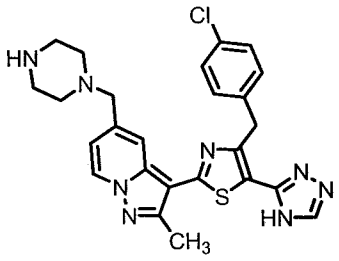
69



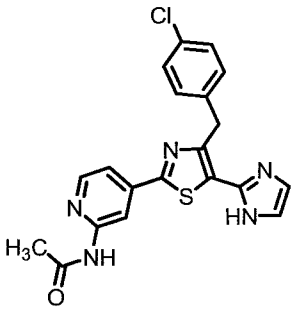
70



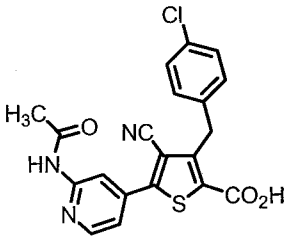
71



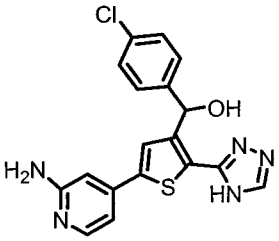
72



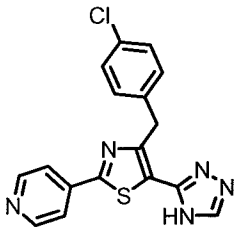
73



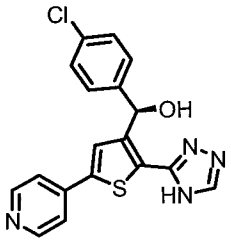
74



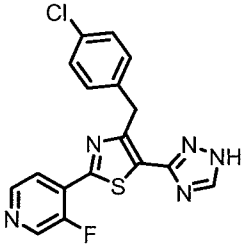
75



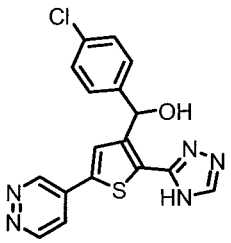
76



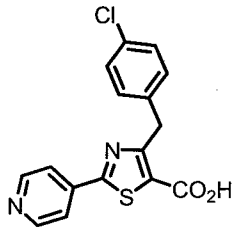
77



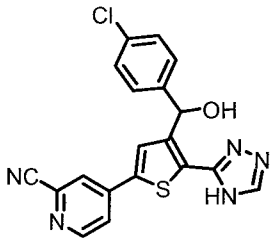
78



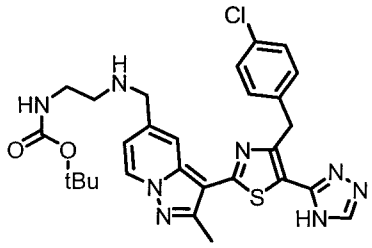
79



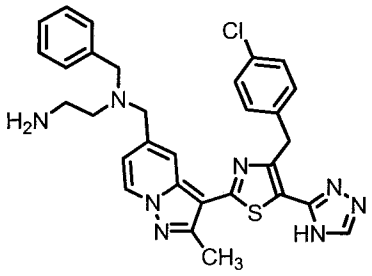
80



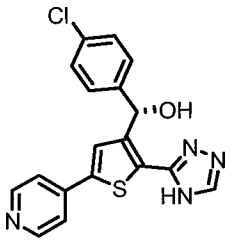
81



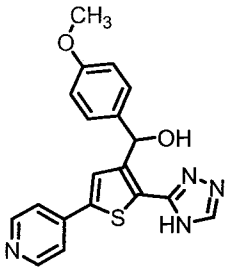
82



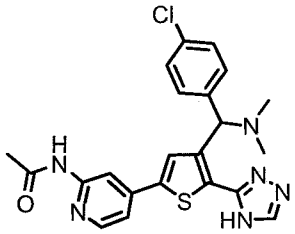
83



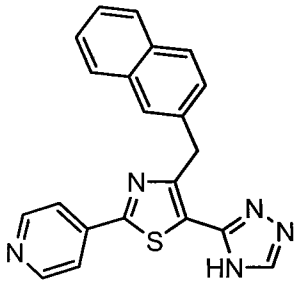
84



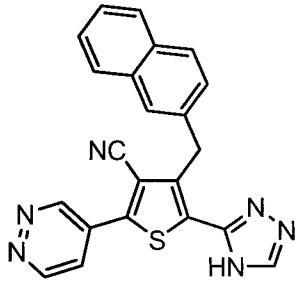
85



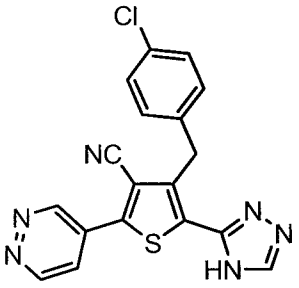
86



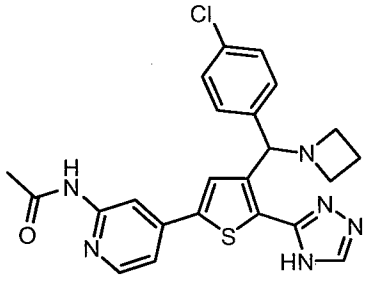
87



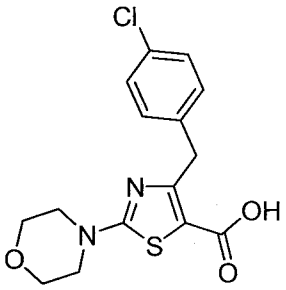
88



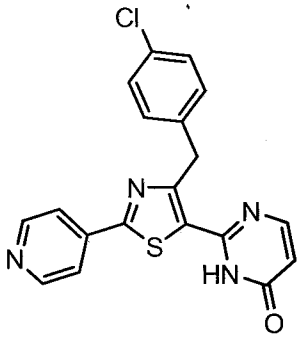
89



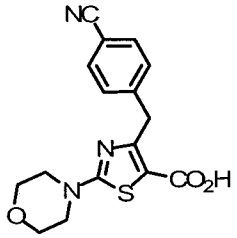
90



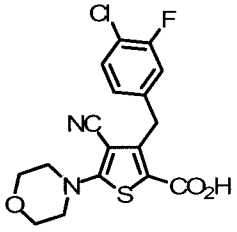
91



92



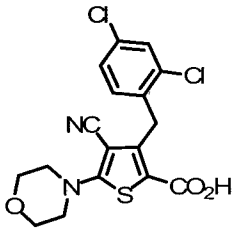
93



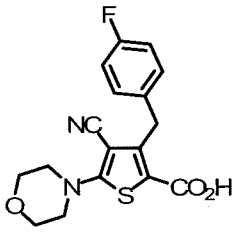
94



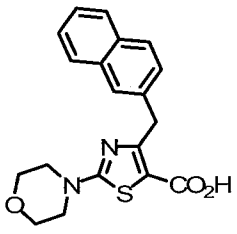
95



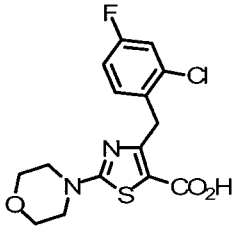
96



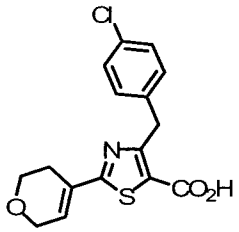
97



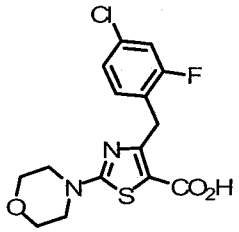
98



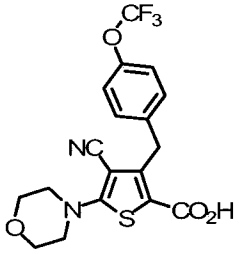
99



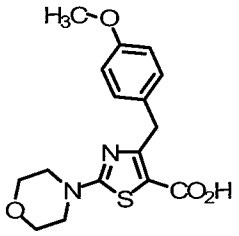
100



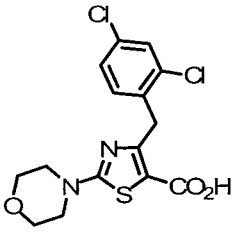
101



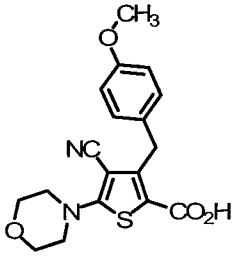
102



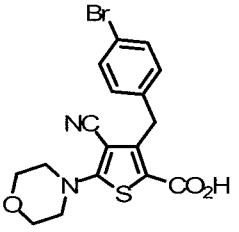
103



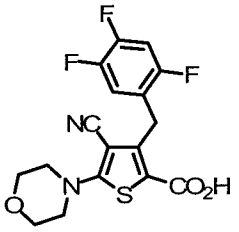
104



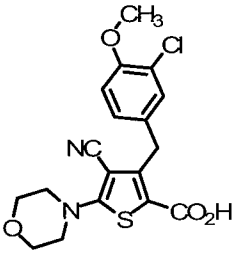
105

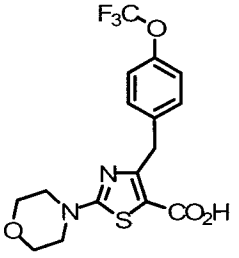


106

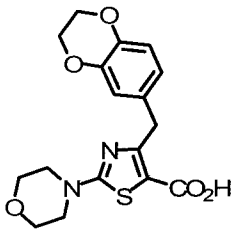


107

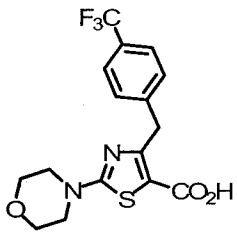




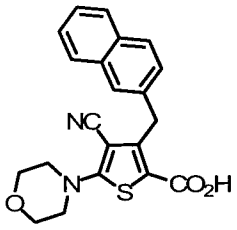
108



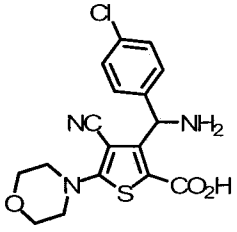
109



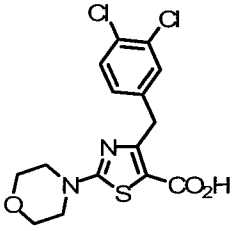
110



111



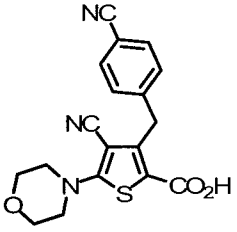
112



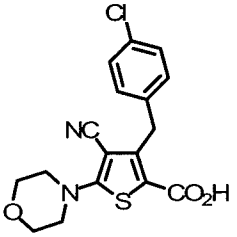
113

114

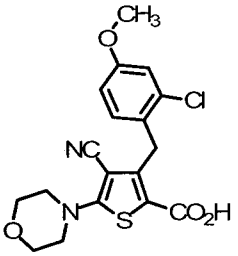
115

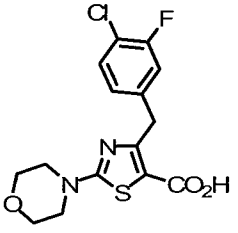


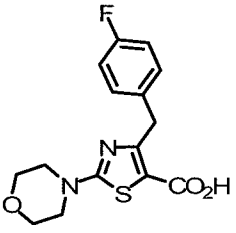
116



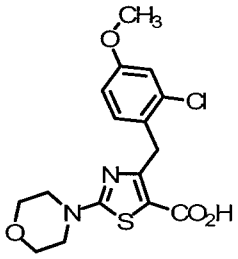
117



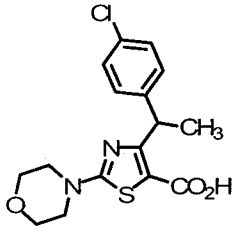




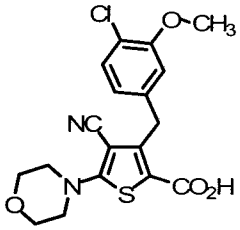
118



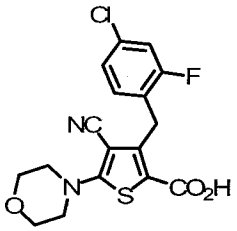
119



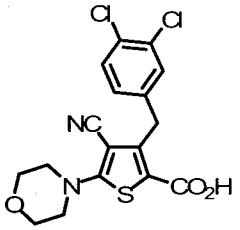
120



121



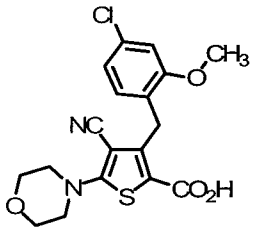
122



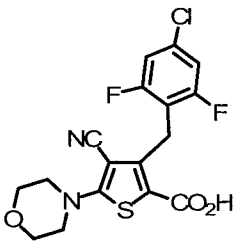
123

124

125

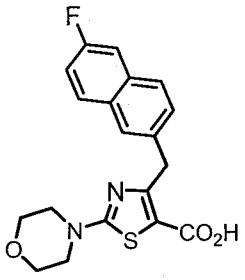


126

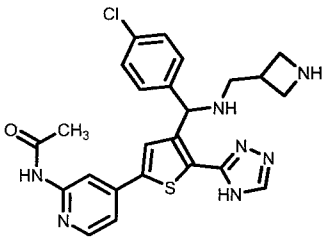


127

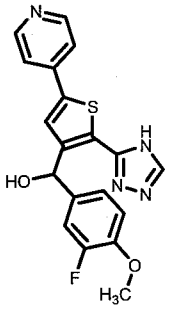




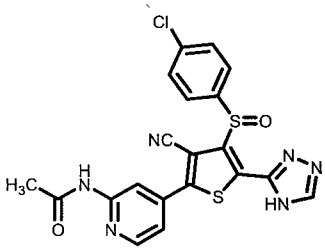
128



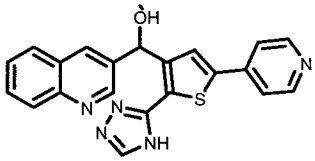
129



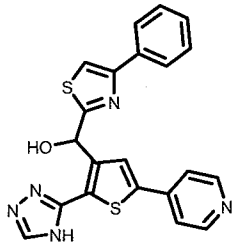
130



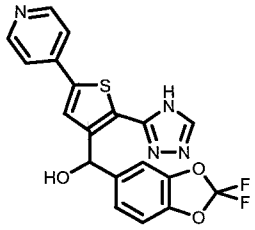
131



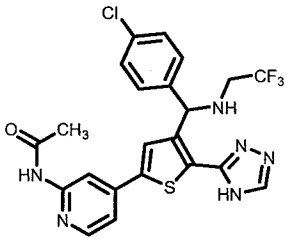
132



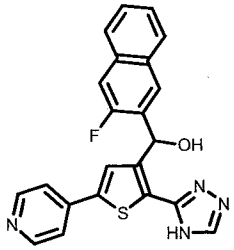
133



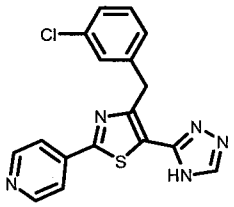
134



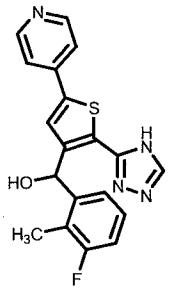
135



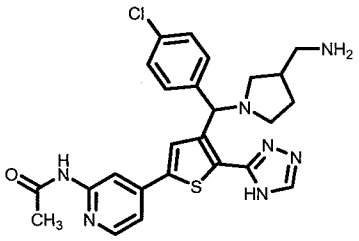
136



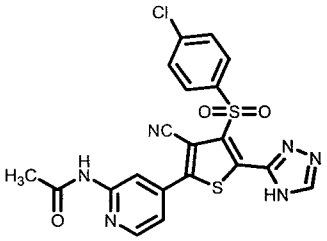
137



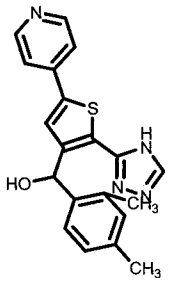
138



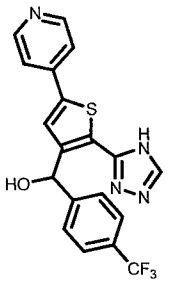
139



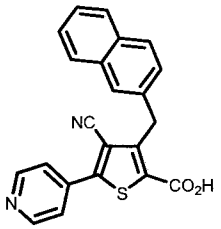
140



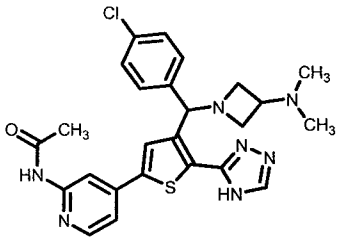
141



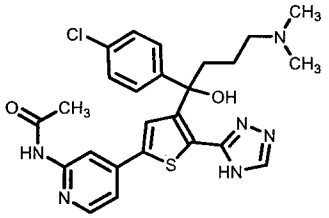
142



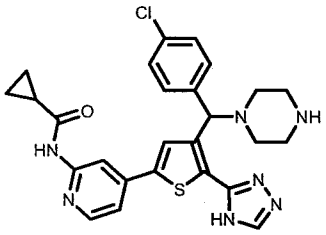
143



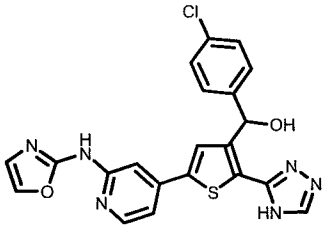
144



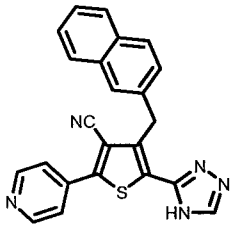
145



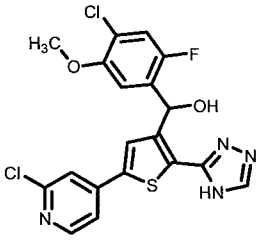
146



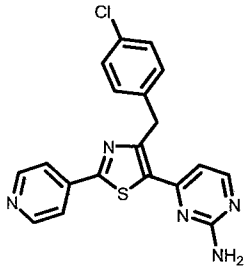
147



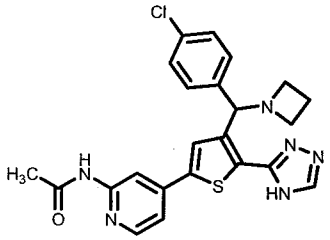
148



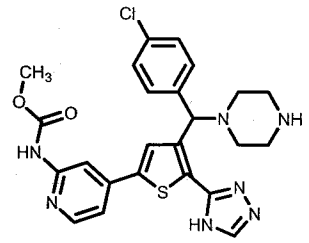
149



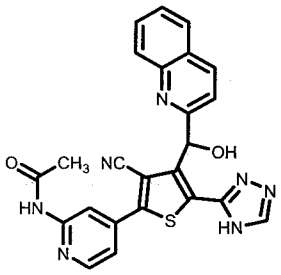
150



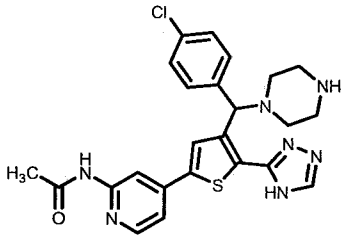
151



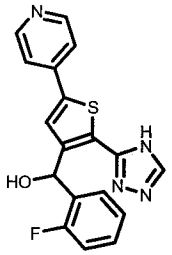
152



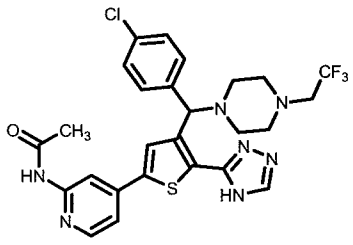
153



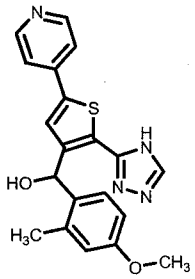
154



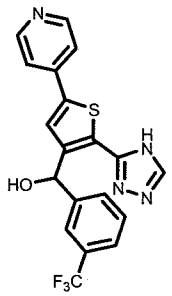
155



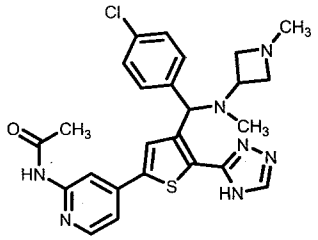
157



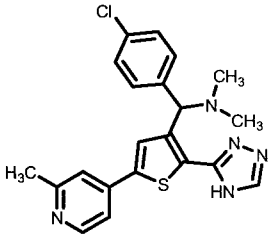
158



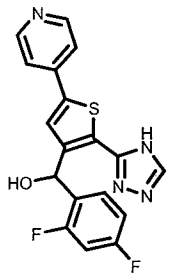
159



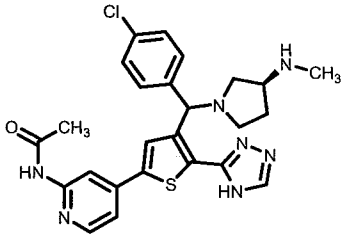
160



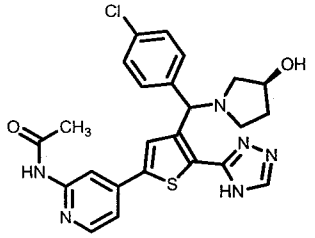
161



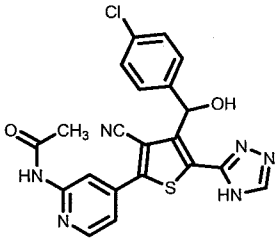
162



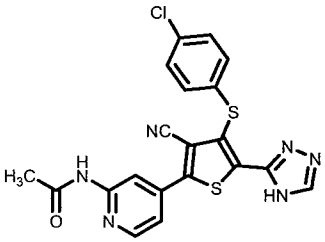
163



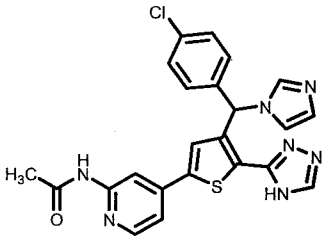
164



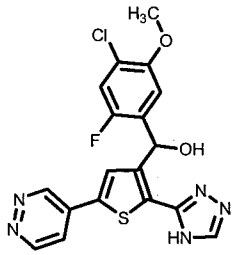
165



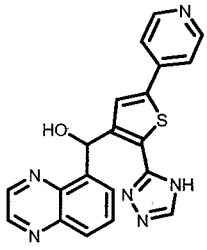
166



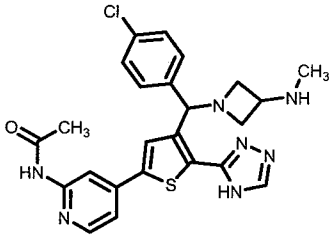
167



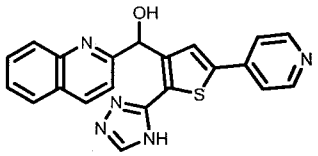
168



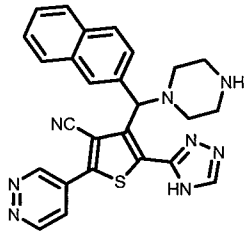
169



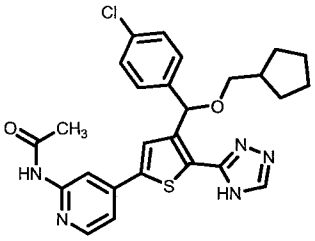
170



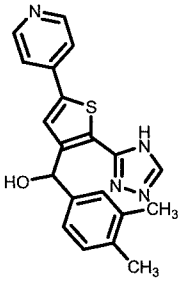
171



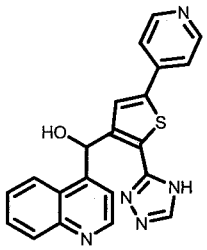
172



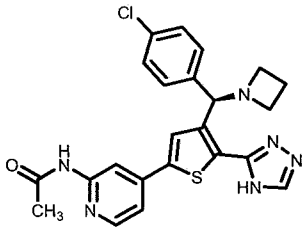
173



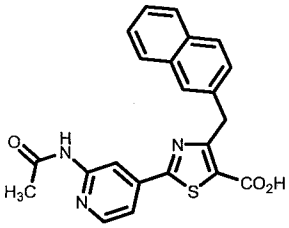
174



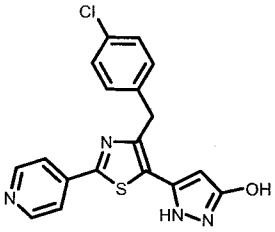
175



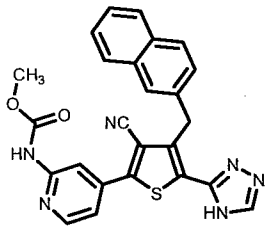
176



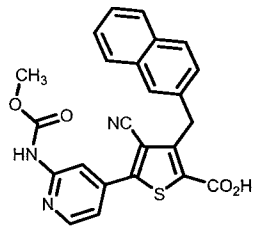
177



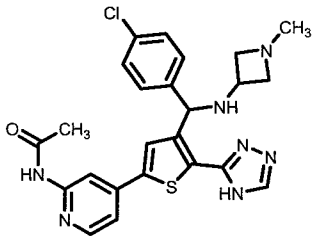
178



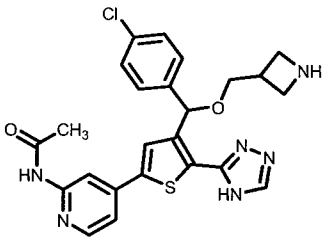
179



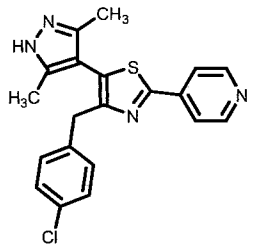
180



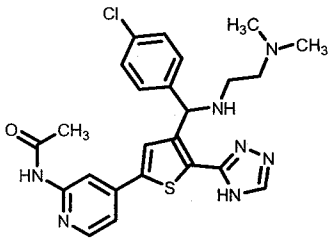
181



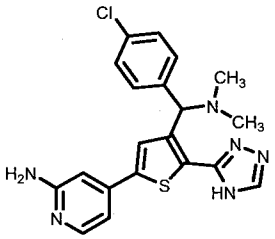
182



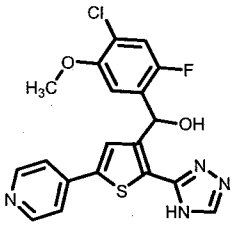
183



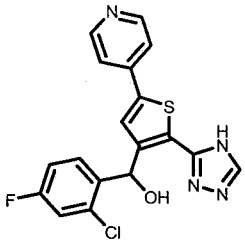
184



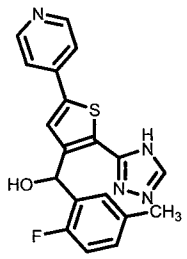
185



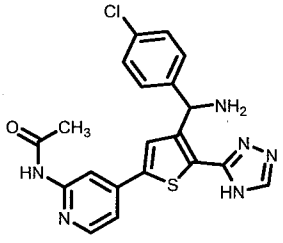
186



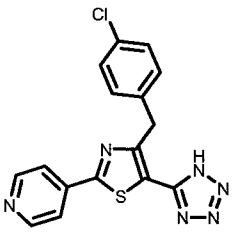
187



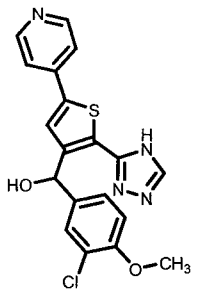
188



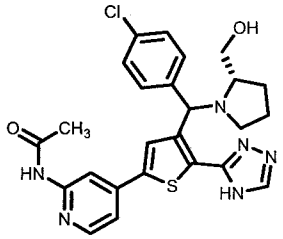
189



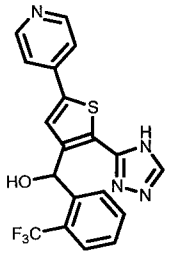
190



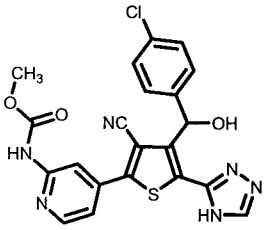
191



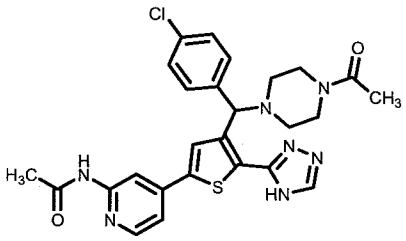
192



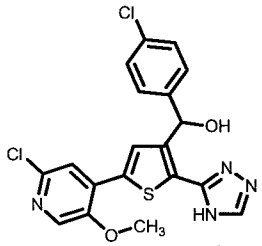
193



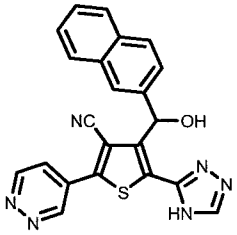
195



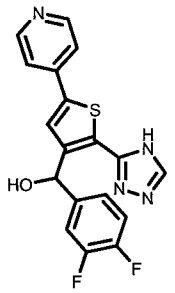
196



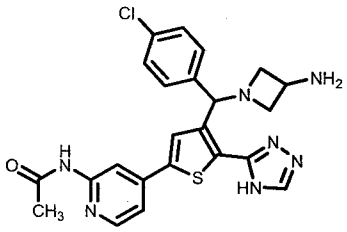
197



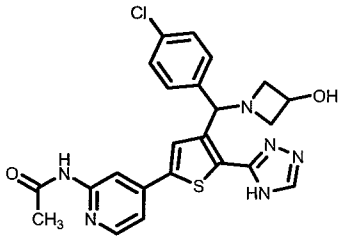
198



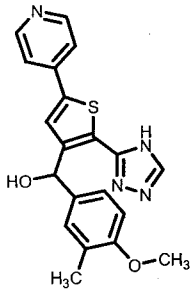
199



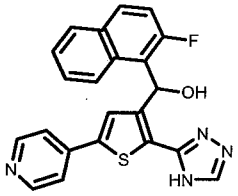
200



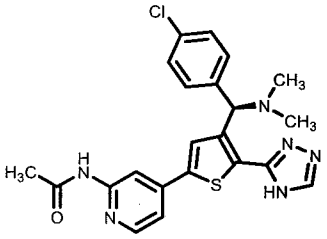
201



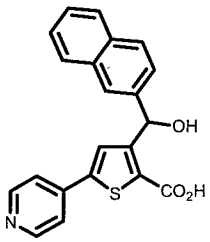
202



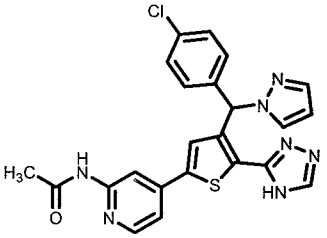
203



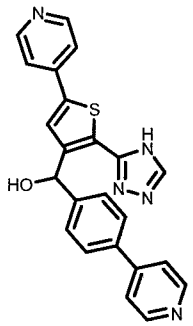
204



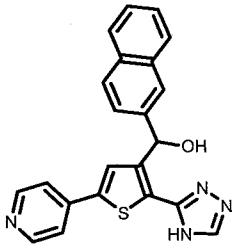
205



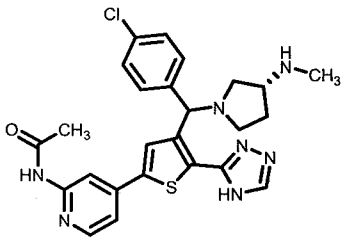
206



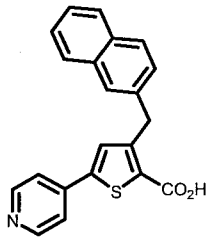
207



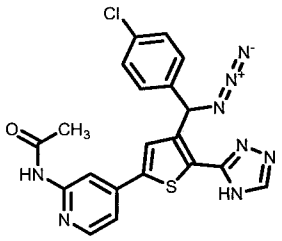
208



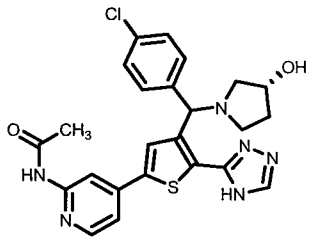
209



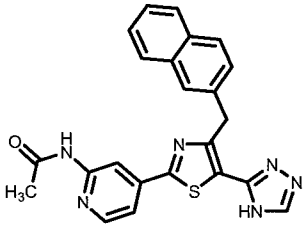
210



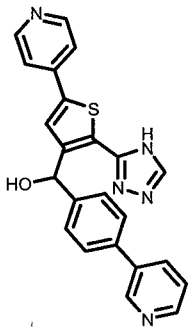
211



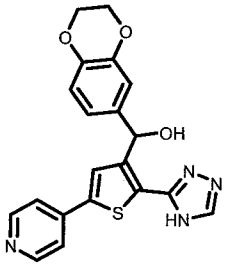
212



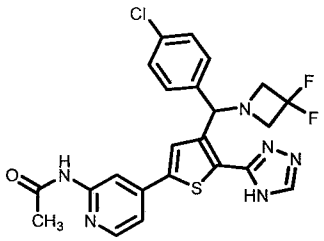
213



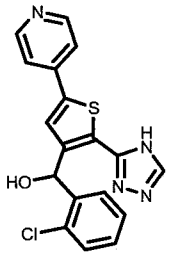
214



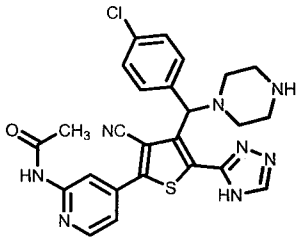
215



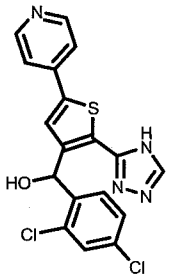
216



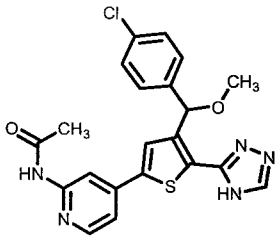
217



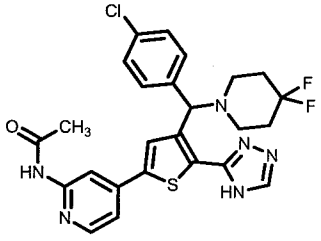
218



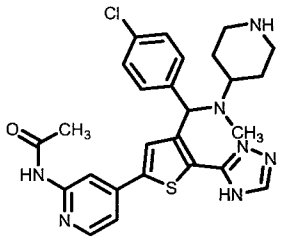
219



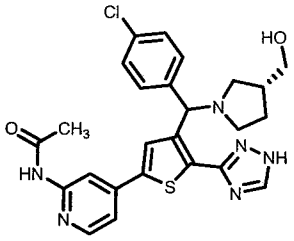
220



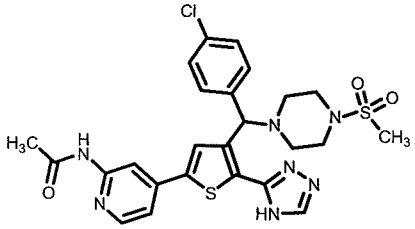
221



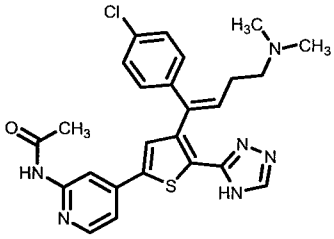
222



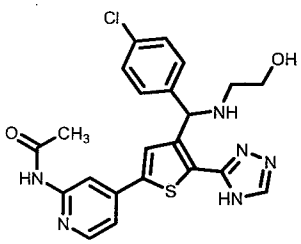
223



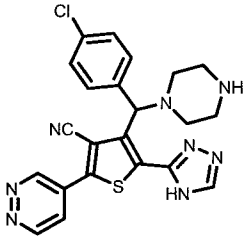
224



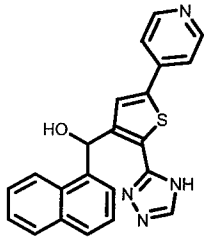
225



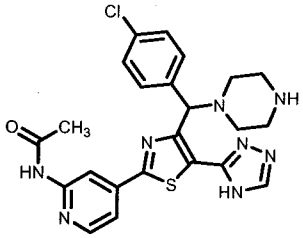
226



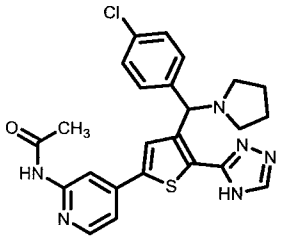
227



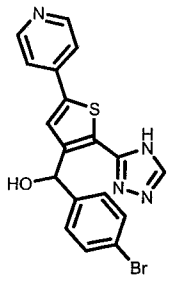
228



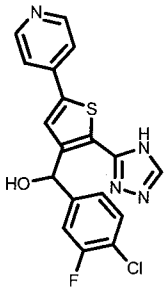
229



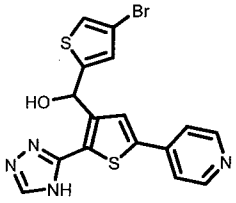
230



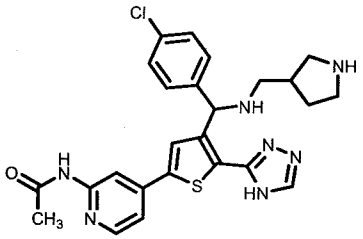
231



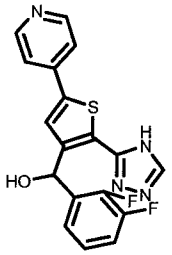
232



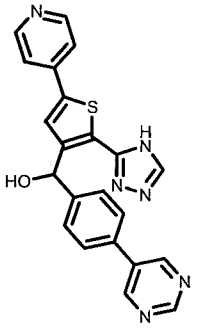
233



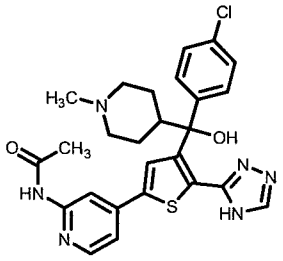
234



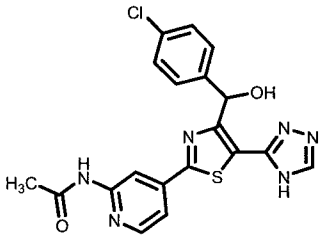
235



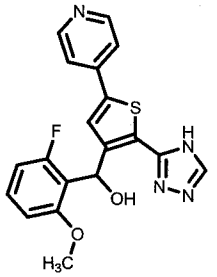
236



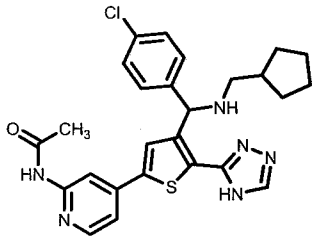
237



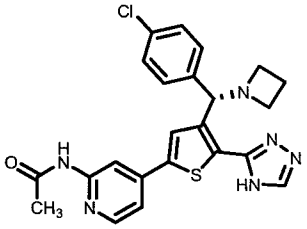
238



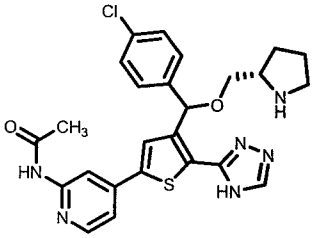
239



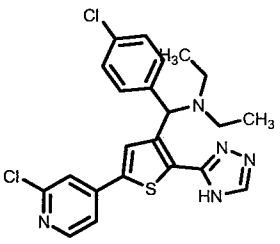
240



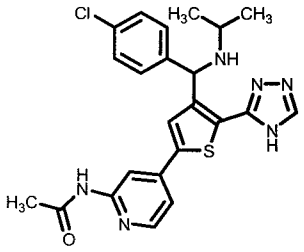
241



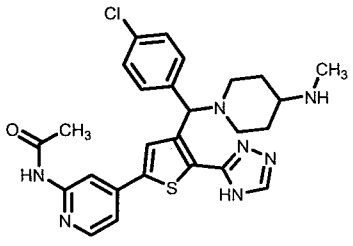
242



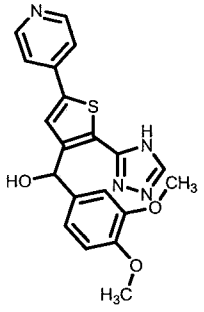
243



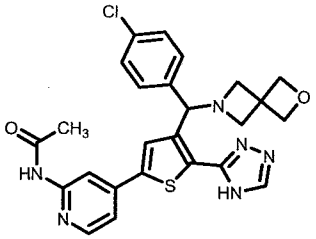
244



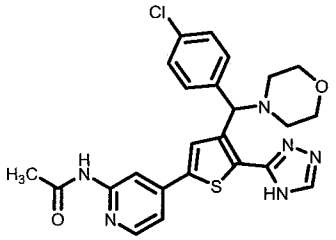
245



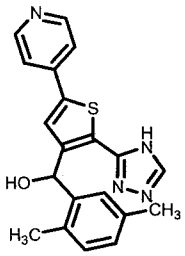
246



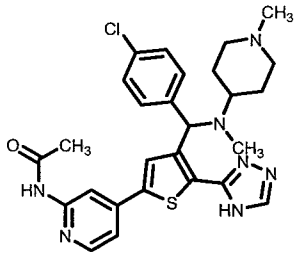
247



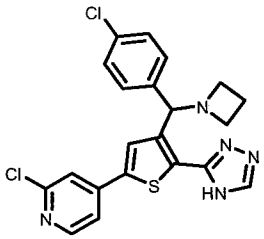
248



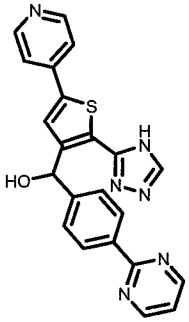
249



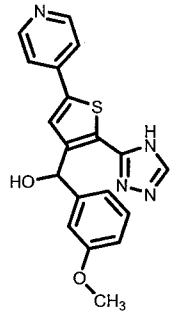
250



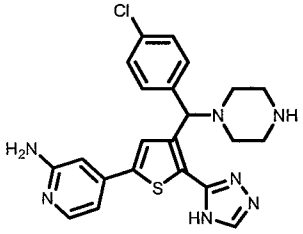
251



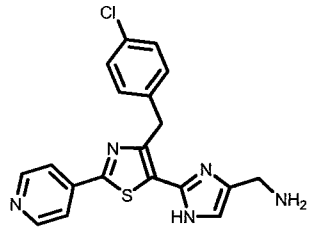
252



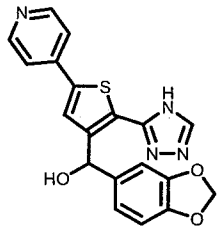
253



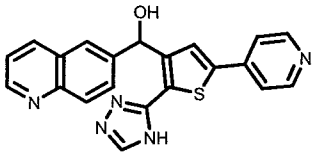
254



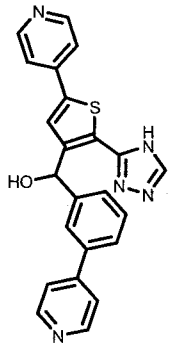
255



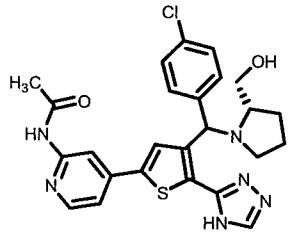
256



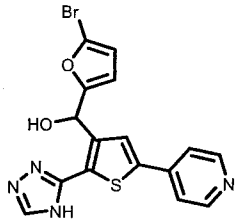
257



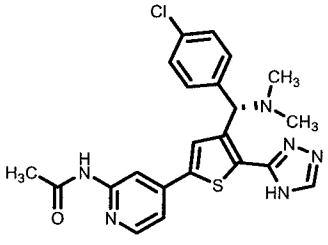
258



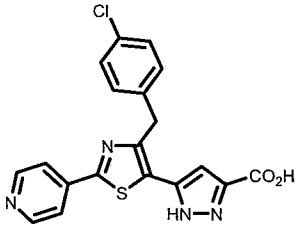
259



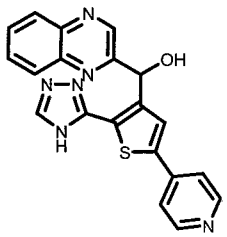
260



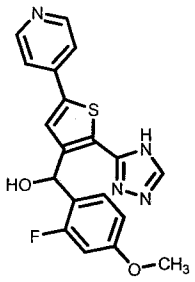
261



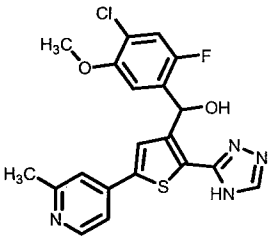
262



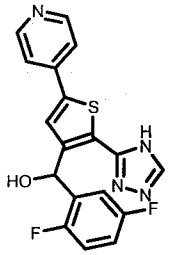
263



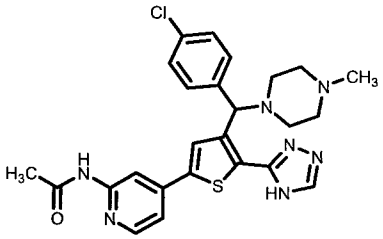
264



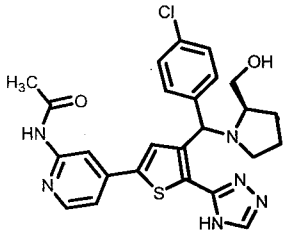
265



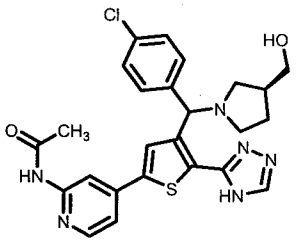
266



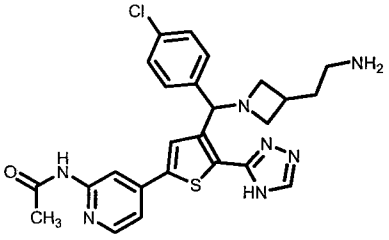
267



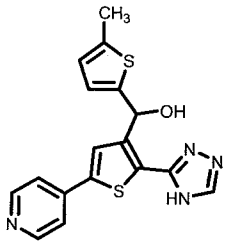
268



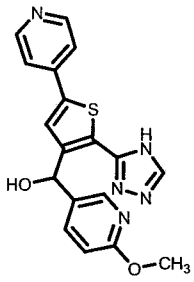
269



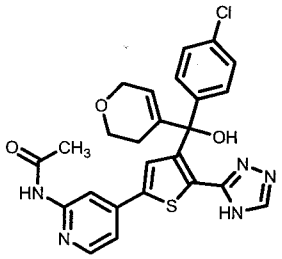
270



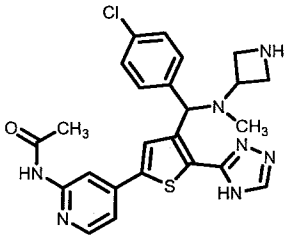
271



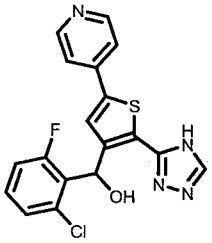
272



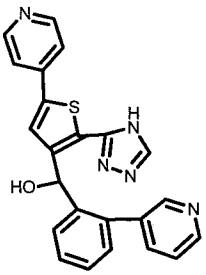
273



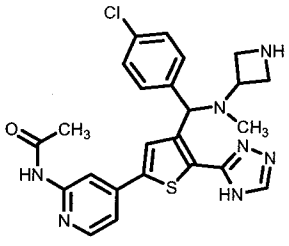
274



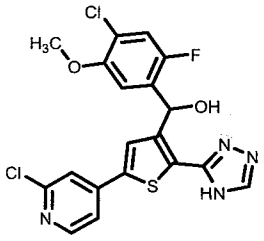
275



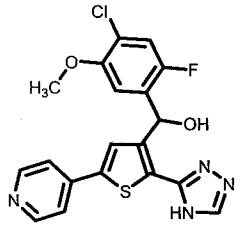
276



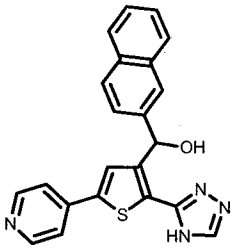
277



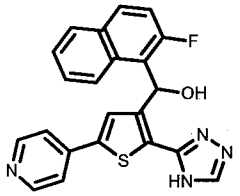
278



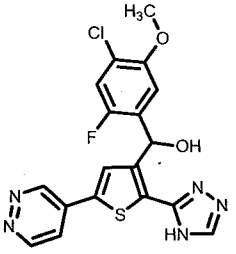
279



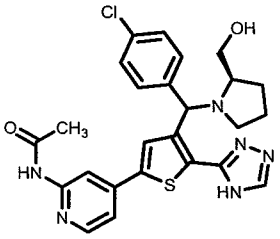
280



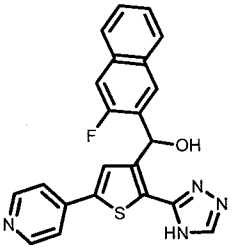
281



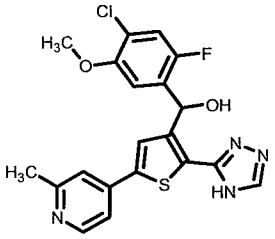
282



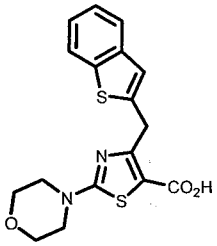
283



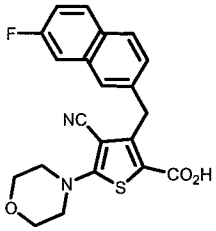
284



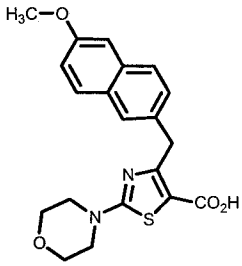
285



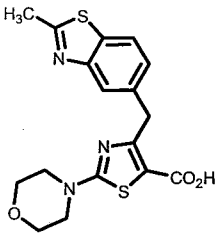
286



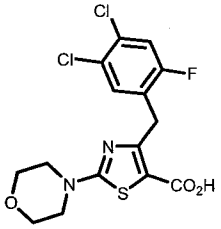
287



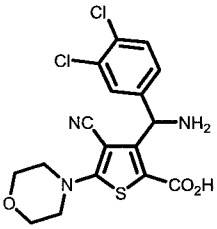
288



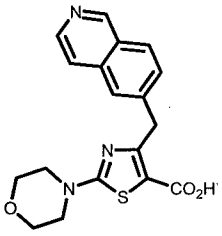
289



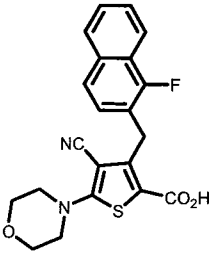
290



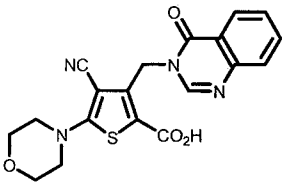
291



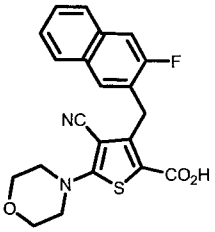
292



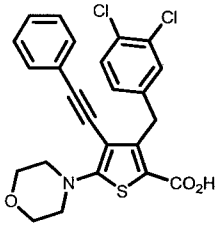
293



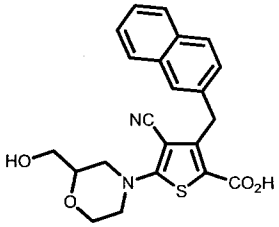
294



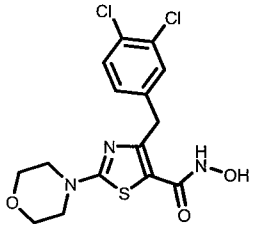
295



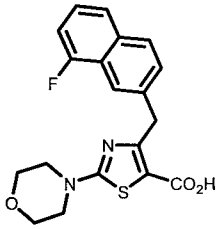
296



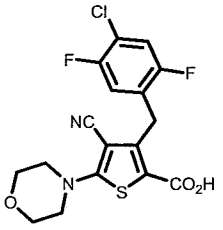
297



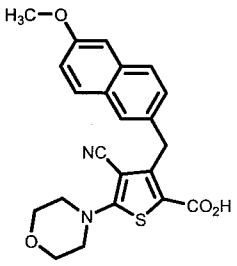
298



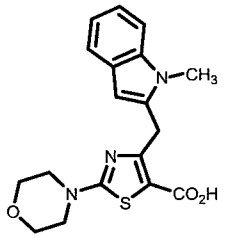
299



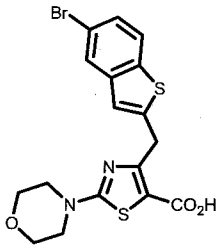
300



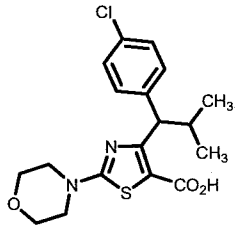
301



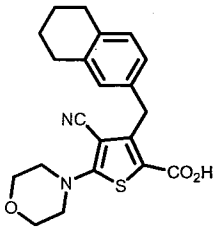
302



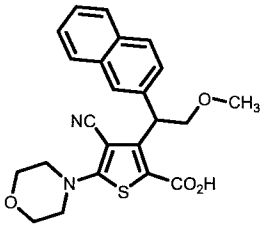
303



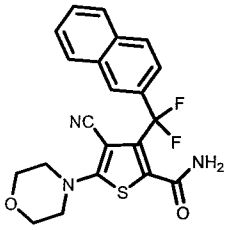
304



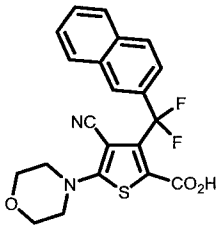
305



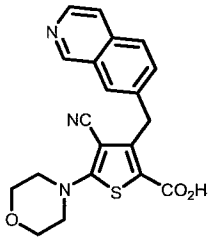
306



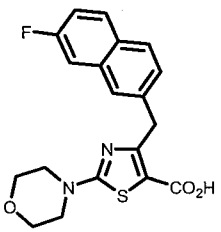
307



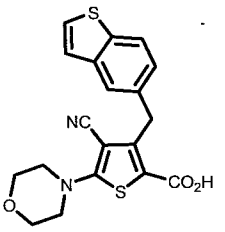
308



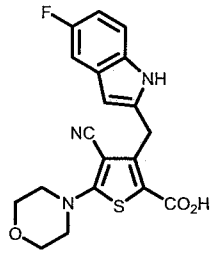
309



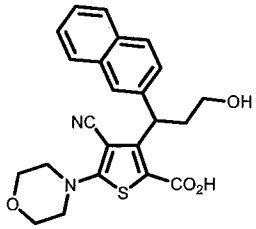
310



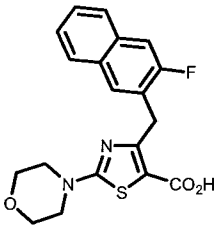
311



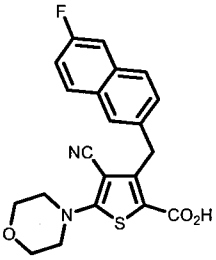
312



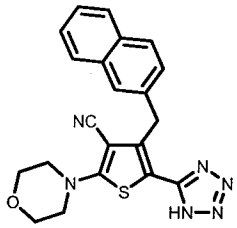
313



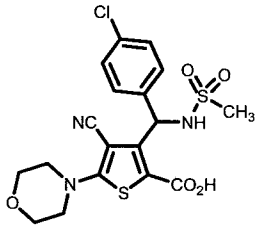
314



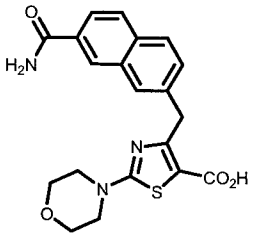
315



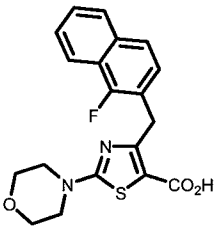
316



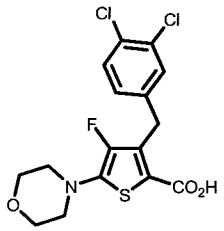
317



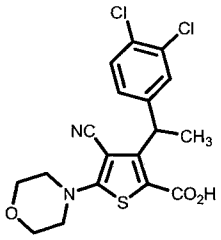
318



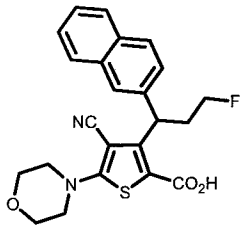
319



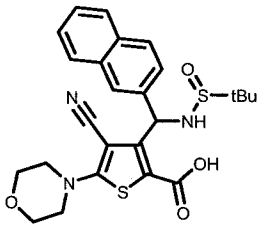
320



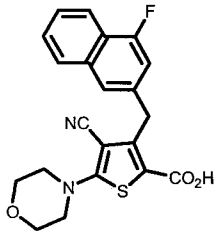
321



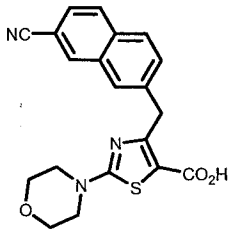
322



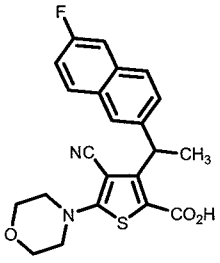
323



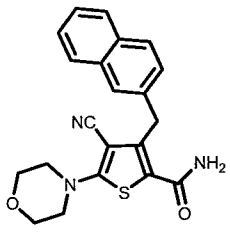
324



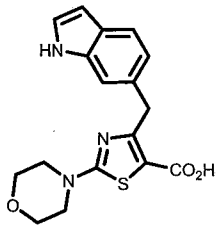
325



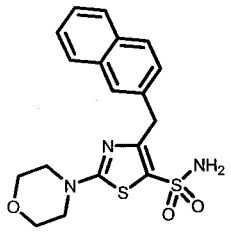
326



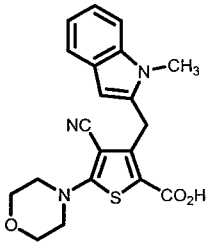
327



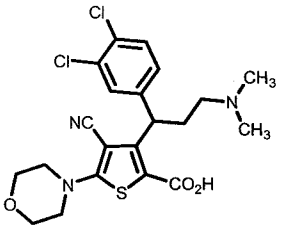
328



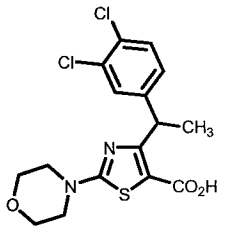
329



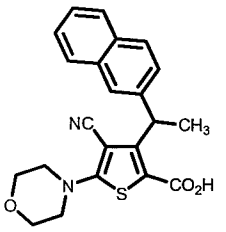
330



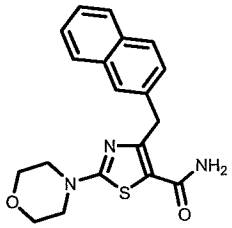
331



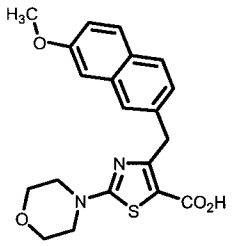
332



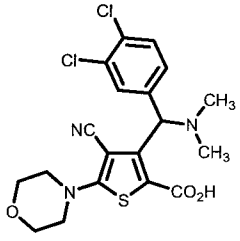
333



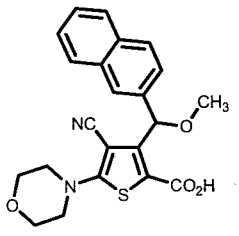
334



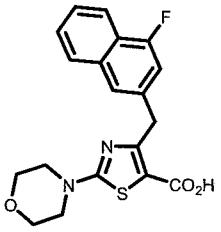
335



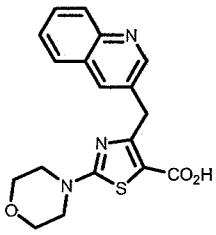
336



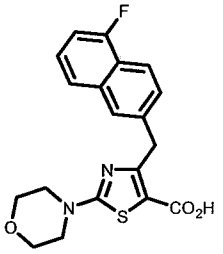
337



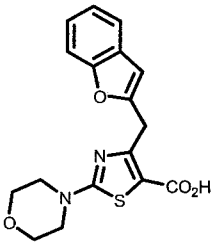
338



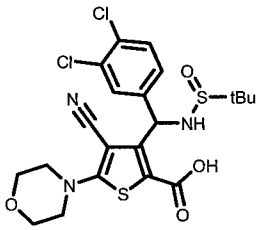
339



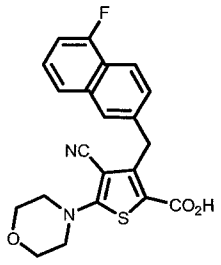
340



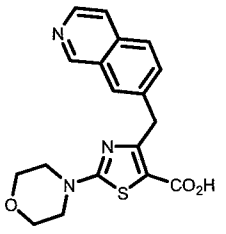
341



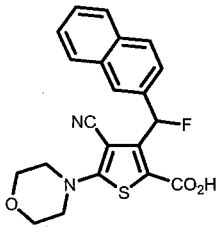
342



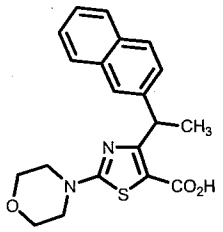
343



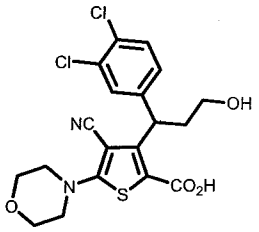
344



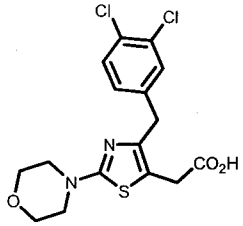
345



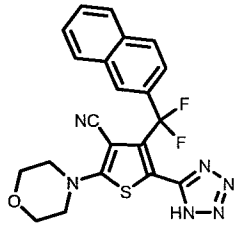
346



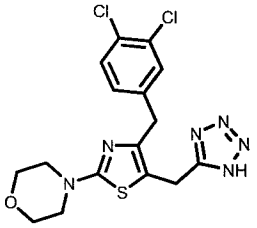
347



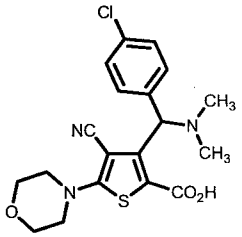
348



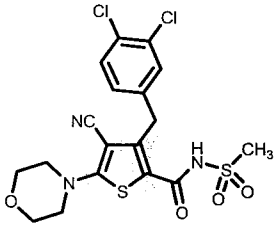
349



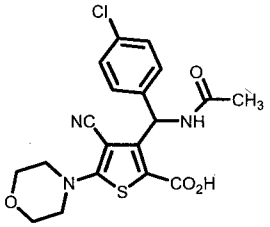
350



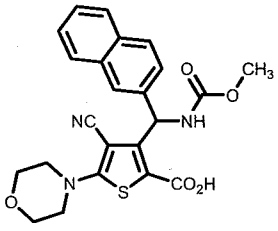
351



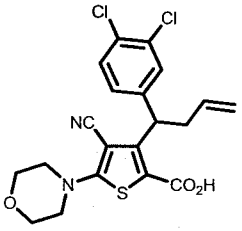
352



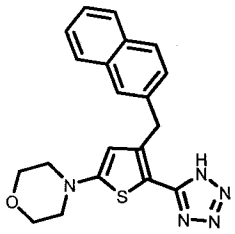
353



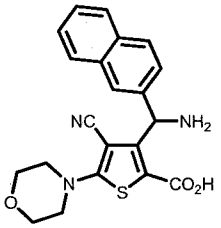
354



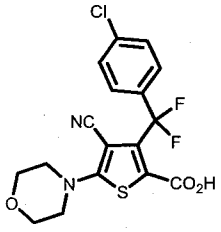
355



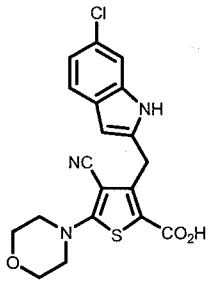
356



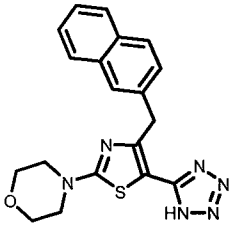
357



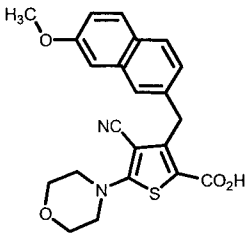
358



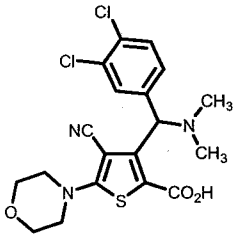
359



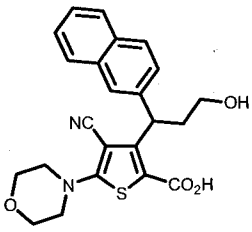
360



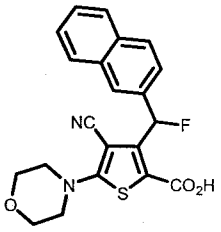
361



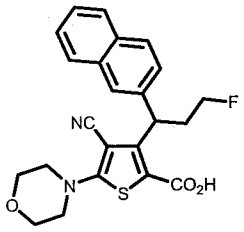
362



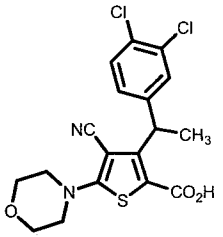
363



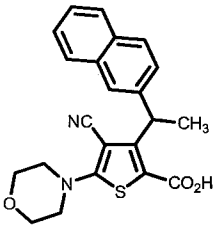
364



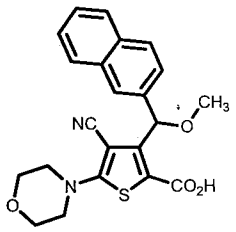
365



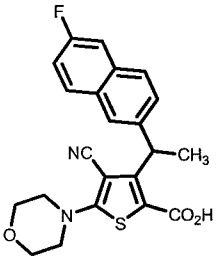
366



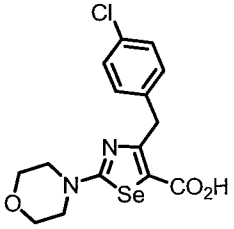
367



368



369



370

[00392] Definitions

AcOH acetic acid

ACN acetonitrile

ATP adenosine triphosphate

br broad

BCA bicinchoninic acid

BSA bovine serum albumin

BOC tert-butoxycarbonyl

BuLi butyllithium

m-CPBA m-chloroperbenzoic acid

d doublet

dd doublet of doublets

DCE dichloroethane

DCM dichloromethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIPEA diisopropylethyl amine

DMAP *N,N*-dimethylaminopyridine

DME 1,2-Dimethoxyethane

DMEM Dulbecco's Modified Eagle's Medium

DMF N, N-dimethylformamide

DMF-DMA N, N-dimethylformamide dimethyl acetal

DMSO dimethylsulfoxide

DPPA diphenylphosphoryl azide

DTT dithiothreitol

dppf diphenylphosphinoferrocene

EDCI N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

EDTA ethylenediaminetetraacetic acid

EtOAc ethyl acetate

EtOH ethanol

FA formic acid

FBS fetal bovine serum

J coupling constant

h hours

Hz: hertz

HATU N, N, N', N'-tetramethyl-o-(7-azabenzotriazole-1-yl)uronium hexafluorophosphate

HBTU o-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate

HEPES N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)

HOBT 1-hydroxybenztriazole hydrate

HRMS high resolution mass spectrum

LAH lithium aluminum hydride

LCMS liquid chromatography mass spectrum

LDA lithium diisopropylamide

LiHMDS Lithium bis(trimethylsilyl)amide

m multiplet

m/z mass to charge

Me methyl

MeOH methanol

min minutes

MS mass spectrum

MTT methylthiazoletetrazolium

MWI microwave irradiation

NBS N-bromosuccinimide

PBS phosphate buffered saline

PKA cAMP-dependent protein kinase

rt room temperature

s singlet

t triplet

TEA triethylamine

TFA: trifluoroacetic acid

TFFA trifluoroacetic anhydride

THF tetrahydrofuran

TMB 3,3′,5,5′-Tetramethylbenzidine

TMEDA Tetramethylethylenediamine

q quartet

WST (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate sodium salt)

[00393] The following analytical methods were used:

[00394] LCMS sectra were run on a Phenominex Luna 5μm C18 50 × 4.6 mm column on a Hewlett-Packard HP1100 using the following gradients:

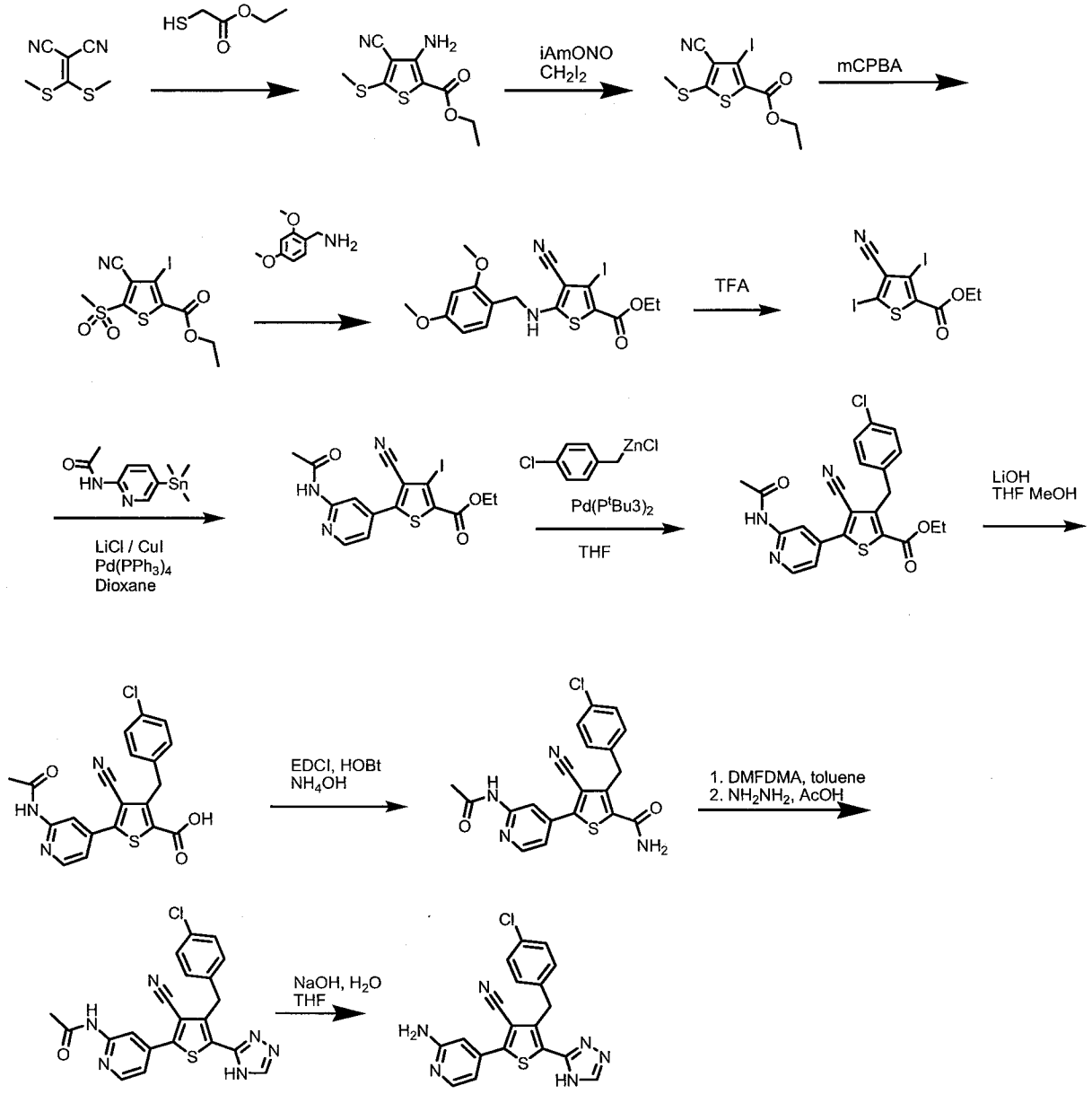
- Method Formic Acid (FA): Acetonitrile containing 0 to 100 percent 0.1 % formic acid in water (2.5 ml/min for a 3 minute run).

- Method Ammonium Acetate (AA): Acetonitrile containing 0 to 100 percent 10 mM ammonium acetate in water (2.5 ml/min for a 3 minute run).

[00395] Chiral isomers were separated using chiral HPLC on a Chiralpak IC 250x25 mm 5 micron column using hexane/ethanol/diethylamine or hexane/isopropylalcohol/ethanol/diethylamine as mobil phase. Absolute configurations of the separated isomers were unknown, structures were assigned arbitrarily.

[00396] NMR spectrum is shown by proton NMR, with tetramethylsilane as the internal standard and using 300MHz Bruker Avance spectrometer equipped with a 5mm QNP probe and 400MHz Bruker Avance II spectrometer equipped with a 5mm QNP probe for the measurement; δ values are expressed in ppm.

[00397] Example 1: Synthesis of *N*-{4-[4-(4-chlorobenzyl)-3-cyano-5-(4*H*-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 71) and 2-(2-aminopyridin-4-yl)-4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound 12)



[00398] **Step 1:** Ethyl 3-amino-4-cyano-5-(methylsulfanyl)thiophene-2-carboxylate

[00399] A mixture of [bis(methylsulfanyl)methylene]malononitrile (40 g, 230 mmol), ethylthioglycolate (29 g , 230 mmol) and TEA (24 mL, 173 mmol) in MeOH (600 mL) was allowed to stir at reflux for 2 h. The reaction mixture was allowed to cool overnight and the precipitate was filtered off then washed with cold MeOH (3x50 mL) to give ethyl 3-amino-4-cyano-5-(methylsulfanyl)thiophene-2-carboxylate (52.4 g, 99 %). LCMS: (FA) ES+ 275.

[00400] **Step 2:** Ethyl 4-cyano-3-iodo-5-(methylsulfanyl)thiophene-2-carboxylate

[00401] Ethyl 3-amino-4-cyano-5-(methylsulfanyl)thiophene-2-carboxylate (10 g, 41.3 mmol) was dissolved in acetonitrile (50 mL) under an atmosphere of argon. Diiodomethane (11.6 mL, 0.144 mol) was added and the mixture was heated at 40°C. Isoamyl nitrite (12.1g, 0.103 mol) was added and the reaction was allowed to cool to room temperature and stirred for 2 hours. The mixture was cooled down to 0°C, diluted with hexane (50 mL) and the precipitate was filtered off, washed with 10:1 hexane-acetonitrile mixture (10 mL), 3:1 hexane-ether (10 mL) and hexane (10 mL). The precipitate was dried to afford ethyl 4-cyano-3-iodo-5-(methylsulfanyl)thiophene-2-carboxylate (6.90 g, 45%). LCMS: (FA) ES+ 354. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.38 (q, 2H), 2.70 (s, 3H), 1.40 (t, 3H).

[00402] **Step 3:** Ethyl 4-cyano-3-iodo-5-(methylsulfonyl)thiophene-2-carboxylate

[00403] Ethyl 4-cyano-3-iodo-5-(methylsulfanyl)thiophene-2-carboxylate (7.2 g, 20.4 mmol) was dissolved in DCM (200 mL) and THF (100 mL) and m-CPBA (9.14 g, 40.8 mmol) was added. The reaction mixture was stired at rt overnight. Sodium sulfite (5.14 g, 40.8 mmol) was added and the mixture was stirred for 10 minutes followed by the addition of potassium carbonate (8.45, 61.2 mmol). The suspension was stirred at rt for 1 hour and filtered through celite, washed with DCM and the solvent was evaporated to afford ethyl 3-iodo-4-cyano-5-(methylsulfonyl)thiophene-2-carboxylate (6.80 g, 78%). LCMS: (FA) ES+ 386. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (q, 2H), 3.38 (s, 3H), 1.43 (t, 3H).

[00404] **Step 4:** Ethyl 4-cyano-5-[(2,4-dimethoxybenzyl)amino]-3-iodothiophene-2-carboxylate

[00405] Ethyl 4-cyano-3-iodo-5-(methylsulfonyl)thiophene-2-carboxylate (5.60g, 0.0145mol) and 2,4-dimethoxybenzylamine (3.51 mL, 0.0234 mol) were combined in tetrahydrofuran (100 mL) and stirred at 60 °C for 3 days. The reaction was concentrated in vacuo, diluted with dichloromethane and hexanes and the resultant precipitate was filtered to yield the title compound (5.56, 81%) as a yellow solid. LCMS: (FA) ES^+, 473. ^{1}H NMR (400MHz, d_6-DMSO) δ: 9.05 (s, 1H) 7.10 (d, 1H, J = 8.57Hz), 6.60-6.50 (m, 2H), 4.30 (s, 2H), 4.22-4.14 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 1.26-1.21 (m, 3H).

[00406] **Step 5:** Ethyl 4-cyano-3,5-diiodothiophene-2-carboxylate

[00407] To a solution of ethyl 4-cyano-5-[(2,4-dimethoxybenzyl)amino]-3-iodothiophene-2-carboxylate (4.50 g, 9.53 mmol) in dichloromethane (100 mL) at room temperature was added trifluoroacetic acid (22.5 mL, 292 mmol). The mixture was then stirred at room temperature for 10 minutes. The solvent was evaporated and the excess trifluoroacetic acid was removed by azeotroping with toluene. The crude material was diluted with ethyl acetate, then treated with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate five times and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield ethyl 5-amino-4-cyano-3-iodothiophene-2-carboxylate (2.85 g, 88%). LCMS: (FA) ES^+, 323. ^{1}H NMR (400MHz, d_6-DMSO) δ: 8.18 (s, 2H), 4.20-4.16 (m, 2H), 2.50-

2.48 (m, 3H). To a suspension of 5-amino-4-cyano-3-iodothiophene-2-carboxylate (2.85 g, 8.85 mmol) in acetonitrile (46.2 mL) under argon was added diiodomethane (2.49 mL, 31.0 mmol). The mixture was heated to 38°C for 30 minutes, then amyl nitrite (2.59 g, 22.1 mmol) was added dropwise over 5 minutes. The reaction was slowly allowed to cool to room temperature then the mixture was concentrated and column chromatography was performed to yield the title compound (3.20 g, 79%). LCMS: (FA) ES^+, 434. ^1H NMR (400MHz, d_6-DMSO) δ: 4.33-4.27 (m, 2H), 2.51-2.47 (m, 3H).

[00408] **Step 6:** Ethyl 5-[2-(acetylamino)pyridin-4-yl]-4-cyano-3-iodothiophene-2-carboxylate

[00409] To a solution of ethyl 4-cyano-3,5-diiodothiophene-2-carboxylate (0.473 g, 1.09 mmol) and N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (0.392 g, 1.31 mmol) in dioxane (10.2 mL) was added lithium chloride (0.139 g, 3.28 mmol), copper(I) iodide (0.0624 g, 0.328 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.0947 g, 0.0819 mmol). The reaction flask was evacuated and backfilled with argon, then the solution was heated at 110°C for 2 hours. The mixture was cooled to room temperature and a mixture of dichloromethane and methanol was added until almost all solids had dissolved. The suspension was filtered through celite and the filtrate was evaporated. Column chromatography was performed to yield the title compound (0.312 g, 65%). LCMS: (FA) ES+ 442. ^1H NMR (400MHz, d_6-DMSO) δ: 8.54-8.49 (m, 2H), 8.31 (s, 1H), 4.38-4.32 (m, 2H), 2.13 (s, 3H), 1.36-1.29 (m, 3H).

[00410] **Step 7:** Ethyl 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylate

[00411] To a solution of ethyl 5-[2-(acetylamino)pyridin-4-yl]-4-cyano-3-iodothiophene-2-carboxylate (0.209 g, 0.474 mmol) in tetrahydrofuran (3.3 mL) was added 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 1.89 mL, 0.947 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.0182 g, 0.0355 mmol) under argon. The solution was stirred at 60°C for 3 hours. The reaction was allowed to cool to room temperature and then the solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (0.159 g, 76%). LCMS: (FA) ES^+, 440. ^1H NMR (400MHz, $CDCl_3$) δ: 8.66 (br s, 1 H), 8.60 (br s, 1H), 8.38 (d, J=5.27Hz ,1H), 7.51-7.47 (m, 1H), 7.33-7.23 (m, 4H), 4.51 (s, 2H), 4.39 (q, J=7.03Hz, 2H), 2.24 (s, 3H), 1.39 (t, J=7.03Hz, 3H).

[00412] **Step 8:** 5-[2-(Acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylic acid

[00413] To a solution of ethyl 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylate (0.080 g, 0.18 mmol) in tetrahydrofuran (1.28 mL) and water (0.85 mL) was added lithium hydroxide (1.0M solution in water, 0.236 mL, 0.236 mmol). The reaction mixture was stirred at room temperature for 16 hours. The mixture was acidified to pH 6 using aqueous 1N HCl (0.300 mL). The

mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, and then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (0.058 g, 78%). LCMS: (FA) ES^+, 412. ^1H NMR (400MHz, d_6-DMSO) δ: 10.72 (s, 1H), 8.46-8.41 (m, 2H), 7.42-7.39 (m, 1H), 7.36-7.32 (m, 4H) 4.53 (s, 2H), 2.11 (s, 3H).

[00414] **Step 9:** 5-[2-(Acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxamide

[00415] To a solution of 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxylic acid (0.0710 g, 0.172 mmol) in dichloromethane (5.0 mL) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.0991 g, 0.517 mmol) and 1-hydroxybenzotriazole hydrate (0.0528 g, 0.345 mmol). The solution was stirred at room temperature for 30 minutes, then added 33% ammonium hydroxide (33:67 ammonia:water, 0.298 mL, 3.45 mmol) was added. The solution was then stirred at room temperature for 16 hours, then the mixture was concentrated and column chromatography was performed to yield the title compound (0.031 g, 42%). LCMS: (FA) ES^+, 411. ^1H NMR (400MHz, d_6-DMSO) δ: 10.79 (s, 1H), 8.50-8.46 (m, 2H), 8.14 (br s, 1H), 7.85 (br s, 1H), 7.47-7.43 (m, 1H), 7.39-7.34 (m, 2H), 7.29-7.24 (m, 2H), 4.41 (s, 2H), 2.12 (s, 3H).

[00416] **Step 10:** *N*-{4-[4-(4-chlorobenzyl)-3-cyano-5-(4*H*-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound **71**)

[00417] To a solution of 5-[2-(acetylamino)pyridin-4-yl]-3-(4-chlorobenzyl)-4-cyanothiophene-2-carboxamide (0.030 g, 0.073 mmol) in toluene (0.75 mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (0.0970 mL, 0.730 mmol), and the mixture was stirred at 100°C for 90 minutes. The mixture was concentrated and the residue was dissolved in acetic acid (0.75 mL). Hydrazine (0.0114 mL, 0.365 mmol) was added and the mixture was stirred at 100°C for 1 hour. The mixture was concentrated and the residue was treated with water. The precipitate was collected, washed with water and dried in a vacuum oven to yield the title compound (0.016 g, 48%). LCMS: (FA) ES^+, 435. ^1H NMR (400MHz, d_6-DMSO) δ: 10.76 (s, 1H), 8.77 (s, 1H), 8.54-8.46 (m, 2H), 7.50-7.47 (m, 1H), 7.37-7.26 (m, 4H), 4.63 (s, 2H), 2.12 (s, 3H).

[00418] **Step 11:** 2-(2-Aminopyridin-4-yl)-4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound **12**)

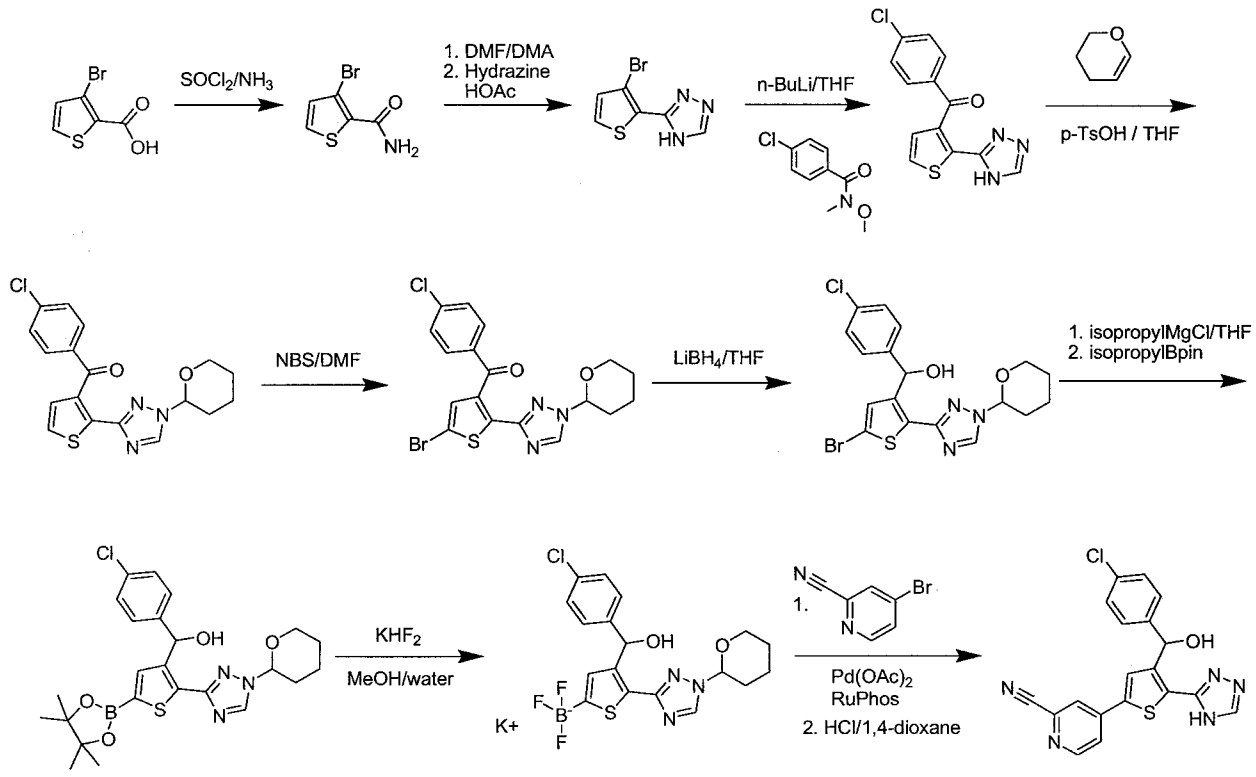
[00419] To a solution of *N*-{4-[4-(4-chlorobenzyl)-3-cyano-5-(4*H*-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (0.020 g, 0.046 mmol) in tetrahydrofuran (5.0 mL) was added sodium hydroxide (1.0M solution in water, 2.0 mL, 2.0 mmol). The solution was stirred at room temperature for 48 hours. The mixture was extracted with ethyl acetate three times, and the combined organic extracts

were then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (0.007 g, 30%). LCMS: (FA) ES^+, 393. ^1H NMR (400MHz, d_6-DMSO) δ: 8.75 (s, 1H), 8.07-8.03 (m, 1H), 7.36-7.26 (m, 4H), 6.83-6.79 (m, 1H), 6.78-6.76 (m, 1H), 6.34-6.29 (m, 1H), 4.61 (s, 2H), 4.04 (s, 2H).

[00420] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 1:

36	LCMS: (FA) ES+ 355, 357
74	LCMS: (FA) ES+, 412, 414.
143	LC/MS: (FA) ES+ 371; ES- 369
148	LCMS: (FA) ES+ 394
179	LC/MS: (FA) ES+ 467
180	LC/MS: (FA) ES+ 444; ES- 442

[00421] Example 2 : Synthesis of 4-(4-((4-chlorophenyl)(hydroxy)methyl)-5-(4H-1,2,4-triazol-3-yl)thiophen-2-yl)picolinonitrile (Compound 81)



[00422] Step 1: 3-Bromothiophene-2-carboxamide

[00423] 3-Bromothiophene-2-carboxylic acid (63.61 g, 307.2 mmol) was weighed into a 1L round bottom flask equipped with reflux condenser and the flask was purged with argon. To this flask was added toluene (636.1 mL, 5972 mmol) and thionyl chloride (44.82 mL, 614.4 mmol) at room temperature, and the resulting mixture was stirred for 3h at 100°C. The reaction mixture was evaporated and the residue was azeotroped with toluene (2 x 100 mL). The resulting residue was dissolved in tetrahydrofuran (954.1 mL, 11760 mmol) then 10 M ammonia in water (170 mL, 2500 mmol) was added slowly into the solution. The mixture was stirred for 5h at room temperature. Thin-layer chromatography showed complete reaction. The reaction mixture was rotovaped to remove THF and the solid residue in water was filtered through a glass frit funnel then washed with water and dried under vacuum to give 3-bromothiophene-2-carboxamide as a white solid (33.26g, 52.5%). LCMS: (FA) ES+ 206.0, 208.0

[00424] **Step 2:** 3-(3-Bromothiophen-2-yl)-4H-1,2,4-triazole

[00425] 3-Bromothiophene-2-carboxamide (33.2 g, 161 mmol) in 1,1-dimethoxy-N,N-dimethylmethanamine (100 mL, 800 mmol) and toluene (100 mL, 900 mmol) was heated at 90 °C for 2h. The solvent was evaporated off and the residue was dissolved in acetic acid (183 mL, 3220 mmol). Hydrazine (20 mL, 600 mmol) was added and the mixture was heated at 90°C again. After 40min, LCMS showed complete reaction. The reaction mixture was evaporated to remove most of the acetic acid. Water was added and the precipitate was collected and dried in air overnight to afford 3-(3-bromothiophen-2-yl)-4H-1,2,4-triazole as a white powder(31.7g, 85.6%). LCMS: (FA) ES+ 230.0, 232.0

[00426] **Step 3:** (4-Chlorophenyl)[2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanone

[00427] To a solution of 3-(3-bromo-2-thienyl)-4H-1,2,4-triazole (15.05 g, 65.41 mmol) in Tetrahydrofuran (500 mL, 6000 mmol) was added dropwise 2.5M BuLi in hexanes (104 mL, 262 mmol) at -70°C (internal temperature) and the solution was stirred for 30 min at -78°C. A solution of 4-chloro-N-methoxy-N-methylbenzamide (41.24 g, 206.6 mmol) in tetrahydrofuran (80 mL, 1000 mmol) was then added dropwise into the suspension. The resulting mixture was stirred for 60 min at -78°C. Ammonium chloride (17.49 g, 327.0 mmol) in water (100 mL, 6000 mmol) was added to the mixture at -78°C and the mixture was stirred for 15min before being warmed to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, and then filtered to remove drying agent. The solvent was evaporated and the residue was purified by chromatography to afford (4-chlorophenyl)[2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanone as white solid (16.8g, 88.5%). LCMS: (FA) ES+ 289.9, 291.8

[00428] **Step 4:** (4-Chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)methanone

[00429] In a 500 mL, round bottomed flask, (4-chlorophenyl)[2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanone (16.89 g, 58.29 mmol) was dissolved in tetrahydrofuran (500.0 mL, 6164 mmol). To

the solution were added dihydropyran (31.9 mL, 3.50E2 mmol) and p-toluenesulfonic acid monohydrate (16.6 g, 87.4 mmol). The mixture was stirred for 3h at rt. The reaction was quenched by the addition of saturated aqueous solution of sodium bicarbonate (200 mL). The aqueous phase was separated and then extracted with EtOAc (300 mL). The combined organic phases were dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography to afford (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)methanone as an oil which was dried under high vacuum overnight (19.4, 89.1%). LCMS: (FA) ES+ 374.2, 376.1.

[00430] **Step 5:** (5-Bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanone

[00431] To a mixture of (4-chlorophenyl){2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanone (20.2 g, 54.0 mmol) in N,N-dimethylformamide (350 mL, 4500 mmol) was added dropwise a solution of N-bromosuccinimide (14.42 g, 81.05 mmol) in N,N-dimethylformamide (50 mL, 600 mmol) under argon. The mixture was stirred at rt with care taken to block the reaction from exposure to ambient light. After 3h reaction, LCMS showed both starting material and product. Additional N-bromosuccinimide (6.732 g, 37.82 mmol) was added and the mixture was stirred at rt again. After stirring overnight, the mixture was diluted with water and sodium bicarbonate solution and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine. The EtOAc layer was dried and evaporated in vacuum to a residue, which was purified by chromatography to afford (5-bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanone as a white solid (18.0, 73.5%). LCMS: (FA) ES+ 451.9, 453.9

[00432] **Step 6:** (5-Bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanol

[00433] To a solution of {5-bromo-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}(4-chlorophenyl)methanone (11.81 g, 26.08 mmol) in tetrahydrofuran (300 mL, 4000 mmol) was added lithium tetrahydroborate (52.17 mmol, 52.17 mmol) in tetrahydrofuran (26 mL, 320 mmol) under argon. The mixture was stirred at rt for 3h and then cooled down in dry ice-acetone bath. Acetic acid (7.1 mL, 120 mmol) was added. The mixture was stirred for 5 min and saturated aqueous sodium bicarbonate solution was added, followed by EtOAc. The organic layer was separated and washed with brine, then dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography to afford (5-bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-3-yl)(4-chlorophenyl)methanol as a white powder (11.2, 94.2%). LCMS: (FA) ES+ 454.0, 456.0

[00434] **Step 7:** (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol

[00435] To a mixture of {5-bromo-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}(4-chlorophenyl)methanol (5.19 g, 11.4 mmol) in tetrahydrofuran (146.9 mL, 1811 mmol) was added isopropylmagnesium chloride (1M in THF, 34.2 mL, 34.2 mmol) at -40°C under argon. After addition, the reaction temperature was raised to rt for 15 min. The mixture was then cooled to -78°C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.149 mL, 39.94 mmol) was added. After the addition, the mixture was brought to rt. After 1h, the mixture was heated at 75°C overnight. The mixture was cooled to rt and quenched with saturated ammonium chloride solution. The mixture was stirred for 10min then extracted with EtOAc. The organic layer was dried and evaporated in vacuum. The mixture was purified by chromatography to afford (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol as a thick oil (5.32g, 65.0%). LCMS: (FA) ES+ 502.2, 504.1.

[00436] **Step 8:** Potassium (4-((4-chlorophenyl)(hydroxy)methyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)trifluoroborate

[00437] To a suspension of (4-chlorophenyl)(2-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)methanol in methanol (3.5 mL, 87 mmol) under argon was added potassium hydrogen fluoride (3.13 g, 40.0 mmol) in one portion at 0 °C. Water (8.06 mL, 447 mmol) was added dropwise. After the addition, the ice-water bath was removed and the mixture was stirred at rt over the weekend. The mixture was evaporated and the residue was dried under high vaccum. The crude mixture was extracted with hot actone 3 times. The extracts were combined and evaporated to dryness to afford potassium (4-((4-chlorophenyl)(hydroxy)methyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)trifluoroborate as a white powder (6.34g, 100%). LCMS: (AA) ES- 442.2, 444.2, ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.71 (d, J = 2.81 Hz, 1H), 7.35-7.24 (m, 2H), 7.45 (td, J = 4.77, 2.42, 2.42 Hz, 2H), 6.69-6.59 (m, 1H), 6.80 (d, J = 4.16 Hz, 1H), 5.81 (dd, J = 4.74, 1.41 Hz, 1H), 5.57 (td, J = 9.49, 2.15, 2.15 Hz, 1H), 4.02-3.89 (m, 1H), 3.74-3.59 (m, 1H), 2.21-1.88 (m, 3H), 1.76-1.47 (m, 3H).

[00438] **Step 9:** 4-(4-((4-Chlorophenyl)(hydroxy)methyl)-5-(4H-1,2,4-triazol-3-yl)thiophen-2-yl)picolinonitrile (Compound **81**)

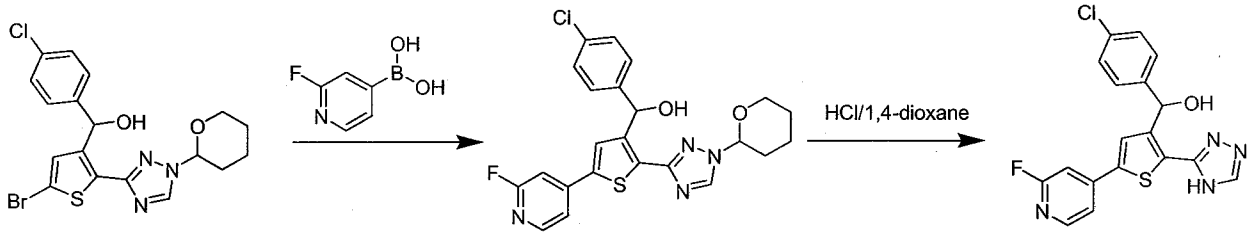
[00439] A mixture of potassium (4-((4-chlorophenyl)(hydroxy)methyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)trifluoroborate (0.133 g, 0.276 mmol), 4-bromo-pyridine-2-carbonitrile (60.6 mg, 0.331 mmol) , 2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl (24.8 mg, 0.0533 mmol), palladium acetate (4.6 mg, 0.020 mmol) and sodium carbonate (77 mg, 0.73 mmol) in ethanol (6.2 mL, 110 mmol) was degassed with argon and then heated at 85°C for 13h. The mixture was absorbed on silica gel and purified by chromatography to afford an intermediate. LCMS: (AA) ES+ 478.1, 480.0. This intermediate in 1,4-dioxane (2.0 mL, 26 mmol), tert-butyl alcohol (2.0 mL, 21 mmol)

and 4.00 M HCl in dioxane(3.0 mL, 14 mmol) was heated at 60°C for 1h. The mixture was evaporated to dryness and then purified by HPLC to afford 4-(4-((4-chlorophenyl)(hydroxy)methyl)-5-(4H-1,2,4-triazol-3-yl)thiophen-2-yl)picolinonitrile (12.4mg, 11.4%). LCMS: (FA) ES+ 394.3, 396.1. 1H NMR (400 MHz, d_6-DMSO) δ: 14.69-13.48 (br, 1H), 8.69 (d, J = 6.79 Hz, 2H), 8.45 (s, 1H), 8.08-7.88 (m, 2H), 7.56 (d, J = 8.39 Hz, 2H), 7.35 (d, J = 8.40 Hz, 2H), 6.79 (s, 1H).

[00440] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 2:

3	LCMS: (AA) ES+ 394, 396.
8	LCMS: (FA) ES+ 399, 401.
10	LCMS: (AA) ES+ 408, 410.
13	LCMS: (AA) ES+ 425, 427.
16	LCMS: (AA) ES+ 387, 389.
17	LCMS: (AA) ES+ 399, 401.
23	LCMS: (FA) ES+ 385, 387.
25	LCMS: (AA) ES+ 403, 405, 407.
42	LCMS: (AA) ES+ 419, 421.
48	LCMS: (AA) ES+ 394, 396.
57	LCMS: (AA) ES+ 425, 427.
64	LCMS: (AA) ES+ 438, 440.
68	LCMS: (FA) ES+ 388, 390.
147	LCMS: (AA) ES+ 451, 453
197	LCMS: (AA) ES- 431, 433, 435

[00441] Example 3: Synthesis of (4-chlorophenyl)[5-(2-fluoropyridin-4-yl)-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound 21)



[00442] **Step 1:** (4-Chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol

A mixture of {5-bromo-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}(4-chlorophenyl)methanol (734 mg, 1.61 mmol), 2-fluoro-4-pyridinylboronicacid (455 mg, 3.23 mmol) , tetrakis(triphenylphosphine)palladium(0) (93.3 mg, 0.0807 mmol) and cesium carbonate (1.58 g, 4.84 mmol) in 1,4-dioxane (10.1 mL, 129 mmol) and water (1.45 mL, 80.7 mmol) was irradiated in a microwave oven at 140 °C under argon for 20 min. The reaction mixture was dry loaded onto silica gel and purified by column chromatography (SiO_2, elution with EtOAc in hexanes, 0-80% gradient) to afford (4-chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol as a white solid (0.71g, 92.8%). LCMS: (AA) ES+ 471.1, 473.1

[00443] **Step 2:** (4-chlorophenyl)[5-(2-fluoropyridin-4-yl)-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound **21**)

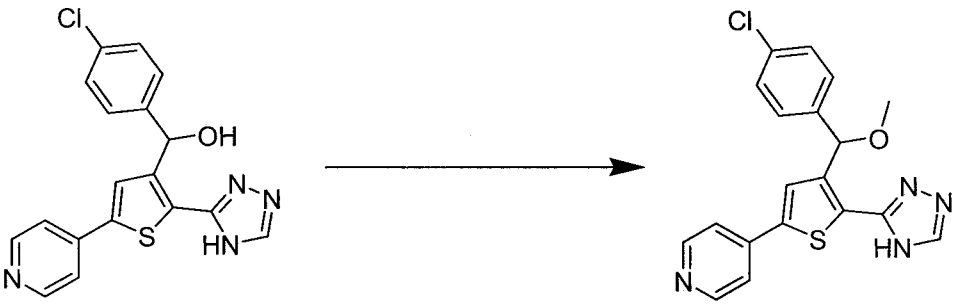
[00444] A mixture of (4-Chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol (0.261 g, 0.554 mmol), tert-butyl alcohol (3.9 mL, 41 mmol), 1,4-dioxane (2.6 mL, 33 mmol) and 4.00 M HCl in dioxane(3.66 mL, 16.6 mmol) was heated at 70 °C for 2 h. The mixture was cooled down. A small amount of water was added, followed by the addition of sodium bicarbonate (0.745 g, 8.87 mmol). The mixture was stirred for 10 min and then evaporated in vacuum. The residue was purified by (HPLC to afford 4-chlorophenyl)[5-(2-fluoropyridin-4-yl)-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol as a white solid. LCMS: (AA) ES+ 387.2, 389.1; 1H NMR (300 MHz, d_4-methanol) δ: 8.51 (s, 1H), 8.18 (d, J = 5.41 Hz, 1H), 7.73 (s, 1H), 7.60-7.44 (m, 3H), 7.37-7.23 (m, 3H), 6.76 (s, 1H).

[00445] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 3:

11	LCMS: (AA) ES+ 383, 385.
14	LCMS: (AA) ES+ 403, 405, 407.
26	LCMS: (AA) ES+ 387, 389.

30	LCMS: (AA) ES+ 403, 405, 407.
34	LCMS: (AA) ES+ 387, 389.
40	LCMS: (AA) ES+ 403, 405, 407.
41	LCMS: (AA) ES+ 426, 428.
43	LCMS: (AA) ES+ 383, 385.
45	LCMS: (AA) ES+ 387, 389.
52	LCMS: (AA) ES+ 369, 371.
55	LCMS: (AA) ES+ 370, 372.
59	LCMS: (AA) ES+ 370, 372.
69	LCMS: (AA) ES+ 383, 385.
75	LCMS: (AA) ES+ 384, 386.
77	LCMS: (AA) ES+ 369, 371.
79	LCMS: (AA) ES+ 370, 372.
84	LCMS: (AA) ES+ 369, 371.

[00446] Example 4: Synthesis of 4-[4-[(4-chlorophenyl)(methoxy)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (Compound 6)



[00447] To a solution of (4-chlorophenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (100 mg, 0.271 mmol) in methanol (10 mL) was added conc. HCl (2.0 mL, 24 mmol) and the mixture was stirred at rt overnight. The reaction mixture was concentrated and basified by sodium bicarbonate, loaded on silica gel and purified by column chromatography (SiO2, elution with 0-5% MeOH in DCM) to afford the title compound (80 mg, 78%). LCMS: (AA) ES+ 383.3, 385.2; 1H NMR (300 MHz, , d_6-

DMSO) δ: 8.70 (s, 1H), 8.57 (d, J = 4.80 Hz, 2H), 7.79 (s, 1H), 7.68 (d, J = 4.79 Hz, 2H), 7.56 (d, J = 8.25 Hz, 2H), 7.38 (d, J = 8.30 Hz, 2H), 6.50 (s, 1H), 3.31 (d, J = 9.06 Hz, 3H).

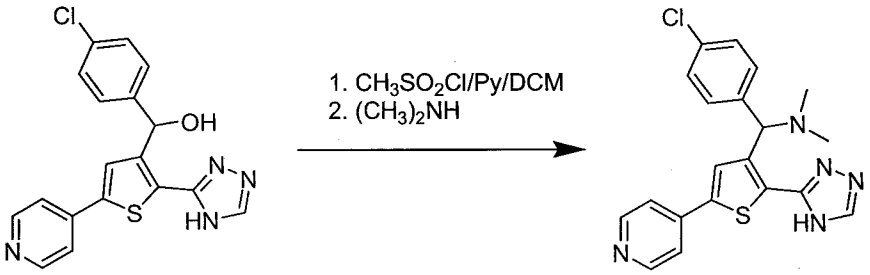
[00448] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 4:

220	LCMS: (AA) ES+ 440, 442.

[00449]

[00450] Example 5: Synthesis of 1-(4-chlorophenyl)-N,N-dimethyl-1-[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3- yl)-3-thienyl]methanamine (Compound 9)

[00451]



[00452] To a mixture of (4-chlorophenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (141 mg, 0.382 mmol) (synthesized in an analogous way as described in Example 3) in methylene chloride (2.8 mL) was added pyridine (6.0 mL, 74 mmol) and methanesulfonyl chloride (0.148 mL, 1.91 mmol) at 0°C. After the addition, the mixture was warmed to rt and stirred for 30min and then heated at 60°C for 20min. The mixture was cooled in an ice bath and dimethylamine (0.553 mL, 11.5 mmol) in THF was added to the mixture. After the addition, the ice bath was removed and the mixture was stirred at rt for 30min and then heated at 55°C for 2h. The mixture was cooled, concentrated, and the residue was purified by HPLC to afford 1-(4-chlorophenyl)-N,N-dimethyl-1-[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanamine as white powder (115mg, 76%). LCMS: (AA) ES+ 396.3, 398.1; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 14.48-14.27 (m, 1H), 8.71 (s, 1H), 8.57 (dd, J = 4.55, 1.62 Hz, 2H), 7.95 (s, 1H), 7.73-7.63 (m, 4H), 7.39-7.30 (m, 2H), 5.53 (s, 1H), 2.13 (s, 6H).

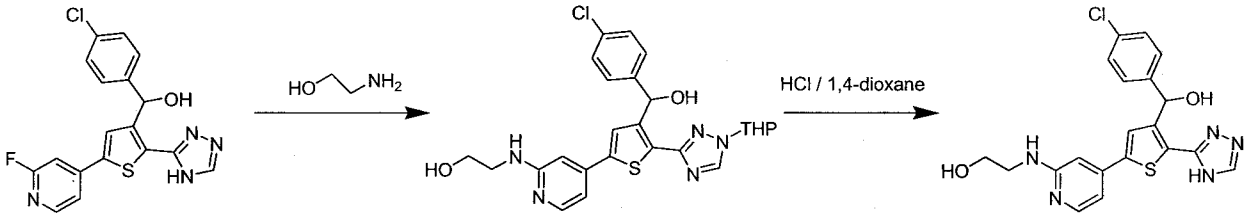
[00453] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 5:

33	LCMS: (AA) ES+ 410, 412.
44	LCMS: (AA) ES+ 396, 398.
51	LCMS: (AA) ES+ 408, 410.
65	LCMS: (AA) ES+ 396, 398.

86	LCMS: (AA) ES+ 453, 455.
90	LCMS: (AA) ES+ 465, 467
135	LCMS: (AA) ES+ 507, 509.
139	LCMS: (AA) ES+ 508, 510
146	LCMS: (FA) ES+ 520, 522
151	LCMS: (AA) ES+ 465, 467
152	LCMS: (FA) ES+ 510, 512
154	LCMS: (FA) ES+ 494, 496
161	LCMS: (AA) ES+ 410, 412
163	LCMS: (AA) ES+ 508, 510
164	LCMS: (AA) ES+ 495, 497.
167	LCMS: (AA) ES+ 476, 478
173	LCMS: (AA) ES+ 508, 510
176	LCMS: (AA) ES+ 465, 467
182	LCMS: (AA) ES+ 495, 497
183	LCMS: (AA) ES+ 496, 498.
185	LCMS: (AA) ES+ 411, 413
192	LCMS: (AA) ES+ 509, 511.
196	LCMS: (AA) ES+ 536, 538
200	LCMS: (AA) ES+ 480, 482
201	LCMS: (AA) ES+ 481, 483
204	LCMS: (AA) ES+ 453, 455
206	LCMS: (AA) ES+ 476, 478
208	LCMS: (AA) ES+ 508, 510
209	LCMS: (AA) ES+ 508, 510

212	LCMS: (AA) ES+ 495, 497.
216	LCMS: (AA) ES+ 501, 503
221	LCMS: (AA) ES+ 529, 531
224	LC/MS: (FA) ES+ 572, 574; ES- 570, 572.
229	LCMS: (AA) ES+ 495, 497.
234	LCMS: (AA) ES+ 508, 510
240	LCMS: (AA) ES+ 507, 509
241	LCMS: (AA) ES+ 465, 467
242	LCMS: (AA) ES+ 507, 509
243	LCMS: (AA) ES+ 458, 460
247	LCMS: (AA) ES+ 507, 509
248	LCMS: (AA) ES+ 495, 497
251	LCMS: (AA) ES+ 442, 444
254	LCMS: (FA) ES+ 452, 454
259	LCMS: (AA) ES+ 509, 511.
261	LCMS: (AA) ES+ 453, 455
267	LCMS: (AA) ES+ 508, 510
268	LCMS: (AA) ES+ 509, 511.
270	LCMS: (AA) ES+ 508, 510
283	LCMS: (AA) ES+ 509, 511.

[00454] Example 6: Synthesis of 2-({4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(4H-1,2,4-triazol-3-yl)-2- thienyl]pyridin-2-yl}amino)ethanol (Compound 49)

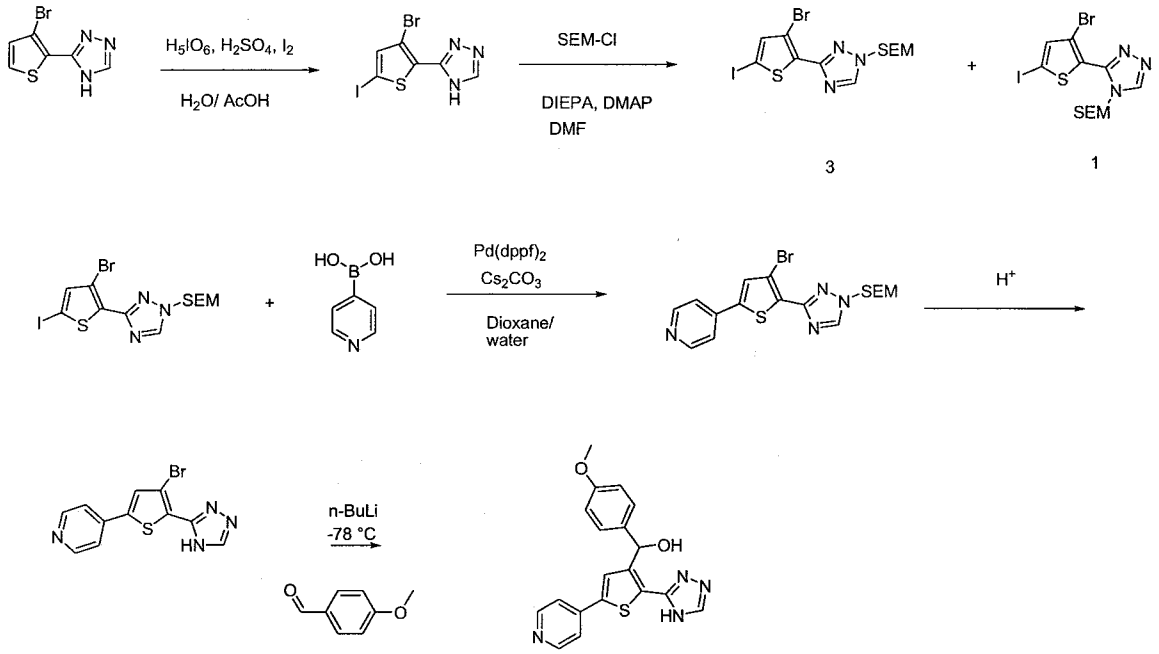


[00455] A mixture of (4-chlorophenyl){5-(2-fluoropyridin-4-yl)-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-3-thienyl}methanol (80.0 mg, 0.170 mmol), ethanolamine (0.104 g, 1.70 mmol) and N,N-diisopropylethylamine (0.118 mL, 0.679 mmol) in dimethylsulfoxide (0.5 mL, 7 mmol) was heated at 200°C for 1h under argon. The reaction mixture was cooled, diluted with water and extracted with butanol. The butanol layer was collected and evaporated to a residue which was purified by chromatography (SiO_2, elution with 0-20 % MeOH in DCM) to afford the intermediate. The intermediate in 1,4-dioxane (1.0 mL, 13 mmol) and conc HCl (1.0 mL, 12 mmol) was stirrred at rt for 1h. The solvent was evaporated and the residue was purified by chromatography (SiO_2, elution with 0-70% (MeOH/DCM/NH4OH, 13/85/2) in DCM) to afford 2-({4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}amino)ethanol (17.6mg, 24.2%). LCMS: (AA) ES+ 428.2, 430.0; ^{1}H NMR (400 MHz, d_6-DMSO) δ: 14.66-14.13 (m, 1H), 8.68 (s, 1H), 7.94 (d, J = 5.30 Hz, 1H), 7.58-7.48 (m, 3H), 7.38-7.30 (m, 2H), 6.81-6.68 (m, 3H), 6.60 (s, 1H), 4.72 (s, 1H), 3.57-3.45 (m, 2H), 3.34 (d, J = 5.88 Hz, 3H).

[00456] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 6:

28	LCMS: (AA) ES+ 435, 437.
62	LCMS: (AA) ES+ 398, 400.

[00457] Example 7: Synthesis of (4-methoxyphenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound 85)



[00458] **Step 1:** 3-(3-Bromo-5-iodo-2-thienyl)-4H-1,2,4-triazole.

To a mixture of 3-(3-bromo-2-thienyl)-4H-1,2,4-triazole (1.12 g, 4.87 mmol), iodine (1.12 g, 4.41 mmol) and periodic acid (4.80 g, 24.8 mmol) in acetic acid (11.0 mL, 200 mmol) were added water (8.0 mL, 400 mmol) and sulfuric acid (2.0 mL, 40 mmol) and the reaction mixture was stirred at rt for two days. The resulting white precipitate was collected by filtration. The solid cake was washed with water and dried under high vacuum at 40°C to yield product as a white solid (1.74 g, 100% yield, as a white solid). LCMS: (FA) ES^+, 357.7. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.63(s, 1H), 7.43 (s, 1H)

[00459] **Step 2**: 3-(3-Bromo-5-iodo-2-thienyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole.

[00460] Into a solution of 3-(3-bromo-5-iodo-2-thienyl)-4H-1,2,4-triazole (500.0 mg, 1.40 mmol), N,N-dimethylaminopyridine (17.2 mg, 0.140 mmol) and N,N-diisopropylethylamine (0.32 mL, 1.83 mmol) in N,N-dimethylformamide (17.0 mL, 220 mmol) was added [β-(Trimethylsilyl)ethoxy]methyl chloride (0.270 mL, 1.55 mmol) was added and the solution was stirred for 2 h at rt. Water(5.0 mL) and EtOAc (5mL) were added , the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 0-30% EtOAc in hexane) to give the title compound as a yellowish oil (653 mg, (87% major isomer, 13% minor isomer) LCMS: (FA) ES^+, 486, 488. (major isomer)^1H NMR (400 MHz, d_6-DMSO) δ: 8.81(s, ,1H), 7.45 (s, 1H), 5.540-5.545 (s, br, 2H), 3.62-3.66 (m, 2H), 0.840-0.880(m, 2H), -0.05 (s, 9H). LCMS: (FA) ES^+, 486, 488. (minor isomer)^1H NMR (400 MHz, d_6-DMSO) δ: 8.215(s, ,1H), 7.615 (s, 1H), 5.48(s, br, 2H), 3.44-3.50 (m, 2H), 0.75-0.80(m, 2H), -0.08 (s, 9H).

[00461] **Step 3:** 4-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine.

[00462] A mixture of 3-(3-bromo-5-iodo-2-thienyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (653.0 mg, 1.34 mmol), pyridine-4-boronic acid (248 mg, 2.02 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (55.2 mg, 0.067 mmol) and cesium carbonate (1.80 g, 5.37 mmol) in 1,4-dioxane (8.40 mL, 107 mmol) and water (1.2mL, 67.1 mmol) was heated at 110°C under an atmosphere of argon overnight. Water(3mL) and EtOAc (3mL) were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 0-10 % MeOH in DCM) to give the title compound as a white solid (438 mg, 74.6 %). LCMS: (FA) ES^+, 438, 440. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.87(s, 1H), 8.62-8.64 (dd, J = 1.5 Hz, 2H), 7.98 (s, 1H), 7.30-7.75 (dd, J = 1.5, 2H), 5.58-5.59 (s, br, 2H), 3.40-3.69 (m, 2H), 0.840-0.890(m, 2H), -0.04 (s, 9H).

[00463] **Step 4:** 4-[4-Bromo-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine.

[00464] 4-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (111.0 mg, 0.224 mmol) was dissolved in methylene chloride (3.0 mL, 47 mmol). Trifluoroacetic acid (3.0 mL, 39 mmol) was added and the solution was stirred at rt overnight. After the reaction was completed saturated $NaHCO_3$ (1mL) was added and the reaction was stirred at rt for 20 min. EtOAc (5mL) was added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 2-20 % MeOH in DCM) to give the title compound as a yellow solid (222 mg, 54 %). LCMS: (FA) ES^+, 307, 309. ^1H NMR (400 MHz, d_6-DMSO)) δ: 14.5(s,br,1H), 8.70-8.72 (dd, J = 1.5 Hz, 2H), 8.10 (s, 1H), 7.90-7.94 (dd, J = 1.5 Hz, 2H)

[00465] **Step 5**: (4-Methoxyphenyl)[5-pyridin-4-yl-2-(4H-1,2,4-triazol-3-yl)-3-thienyl]methanol (Compound **85**)

[00466] To a mixture of 4-[4-bromo-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (222.0 mg, 0.730 mmol) in tetrahydrofuran (5.9 mL, 72.3 mmol) cooled to -78°C was added dropwise n-BuLi in hexanes(2.50 M, 1.2 mL, 2.90 mmol) under an atmosphere of argon and and the mixture was stirred at -78°C for 30 min. To the solution was added dropwise a solution of 4-methoxybenzaldehyde (0.53 mL, 4.34 mmol) in tetrahydrofuran (5.0 mL, 60 mmol) and the resulting solution was stirred for 30 min at -78°C. The reaction mixture was quenched by the addition of water (2mL) and the resulting mixture was warmed to room temperature and stirred for 30 min. The mixture was extracted with EtOAc (5mL) then the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under the reduced pressure. The obtained residue was purified by prep HPLC to yield 62.0 mg as a yellow solid (23.5%). LCMS: (FA) ES^+, 365. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.68(s, 1H), 8.55-8.57 (dd, J = 1.5

Hz , 2H), 7.81(s, br, 1H), 7.63-7.65(dd, J = 1.5 Hz , 2H), 7.40-7.44(d, , J = 8.78 Hz, 2H), 6.82-6.84(d, J = 8.78 Hz, 2H), 6.72 (s, br, 1H), 3.68-3.69 (s, br, 3H).

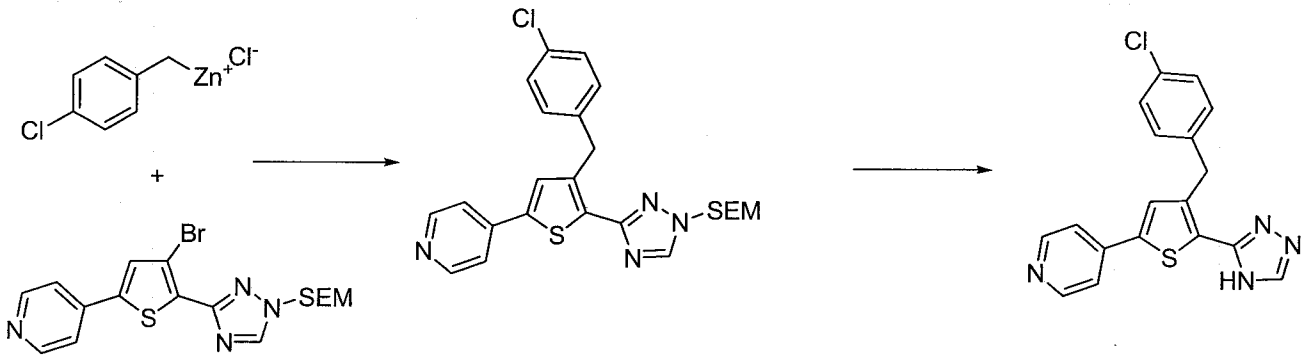
[00467] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 7:

130	LCMS: (FA) ES+ 383.4
132	LCMS: (FA) ES+ 386.3
133	LCMS: (FA) ES+ 418.3
134	LCMS: (FA) ES+ 415.3
136	LCMS: (FA) ES+ 403
138	LCMS: (FA) ES+ 367.4
141	LCMS: (FA) ES+ 363.3
142	LCMS: (FA) ES+ 403.3
155	LCMS: (FA) ES+ 353.4
158	LCMS: (FA) ES+ 379.4
159	LCMS: (FA) ES+ 403.3
162	LCMS: (FA) ES+ 371.3
169	LCMS: (FA) ES+ 387.3
171	LCMS: (FA) ES+ 386.4
174	LCMS: (FA) ES+ 363.5
175	LCMS: (FA) ES+ 386.4
183	LCMS: (FA) ES+ 381.4
186	LCMS: (FA) ES+ 417, 419.
187	LCMS: (FA) ES+ 387.3
188	LCMS: (FA) ES+ 367.4
191	LCMS: (FA) ES+ 399.4
193	LCMS: (FA) ES+ 403.4

198	LCMS: (FA) ES+ 411.
199	LCMS: (FA) ES+ 371.4
202	LCMS: (FA) ES+ 379.4
203	LCMS: (FA) ES+ 403.
207	LCMS: (FA) ES+ 412.3
208	LCMS: (FA) ES+ 385.
214	LCMS: (FA) ES+ 412.4
215	LCMS: (FA) ES+ 393.
217	LCMS: (FA) ES+ 369.4
219	LCMS: (FA) ES+ 403.4
228	LCMS: (FA) ES+ 385.4
231	LCMS: (FA) ES+ 413.3
232	LCMS: (FA) ES+ 387.3
233	LCMS: (FA) ES+ 419.2
235	LCMS: (FA) ES+ 371.3
236	LCMS: (FA) ES+ 413.4
239	LCMS: (FA) ES+ 383.4
246	LCMS: (FA) ES+ 395.4
249	LCMS: (FA) ES+ 365.3
252	LCMS: (FA) ES+ 413.4
253	LCMS: (FA) ES+ 363.3
256	LCMS: (FA) ES+ 379.4
257	LCMS: (FA) ES+ 386.4
258	LCMS: (FA) ES+ 412.3
260	LCMS: (FA) ES+ 403.2

263	LCMS: (FA) ES+ 387.3
264	LCMS: (FA) ES+ 383.4
266	LCMS: (FA) ES+ 371.3
271	LCMS: (FA) ES+ 355.4
272	LCMS: (FA) ES+ 366.3
275	LCMS: (FA) ES+ 387.4
276	LCMS: (FA) ES+ 412.3
279	LCMS: (FA) ES+ 417, 419.
280	LCMS: (FA) ES+ 385.
281	LCMS: (FA) ES+ 403.
284	LCMS: (FA) ES+ 403

[00468] Example 8: Synthesis of 4-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (Compound 5)



[00469] Step 1: 4-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4- triazol-3-yl)-2-thienyl]pyridine

[00470] Bis(tri-*t*-butylphosphine)palladium(0) (4.38 mg, 0.00857 mmol) and 4-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (0.075 g, 0.17 mmol) were combined in a dry round bottomed flask fitted with a stirbar and sealed with a septum. The flask was evacuated/refilled with nitrogen three times then a solution of 4-chlorobenzylzinc chloride in tetrahydrofuran (0.50M, 0.720 mL, 0.360 mmol) was added dropwise via a syringe. A nitrogen line was

attached and the reaction was stirred at rt for 30 minutes, then at 60°C for ~2 hours. The reaction was cooled to rt, diluted with EtOAc and saturated ammonium chloride solution, then the mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice more with EtOAc. The organics were combined, washed with bicarbonate solution, then brine, then dried over sodium sulfate. The mixture was filtered then evaporated in vacuo and the residue was purified by column chromatography on silica, elution 100% hexane to 100% EtOAc to afford the title compound as a light yellow oil. Yield 63 mg (76% yield). LCMS: (FA) ES+, 483, 485.

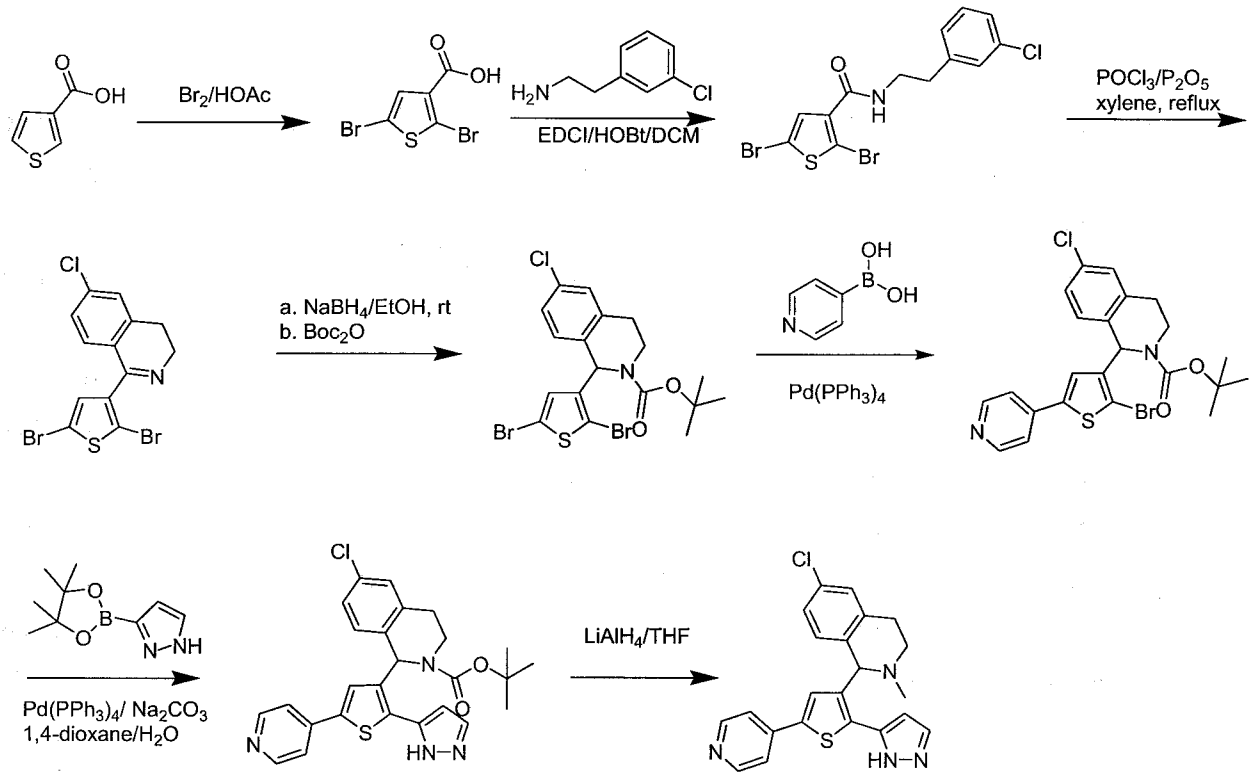
[00471] **Step 2:** 4-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (Compound **5**)

[00472] The 4-[4-(4-chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridine (58 mg, 0.12 mmol) and methylene chloride (4.0 mL, 62 mmol) were combined in a round bottomed flask equipped with a stirbar. The mixture was stirred and trifluoroacetic acid (1.1 mL, 14 mmol) was added in one portion. The resulting yellow solution was stirred overnight at rt under an atmosphere of nitrogen. Excess solvent was removed on the rotovap and the residue was digested in a mixture of EtOAc and aqueous sodium bicarbonate solution. The mixture was stirred then transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice more with EtOAc. The organics were combined, washed with bicarbonate solution, then saline, and then dried over sodium sulfate. The mixture was filtered then evaporated in vacuo and the residue was purified by column chromatography on silica, elution 100% DCM to 100% EtOAc to afford the title compound as an off-white powder. Yield 41 mg (97% yield). LCMS: (FA) ES+, 353, 355. ^{1}H NMR (400MHz, d_6-DMSO) δ: 14.31 (1H, br s), 8.67 (1H, br s), 8.55 (2H, d, J = 6.3 Hz), 7.69 (1H, s), 7.63 (2H, d, J = 6.3 Hz), 7.36-7.30 (4H, m), 4.47 (2H, s).

[00473] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 8:

87	LCMS: (FA) ES+ 370.

[00474] **Example 9: Synthesis of 6-chloro-2-methyl-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-1,2, 3,4-tetrahydroisoquinoline (Compound 58)**



[00475] **Step 1:** 2,5-Dibromo-3-thenoic Acid

[00476] In a 500 mL round bottomed flask was placed 3-thenoic acid (16.04 g, 125.2 mmol) and acetic acid (200 mL, 4000 mmol). To the mixture was added bromine (32.24 mL, 625.8 mmol) and the mixture was stirred for 18 h at 60 °C. The mixture was allowed to cool to rt then was diluted with ice-water. Sodium bisulfite (52.10 g, 500.7 mmol) was added. The resulting precipitate was collected by filtration and then washed with water to give 5-dibromo-3-thenoic acid as an off-white powder (33.4, 93.3%). LCMS (FA) ES+ 284.9, 286.9.

[00477] **Step 2:** 2,5-dibromo-N-[2-(3-chlorophenyl)ethyl]thiophene-3-carboxamide

[00478] To a mixture of 2,5-dibromo-3-thenoic Acid (10.0 g, 35.0 mmol), 2-(3-chlorophenyl)ethanamine (7.08 g, 45.5 mmol) and 1-hydroxybenzotriazole hydrate (5.89 g, 38.5 mmol) in methylene chloride (291 mL, 4550 mmol) was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (12.1 g, 62.9 mmol). The mixture was stirred at rt overnight. The reaction mixture was washed with 1NHCl, water, saturated sodium bicarbonate and brine. The DCM layer was dried and evaporated to afford 5-dibromo-N-[2-(3-chlorophenyl)ethyl]thiophene-3-carboxamide (14.7, 99.2%). LCMS (FA) ES+ 423.9, 425.9.

[00479] **Step 3:** 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline

[00480] To a mixture of 2,5-dibromo-N-[2-(3-chlorophenyl)ethyl]thiophene-3-carboxamide (5.15 g, 12.2 mmol) in xylenes (25.98 mL, 70.32 mmol) at 70°C was added phosphorus pentoxide (13.0 g, 45.8

mmol) and then phosphoryl chloride (12.0 mL, 129 mmol). The mixture was heated at 150°C for 60h, then the mixture was cooled to rt. The solution was removed by decantation and washed with toluene twice. Water (20mL) and 20% NaOH (20mL) were added and the mixture was sonicated. The mixture was extracted with EtOAc. The organic layer was washed with water, dried over MgSO4, and evaporated in vacuo to give a residue which was purified by chromatography to afford 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline as foam solid (2.8g, 57%).

[00481] **Step 4:** tert-Butyl 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[00482] To a mixture of 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline (2.60 g, 6.41 mmol) in ethanol (37.43 mL, 641.1 mmol) was added di-tert-butyldicarbonate (2.80 g, 12.8 mmol) and sodium tetrahydroborate (0.485 g, 12.8 mmol) at 0°C. The mixture was stirred for 20min at 0°C and then overnight at rt. The reaction mixture was concentrated and the residue was extracted with EtOAc. The organic layer was separated, washed with water, washed with brine, and then dried over MgSO4. The solvent was evaporated and the residue was purified by chromatography to afford tert-butyl 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline-2(1H)- carboxylate as a white powder (2.45g, 75.3%).

[00483] **Step 5:** tert-Butyl 1-(2-bromo-5-pyridin-4-yl-3-thienyl)-6-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate

[00484] A mixture of tert-butyl 6-chloro-1-(2,5-dibromo-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (177.0 mg, 0.3486 mmol), pyridine-4-boronic acid (51.43 mg, 0.4184 mmol) tetrakis(triphenylphosphine)palladium(0) (20.1 mg, 0.0174 mmol) and cesium carbonate (0.341 g, 1.04 mmol) in 1,4-dioxane (6.0 mL, 77 mmol) and water (2.0 mL, 110 mmol) was degassed and heated at 100 °C for 1h. The mixture was extracted with EtOAc. The organic layer was separated and washed with water. The organic layer was dried and evaporated to leave a residue which was purified by chromatography to afford tert-butyl 1-(2-bromo-5-pyridin-4-yl-3-thienyl)-6-chloro-3,4-dihydroisoquinoline- 2(1H)-carboxylate as a white solid (72mg, 41%). LCMS AA ES+ 505.1, 507.1

[00485] **Step 6:** tert-Butyl 6-chloro-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-3, 4-dihydroisoquinoline-2(1H)-carboxylate

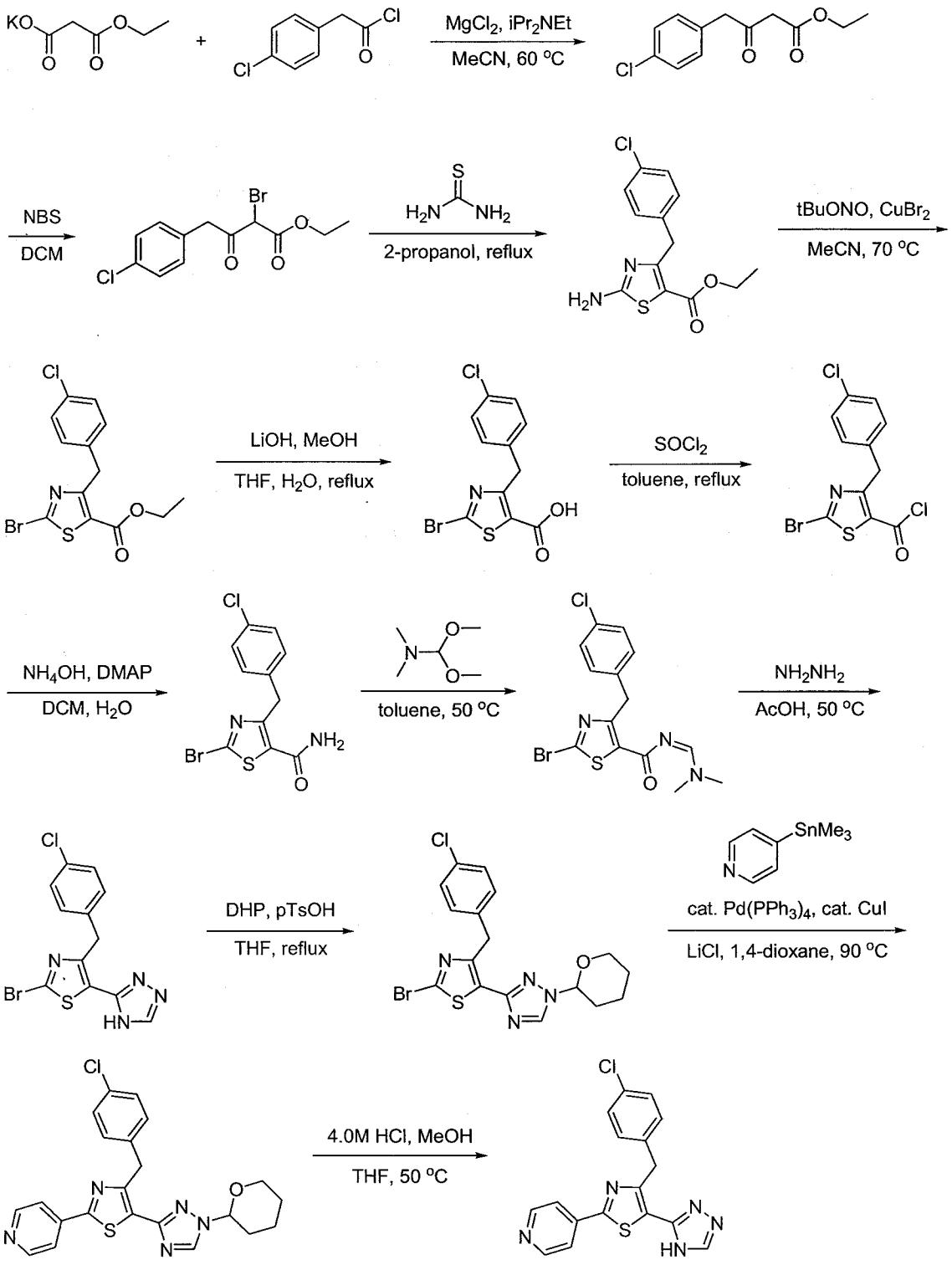
[00486] A mixture of tert-butyl 1-(2-bromo-5-pyridin-4-yl-3-thienyl)-6-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (72.0 mg, 0.142 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxabolone)-pyrrazole (27.6 mg, 0.142 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (11.7 mg, 0.0142 mmol) and sodium carbonate (29 mg, 0.27 mmol) in 1,2-dimethoxyethane (3.0 mL, 29 mmol) and water (1.0 mL, 56 mmol) was heated at 95°C for 4.5h. A LCMS showed the desired product together with unreacted starting material. Aditional [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (11.7 mg, 0.0142 mmol) 3-

(4,4,5,5-Tetramethyl-1,3,2-dioxabolone)-pyrrazole (56 mg, 0.29 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol), sodium carbonate (100 mg, 0.9 mmol) and 1,2-dimethoxyethane (3.0 mL, 29 mmol) were added. The mixture was heated at 100°C for another 4h. The mixture was dry-loaded onto silica gel and purified by chromatography to afford tert-butyl 6-chloro-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-3, 4-dihydroisoquinoline-2(1H)-carboxylate (41mg, 58%). LCMS AA ES+ 493.2, 495.1.

[00487] **Step 7:** 6-Chloro-2-methyl-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-1,2, 3,4-tetrahydroisoquinoline (Compound **58**)

[00488] To a solution of tert-butyl 6-chloro-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-3,4-dihydroisoquinoline-2(1H)-carboxylate (41 mg, 0.083 mmol) in tetrahydrofuran (3.0 mL, 37 mmol) was added lithium tetrahydroaluminate (0.249 mmol, 0.249 mmol) in THF (2.0mM) at -78°C. After the addition, the temperature of the reaction was raised to rt for 30 min and then heated at 85°C for 5h. The mixture was quenched with water, diluted with methanol, and extracted with ethyl acetate. The organic phase was dried, filtered and evaporated. The residue was loaded onto silica gel and purified by chromatography to afford 6-chloro-2-methyl-1-[2-(1H-pyrazol-5-yl)-5-pyridin-4-yl-3-thienyl]-1,2, 3,4-tetrahydroisoquinoline (5.1mg, 15%). LCMS AA ES+ 407.2, 409.1; ^{1}H NMR (400 MHz, d_4-methanol) δ: 8.48 (d, J = 5.06 Hz, 2H), 7.89-7.66 (m, 1H), 7.61 (s, 2H), 7.50-7.31 (br, 1H), 7.17 (s, 1H), 7.00 (d, J = 7.98 Hz, 1H), 6.87-6.48 (m, 2H), 5.16-4.94 (m, 1H), 3.34 (s, 1H), 3.28-3.10 (m, 2H), 2.94-2.79 (m, 1H), 2.72-2.56 (m, 1H), 2.26 (s, 3H)

[00489] **Example 10: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound 76)**



[00490] **Step 1:** Ethyl 4-(4-chlorophenyl)-3-oxobutanoate.

[00491] To a suspension of potassium ethyl malonate (17.12 g, 100.6 mmol) in acetonitrile (150 mL) were added N,N-diisopropylethylamine (28 mL, 160 mmol) and magnesium chloride (12.11 g, 127.2

mmol). The resulting mixture was stirred for 1 hour. A solution of 4-chlorophenylacetyl chloride (10.12 g, 53.53 mmol) in acetonitrile (100 mL) was then added and the mixture was heated to 60° C and stirred for 20 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was suspended in 1N aqueous HCl (250 mL) and was extracted with EtOAc (100 mL x 2). The combined organic phases were dried over anhydrous MgSO4 and insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica, elution with a 0%-80% mixture of EtOAc in hexane (linear gradient, 45 min) to obtain ethyl 4-(4-chlorophenyl)-3-oxobutanoate (5.0 g, 39%) as a yellow oil. LC/MS (FA) ES- 239. ^{1}H NMR (d_6-DMSO, 400 MHz): δ: 7.37 (2H, d, J = 13.8 Hz), 7.20 (2H, d, J = 13.8 Hz), 4.07 (2H, q, J = 7.2 Hz), 3.89 (2H, s), 3.66 (2H, s), 1.17 (3H, t, J = 7.2 Hz).

[00492] **Step 2:** Ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate

[00493] In a 250 mL round bottomed flask were placed ethyl 4-(4-chlorophenyl)-3-oxobutanoate (4.04 g, 16.8 mmol) and methylene chloride (100 mL). To the solution was added N-bromosuccinimide (3.13 g, 17.6 mmol) and the mixture was stirred for 3 h at rt. To the mixture was added a freshly prepared 10% aqueous solution of NaHSO3 (5 g $NaHSO_3$ dissolved in 50 mL water) and the resulting biphasic mixture was vigorously stirred for 15 min at rt. The organic phase was separated and the aqueous phase was extracted with DCM (30 mL). The organic phases were combined and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual yellow oil was essentially pure and was used in the next step without further purification. LC/MS (FA) ES- 319.

[00494] **Step 3:** Ethyl 2-amino-4-(4-chlorobenzyl)thiazole-5-carboxylate

[00495] In a 100 mL round bottomed flask were placed ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate (990 mg, 3.1 mmol) and isopropyl alcohol (20 mL). To the mixture was added thiourea (590 mg, 7.8 mmol) and the reaction was then refluxed for 16 h with stirring. The mixture was allowed to cool to rt and was then concentrated under reduced pressure. The residue was suspended in EtOAc (50 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), brine (50 mL), and dried over anhydrous MgSO4. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual off-white yellowish crystalline solid was essentially pure by LCMS and was used in the next step without further purification. LC/MS (FA) ES+ 296. ^{1}H NMR (d_6-DMSO, 400 MHz): δ: 7.80 (2H, br s), 7.32 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.8 Hz), 4.14—4.20 (4H, m), 1.22 (3H, t, J = 7.1 Hz).

[00496] **Step 4:** Ethyl 2-bromo-4-(4-chlorobenzyl)thiazole-5-carboxylate.

In a 250 mL round bottomed flask were placed ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (786 mg, 2.65 mmol) and acetonitrile (75 mL). To the mixture was added copper (II) bromide

(963 mg, 4.31 mmol). The suspension was stirred for 15 min at rt. To the mixture was added tert-butyl nitrite (0.630 mL, 5.30 mmol) and the stirring was continued for an additional 1.5 h at 70° C. The reaction mixture was allowed to cool to rt and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica, elution with a 10%-50% mixture of EtOAc in hexane to obtain ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (820 mg; 86%) as an yellow syrup, which spontaneously solidified on standing at rt to afford off-white crystalline solid. LC/MS (FA) ES+ 362. ^{1}H NMR (CDCl3, 400 MHz): δ: 7.29 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 4.44 (2H, s), 4.35 (2H, q, J = 7.3 Hz), 1.36 (3H, t, J = 7.3 Hz).

[00497] **Step 5:** Ethyl 2-bromo-4-(4-chlorobenzyl)thiazole-5-carboxylic acid.

[00498] In a 100 mL round bottomed flask were placed ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (955 mg, 2.65 mmol) and tetrahydrofuran (50 mL, 600 mmol). To this solution was added a freshly prepared aqueous solution of lithium hydroxide [(lithium hydroxide•H_2O (177 mg, 4.22 mmol) and water (15 mL, 830 mmol)). The mixture was stirred for 4 h at rt then MeOH (20 mL) was added and the mixture was refluxed for 3 h. The mixture was allowed to cool to rt and then acidified by the addition of 1.0N HCl aq (4.5 mL). The mixture was stirred for 1 h at rt. The mixture was then concentrated under reduced pressure until reduced to ca 5 mL volume. EtOAc (50 mL) was added and the mixture was washed with water (50 mL), then brine (50 mL), then was dried over anhydrous MgSO4. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual yellow crystalline solid was used in the next step without further purification. LC/MS (FA) ES+ 332.

[00499] **Steps 6 and 7:** 2-Bromo-4-(4-chlorobenzyl)thiazole-5-carboxamide.

[00500] In a 250 mL round bottomed flask were placed 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylic acid (800 mg, 2 mmol) and toluene (30 mL, 300 mmol). To the suspension was added thionyl chloride (700 uL, 10 mmol) and the mixture was refluxed for 2 h during which time the suspension turned into a solution. The reaction was allowed to cool to rt and then was concentrated under reduced pressure. The residue was co-evaporated with toluene (10 mL). The residual orange oil was dissolved in methylene chloride (30 mL, 500 mmol) then N,N-dimethylaminopyridine (21.2 mg, 0.174) was added. To the mixture was added ammonium hydroxide in water (8.5 M, 20 mL) and the mixture was stirred for 1.5 h at rt. The organic phase was separated and the aqueous phase was extracted with DCM (30 mL). The organic phase and extract were combined and dried over anhydrous MgSO4. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residual yellow syrup was used in the next step without further purification. LC/MS (FA) ES+ 333.

[00501] **Step 8:** (Z)-2-bromo-4-(4-chlorobenzyl)-N-((dimethylamino)methylene)thiazole-5-carboxamide.

[00502] In a 250 mL round bottomed flask were placed 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxamide (0.66 g, 2.0 mmol) and toluene (30 mL, 300 mmol). The mixture was turned into a suspension by ultrasonication. To the suspension was added 1,1-dimethoxy-N,N-dimethylmethanamine (80 uL, 6.0 mmol) and the mixture was stirred for 2 h at 50°C. The mixture was allowed to cool to rt then was concentrated under reduced pressure. The residue was used in the next step without further purification. LC/MS (FA) ES+ 388.

[00503] **Step 9**: 2-Bromo-4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)thiazole.

[00504] In a 250 mL round bottomed flask were placed 2-bromo-4-(4-chlorobenzyl)-N-[(1Z)-(dimethylamino)methylene]-1,3-thiazole-5-carboxamide and acetic acid (50 mL, 900 mmol). Hydrazine hydrate (490 uL, 10 mmol) was added and the mixture was stirred for 1 h at 50°C. The mixture was allowed to cool to rt, then was concentrated under reduced pressure to obtain 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-4H-1,2,4-triazole as a yellowish off-white crystalline solid. The crude material was used in the next step without further purification. LC/MS (FA) ES+ 357.

[00505] **Step 10:** 2-Bromo-4-(4-chlorobenzyl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiazole

[00506] In a 250 mL round bottomed flask were placed 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-4H-1,2,4-triazole (0.7 g, 2 mmol) and tetrahydrofuran (50 mL, 600 mmol). To the mixture were added dihydropyran (2 mL, 20 mmol) and p-toluenesulfonic acid monohydrate (911.3 mg, 4.791 mmol). The mixture was refluxed for 2 h then was allowed to cool to rt and then a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The resulting biphasic mixture was vigorously stirred for 30 min at rt. The aqueous phase was separated then was extracted with EtOAc (50 mL x 2). The combined organic phases were dried over anhydrous $MgSO_4$. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica, elution with a 10%-80% mixture of EtOAc in hexane (linear gradient, 30 min) to afford 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (778 mg; 67% six steps) as a yellow syrup which spontaneously solidified on standing at rt for 2 days. LC/MS (FA) ES+ 441. ^1H NMR (d_6-DMSO, 400 MHz): δ: 8.89 (1H, s), 7.28—7.34 (4H, m), 5.62 (1H, dd, J = 2.8 and 9.6 Hz), 4.52 (2H, s), 3.92—3.96 (1H, m), 3.63—3.70 (1H, m), 1.91—2.14 (3H, m), 1.52—1.72 (3H, m)

[00507] **Step 11:** 4-(4-Chlorobenzyl)-2-(pyridin-4-yl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiazole.

[00508] To a 20 mL vial was added a solution of 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (0.1500 g, 0.3411 mmol) and 4-(tributylstannyl)pyridine (0.2511 g, 0.6822 mmol) in anhydrous 1,4-dioxane (5.000 mL). The solution was degassed for 10 minutes. Lithium chloride (0.108 g, 2.56 mmol) and copper (I) iodide (0.0487 g, 0.256 mmol) were added

followed by tetrakis(triphenylphosphine)palladium(0) (0.0492 g, 0.0426 mmol). The reaction mixture was heated to 90°C and allowed to stir for 18 h. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL). The quench mixture was extracted with EtOAc (10 mLx3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica (gradient DCM to 10% MeOH over 30 min) to afford the product (0.2245 g, 73%) as a yellow solid. LC/MS (AA) ES+ 438. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.92 (s, 1H), 7.90 (d, J = 4.8 Hz, 2H), 7.65 (d, J = 1.2 Hz, 2H), 7.38-7.32 (m, 4H), 5.66 (dd, J = 9.6, 2.8 Hz, 1H), 4.65 (s, 2H), 3.97-3.94 (m, 1H), 3.72-3.66 (m, 1H), 1.59-1.48 (m, 2H), 1.32-1.23 (m, 2H), 1.10-1.06 (m, 2H).

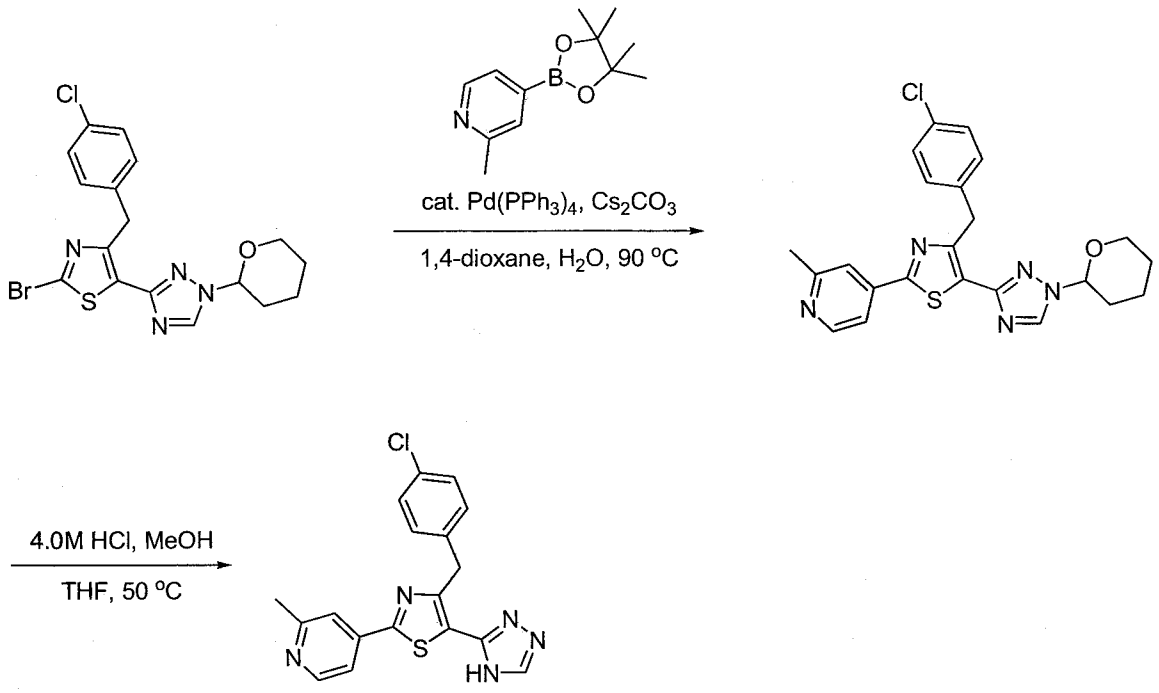
[00509] **Step 12:** 4-(4-Chlorobenzyl)-2-(pyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound **76**).

[00510] To a 20 mL vial was added a solution of 4-{4-(4-chlorobenzyl)-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-1,3-thiazol-2-yl}pyridine (0.2245 g, 0.635 mmol) in anhydrous tetrahydrofuran (2.000 mL) and methanol (2.000 mL). 4.0 M Hydrochloric acid in 1,4-dioxane (1.0 mL, 4.0 mmol) was added and the reaction mixture was allowed to stir at 50°C for 18 hours. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL) and extracted with EtOAc (10 mLx3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by HPLC to afford the product (0.0423 g, 45%) as an off white solid. LC/MS (AA) ES+ 354. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 14.48 (s, 1H), 8.71 (dd, J = 4.4, 1.2 Hz, 2H), 7.89-7.87 (m, 2H), 7.38-7.32 (m, 4H), 4.67 (s, 2H).

[00511] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 10:

37	LCMS: (FA) ES+ 372, 374.
39	LCMS: (AA) ES+ 355, 357.
46	LCMS: (AA) ES- 370, 372.
63	LCMS: (FA) ES+ 383, 385.
78	LCMS: (AA) ES+ 372, 374.

[00512] **Example 11: Synthesis of 4-(4-Chlorobenzyl)-2-(2-methylpyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound 18)**



[00513] **Step 1:** 4-(4-chlorobenzyl)-2-(2-methylpyridin-4-yl)-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiazole.

[00514] To a 20 mL vial was added a solution of 3-[2-bromo-4-(4-chlorobenzyl)-1,3-thiazol-5-yl]-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (0.1000 g, 0.2274 mmol) and 2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine (0.0931 g, 0.425 mmol) in a solution of 1,4-dioxane (2.5000 mL, 32.036 mmol) and water (0.2500 mL). Cesium carbonate (0.2223 g, 0.6822 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (0.031533 g, 0.027288 mmol). The reaction mixture was heated to 90°C and allowed to stir for 18 h. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL) and extracted with EtOAc (10 mLx3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was dry loaded onto silica gel then was purified by column chromatography on silica (gradient DCM to 10% MeOH over 30 min) to afford the product with Ph_3PO impurities (0.1654 g, 96.6%) as a brown oil. LC/MS (AA) ES+ 452. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.91 (s, 1H), 7.64-7.53 (m, 3H), 7.37-7.31 (m, 4H), 5.66 (dd, J = 9.6, 2.8 Hz, 1H), 4.61 (s, 2H), 3.72-3.66 (m, 2H), 2.55 (s, 3H), 1.70-1.68 (m, 2H), 1.62-1.48 (m, 2H), 1.45-1.38 (m, 2H).

[00515] **Step 2:** 4-(4-Chlorobenzyl)-2-(2-methylpyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound **18**).

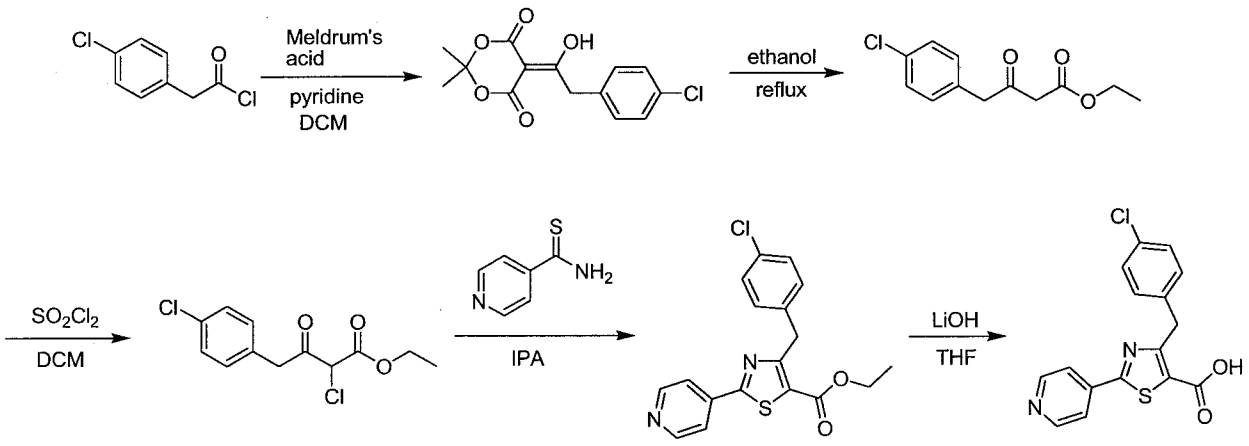
[00516] To a 20 mL vial was added a solution of 4-{4-(4-chlorobenzyl)-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-1,3-thiazol-2-yl}-2-methylpyridine (0.1654 g, 0.365 mmol) in anhydrous tetrahydrofuran (2.000 mL) and methanol (2.000 mL). 4.0 M hydrochloric acid in 1,4-dioxane (1.0 mL, 4.0 mmol) was added and the reaction mixture was allowed to stir at 50°C for 18 hours. The reaction was cooled to ambient temperature and quenched by the addition of a saturated aqueous solution of sodium bicarbonate (10 mL) then was extracted with EtOAc (10 mLx3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by HPLC to afford the product (0.0351 g, 39.9%) as a white solid. LC/MS (AA) ES+ 368, 370. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.73 (s, 1H), 8.56 (d, J = 5.2 Hz, 1H), 7.75 (s, 1H), 7.67 (dd, J = 5.2, 1.6 Hz, 1H), 7.37-7.32 (m, 4H), 4.65 (s, 2H) 2.55 (s, 3H).

[00517] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 11:

137	LCMS: (FA) ES+ 354, 356.
213	LCMS: (FA) ES+ 427.

[00518]

[00519] Example 12: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (Compound 80)



[00520] **Step 1:** 5-(2-(4-Chlorophenyl)-1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione.

[00521] To a mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (52.7 g, 366 mmol) in DCM (205 mL) at -10°C in an ice/methanol bath was added pyridine (72.5 mL, 897 mmol) over 10 minutes. To the resulting solution at -10°C was added a solution of 2-(4-chlorophenyl)acetyl chloride (69.1 g, 366 mmol) in DCM (144 mL) dropwise over 1 hour. The mixture was stirred at -10°C for 1 hour, then at room temperature for

1 hour. The mixture was poured into a mixture of 2 M HCl (820 mL) and ice (400 mL) and the aqueous layer was extracted with DCM (2 x 200 mL). The combined DCM layers were washed with 1 N HCl (100 mL) and brine (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 103 g of title compound. (95 % yield). LC/MS (FA) ES- 295. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.25 (br s, 1H), 7.34-7.26 (m, 4H), 4.37 (s, 2H), 1.72 (s, 6H).

[00522] **Step 2:** Ethyl 4-(4-chlorophenyl)-3-oxobutanoate

[00523] A solution of 5-(2-(4-chlorophenyl)-1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (103 g, 347 mmol) in ethanol (718 mL) was refluxed for 3 hours. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→20/80) to give 61 g of the title compound as an orange oil. (73 % yield). LC/MS (FA) ES+ 241. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.28 (m, 2H), 7.15-7.11 (m, 2H), 4.17 (q, 2H, J = 7.2 Hz), 3.81 (s, 2H), 3.45 (s, 2H), 1.26 (t, 3H, J = 7.2 Hz).

[00524] **Step 3:** Ethyl 2-chloro-4-(4-chlorophenyl)-3-oxobutanoate

[00525] To a solution of ethyl 4-(4-chlorophenyl)-3-oxobutanoate (61.0 g, 253 mmol) in DCM (811 mL) in an ice bath was added sulfuryl chloride (34.2 g, 253 mmol) and the resulting solution was allowed to stir at room temperature overnight. The reaction was quenched with saturated sodium bicarbonate solution (200 mL) and the layers separated. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give 70.8 g of title compound. (100 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.30 (m, 2H), 7.17-7.14 (m, 2H), 4.85 (s, 1H), 4.26 (dq, 1H, J = 7.2, 1.2 Hz), 4.02 (d, 1H, J = 16.8 Hz), 3.97 (d, J = 16.8 Hz, 1H), 1.29 (t, 3H, J = 7.2 Hz).

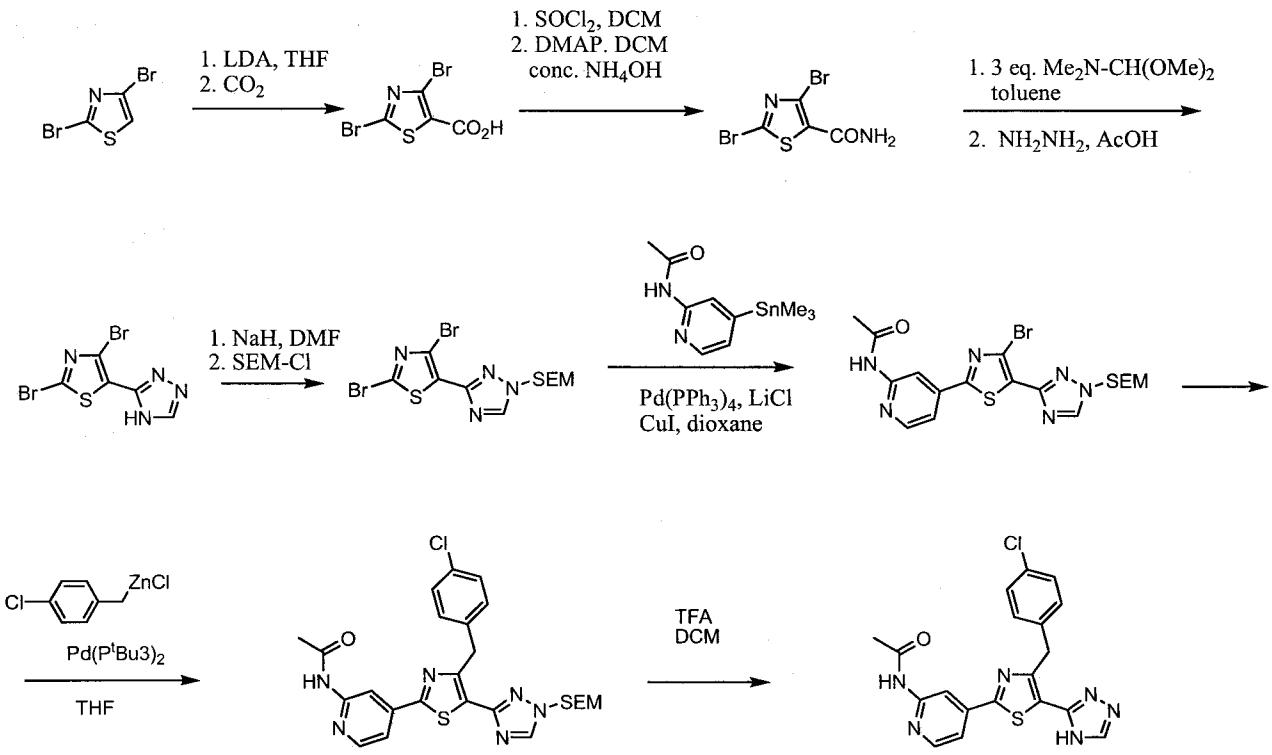
[00526] **Step 4:** Ethyl 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylate

[00527] To a solution of ethyl 2-chloro-4-(4-chlorophenyl)-3-oxobutanoate (70.8 g, 257 mmol) in IPA (2.96 L) was added thioisonicotinamide (71.1 g, 515 mmol) and the resulting mixture was refluxed for 3 days. The reaction was cooled and concentrated in vacuo and the residue was partitioned between DCM (300 ml) and saturated sodium bicarbonate solution (200 mL). The layers were separated and the aqueous layer was extracted with DCM (100 mL). The combined DCM layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product which was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→40/60) followed by recrystallization from ethyl acetate/hexanes to give 33 g of the title compound as yellow crystals. (36 % yield). LC/MS (FA) ES+ 359. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74-8.72 (m, 2H), 7.81-7.80 (m, 2H), 7.36-7.32 (m, 2H), 7.27-7.23 (m, 2H), 4.54 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz).

[00528] **Step 5:** 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (Compound **80**)

[00529] To a solution of ethyl 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylate (12.8 g, 35.7 mmol) in THF (200 mL) and water (100 mL) was added 1.0 M LiOH (46.4 mL, 46.4 mmol) and the resulting solution was stirred at room temperature overnight. The mixture was acidified to pH 4 with 1 N HCl. The precipitated solids were filtered, washed with water and dried to give 11 g of the title compound as an a white solid. (93 % yield). LC/MS (FA) ES+ 331. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 13.86 (br s, 1H), 8.72-8.71 (m, 2H), 7.89-7.87 (m, 2H), 7.36-7.29 (m, 4H), 4.50 (s, 2H).

[00530] Example 13: Synthesis of *N*-{4-[4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound 56)



[00531] **Step 1:** 2,4-Dibromo-1,3-thiazole-5-carboxylic acid:

[00532] To a 500mL 3-neck round bottom flask equipped with dropping funnel and internal temperature monitor was added THF (200 mL) and N,N-diisopropylamine (14.7 mL, 105 mmol) under atmosphere of argon. After cooling at -75°C, 2.50 M of n-Butyllithium in hexane (41.1 mL, 103 mmol) was added dropwise into the solution over 30 min. The internal temperature was kept below -70°C and the resulting solution was stirred for 15 min at -75 °C. To this LDA solution was added a solution of 2,4-dibromothiazole (25.0 g, 99.8 mmol) in THF (60 mL) via dropping funnel over 40 min and the internal

temperature was kept below -70°C, then this solution was stirred for 20 min at -75°C. To this solution was added crushed dry ice at -75°C and the mixture was stirred for 15min. At that time, 10mL water was added dropwise. The cooling bath was removed and the mixture was brought to rt over 1 h with a water bath. The solvent was evaporated under reduced pressure to give a solid residue. The residue was suspended in 100 mL water, basified with 1.00 M of sodium hydroxide in water (110 mL) and extracted with 100 mL ether. The ether layer was washed with 0.5 N NaOH (2 x 30 mL). The combined aqueous solution was acidified with conc. HCl to ~pH 2, extracted with ether (5 x 100 mL, adjusting the pH to ~2 each time after separation). The combined ether solutions were washed with brine, dried over Na_2SO_4, filtered, evaporated to give a solid product (28.04 g, 98%). LCMS: (FA) ES+ 288, ES- 286.

[00533] **Step 2:** 2,4-Dibromo-1,3-thiazole-5-carboxamide:

[00534] A suspension of 2,4-dibromo-1,3-thiazole-5-carboxylic acid (16.33 g, 56.91 mmol) in dry DCM (250 mL) and DMF (0.400 mL) was cooled in an ice bath. Thionyl chloride (40.0 mL, 548 mmol) was added dropwise. The cooling bath was removed and the suspension was stirred at rt for 2.5 hours. Toluene (80 mL, 800 mmol) was added and the suspension was heated to reflux for 1 hour. The mixture was cooled to room temperature, the solvent was removed and the residue was azeotroped with toluene (2 x 100 mL) to give a crude intermediate. This material was suspended in DCM (230 mL) and cooled in an ice bath. N,N-Dimethylaminopyridine (0.70 g, 5.7 mmol) was added, followed by the slow addition of 8.5 M ammonium hydroxide in water (100.0 mL, 850.0 mmol). The mixture was stirred at room temperature overnight. The mixture was filtered and the aqueous layer was separated and extracted with DCM (3 x 100 mL). The combined DCM layers were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give a solid product (11.2 g, 69%). LCMS: (FA) ES+ 287 and ES- 285.

[00535] **Step 3:** 3-(2,4-Dibromo-1,3-thiazol-5-yl)-4H-1,2,4-triazole :

[00536] To a suspension of 2,4-dibromo-1,3-thiazole-5-carboxamide (0.110 g, 0.385 mmol) in dry toluene (8.0 mL, 75 mmol) was added DMF-DMA (0.204 mL, 1.54 mmol). The mixture was stirred at 60°C under a nitrogen atmosphere for 3 hours. The solvent was removed and to the intermediate was added acetic acid (2.0 mL, 35 mmol), followed by hydrazine (0.0604 mL, 1.92 mmol). The mixture was heated to 120°C for 30 min. The mixture was cooled to room temperature, the solvent was removed and the residual acetic acid was azeotroped with toluene (2 x 5 mL) to give an oily material, which was basified with saturated aqueous NaHCO3 to pH~8 and extracted with EtOAc (3 x 30 mL). The EtOAc layer was washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give a crude product. Chromatography on a silica column using EtOAc/hexane (0/100 to 50/50) gave a solid product (0.073 g, 61%). LCMS: (FA) ES+ 311 and ES- 309. ^{1}H NMR (400MHz, d_4-methanol) δ: 8.53 (s, 1H).

[00537] **Step 4:** 3-(2,4-Dbromo-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole

[00538] To the solution of 3-(2,4-dibromo-1,3-thiazol-5-yl)-4H-1,2,4-triazole (1.16 g, 3.74 mmol) in dry DMF (5.0 mL) at 0°C was added portionwise sodium hydride (60%, 0.180 g, 4.49 mmol). The ice bath was removed, mixture was stirred for 5 min at ambient temperature then cooled in an ice bath. [β-(Trimethylsilyl)ethoxy]methyl chloride (0.795 mL, 4.49 mmol) in dry DMF (2.0 mL) was added dropwise and the mixture was stirred at room temperature for 2 hours. The mixture was quenched with ice-water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, evaporated to give a crude oil. The product was purified by column chromatography on silica gel , eluting with EtOAc/hexane (0/100 to 20/80) to afford a white solid product (1.10 g, 67%). LCMS: (FA) ES+ 441. ^{1}H NMR (400MHz, $CDCl_3$) δ: 8.29 (s, 1H), 5.54 (s, 2H), 3.71 (t, J = 8.28 Hz, 2H), 0.95 (t, J = 8.28 Hz, 2H), 0.00 (s, 9H) .

[00539] **Step 5:** N-{4-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide:

[00540] The mixture of 3-(2,4-dibromo-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (1.10 g, 2.50 mmol), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (0.896 g, 3.00 mmol), tetrakis(triphenylphosphine)palladium (0) (0.155 g, 0.125 mmol), copper(I) iodide (0.143 g, 0.750 mmol) and lithium chloride (0.318 g, 7.50 mmol) in dry 1,4-dioxane (100 mL) was sonicated for 2 min, degassed and backfilled with nitrogen 5 times. The mixture was heated under nitrogen atmosphere to reflux for 90 min, then cooled to room temperature, filtered through celite and washed with dioxane/DCM. The filtrate was evaporated under reduced pressure to give a crude residue, which was purified by column chromatography on silica gel eluting with MeOH/DCM (0/100 to 5/95) to give a product, which was further purified on a silica column using MeOH/EtOAc/hexane (0/0/100 to 5/45/50) to give pure product (0.150 g, 13%). LCMS: (FA) ES+ 495, 497. ^{1}H NMR (400MHz, $CDCl_3$) δ: 8.72 (s, 1H), 8.37 (m, 1H), 8.33 (s, 1H), 8.26 (s, 1H), 7.68 (m, 1H), 5.57 (s, 2H), 3.73 (t, J = 8.28 Hz, 2H), 2.25 (s, 3H), 0.97 (t, J = 8.28 Hz, 2H), 0.00 (s, 9H) .

[00541] **Step 6:** *N*-{4-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-5-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00542] To a solution of *N*-{4-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-5-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.292 g, 0.589 mmol) in tetrahydrofuran (4.1 mL) was added 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 2.36 mL, 1.18 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.0226 g, 0.0442 mmol) under argon. The solution was stirred at 60°C for 2 hours. The reaction was incomplete by LCMS, so additional 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 2 mL, 1 mmole) was added, then the reaction was stirred at 60°C for an additional 2 hours. The reaction was allowed to cool to room temperature then the solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (0.112 g,

35%). LCMS: (FA) ES^+, 542. ^1H NMR (400MHz, d_4-methanol) δ: 8.73-8.69 (m, 1 H), 8.42-8.38 (m, 1H), 8.14 (s ,1H), 7.58-7.55 (m, 1H), 7.27-7.20 (m, 4H), 5.52 (s, 2H), 4.32 (s, 2H), 3.68-3.61 (m, 2H), 2.20 (s, 3H), 0.90-0.84 (m, 2H), 0.040 (s, 9H).

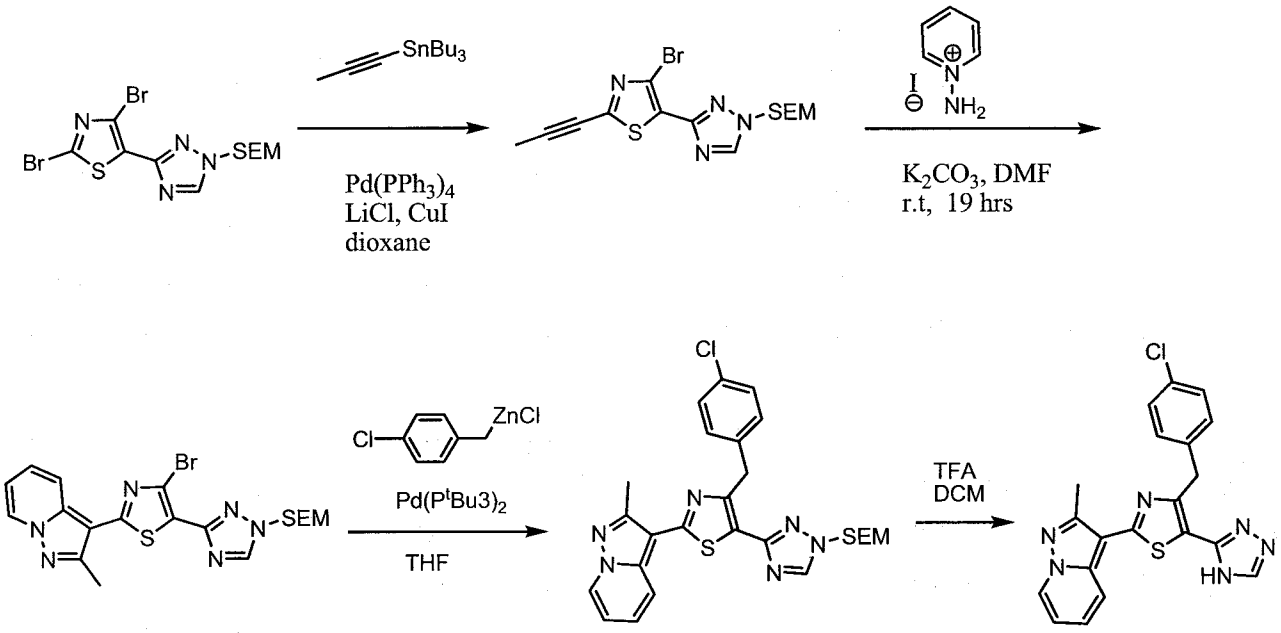
[00543] **Step 7:** *N*-{4-[4-(4-Chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound **56**)

[00544] To a solution of *N*-{4-[4-(4-chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-5-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.112 g, 0.207 mmol) in dichloromethane (2.0 mL) at room temperature was added trifluoroacetic acid (3.1 mL, 40 mmol). The mixture was then stirred at room temperature for 4 hours. The solvent was evaporated and the excess trifluoroacetic acid was removed by azeotroping with toluene. Column chromatography was performed to yield the title compound (0.0520 g, 61%). LCMS: (FA) ES^+, 411. ^1H NMR (400MHz, d_6-DMSO) δ: 14.46 (s, 1H), 10.69 (s, 1H), 8.80-8.73 (m, 1H), 8.64-8.60 (m, 1H), 8.43-8.37 (m, 1H), 7.59-7.54 (m, 1H), 7.37-7.28 (m, 4H), 4.66 (s, 2H), 2.12 (s, 3H).

[00545] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 13:

7	LCMS: (FA) ES+ 388, 390.
27	LCMS: (AA) ES+ 369, 371.
53	LCMS: (AA) ES+ 393, 395.

[00546] **Example 14: Synthesis of 3-[4-(4-chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (Compound 4)**



[00547] **Step 1:** 3-(4-Bromo-2-prop-1-yn-1-yl-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole

[00548] A mixture of 3-(2,4-dibromo-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (6.00 g, 13.6 mmol), lithium chloride (1.73 g, 40.9 mmol), copper(I) iodide (0.779 g, 4.09 mmol) and tetrakis(triphenylphosphine)platinum (0) (0.848 g, 0.681 mmol) in anhydrous 1,4-dioxane (120 mL, 1500 mmol) was sonicated under an argon atmosphere for 2 minutes in a 250 mL RBF. Tributyl(1-propynyl)tin (4.80 mL, 15.0 mmol) was added. The mixture was heated to 100°C for 1 hour under an argon atmosphere. The mixture was cooled to rt., diluted with DCM (~150 mL), filtered through celite, and washed with DCM. The filtrate was rotavaped to give a crude residue which was then purified by column chromatography (SiO2, elution with 0-100% EtOAc in hexane) to afford a pure solid product (4.14 g, 76 % yield). LCMS: (FA) ES^+ 399, 401. ^1H NMR (400MHz, $CDCl_3$) δ: 8.29 (s, 1H), 5.54 (s, 2H),3.69-3.74 (m, 2H), 2.15 (s, 3H), 0.93-0.97 (m, 2H), 0.00 (s, 9H) .

[00549] **Step 2**: 3-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine

[00550] A mixture of 3-(4-bromo-2-prop-1-yn-1-yl-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole (0.514 g, 1.29 mmol), 1-aminopyridinium iodide (0.343 g, 1.54 mmol) and potassium carbonate (0.231 g, 1.67 mmol) in N,N-dimethylformamide (8.0 mL, 1.0E2 mmol) was stirred at rt for 29 hours. The mixture was quenched with ice water (80 mL) then extracted

with EtOAc 3 times. The combined EtOAc solution was washed with water, brine, dried over Na_2SO_4, filtered and purified by column chromatography (SiO2, elution with 0-100% EtOAc in hexane) to afford a solid product. (0.410 g, 64.8 % yield). LCMS: (FA) ES^+ 491, 493. ^1H NMR (400MHz, $CDCl_3$) δ: 8.43-8.46 (m, 2H), 8.32 (s, 1H), 7.39-7.42 (m, 1H), 6.90-6.93 (m, 1H), 5.57 (m, 2H), 3.72-3.76 (m, 2H), 2.76 (s, 3H), 0.96-1.00 (m, 2H),0.00 (s, 9H) .

[00551] **Step 3:** 3-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine

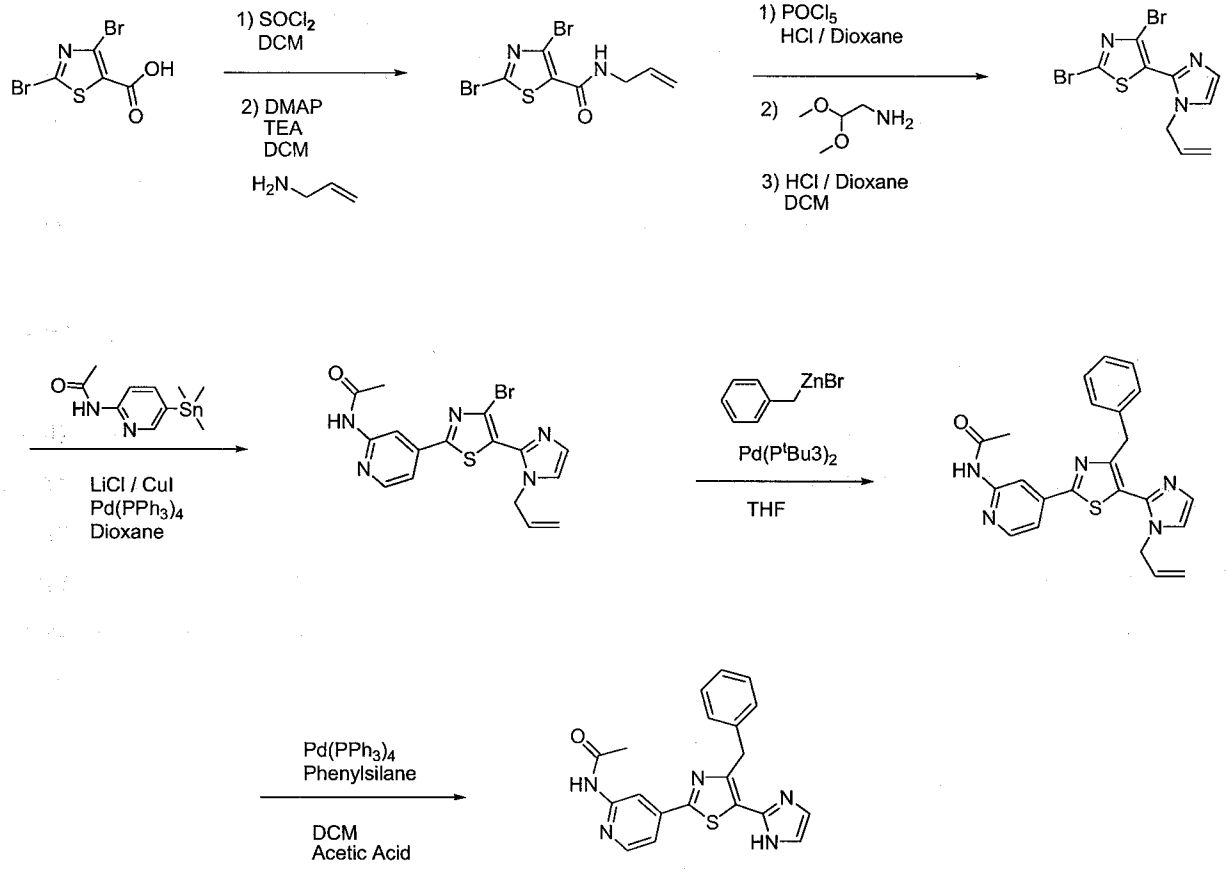
[00552] To a solution of 3-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (0.200 g, 0.407 mmol) in tetrahydrofuran (2.8 mL) were added 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 1.63 mL, 0.814 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.0156 g, 0.0305 mmol) under argon. The solution was stirred at 60°C for 3 hours. The reaction was incomplete by LCMS, so additional 4-chlorobenzylzinc chloride (0.50M solution in tetrahydrofuran, 1.0 mL, 0.5 mmole) was added then the reaction was stirred at 60°C for an additional 3 hours. The reaction was cooled to room temperature then the solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO2, elution with EtOAc in hexanes 10-100% gradient) to yield the title compound (0.188 g, 86%). LCMS: (FA) ES^+, 538. ^1H NMR (400MHz, d_6-DMSO) δ: 8.87 (s, 1 H), 8.76-8.72 (m, 1H), 8.28-8.24 (m,1H), 7.54-7.48 (m, 1H), 7.44-7.40 (m, 2H), 7.35-7.30 (m, 2H), 7.09-7.03 (m, 1H), 5.58 (s, 2H), 4.63 (s, 2H), 3.68-3.62 (m, 2H), 2.66 (s, 3H), 0.91-0.84 (m, 2H), 0.050 (s, 9H).

[00553] **Step 4:** 3-[4-(4-Chlorobenzyl)-5-(4*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (Compound **4**)

[00554] To a solution of 3-[4-(4-chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-*a*]pyridine (0.182 g, 0.339 mmol) in dichloromethane (3.3 mL) at room temperature was added trifluoroacetic acid (5.1 mL, 66 mmol). The mixture was then stirred at room temperature for 3 hours. The solvent was evaporated and the excess trifluoroacetic acid was removed by azeotroping with toluene. The crude product was purified by column chromatography (SiO2, elution with hexane to 100% ethyl acetate) to yield the title compound (0.0884 g, 64%). LCMS: (FA) ES^+, 407. ^1H NMR (400MHz, d_6-DMSO) δ: 8.76-8.70 (m, 2H), 8.28-8.22 (m, 1H), 7.53-7.46 (m, 1H), 7.45-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.07-7.01 (m, 1H), 5.55-5.50 (m, 1H), 4.64 (s, 2H), 2.65 (s, 3H).

[00555] **Example 15: Synthesis of N-{4-[4-benzyl-5-(1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound 2)**

[00556]



[00557] **Step 1:** *N*-allyl-2,4-dibromo-1,3-thiazole-5-carboxamide

[00558] To a solution of 2,4-dibromo-1,3-thiazole-5-carboxylic acid (25.0 g, 87.1 mmol) in dichloromethane (600 mL) at 0°C was added thionyl chloride (66.1 mL, 906 mmol) followed by N,N-dimethylformamide (7.02 mL, 90.6 mmol). The mixture was allowed to warm to room temperature and stir for 2 hours. The solvent was evaporated and the excess thionyl chloride was removed by azeotroping with toluene. The residue was dissolved in dichloromethane (600 mL) and cooled to 0°C, then added triethylamine (63.2 mL, 453 mmol) was added followed by 2-propen-1-amine (23.8 mL, 317 mmol) and N,N-dimethylaminopyridine (1.11 g, 9.06 mmol). The mixture was allowed to warm to room temperature and stirred for 2 hours. The solution was then diluted with dichloromethane and water and the layers were separated. The aqueous phase was then extracted with dichloromethane twice, then the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (14.3 g, 50%). LCMS: (FA) ES^+, 327. ^1H NMR (400MHz, d_4-methanol) δ: 5.97-5.85 (m, 1H), 5.32-5.24 (m, 1H), 5.20-5.14 (m, 1H), 4.02-3.95 (m, 2H).

[00559] **Step 2:** 5-(1-allyl-1*H*-imidazol-2-yl)-2,4-dibromo-1,3-thiazole

[00560] To a solution of *N*-allyl-2,4-dibromo-1,3-thiazole-5-carboxamide (13.0 g, 39.9 mmol) in dichloromethane (260 mL) was added phosphorus pentachloride (9.93 g, 47.7 mmol) and 4M hydrochloric acid in dioxane (1.52 mL, 6.06 mmol). The reaction was heated to 60°C for 90 minutes under an atmosphere on nitrogen. The reaction was allowed to cool to room temperature and then aminoacetaldehyde dimethyl acetal (47.8 mL, 439 mmol) was added slowly through the condenser. The mixture was heated to 60°C for 2 hours under an atmosphere of nitrogen then cooled to room temperature, and water was added (200 mL). The layers were separated and the organic phase was washed with water again (2 x 200 mL). The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and washed with dichloromethane (200 mL). To this dichloromethane solution of the intermediate was added 4M hydrochloric acid in dioxane (120 mL, 480 mmol) and the solution was stirred at 60°C for 16 hours. The solution was decanted (leaving behind an oily black residue on the flask) then the solvent was evaporated and the residue was diluted with ethyl acetate and saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted three more times with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (8.04 g, 58%). LCMS: (FA) ES^+, 306 (parent minus allyl group). ^1H NMR (300MHz, d_4-methanol) δ: 7.37-7.31 (m, 1H), 7.20-7.16 (m, 1H), 6.02-5.86 (m, 1H), 5.26-5.18 (m, 1H), 5.07-4.96 (m, 1H), 4.68-4.59 (m, 2H).

[00561] **Step 3:** Synthesis of *N*-{4-[5-(1-allyl-1*H*-imidazol-2-yl)-4-bromo-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00562] To a solution of 5-(1-allyl-1*H*-imidazol-2-yl)-2,4-dibromo-1,3-thiazole (5.00 g, 14.3 mmol) in 1,4-dioxane (133 mL) was added N-[4-(trimethylstannyl)pyridine-2-yl]acetamide (5.14 g, 17.2 mmol), lithium chloride (1.82 g, 43.0 mmol), copper (I) iodide (0.818 g, 4.30 mmol) and tetrakis (triphenylphosphine)palladium(0) (1.24 g, 1.07 mmol). The flask was purged with argon and then the mixture was heated at 115 °C for 4 hours. The reaction was allowed to cool to room temperature, and then the solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (3.13 g, 54%). LCMS: (FA) ES^+, 406. ^1H NMR (400MHz, d_6-DMSO) δ: 10.77 (s, 1H), 8.66-8.61 (m, 1H), 8.49-8.44 (m, 1H), 7.61-7.56 (m, 1H), 7.49-7.45 (m, 1H), 5.98-5.87 (m, 1H), 5.19-5.12 (m, 1H), 4.95-4.88 (m, 1H), 4.70-4.64 (m, 2H), 2.13 (s, 3H).

[00563] **Step 4:** Synthesis of N-{4-[5-(1-allyl-1H-imidazol-2-yl)-4-benzyl-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00564] To a solution of *N*-{4-[5-(1-allyl-1*H*-imidazol-2-yl)-4-bromo-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.0500 g, 0.124 mmol) in tetrahydrofuran (0.86 mL) was added benzylzinc bromide

(0.50M solution in tetrahydrofuran, 0.495 mL, 0.247 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.00474 g, 0.00928 mmol) under argon. The solution was stirred at 60°C for 2 hours then cooled to room temperature. The solvent was evaporated in vacuo. Column chromatography was performed to yield the title compound (0.0110 g, 21%). LCMS: (FA) ES^+, 416. ^1H NMR (400MHz, d_4-methanol) δ: 8.70-8.65 (m, 1 H), 8.41-8.36 (m, 1H), 7.66-7.61 (m ,1H), 7.34-7.05 (m, 7H), 5.81-5.70 (m, 1H), 5.16-5.10 (m, 1H), 4.95-4.88 (m, 1H), 4.38-4.33 (m, 2H), 4.13 (s, 2H), 2.20 (s, 3H).

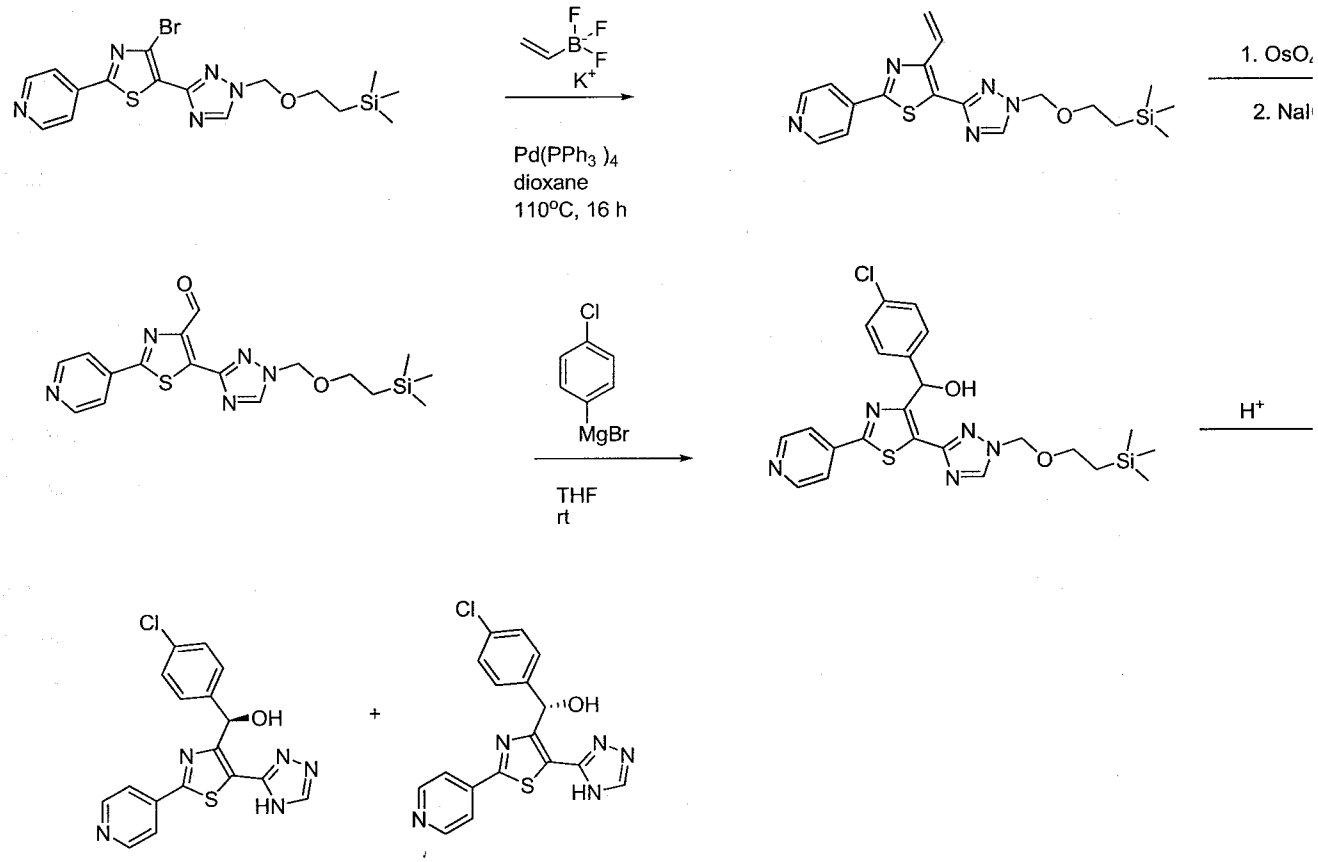
[00565] **Step 5:** Synthesis of N-{4-[4-benzyl-5-(1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (Compound **2**)

[00566] To a solution of N-{4-[5-(1-allyl-1H-imidazol-2-yl)-4-benzyl-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.210 g, 0.0505 mmol) in dichloromethane (0.38 mL) and acetic acid (0.13 mL) was added tetrakis (triphenylphosphine)palladium(0) (0.00292 g, 0.00253 mmol) followed by phenylsilane (0.0318 mL, 0.258 mmol). The solution was stirred at 40°C for 3 hours. The solution was cooled to room temperature then concentrated in vacuo and diluted with ethyl acetate and saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted three more times with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Column chromatography was performed to yield the title compound (0.0100 g, 53%). LCMS: (FA) ES^+, 376. ^1H NMR (400MHz, d_4-methanol) δ: 8.67-8.63 (m, 1H), 8.38-8.35 (m, 1H), 7.63-7.59 (m, 1H), 7.25-7.07 (m, 7H), 4.42 (s, 2H), 2.20 (s, 3H).

[00567] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 15:

24	LCMS: (FA) ES+ 390
67	LCMS: (FA) ES+ 410, 412.
73	LCMS: (FA) ES+ 410, 412.

[00568] **Example 16: Synthesis of (4-chlorophenyl)[2-pyridin-4-yl-5-(1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol (Compounds 19 and 70)**



[00569] **Step 1:** 4-[5-(1-{[2-(Trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-4-vinyl-1,3-thiazol-2-yl]pyridine.

[00570] Into a sealed tube was added potassium vinyltrifluoroborate (1.34 g, 10.0 mmol), 1,4-dioxane (21.0 mL, 269 mmol), 4-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]pyridine (2.0 g, 4.6 mmol) and 2 M sodium carbonate in water (9.10 mL, 18.2 mmol). The reaction was degassed with nitrogen for 15 min then tetrakis(triphenylphosphine)palladium(0) (527 mg, 0.456 mmol) was added. The tube was sealed and the reaction was heated in an oil bath at 110°C with stirring overnight. The reaction solution was cooled to room temperature, water (10 mL) and EtOAc (10 mL) were added, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, elution with 0-10 % MeOH in DCM) to give the title compound as a yellow solid (1.34 g 81%). LCMS: (FA) ES^+, 386. ^1H NMR (400 MHz, *d6*-DMSO) δ:8.92 (s, 1H), δ 8.74-8.76 (dd, J = 1.75 Hz, J = 1.5 Hz 2H), 7.96-7.98 (dd, J = 1.75 Hz, 2H), 6.34-6.40 (dd, J = 2.3 Hz, 1 2H), 5.62-5.65 (dd, J = 2.3 Hz, 1H), 5.60 (s, br, 2H), 3.63-3.68 (m, 2H), 0.86-0.90 (m, 2H), -0.04 (s, 9H).

[00571] **Step 2:** 2-Pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazole-4-carbaldehyde

[00572] To a solution of 4-[5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-4-vinyl-1,3-thiazol-2-yl]pyridine (1.43 g, 2.60 mmol) in a 3:1 mixture of 1,4-dioxane (17.5 mL, 224.6 mmol) and water (5.8 mL, 324.25 mmol) was added 2,6-lutidine (1.50 mL, 12.98 mmol) and the mixture was cooled to 0°C. Sodium metaperiodate (2.80 g, 12.98 mmol) was added followed by the addition of 4% osmium tetroxide in water (0.50 mL, 0.080 mmol) and the reaction mixture was slowly warmed to ambient temperature and allowed to stir overnight. Water (10mL) was added. The resulting yellow precipitate was collected by filtration, washed with water, ether and MeOH. The filtrate was concentrated under reduced pressure and dried on the high vac to give the title compound (1.0g, yield 99%). LCMS: (FA) ES^+, 388. ^1H NMR (400 MHz, d_6-DMSO) δ: 10.70(s, 1H), δ:9.05 (s, 1H), 8.79-8.80 (dd, J = 1.5 Hz, 2H), 7.98-8.0 (dd, J = 1.5 Hz, J = 1.7 Hz, 2H), 5.64-5.66 (s, br, 2H), 3.64-3.68 (m, 2H), 0.870-0.90(m, 2H), -0.03 (s, 9H).

[00573] **Step 3:** (4-Chlorophenyl)[2-pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol

[00574] To a solution of 2-pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazole-4-carbaldehyde (280.0 mg, 0.722 mmol) in tetrahydrofuran (4.0 mL, 40 mmol), 1 M 4-chlorophenyl magnesium bromide in ether (4.0 mL, 4 mmol) was added and the mixture was stirred for 40 min at rt. After the reaction was completed a 5% aqueous solution of NH_4Cl (10 mL) and EtOAc (10 mL) were added and the resulting bi-phasic mixture was vigorously stirred for 15 min then the aqueous phase was discarded. The organic phase was washed with brine (5 mL) then dried over anhydrous $MgSO_4$. Insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, elution with 20-80 % EtOAc in hexane) to give the title compound as a white solid (230 mg, 73.6%). LCMS: (FA) ES^+, 500. ^1H NMR (400 MHz, d_6-DMSO) δ:8.96 (s, 1H), δ 8.70-8.72 (dd, J = 1.75 Hz, 2H), 7.87-7.89 (dd, J = 1.75, 2H), 7.32-7.37(m, 2H), 7.55-7.58(m, 3H), 6.85-6.87(d, J = 5.5 Hz , 1H) , 6.15-6.17(d, J = 5.5 Hz , 1H) , 5.6 (s, br, 2H), 3.65-3.67 (m, 2H), 0.850-0.90(m, 2H), -0.05 (s, 9H).

[00575] **Step 4:** (4-Chlorophenyl)[2-pyridin-4-yl-5-(1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol.

[00576] (4-Chlorophenyl)[2-pyridin-4-yl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-4-yl]methanol(266.0 mg, 0.530 mmol) was dissolved in methylene chloride (3.0 mL, 47 mmol). Trifluoroacetic acid (3.0 mL, 39 mmol) was added and the solution was stirred at rt overnight. After the reaction wass completed, saturated $NaHCO_3$ was added and the reaction was stirred at rt for 20 min, then EtOAc (5mL) was added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, concentrated and the obtained residue was purified by column chromatography (SiO_2, elution with 2-20% MeOH in DCM) to give the title compound as a white solid (200 mg). The racemic isomers were separated by chiral prep HPLC to yield **17** (34 mg, 12.7%) (peak 1, ret. time 13.04 min).

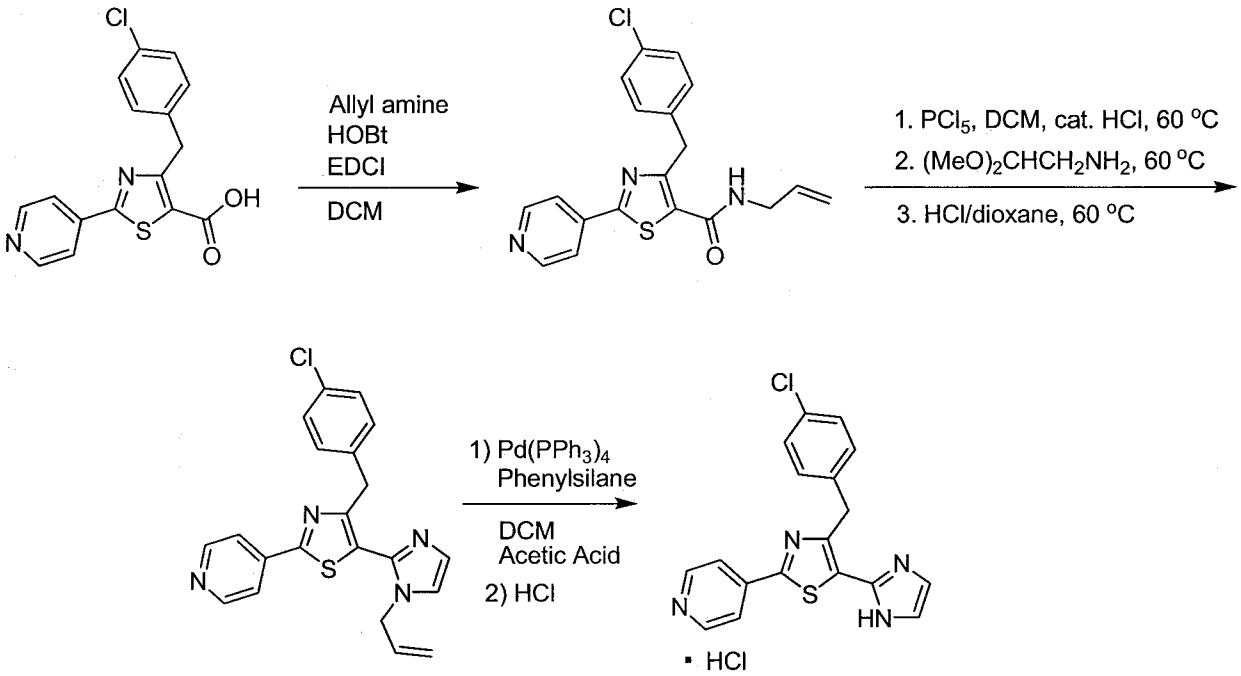
LCMS: (FA) ES^+, 370. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.76(s, 1H), 8.69-8.71 (dd, J = 1.5 Hz, 2H), 7.86-7.88 (dd, J = 1.5, 2H), 7.55-7.58(d, , J = 8.5 Hz, 2H), 7.34-7.38(d, J = 8.5 Hz, 2H), 6.84-6.86 (s, br, 1H) and **70** (34.8 mg, 13.0%) (peak 2, ret. time 13.2 min). LCMS: (FA) ES^+, 370. ^1H NMR (400 MHz, d_6-DMSO) δ: 8.68-8.72(m, 3H), 7.86-7.88 (dd, J = 1.69 Hz , J = 1.5 Hz , 2H), 7.54-7.58(d, , J = 8.47 Hz, 2H), 7.34-7.38(d, J = 8.47 Hz, 2H), 6.81-6.82 (s, br, 1H).

[00577] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 16:

149	LCMS: (AA) ES+ 451, 453, 455
168	LCMS: (FA) ES+ 418, 420
238	LCMS: (AA) ES+ 427, 429
265	LCMS: (AA) ES+ 431, 433
278	LCMS: (AA) ES+ 451, 453, 455
282	LCMS: (FA) ES+ 418, 420
285	LCMS: (AA) ES+ 431, 433

[00578]

[00579] Example 17: Synthesis of 4-(4-chlorobenzyl)-5-(1H-imidazol-2-yl)-2-(pyridin-4-yl)thiazole (Compound 15)



[00580] **Step 1:** N-Allyl-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxamide

[00581] To a stirred solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (220 mg, 0.665 mmol) in DCM (4.05 mL) was added HOBT (98.8 mg, 0.732 mmol) and EDCI (204 mg, 1.06 mmol) at room temperature and the mixture was stirred for 30 min. To the solution was added 2-propen-1-amine (0.200 mL, 2.66 mmol) then the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (10 mL) and washed with water (3 mL) and brine (2 mL), then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→75/25) to give 150 mg of the title compound as a yellow solid (61 % yield). LC/MS (FA) ES+ 370. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74-8.72 (m, 2H), 7.79-7.77 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.25 (m, 2H), 5.94-5.80 (m + bs, 2H), 5.25-5.20 (m, 2H), 4.48 (s, 2H), 4.06-4.02 (m, 2H).

[00582] **Step 2:** 5-(1-Allyl-1H-imidazol-2-yl)-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole

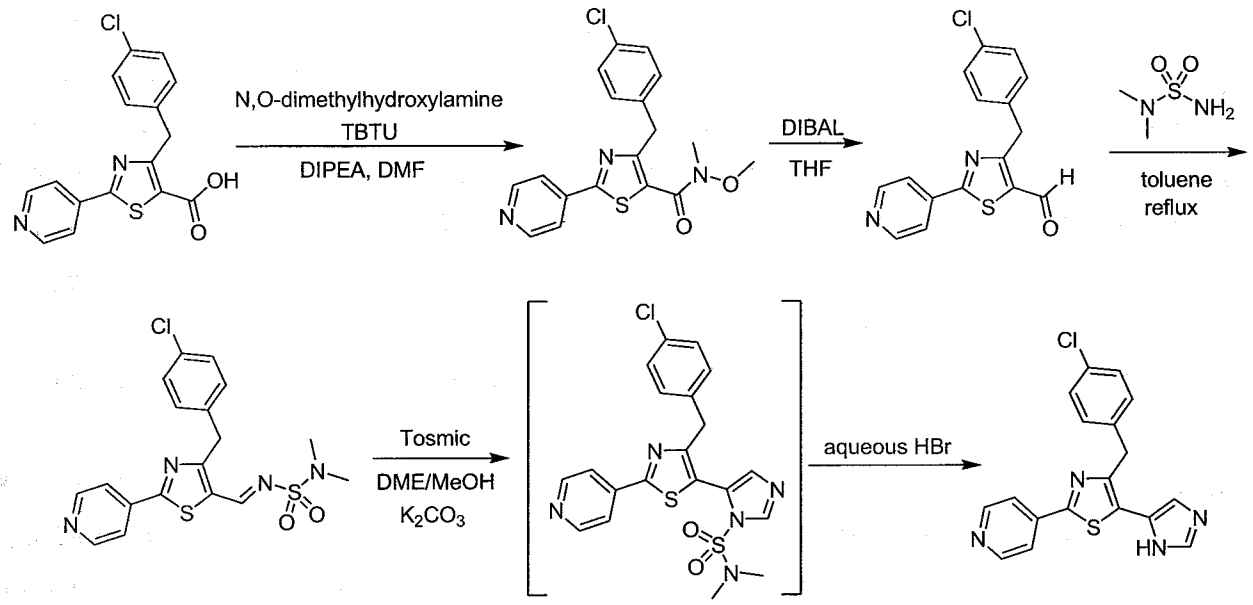
[00583] To a solution of N-allyl-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxamide (150 mg, 0.406 mmol) in DCM (2.64 mL) was added phosphorus pentachloride (101 mg, 0.485 mmol) and 4 M hydrochloric acid in 1,4-dioxane (0.0154 mL, 0.0614 mmol) and the mixture was heated to 60 °C for 1.5 h. The reaction was cooled to room temperature and aminoacetaldehyde dimethyl acetal (0.486 mL, 4.46 mmol) was added. The resulting mixture was heated at 60°C for 2 h. The mixture was cooled to room temperature, diluted with DCM (10 mL), washed with water (2 x 2 mL) and brine (2 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in DCM (3.0 mL) and 4 M hydrochloric acid in 1,4-dioxane (0.608 mL, 2.43 mmol) was added and the mixture was stirred at 60°C

overnight. The reaction was cooled and concentrated in vacuo. The residue was taken up in ethyl acetate (20 mL) and saturated sodium bicarbonate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→5/95) to give 99 mg of the title compound (62 % yield). LC/MS (FA) ES+ 393. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72-8.70 (m, 2H), 7.80-7.72 (m, 2H), 7.26 (m, 1H), 7.22-7.14 (m, 4H), 7.06 (m, 1H), 5.84-5.71 (m, 1H), 5.23-5.19 (m, 1H), 5.01-4.96 (m, 1H), 4.38-4.34 (m, 2H), 4.20 (s, 2H).

[00584] **Step 3:** 4-(4-Chlorobenzyl)-5-(1H-imidazol-2-yl)-2-(pyridin-4-yl)thiazole, hydrochloride salt (Compound **15**)

[00585] To a solution of 5-(1-allyl-1H-imidazol-2-yl)-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole (99.0 mg, 0.252 mmol) and tetrakis(triphenylphosphine)palladium (14.6 mg, 0.0126 mmol) in DCM (3.38 mL) was added acetic acid (0.623 mL, 11.0 mmol) and phenylsilane (0.158 mL, 1.28 mmol) and the mixture was stirred for 2 h at 40°C. The reaction mixture was evaporated to remove volatiles and DCM (10 mL) added. To this solution was added saturated sodium bicarbonate (4 mL) and the resulting mixture was stirred for 30 min. The mixture was extracted with DCM (3 x 10 mL) and the combined DCM layers were washed with brine. The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→10/90) to give 57 mg of the title compound as a yellow solid (64 % yield). The HCl salt was made as follows. To a mixture of the free base (57 mg, 0.162 mmol) in ethanol (5 mL) was added 1.0 M HCl in ether (0.178 mL, 0.178 mmol) and the mixture was stirred for 2 hours then concentrated in vacuo. The residue was taken up in a minimum of methanol, and acetonitrile was added to give a precipitate. Ether was added and the precipitate was filtered, washed with ether and dried to give the title compound as an orange solid. LC/MS (FA) ES+ 353. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.78-8.74 (m, 2H), 7.96-7.91 (m, 2H), 7.48-7.43 (m, 2H), 7.34-7.28 (m, 4H), 4.51 (s, 2H).

[00586] **Example 18: Synthesis of 4-(4-chlorobenzyl)-5-(1H-imidazol-5-yl)-2-(pyridin-4-yl)thiazole (Compound 66)**



[00587] **Step 1:** 4-(4-Chlorobenzyl)-N-methoxy-N-methyl-2-(pyridin-4-yl)thiazole-5-carboxamide

[00588] To a solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylic acid (850 mg, 2.57 mmol) in DMF (11.9 mL) was added N,O-dimethylhydroxylamine hydrochloride (852 mg, 8.74 mmol), HATU (1.95 g, 5.14 mmol) and diisopropylethylamine (2.42 mL, 13.9 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was diluted with water (30 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with water (3 x 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→80/20) to give 775 mg of the title compound as a yellow solid (80 % yield). LC/MS (FA) ES+ 374. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72-8.70 (m, 2H), 7.84-7.82 (m, 2H), 7.37-7.34 (m, 2H), 7.25-7.22 (m, 2H). 4.56 (s, 2H), 3.70 (s, 3H), 3.37 (s, 3H).

[00589] **Step 2:** Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbaldehyde

[00590] To a solution of 4-(4-chlorobenzyl)-N-methoxy-N-methyl-2-(pyridin-4-yl)thiazole-5-carboxamide (1.13 g, 3.02 mmol) in THF (36.8 mL) at -50°C was added 1.0 M diisobutylaluminum hydride in hexane (15.1 mL, 15.1 mmol) and the resulting solution was stirred at -50°C to -30°C for 2 hours. The reaction was quenched with saturated ammonium chloride (10 mL) and allowed to warm to room temperature. Water (25 mL) was added and the mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→70/30) to give 699 mg of the title compound as a white solid (73 % yield). LC/MS (FA) ES+ 315. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.16 (s, 1H), 8.78-8.76 (m, 2H), 7.85-7.83 (m, 2H), 7.30-7.25 (m, 4H), 4.47 (s, 2H).

[00591] **Step 3:** N'-{(1E)-[4-(4-chlorobenzyl)-2-pyridin-4-yl-1,3-thiazol-5-yl]methylene}-N,N-dimethylsulfamide

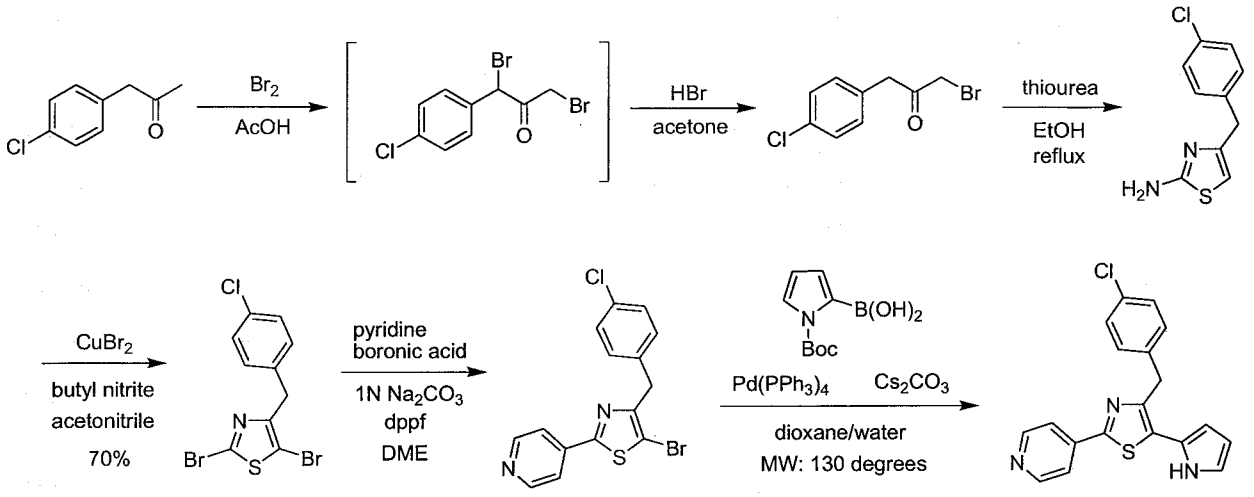
[00592] A solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbaldehyde (186 mg, 0.591 mmol) and N,N-dimethylsulfonamide ((75.6 mg, 0.608 mmol) (prepared according to Li, *Tetrahedron Letters*, 50(19), 2232-2235) in toluene (5.0 mL) was refluxed overnight using a Dean Stark trap to azeotrope water. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→60/40) to give 699 mg of the title compound as a yellow solid (60% yield). LC/MS (FA) ES+ 421. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.08 (s, 1H), 8.78-8.76 (m, 2H), 7.84-7.82 (m, 2H), 7.32-7.22 (m, 4H), 4.38 (s, 2H), 2.86 (s, 6H).

[00593] **Step 4:** 5-(4-(4-Chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide and 4-(4-chlorobenzyl)-5-(1H-imidazol-5-yl)-2-(pyridin-4-yl)thiazole (Compound **66**).

[00594] A solution of N'-{(1E)-[4-(4-chlorobenzyl)-2-pyridin-4-yl-1,3-thiazol-5-yl]methylene}-N,N-dimethylsulfamide (148 mg, 0.352 mmol), p-tolylsulfonylmethyl isocyanide (75.5 mg, 0.387 mmol) and potassium carbonate (146 mg, 1.05 mmol) in DME (2.50 mL) was heated at 78°C for 2 hours. The reaction was diluted with DCM (10 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with DCM (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give 50 mg of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide. LC/MS (FA) ES+ 460. (Some of the deprotected product, 4-(4-chlorobenzyl)-5-(1H-imidazol-5-yl)-2-(pyridin-4-yl)thiazole, was also obtained (19 mg). This material was combined with the material obtained in the following deprotection step.)

A solution of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (50 mg, 0.109 mmol) in 48% HBr in water (3.0 mL) was heated to 90°C for 2.5 hours. The cooled solution was taken up in DCM (20 mL) and saturated sodium bicarbonate (20 mL). The layers were separated and the aqueous extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. To this crude material was added the 19 mg of deprotected material obtained in the previous step. The combined material was purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give 34 mg of the title compound as a white solid (27 % yield). LC/MS (FA) ES+ 353. ^{1}H NMR (300 MHz, d_4-MeOH) δ: 8.63-8.61 (m, 2H), 7.93-7.91 (m, 2H), 7.80 (d, 1H, J = 1.1 Hz), 7.30-7.19 (m, 5H), 4.35 (s, 2H).

[00595] **Example 19: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-pyrrol-2-yl)thiazole (Compound 22)**



[00596] **Step 1:** 1-Bromo-3-(4-chlorophenyl)propan-2-one

[00597] To a solution of 1-(4-chlorophenyl)propan-2-one (25.0 g, 148 mmol) in acetic acid (37.9 mL) was added 48% aqueous HBr (19.0 mL, 168 mmol). A solution of bromine (16.3 mL, 316 mmol) in acetic acid (63.2 mL) was then added over 10 minutes and the resulting solution was stirred for 4 hours at room temperature. Acetone (190 mL) was added and the resulting solution was stirred at room temperature for 3 days. The reaction was concentrated in vacuo and the residue was taken up in DCM (300 mL) and brine (100 mL). The layers were separated and the aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexanes = 0/100→15/85) to give 25.4 grams of the title compound as a dark gray solid (69 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.31 (m, 2H), 7.18-7.15 (m, 2H), 3.94 (s, 2H), 3.91 (2, 2H).

[00598] **Step 2:** 4-(4-Chlorobenzyl)thiazol-2-amine

[00599] A mixture of 1-bromo-3-(4-chlorophenyl)propan-2-one (25.4 grams, 103 mmol) and thiourea (8.59 g, 113 mmol) in ethanol (1.51 L) was heated at 85°C for 2 hours. The reaction was cooled and concentrated in vacuo and the residue was taken up in ethyl acetate (300 mL) and saturated sodium bicarbonate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was recrystallized from ethyl acetate/hexanes to give 19.9 grams of the title compound as a tan powder (86 % yield). LC/MS (FA) ES+ 225. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29-7.24 (m, 2H), 7.20-7.15 (m, 2H), 6.04 (m, 1H), 5.00 (bs, m, 2H), 3.83 (s, 2H).

[00600] **Step 3:** 2,5-Dibromo-4-(4-chlorobenzyl)thiazole

[00601] To a mixture of 4-(4-chlorobenzyl)thiazol-2-amine (6.90 g, 30.7 mmol) in acetonitrile (367 mL) was added copper(II) bromide (10.3 grams, 46.0 mmol) and the resulting mixture was stirred at room temperature for 4 hours. Butyl nitrite (5.21 mL, 46.0 mmol) was added and the mixture was stirred at

room temperature for 30 minutes. The reaction was concentrated in vacuo and the residue was slurried in DCM (250 mL) for 30 minutes. The mixture was filtered through Celite and washed with DCM (50 mL). The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography (ethyl acetate/hexanes = 0/100→10/90) to give 8.47 grams of the title compound as an orange oil (75 % yield). LC/MS (FA) ES+ 368, 370. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.18 (m, 4H), 4.03 (s, 2H).

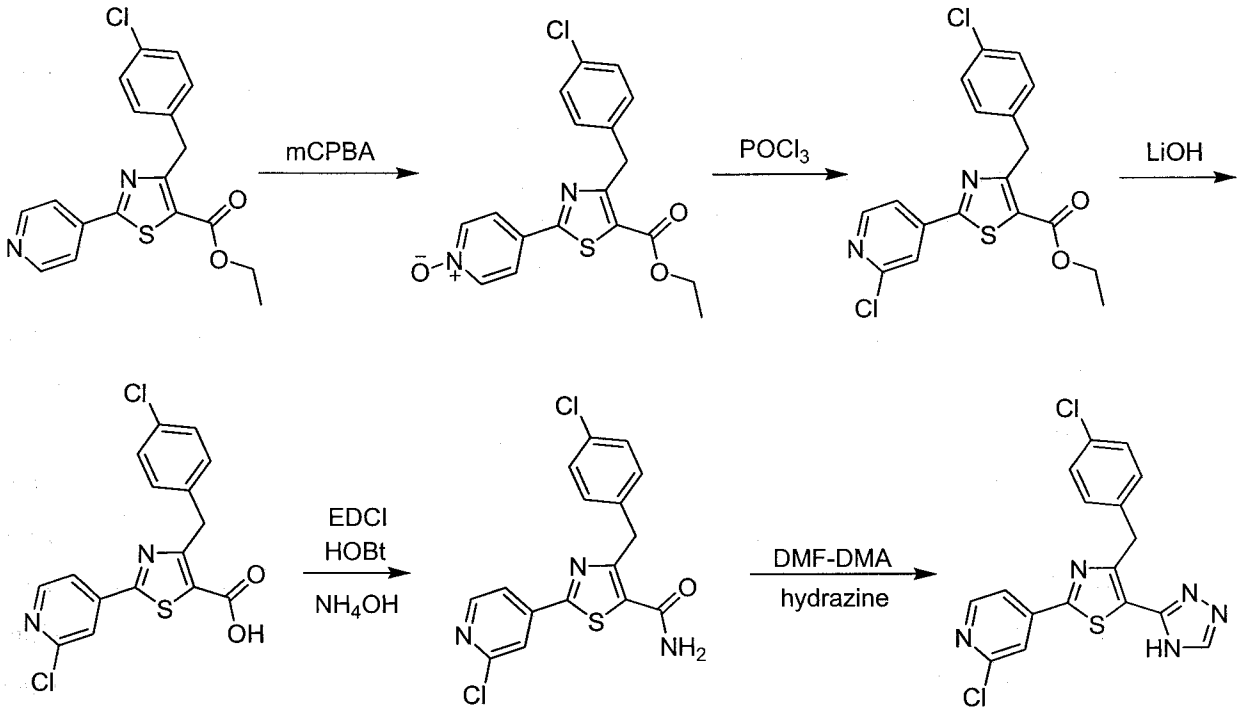
[00602] **Step 4:** 5-Bromo-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole

[00603] To a solution of 2,5-dibromo-4-(4-chlorobenzyl)thiazole (12.9 grams, 35.1 mmol) in DME (365 mL) was added pyridine-4-boronic acid (5.61 g, 45.6 mmol), 1M sodium carbonate (70.2 mL, 70.2 mmol), and $PdCl_2$(dppf) (2.89 g, 3.51 mmol). The reaction was degassed with argon and stirred at 85°C overnight. The reaction was cooled and taken up in ethyl acetate (400 mL) and saturated sodium bicarbonate (200 mL). The insolubles were filtered through celite and the bed was washed with ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→70/30) followed by another silica gel chromatography (ethyl acetate/hexanes = 0/100→100/0) to give 3.3 grams of the title compound as a brown solid (26% yield). LC/MS (FA) ES+ 365, 367. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70-8.67 (m, 2H), 7.70-7.67 (m, 2H), 7.28-7.26 (m, 4H), 4.13 (s, 2H).

[00604] **Step 5:** 4-(4-Chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-pyrrol-2-yl)thiazole (Compound **22**).

[00605] To a solution of 5-bromo-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole (94.0 mg, 0.257 mmol) in 4:1 dioxane:water (3.0 mL) was added 1-(t-butoxycarbonyl)pyrrole-2-boronic acid (57 mg, 0.27 mmol), cesium carbonate (251 mg, 0.771 mmol), and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol). The solution was degassed with argon and heated in a microwave reactor at 130°C for 105 minutes. The reaction was concentrated in vacuo and the residue taken up in DCM (25 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→80/20) followed by HPLC purification (formic acid method) to give 26 mg of the title compound as a yellow solid (29 % yield). LC/MS (FA) ES+ 352. ^{1}H NMR (300 MHz, d_4-MeOH) δ: 8.62-8.60 (m, 2H), 7.90-7.88 (m, 2H), 7.66-7.55 (m, 1H), 7.26-7.24 (m, 2H), 7.20-7.17 (m, 2H), 6.92 (dd, 1H, J = 2.7, 1.5 Hz), 6.32 (dd, 1H, J = 3.5, 1.5 Hz), 6.21 (dd, 1H, J = 3.5, 2.7 Hz), 4.28 (s, 2H).

[00606] **Example 20: Synthesis of 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound 47)**



[00607] **Step 1:** 4-(4-(4-Chlorobenzyl)-5-(methoxycarbonyl)thiazol-2-yl)pyridine 1-oxide

[00608] To a solution of ethyl 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboxylate (430 mg, 1.20 mmol) in DMF (6.0 mL) was added mCPBA (322 mg, 1.44 mmol) and the mixture was stirred at room temperature overnight. To the reaction was added DCM (30 mL) and saturated sodium bicarbonate (25 mL). The layers were separated and the aqueous layer extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 50/50→100/0) to give 449 mg of the title compound as a white solid (100 % yield). LC/MS (FA) ES+ 375. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23-8.20 (m, 2H), 7.84-7.81 (m, 2H), 7.33-7.23 (m, 4H), 4.51 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 1.39 (t, 3H, J = 7.2 Hz).

[00609] **Step 2:** Ethyl 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylate

[00610] A solution of 4-(4-(4-chlorobenzyl)-5-(methoxycarbonyl)thiazol-2-yl)pyridine 1-oxide (334 mg, 0.891 mmol) in phosphoryl chloride (1.66 mL, 17.8 mmol) was heated at 100°C for 2 hours. The reaction was cooled and poured onto ice and saturated sodium bicarbonate (50 mL). The mixture was extracted with ethyl acetate (2 x 40 mL) and the combined organic layers were washed with water (20 mL), brine (10 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (DCM/hexanes = 50/50→100/0) to give 191 mg of the title compound as a white solid (54 % yield). LC/MS (FA) ES+ 393, 395. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (dd, 1H, J = 5.3, 0.7 Hz), 7.88 (dd, 1H, J = 1.5, 0.7 Hz), 7.71 (dd, 1H, J = 5.3, 1.5 Hz), 7.36-7.31 (m, 2H), 7.27-7.23 (m, 2H), 4.53 (s, 2H), 4.39 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz).

[00611] **Step 3:** 4-(4-Chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylic acid

[00612] To a solution of ethyl 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylate (199 mg, 0.506 mmol) in THF (2.84 mL) and water (1.42 mL) was added 1.0 M LiOH (0.658 mL, 0.658 mmol) and the resulting solution was stirred at room temperature overnight. The mixture was acidified to pH = 4 with 1 N HCl. The precipitated solids were filtered, washed with water and dried to give 179 mg of the title compound as an a white solid. (96 % yield). LC/MS (FA) ES+ 365, 367.

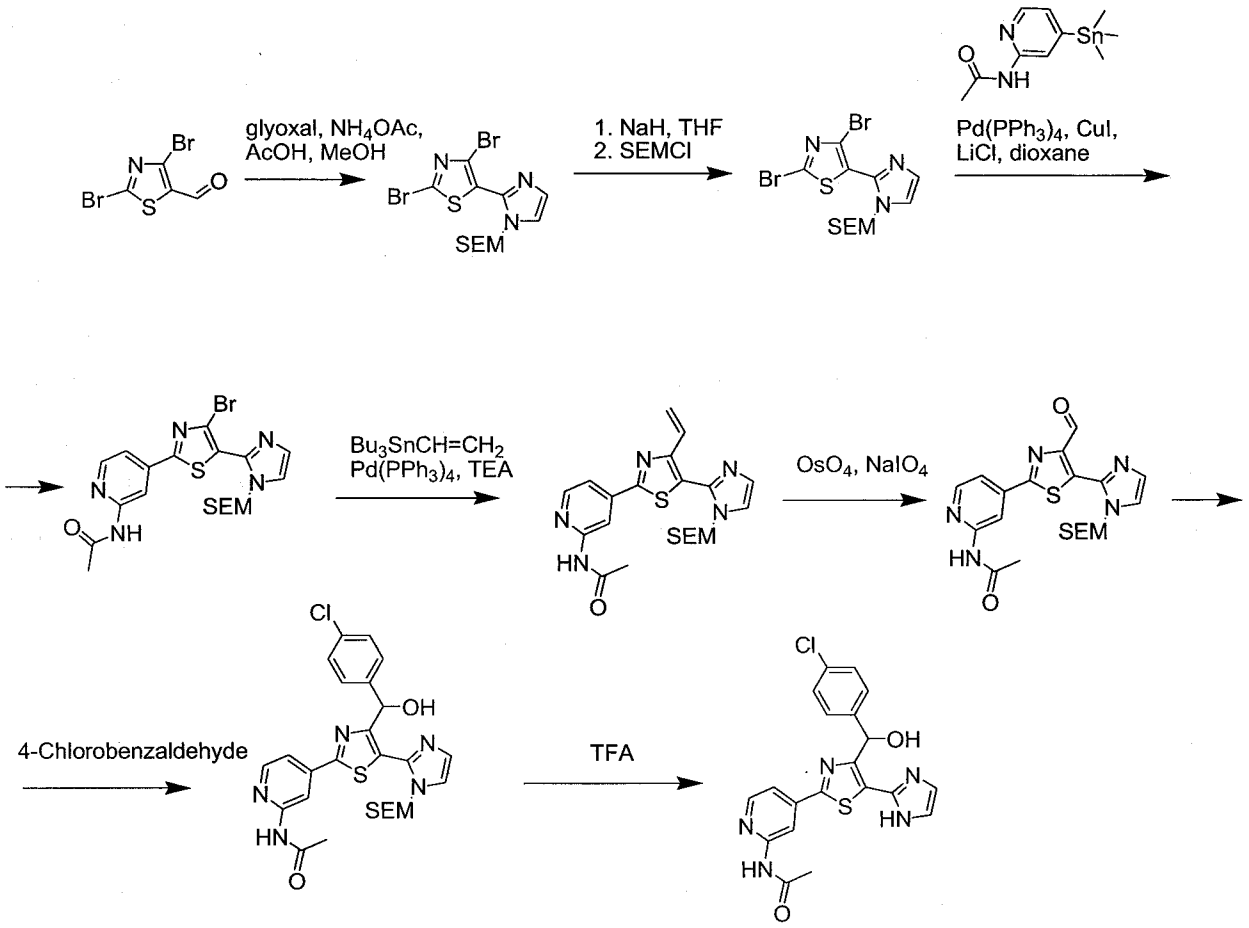
[00613] **Step 4**: 4-(4-Chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxamide

[00614] To a mixture of 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxylic acid (179 mg, 0.490 mmol) in DCM (27.5 mL) was added EDCI (282 mg, 1.47 mmol) and 1-hydroxybenzotriazole hydrate (150 mg, 0.980 mmol) and the solution was stirred for 10 minutes. 28% ammonium hydroxide (2.12 mL, 24.5 mmol) was added and the resulting mixture was stirred at room temperature overnight. Water (20 mL) was added and the mixture was extracted with DCM (2 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give 121 mg of the title compound as a white solid (67 % yield). LC/MS (FA) ES+ 364, 366. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.54 (dd, 1H, J = 5.2, 0.7 Hz), 8.02 (bs, 1H), 7.91 (dd, 1H, J = 1.5, 0.7 Hz), 7.84 (dd, 1H, J = 5.2, 1.5 Hz), 7.79 (bs, 1H), 7.36-7.29 (m, 4H), 4.43 (s, 2H).

[00615] **Step 5:** 4-(4-Chlorobenzyl)-2-(2-chloropyridin-4-yl)-5-(4H-1,2,4-triazol-3-yl)thiazole (Compound **47**).

[00616] A solution of 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)thiazole-5-carboxamide (128 mg, 0.351 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (0.467 mL, 3.51 mmol) in toluene (3.75 mL) was heated at 100 °C for 1 hour. The reaction was cooled and concentrated in vacuo to give the intermediate, 4-(4-chlorobenzyl)-2-(2-chloropyridin-4-yl)-N-((dimethylamino)methylene)thiazole-5-carboxamide, as a solid. LC/MS (FA) ES+ 419, 421. The intermediate was dissolved in acetic acid (3.60 mL). Hydrazine hydrate (0.0855 mL, 1.76 mmol) was added and the resulting solution was heated at 90°C for 2 hours. The mixture was cooled and concentrated in vacuo, and the residue was azeotroped with toluene. The residue was slurried in DCM (30 mL) and saturated sodium bicarbonate (20 mL). Some undissolved solids were filtered to give one batch of desired product. The layers of the filtrate were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give another batch of desired product. The two product batches were combined and purified by silica gel chromatography (methanol/DCM = 0/100→20/80) to give 85 mg of the title compound as a beige solid (62 % yield). LC/MS (FA) ES+ 388, 390. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 14.48 (bs, 1H), 8.76 (s, 1H), 8.54-8.51 (m, 1H), 7.96-7.95 (m, 1H), 7.92-7.89 (m, 1H), 7.38-7.30 (m, 4H), 4.65 (s, 2H).

[00617] Example 21: Synthesis of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1H-imidazol-2-yl)-1,3-thiazol- 2-yl]pyridin-2-yl}acetamide (Compound 60)



[00618] Step 1: 2,4-Dibromo-5-(1H-imidazol-2-yl)thiazole

[00619] A mixture of 2,4-dibromo-thiazole-5-carbaldehyde (14.8 g, 54.6 mmol), glyoxal trimer dihydrate (22.96 g, 109.2 mmol) and ammonium acetate (25.26 g, 327.8 mmol) in MeOH (450 mL) and acetic acid (31.06 mL) was stirred at rt overnight. The reaction mixture was concentrated in vacuo to a thick liquid mixture. Remaining acetic acid was removed by azeotroping with toluene (3 x 100 mL) to afford a dark brown solid. The mixture was purified by column chromatography on silica gel (0 to 25% EtOAc in hexanes) to give pure product (9.12 g, 54%). LCMS: (AA) ES+, 310, 312. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 12.50 (br, 1H), 7.21 (br, 2H).

[00620] Step 2: 2,4-Dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole

[00621] To a mixture of sodium hydride (2.89 g, 72.2 mmol) in THF (431 mL) was added 2,4-dibromo-5-(1H-imidazol-2-yl)thiazole (18.8 g, 60.9 mmol) in THF (60 mL) at 0 °C . After stirring 30

min, 2-(trimethylsilyl)ethoxymethyl chloride (11.8 mL, 66.9 mmol) in THF (24 mL) was slowly added at 0 °C . After 30min at this temperature, the reaction was quenched by the addition of MeOH (20 mL). The solvent was evaporated and the residue was purified by column chromatography on silica gel (0 to 25% EtOAc in hexanes). Product was obtained as colorless oil (21.8 g, 81.6%). LCMS: (AA) ES+, 440, 442. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (dd, 2H), 5.27 (s, 2H), 3.39 (t, 2H), 0.85 (t, 2H), -0.03(s, 9H).

[00622] **Step 3:** N-(4-(4-Bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol-2-yl)pyridin-2-yl)acetamide

[00623] A mixture of 2,4-dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole (13.6 g, 31.0 mmol), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (11.1 g, 37.2 mmol), tetrakis(triphenylphosphine)palladium(0) (1.792 g, 1.550 mmol), copper(I) iodide (1.77 g, 9.30 mmol) and lithium chloride (3.94 g, 93.0 mmol) in 1,4-dioxane (569 mL) was degassed with argon. The mixture was sonicated for 20min and then heated at 120°C for 5 h. The solvent was evaporated and the crude reaction mixture was purified by ISCO chromatography (0 to 3% MeOH in DCM). Product was obtained as an orange solid (10.1 g, 66.0%). LCMS: (AA) ES+, 494, 496. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.44 (br, 1H), 8.34 (d, 1H), 7.60 (dd, 1H), 7.30 (d, 2H), 5.30 (s, 2H), 3.40 (t, 2H), 2.25 (s, 3H), 0.86 (t, 2H), -0.05 (s, 9H).

[00624] **Step 4:** N-{4-[5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-4-vinyl- 1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00625] N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol-2-yl)pyridin-2-yl)acetamide (0.80 g, 1.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.187 g, 0.162 mmol) were placed in a microwave vial and sealed under atmosphere of argon. Triethylamine (7.0 mL, 50 mM), THF (7 mL) and tributylethenyl stannane (0.708 mL, 2.43 mmol) were added and the mixture was irradiated at 95°C for 3 hours. The solvent was evaporated and the residue was purified using column chromatography on silica gel (0 to 60% EA in hexane) to give the title compound (0.65 g, 72%). LCMS: (FA) ES+, 442. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.41-8.31 (m, 1H), 8.09 (s, 1H), 7.70-7.40 (m, 3H), 6.81 (dd, J = 17.2, 10.7 Hz, 1H), 6.38 (dd, J = 17.2, 1.9 Hz, 1H), 5.54 (dd, J = 10.7, 1.9 Hz, 1H), 5.27 (s, 2H), 3.48-3.34 (m, 2H), 2.25 (s, 3H), 0.90-0.84 (m, 2 H), -0.04 (s, 9 H).

[00626] **Step 5:** N-{4-[4-formyl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)- 1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00627] N-{4-[5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-4-vinyl-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.650 g, 1.47 mmol) was dissolved in tetrahydrofuran (20 mL) and water (10 mL) at ambient temperature and 0.157 M osmium tetraoxide in water (93 uL, 0.014 mmol) was added. The mixture was stirred at room temperature for 5 minutes. Sodium metaperiodate (0.661 g, 3.09 mmol)

was then added in portions over 20 minutes and the mixture was stirred at room temperature overnight. Solids were removed by filtration and washed with THF (2 x 50 mL) and ethyl acetate (2 x 5 mL). The filtrate was extracted with ethyl acetate (3 x 100 mL). The extracts were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Crude material was purified by silica gel chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.25 g, 38%). LCMS: (FA) ES+, 444. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 10.21 (s, 1H), 8.41 (d, J = 5.18 Hz, 1H), 8.20-8.07 (m, 1H), 7.76 (dd, J = 5.21, 1.58 Hz, 1H), 7.30 (dd, J = 2.87, 1.21 Hz, 2H), 5.32 (s, 2H), 3.50-3.33 (m, 2H), 2.26 (s, 3H), 0.93-0.78 (m, 2H), -0.04 (s, 9H).

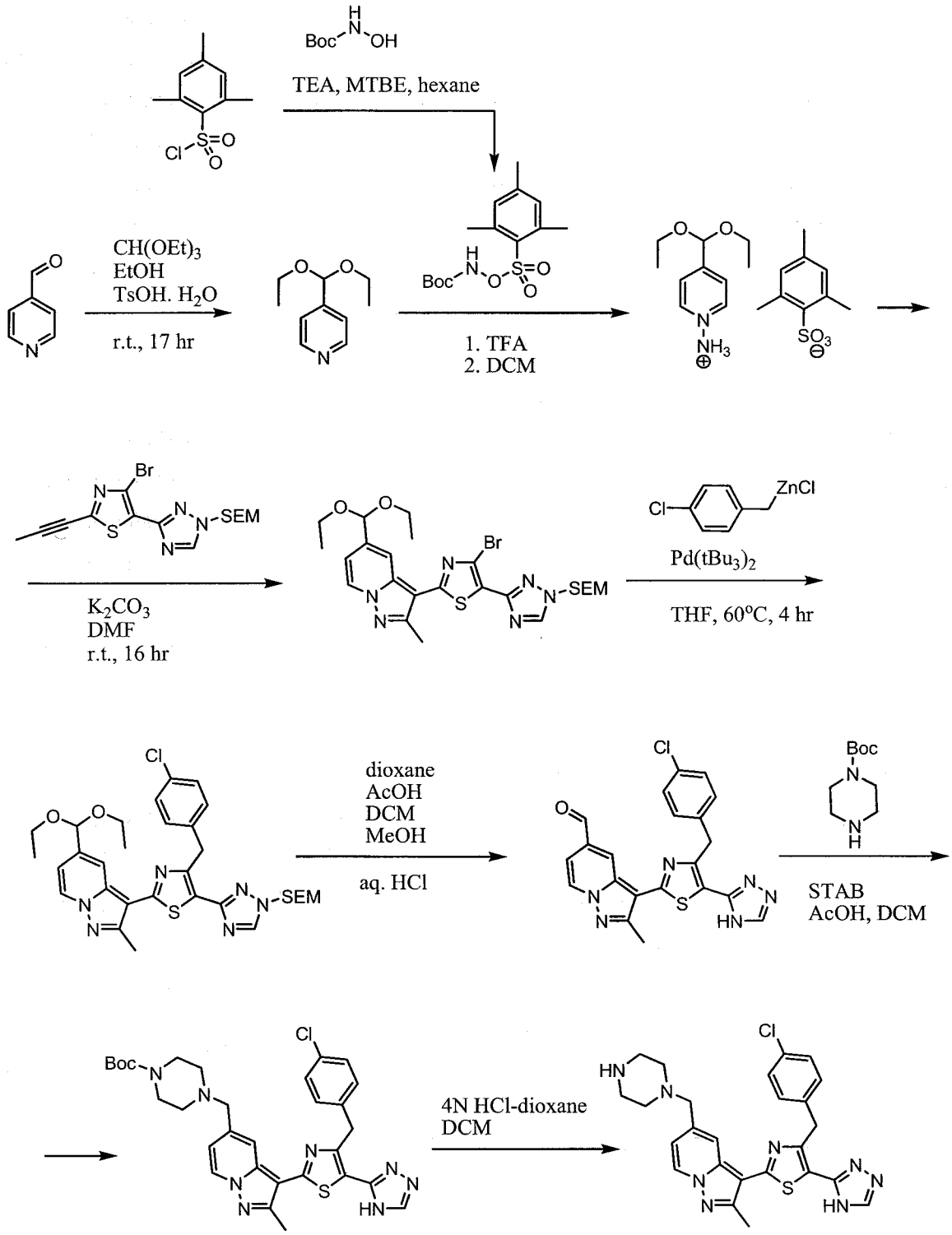
[00628] **Step 6:** N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide

[00629] N-{4-[4-formyl-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.250 g, 0.564 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled at 0°C. 1.0 M 4-Chlorophenylmagnesium bromide in ether (1.41 mL, 1.41 mmol) was added and the solution was stirred at 0°C for 30 minutes. The reaction was quenched by the addition of MeOH (10 mL), and was evaporated under reduced pressure. The residue was purified using column chromatography (20 to 100% ethyl acetate in hexane) to give the title compound (0.150 g, 48%). LCMS: (FA) ES+, 556, 558. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 8.34 (d, J = 5.23 Hz, 1H), 8.21 (s, 1H), 7.65 (dd, J = 5.23, 1.55 Hz, 1H), 7.31 (d, J = 8.28 Hz, 2H), 7.21-7.16 (m, 3H), 7.07 (d, J = 1.31 Hz, 1H), 6.26-6.15 (m, 1H), 5.30 (s, 1H), 3.46-3.36 (m, 2H), 2.24 (s, 3H), 0.94-0.84 (m, 2H), -0.02 (s, 9H).

[00630] **Step 7:** N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1H-imidazol-2-yl)-1,3-thiazol- 2-yl]pyridin-2-yl}acetamide (Compound 60)

[00631] N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)-1,3-thiazol-2-yl]pyridin-2-yl}acetamide (0.120 g, 0.216 mmol) was dissolved in DCM (5 mL) and trifluoroacetic acid (5.0 mL, 65 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated, azeotroped with toluene and purified using column chromatography on silica gel (0 to 10% MeOH in DCM) to give the title compound (0.050 g, 50%). LCMS: (FA) ES+, 426, 428. ^{1}H NMR (400 MHz, d_4-methanol) δ: 8.68 (s, 1H), 8.38 (d, J = 5.24 Hz, 1H), 7.64 (dd, J = 5.25, 1.60 Hz, 1H), 7.45-7.37 (m, 2H), 7.30-7.23 (m, 2H), 7.25-7.09 (m, 2H), 6.37 (s, 1H), 2.20 (s, 3H).

[00632] **Example 22: Synthesis of 3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methyl-5-(piperazin-1-ylmethyl)pyrazolo[1,5-a]pyridine (Compound 72)**



[00633] **Step 1:** 4-(Diethoxymethyl)pyridine:

[00634] p-Toluenesulfonic acid monohydrate (11.8 g, 62.0 mmol) was dissolved in dry ethanol (80 mL) at rt. 4-Pyridinecarboxaldehyde (4.71 mL, 50.0 mmol) was added, followed by ethyl orthoformate

(20.79 mL, 125.0 mmol). The mixture was stirred at rt for 17 hours. The mixture was concentrated and the residue was basified with aqueous saturated $NaHCO_3$ solution to ~pH 8, extracted with EtOAc (150 mL), washed with brine, dried over Na_2SO_4, filtered, evaporated, and dried under high vacuum to give a liquid product. (9.06 g, yield 97.2%). LCMS: (FA) ES^+ 182. ^1H NMR (400MHz, $CDCl_3$) δ: 8.60-8.62 (m, 2H), 7.38-7.40 (m, 2H), 5.50 (s, 1H), 3.53-3.62 (m, 4H), 1.23-1.27 (m, 6H).

[00635] **Step 1A:** N-tert-Butoxycarbonyl-O-(mesitylsulfonyl)hydroxylamine

[00636] tert-Butyl-N-hydroxycarbamate (5.00 g, 37.6 mmol) and mesitylenesulfonyl chloride (8.21 g, 37.6 mmol) were dissolved in 2-methoxy-2-methylpropane (90 mL), flushed with nitrogen and cooled in an ice bath to an internal temperature of 1°C. Triethylamine (5.34 mL, 38.3 mmol) was added dropwise over 25 min during which time the temperature increased to 6°C. The mixture was stirred with cooling for 2 hours at which time the internal reaction temperature was 8°C. The suspension was filtered and the solids were washed with 2-methoxy-2-methylpropane (60 mL). The filtrate was concentrated to ~20 mL volume, diluted with hexane (70 mL) and allowed to sit at rt for 30 min. The resulting crystalline solid was collected by filtration and washed with hexane (20 mL). The mother liquor was evaporated, diluted with hexane (50 mL), and allowed to sit, giving a second crop of crystals. The combined collected solids were dried in vacuum for 1 hour to give a white crystal product (11.06g, yield 93.4%). LCMS: (AA) ES^+ 316 and 333 for M^++NH_3. ^1H NMR (400MHz, $CDCl_3$) δ: 7.54 (s, 1H), 6.99 (s, 2H), 2.68 (s, 6H), 2.32 (s, 3H), 1.31 (s, 9H).

[00637] **Step 2:** 1-Amino-4-(diethoxymethyl)pyridinium 2,4,6-trimethylbenzenesulfonate

[00638] Trifluoroacetic acid (12.0 mL, 156 mmol) was cooled in an ice bath. N-tert butoxycarbonyl-O-(mesitylsulfonyl)hydroxylamine (7.91 g, 25.1 mmol) was portionwise added over 15 min. The mixture was stirred with cooling for 2 hours then ~50 g of ice was added, followed by ~100 mL of ice water. The resulting white solid was collected by filtration and washed with water until the washings were ~pH 6. The solid was dried in air for 15 min to afford a still damp intermediate (6.25 g). The solid then was dissolved in methylene chloride (160 mL, 2500 mmol), dried over Na_2SO_4, and filtered. The filtrate was cooled in an ice bath and a solution of 4-(diethoxymethyl)pyridine (5.91 g, 32.6 mmol) in dry methylene chloride (20 mL, 300 mmol) was slowly added over 10 min. The ice bath was removed and the mixture was stirred at rt for 50 min. The mixture was concentrated to ~30 mL volume. The oily residue was azeotroped with 15 mL of diethyl ether, then the residue was diluted with 250 mL of diethyl ether and cooled in an ice bath for 1 hour, then stored in a freezer (-20°C) overnight. An oily residue appeared. The clear solution was decanted and the oily residue was dried under high vacuum to give a first crop of oily product (2.15g). The decanted solution was concentrated to give an oily residue which was triturated with hexane (2 x 100 mL), then dried under high vacuum to give a second crop of oily product (6.15g, yield 79.7% for 2 crops). LCMS: (FA) ES^+ 197; ES^- 199. ^1H NMR (400MHz, $CDCl_3$) δ: 9.00-9.05 (m, 4H),

7.69-7.71 (m, 2H),6.85 (s, 2H), 5.50 (s, 1H), 3.52-3.57 (m, 4H), 2.67 (s, 6H), 2.25 (s, 3H), 1.22-1.26 (m, 6H).

[00639] **Step 3:** 3-[4-Bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine

[00640] To a mixture of 3-(4-bromo-2-prop-1-yn-1-yl-1,3-thiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazole [Prepared as described in Example 14 (4.37 g, 10.9 mmol)] and potassium carbonate (3.00 g, 21.7 mmol) in dry N,N-dimethylformamide (20.0 mL) was added a solution of 1-amino-4-(diethoxymethyl)pyridinium 2,4,6-trimethylbenzenesulfonate (6.37 g, 15.6 mmol) in dry N,N-dimethylformamide (20.0 mL) over 10 min. The resulting dark brown solution was stirred at rt for 40 hours. The mixture was added to ~250 mL of ice water with stirring, then was extracted with EtOAc (100 mL x 5) until the aqueous layer turned into a clear solution. The combined EtOAc extracts were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography on silica gel, using EtOAc/hexane (0/100 to 50/50) as an eluant to give a solid product (4.56g, 70.2%). LCMS: (FA) ES^+ 593, 595. ^1H NMR (400MHz, $CDCl_3$) δ: 8.46 (d, J = 2.01 Hz, 1H), 8.40-8.42 (d, J = 7.28 Hz, 1H), 8.32 (s, 2H), 7.05-7.08 (dd, J = 2.01, 7.03 Hz, 1H),5.57(s, 2H)3.68-3.77 (m, 4H), 3.58-3.63 (m, 2H), 2.75 (s, 3H), 1.28-1.32 (m, 6H), 0.95-1.00 (m, 2H),0.02 (s, 9H)

[00641] **Step 4:** 3-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine

[00642] A mixture of 3-[4-bromo-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine (0.907 g, 1.53 mmol) and bis(tri-t-butylphosphine)palladium(0) (39.0 mg, 0.0764 mmol) in a 40 mL vial was evacuated under low vacuum and backfilled with nitrogen four times. 4-Chlorobenzylzinc chloride in tetrahydrofuran (0.50 M, 7.0 mL, 3.5 mmol) was added and the solution was again evacuated under low vacuum and backfilled with nitrogen twice. The solution was heated to 60°C for 4 hours. The reaction mixture was cooled to rt, quenched with water, adjusted to ~ pH 6 with acetic acid, and extracted with EtOAc (2x). The organic layers were combined, washed with water, brine, dried over Na_2SO_4, filtered and evaporated to give a crude residue which was purified by column chromatography on silica gel column using EtOAc/hexane (0/100 to 40/60) as an eluant to give a solid product (0.806g, 85% pure by 1H-NMR, yield 70.5%). LCMS: (FA) ES^+ 639, 641. ^1H NMR of pure fraction (400MHz, $CDCl_3$) δ: 8.36-8.39 (m, 2H), 8.27 (s, 1H), 7.45-7.47 (m, 2H), 7.23-7.25 (m, 2H), 6.99-7.01 (m, 1H),5.54 (s, 2H, 5.50 (s, 1H), 4.67 (s, 2H), 3.66-3.74 (m, 4H), 3.57-3.62 (m, 2H), 2.74 (s, 3H), 1.26-1.30 (m, 6H), 0.95-0.99 (m, 2H),0.00 (s, 9H).

[00643] **Step 5:** 3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine-5-carbaldehyde

[00644] 3-[4-(4-Chlorobenzyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-5-(diethoxymethyl)-2-methylpyrazolo[1,5-a]pyridine (1.17 g, 1.83 mmol) was dissolved in 1,4-dioxane (45 mL) and cooled in a water bath. 12 M hydrochloric acid (15 mL) was added and the mixture was stirred at rt for 15 hours. Acetic acid (40 mL, 700 mmol) was added and the suspension was stirred at rt for 24 hours then heated to 70° C for 2 hours, then evaporated. The solid residue was stirred with 1.00 hydrochloric acid (100 mL) and methanol (120 mL) at rt for 14 hours. The mixture was evaporated on a rotovap at 45°C to dryness and then azeotroped with DCM to give a crude product. The crude product was suspended in water, basified with $NaHCO_3$ to ~pH 8, extracted with EtOAc (300 mL, 3 x 80 mL), washed with brine, dried over Na_2SO_4, filtered, and evaporated to afford a yellow solid product (0.773 g, yield 97.2%). LCMS: (FA) ES^+ 435, 437. ^1H NMR (400MHz, $CDCl_3$) δ: 10.84 (s, br, 1H), 9.99 (s, 1H), 8.75 (m, 1H), 8.43-8.46 (d, J = 7.28 Hz, 1H), 8.36 (s, 1H), 7.41-7.44 (d, J = 8.53 Hz, 2H), 7.32-7.35 (dd, J = 7.03, 2.01 Hz, 1H), 7.27-7.30 (d, J = 8.53 Hz, 2H), 4.69 (s, 2H), 2.79 (s, 3H).

[00645] **Step 6:** tert-Butyl 4-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)piperazine-1-carboxylate

[00646] A mixture of 3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine-5-carbaldehyde (0.0563 g, 0.109 mmol), tert-butyl 1-piperazinecarboxylate (60.8 mg, 0.326 mmol) and acetic acid (0.0800 mL, 1.41 mmol)in dry methylene chloride (10 mL) was stirred at rt for 15 min. Sodium triacetoxyborohydride (69.1 mg, 0.326 mmol) was added and the mixture was stirred at rt for 15 hours. The mixture was washed with saturated $NaHCO_3$ solution and the aqueous layer was extracted with DCM. The DCM extract was washed with water, brine, dried over Na_2SO_4, filtered and evaporated to give a crude product which was purified by column chromatography on silica gel column using MeOH/DCM (0/100 to 5/95) to give solid product (0.0464g, yield 70.5%). LCMS: (FA) ES^+ 605, 607; ES^- 603, 605. ^1H NMR (400MHz, $CDCl_3$ and d_4-methanol) δ: 8.23-8.25 (d, J = 7.03 Hz, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.29-7.31 (d, J = 8.28 Hz, 2H), 7.15-7.17 (d, J = 8.53 Hz, 2H), 6.86-6.89 (dd, J = 7.28, 1.76 Hz, 1H), 4.53 (s, 2H), 3.45 (s, 2H), 3.33-3.36 (m, 4H), 2.62 (s, 3H), 2.35 (s, br, 4H), 1.37 (s, 9H).

[00647] **Step 7:** 3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methyl-5-(piperazin-1-ylmethyl)pyrazolo[1,5-a]pyridine (Compound **72**)

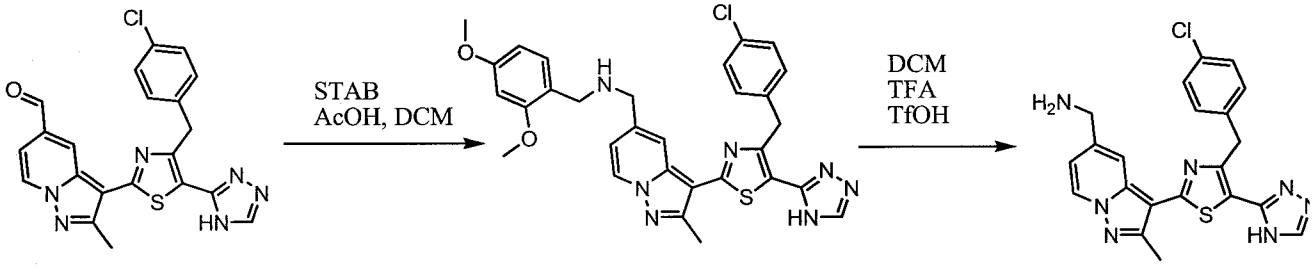
[00648] To a solution of tert-butyl 4-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)piperazine-1-carboxylate (0.0435 g, 0.0719 mmol) in methylene chloride (2.0 mL) and methanol (2.0 mL) was added 4 M hydrochloric acid in 1,4-dioxane (2.0 mL, 7.8 mmol). The mixture was stirred at rt for 5 hours then was evaporated, azeotroped with MeOH, and dried under high vacuum to give a solid (~50 mg). The solid was triturated with diethyl ether (10 ml x 2) then dried under high vacuum to give product as a pale yellow powder (0.0424g, yield 100%) as a bis

HCl salt. LCMS: (FA) ES^+ 505, 507; ES^- 503, 505. ^1H NMR (400MHz, d_4-methanol) δ: 8.71 (s, 1H), 8.62-8.64 (d, J = 7.03 Hz, 1H), 8.41 (s, 1H), 7.39-7.41 (d, J = 8.78 Hz, 2H), 7.27-7.29 (d, J = 8.53 Hz, 2H), 7.20-7.23 (dd, J = 7.03, 2.01 Hz, 1H), 4.66 (s, 2H), 4.38 (s, 2H), 3.54 (s, br, 4H), 3.43 (s, br, 4H), 2.73 (s, 3H).

[00649] Compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 22:

31	LCMS: (FA) ES+ 570, 572.
32	LCMS: (FA) ES+ 526, 528.
38	LCMS: (FA) ES+ 493, 495.
54	LCMS: (FA) ES+ 479, 481.
61	LCMS: (FA) ES+ 519, 521.
82	LCMS: (FA) ES+ 579, 581.
83	LCMS: (FA) ES+ 569, 571.

[00650] **Example 23: Synthesis of 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (Compound 1)**



[00651] **Step 1:** 1-{3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}-N-(2,4-dimethoxybenzyl)methanamine

[00652] To a suspension of 3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridine-5-carbaldehyde (0.300 g, 0.690 mmol) in acetic acid (0.20 mL, 3.5 mmol) and dry methylene chloride (10 mL, 200 mmol) was added 2,4-dimethoxybenzylamine (0.207 mL, 1.38 mmol), followed by additional of sodium triacetoxyborohydride (0.363 g, 1.71 mmol). The mixture was stirred at rt. for 16 hours. The mixture was basified with $NaHCO_3$ solution to ~pH 8 then extracted with DCM. The DCM solution was washed with water. The crude product was purified by column chromatography (SiO2, elution with 0-100% MeOH in DCM) to afford a solid product (0.252 g, yield

62%). LCMS: (FA) ES^+ 586, 588; ES^- 584, 586. ^1H NMR (400MHz, $CDCl_3$ and d_4-methanol) δ: 8.23-8.25 (d, J = 7.03 Hz, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.28-7.30 (d, J = 8.53 Hz, 2H), 7.09-7.11 (d, J = 8.53 Hz, 2H), 7.01-7.03 (d, J = 8.28 Hz, 1H), 6.78-6.80 (d, J = 7.03 Hz, 1H), 6.33-6.37 (m, 2H), 4.53 (s, 2H), 3.65 (s, 2H), 3.64 (s, 6H), 3.61 (s, 2H), 2.61 (s, 3H).

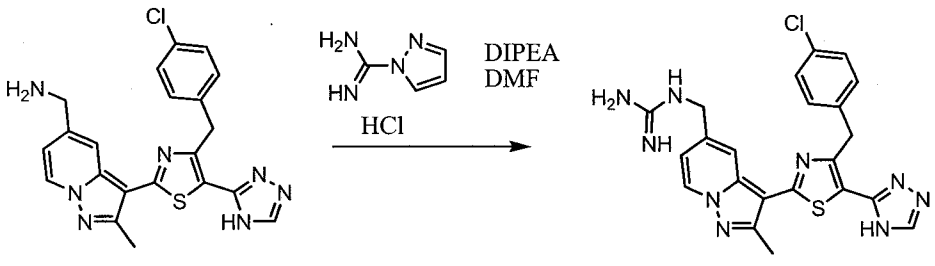
[00653] **Step 2:** 1-{3-[4-(4-Chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (Compound **1**)

[00654] 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}-N-(2,4-dimethoxybenzyl)methanamine (0.257 g, 0.438 mmol) was dissolved in methylene chloride (6.0 mL) and trifluoroacetic acid (6.0 mL). Trifluoromethanesulfonic acid (0.050 mL, 0.56 mmol) was added and the mixture was heated to 60°C for 6 days. The mixture was evaporated in a rotary evaporator, azeotroped with EtOAc (3 x), and evaporated to give a crude residue. The residue was suspended in ~1 mL of MeOH and diluted with ~20 mL of Et_2O. The resulting powder was collected by filtration and dried under high vacuum to afford a pale pink solid product. The solid was taken up in EtOAc / water (20 mL / 10 mL) and adjusted to ~pH 8 with $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with EtOAc (2x30 mL). The combined EtOAc solutions were washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to ~5 mL volume and the precipitated solid was collected by filtration to give a pure crop of product (0.0069 g). The filtrate was evaporated then dried under high vacuum to afford a second crop of solid product (0.171g, yield for 2 crops 89.9%). LCMS: (FA) ES^+ 436, 438; ES^- 434, 436. ^1H NMR (400MHz, d_4-methanol) δ: 8.33-8.35 (d, J = 7.29 Hz, 1H), 8.24 (s, 1H), 8.09 (s, 1H), 7.31-7.33 (d, J = 8.78 Hz, 2H), 7.20-7.22 (d, J = 8.53 Hz, 2H), 6.98-7.00 (m, 1H), 4.59 (s, 2H), 4.06 (s, 2H), 2.67 (s, 3H).

[00655] Compound in the following table was prepared from the appropriate starting materials in a method analogous to that of Example 23:

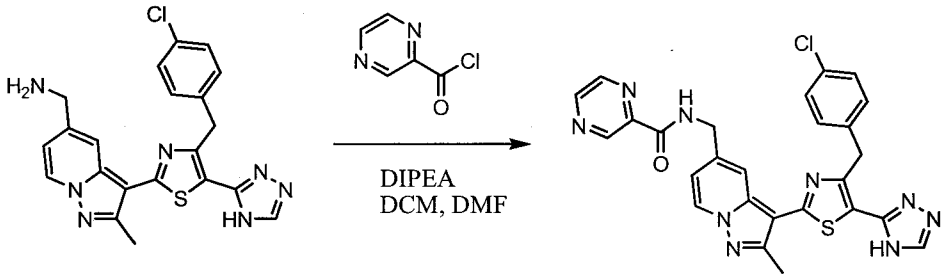
20	LCMS: (FA) ES+ 586, 588.

[00656] **Example 24: Synthesis of N-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)guanidine (Compound 35)**



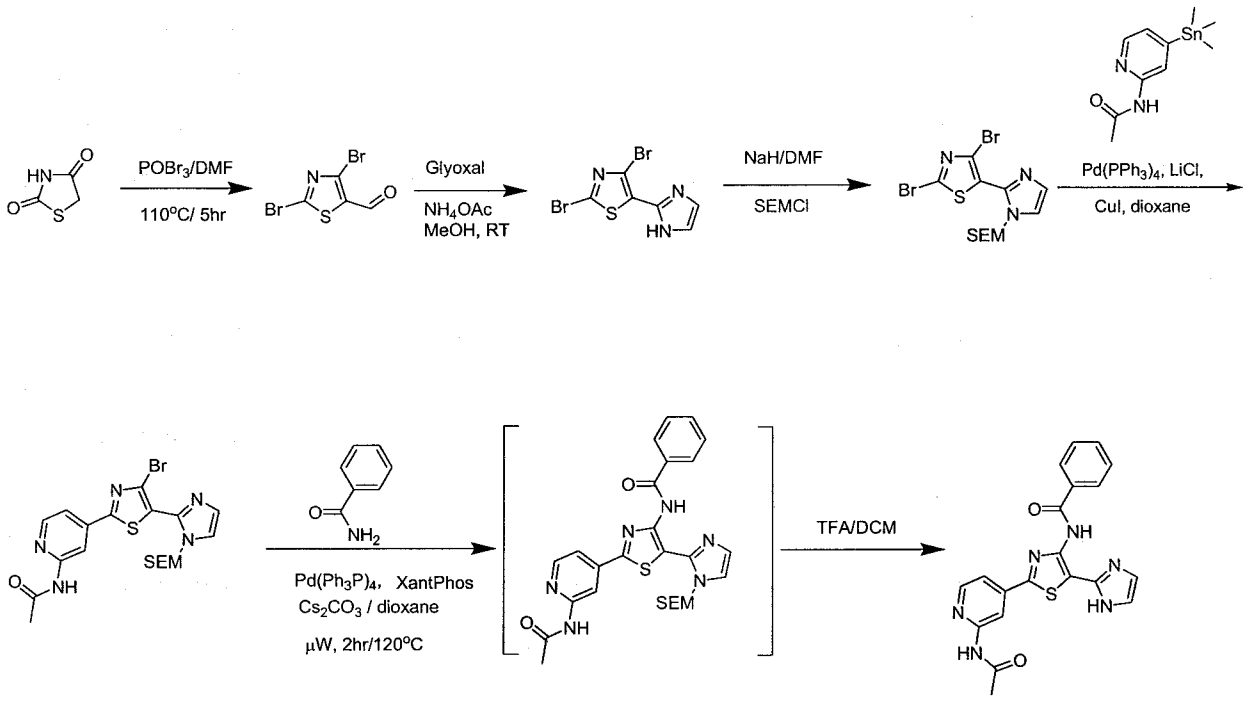
[00657] To a mixture of 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (0.0250 g, 0.0553 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (8.20 mg, 0.0559 mmol) in dry N,N-dimethylformamide (0.50 mL) was added N,N-diisopropylethylamine (7.15 mg, 0.0553 mmol). The solution was stirred at rt for 23 hours. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (5 x 15 mL). The EtOAc solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated in a rotary evaporator to give a crude residue. The residue was dissolved in ~0.2 mL of MeOH, then diluted with ~5 mL of EtOAc. The resulting solid was collected by filtration to give a pale yellow powder product (0.008 g, 30%). LCMS: (FA) ES^+ 478, 480; ES^- 476, 478. ^1H NMR (400MHz, $CDCl_3$ and d_4-methanol) δ: 8.25-8.27 (d, J = 7.28 Hz, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.21-7.23 (d, J = 8.53 Hz, 2H), 7.08-7.10 (d, J = 8.28 Hz, 2H), 6.72-6.74 (dd, J = 7.28, 1.76 Hz, 1H), 4.48 (s, 2H), 4.30 (s, 2H), 2.57 (s, 3H).

[00658] Example 25: Synthesis of N-({3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methyl)pyrazine-2-carboxamide (Compound 50)



[00659] A mixture of 1-{3-[4-(4-chlorobenzyl)-5-(4H-1,2,4-triazol-3-yl)-1,3-thiazol-2-yl]-2-methylpyrazolo[1,5-a]pyridin-5-yl}methanamine (0.0222 g, 0.0491), pyrazine-2-carboxylic acid chloride (8.0 mg, 0.056 mmol) and N,N-diisopropylethylamine (10 mg, 0.08 mmol) in dry Methylene chloride (5.0 mL) in dry N,N-dimethylformamide (1.0 mL) was sonicated for 2 min. The mixture was stirred at rt for 22 hours. N,N-diisopropylethylamine (13 mg, 0.10 mmol) and pyrazine-2-carboxylic acid chloride (9.11 mg, 0.0639 mmol) were added and the mixture was stirred at rt for 3 days. The mixture was quenched with water, then extracted with DCM (3 x 30 mL). The combined DCM solutions were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated to give a crude product (80 mg). The crude product was purified by HPLC to give a solid product (0.0007 g, yield 3%). LCMS: (AA) ES^+ 542, 544. ^1H NMR (400MHz, d_6-DMSO) δ: 9.72-9.74 (d, J = 6.53 Hz, 1H), 9.23 (s, 1H), 8.87 (s, 1H), 8.75 (s, 1H), 8.67-8.69 (d, J = 6.53 Hz, 1H), 8.63 (s, 1H), 8.22 (s, 1H), 7.24-7.30 (m, 4H), 7.03-7.05 (d, J = 7.28 Hz, 1H), 4.62-4.64 (d, J = 6.78 Hz, 2H), 4.47 (s, 2H), 2.63 (s, 3H).

[00660] Example 26: Synthesis of N-(2-(2-acetamidopyridin-4-yl)-5-(1H-imidazol-2-yl)thiazol-4-yl)benzamide (Compound 29)



[00661] **Step 1:** 2,4-Dibromo-thiazole-5-carbaldehyde

[00662] 2,4-Thiazolidinedione (3.50 g, 0.0299 mol) and phosphorus oxybromide (42.76 g, 0.1491 mol) were placed into a two-neck round bottomed flask and the solid mixture was well mixed. The flask was evacuated and filled with argon. N,N-dimethylformamide (2.54 mL, 0.0329 mol) was added via syringe with hand shaking of the flask at the sametime. The mixture was stirred at rt for 2 hours and then heated slowly to 105°C, until the evolution of hydrogen bromide had ceased, (approximately 4h). The reaction was cooled to rt then the mixture was transferred to a beaker containg 200g of ice. The aqueous mixture was stirred with DCM then filtered. The DCM phase was separated and the aqueous phase was extracted with DCM twice. THe DCM layers were combined and washed with saturated sodium bicarbonate solution, then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The mixture was dry loaded on silica gel and purified by chromatography to afford 2,4-dibromo-thiazole-5-carbaldehyde (2.50g, 30.9%). LCMS (FA) ES+ 272, 274.

[00663] **Step 2:** 2,4-Dibromo-5-(1H-imidazol-2-yl)thiazole

[00664] 2,4-Dibromo-thiazole-5-carbaldehyde (14.8 g, 54.6 mmol), hexahydro-[1,4]dioxino[2,3-b][1,4]dioxine-2,3,6,7-tetraol (22.96 g, 109.2 mmol), and ammonium acetate (25.26 g, 327.8 mmol) were added to a round bottomed flask followed by methanol (450 mL, 11000 mmol). The mixture was stirred and acetic acid (31.06 mL, 546.3 mmol) was added. The reaction was stirred overnight then the reaction mixture was concentrated under vaccuum to provide a thick liquid mixture. Toluene (100mL) was then added and reevaporated and this process was repeated several times to give a dark brown solid. Methanol

was added and the mixture was loaded on silica gel. Purification by column chromatography on silica gel afforded 2,4-dibromo-5-(1H-imidazol-2-yl)thiazole (9.12g, 54%). LCMS (AA) ES+ 310, 312, 308.

[00665] **Step 3:** 2,4-Dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole

[00666] To a mixture of sodium hydride (2.89 g, 72.2 mmol) in tetrahydrofuran (431 mL, 5310 mmol) was added 2,4-dibromo-5-(1H-imidazol-2-yl)thiazole (18.81 g, 60.88 mmol) in tetrahydrofuran (60 mL, 700 mmol) at 0°C . The mixture was stirred for 30 min before [β-(Trimethylsilyl)ethoxy]methyl chloride (11.85 mL, 66.96 mmol) in tetrahydrofuran (24 mL, 3.0E2 mmol) was added slowly at 0°C . The reaction was quenched with MeOH. The solvent was evaporated and the residue was purified by column chromatography on silica gel to afford 2,4-dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole (13.6g, 81.7%). LCMS (AA) ES+ 440, 442.

[00667] **Step 4:** N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol- 2-yl)pyridin-2-yl)acetamide

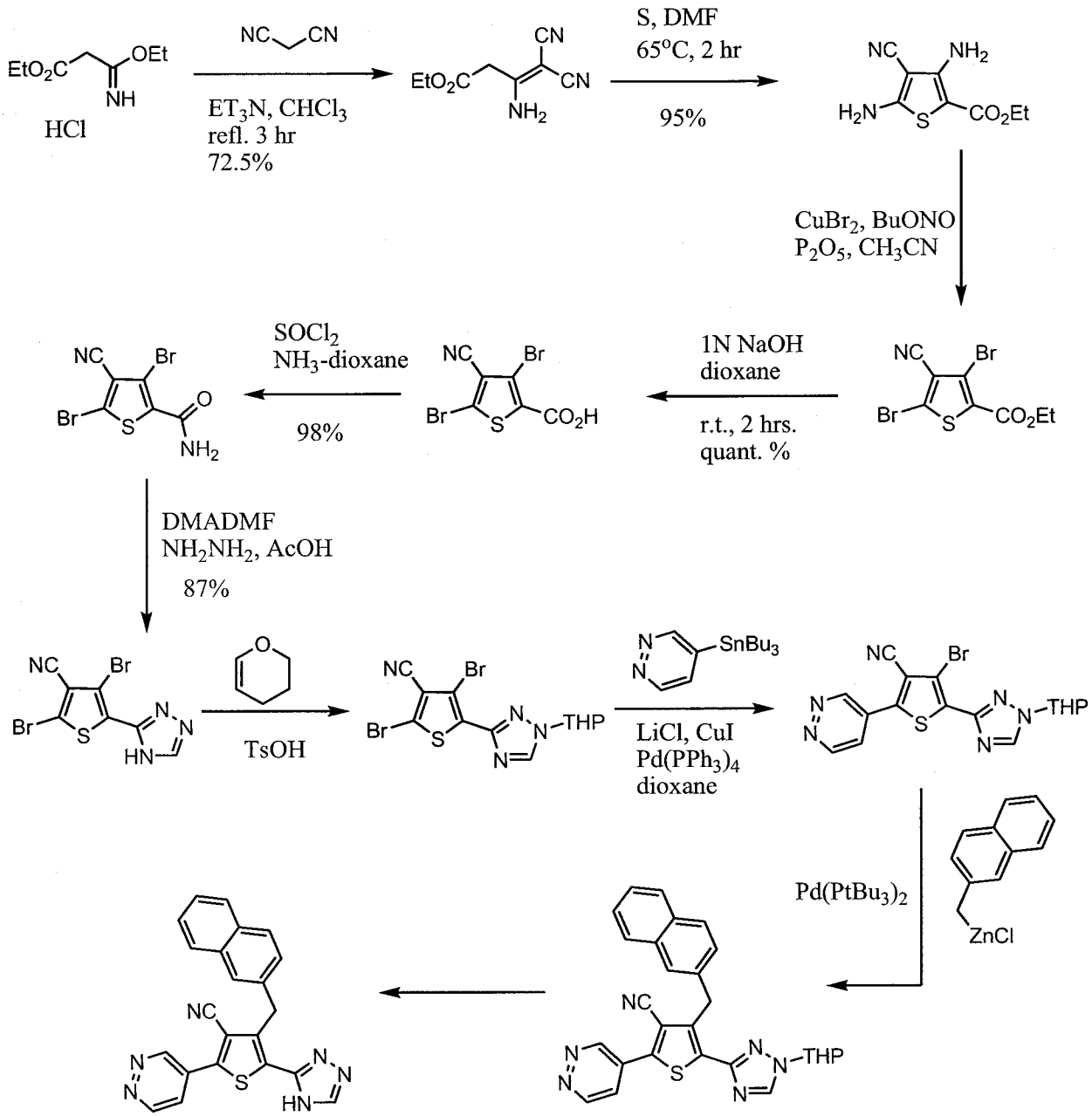
[00668] A mixture of 2,4-dibromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazole (13.62 g, 31.01 mmol), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (11.1 g, 37.2 mmol), tetrakis(triphenylphosphine)palladium(0) (1.792 g, 1.550 mmol), copper(I) iodide (1.772 g, 9.302 mmol) and lithium chloride (3.944 g, 93.02 mmol) in 1,4-dioxane (569 mL, 7290 mmol) was degassed and filled with argon three times. The mixture was sonicated for 20min and then heated at 120°C for 5h. The reaction mixture was dry loaded onto a silica gel column and purified by chromatography to afford N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol- 2-yl)pyridin-2-yl)acetamide as an orange solid. LCMS (AA) ES+ 494, 496.

[00669] **Step 5:** N-(2-(2-acetamidopyridin-4-yl)-5-(1H-imidazol-2-yl)thiazol-4-yl)benzamide (Compound **29**).

[00670] A mixture of N-(4-(4-bromo-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)thiazol-2-yl)pyridin-2-yl)acetamide (80.9 mg, 0.164 mmol), benzamide (99.1 mg, 0.818 mmol), tris(dibenzylideneacetone)dipalladium(0) (21.3 mg, 0.0233 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (39.9 mg, 0.0690 mmol) and cesium carbonate (303 mg, 0.930 mmol) in 1,4-dioxane (7.66 mL, 98.2 mmol) was evacuated then filled with argon and then irradiated in microwave at 130°C for 3h. The reaction mixture was filtered and the filtrate was purified by column chromatography to afford the desired intermediate. LCMS (AA) ES+ 535, 536. To the above intermediate were added methylene chloride (1.2 mL, 19 mmol) and trifluoroacetic acid (1.8 mL, 23 mmol). The mixture was stirred at rt for 2h. The excess trifluoroacetic acid and solvent was evaporated and the residue was purified by HPLC to afford N-(2-(2-acetamidopyridin-4-yl)-5-(1H-imidazol-2-yl)thiazol-4-yl)benzamide (11.3mg, 17.1%). LCMS (FA) ES+ 406, 407; ^{1}H NMR (300 MHz, d_4-methanol) δ: 8.67 (d, J = 0.45 Hz, 1H), 8.40 (d, J =

5.23 Hz, 1H), 8.17-8.07 (m, 2H), 7.84-7.78 (m, 1H), 7.59 (dd, J = 13.90, 7.27 Hz, 3H), 7.22 (s, 2H), 2.22 (s, 3H).

[00671] Example 27: Synthesis of 4-(2-naphthylmethyl)-2-pyridazin-4-yl-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound 88)



[00672] Step 1: Ethyl 3-amino-4,4-dicyano-3-butenoate

[00673] Ethyl 3-ethoxy-3-iminopropionate hydrochloride (166 g, 721 mmol.) was suspended in dry methylene chloride (400 mL, 6000 mmol). Malononitrile (46.7 g, 707 mmol) was added, followed by

Triethylamine (1.00 mL, 721 mmol). The mixture was heated to reflux for 3 hours. The mixture was cooled to rt then quenched with 200 mL of water. The separated organic layer was washed with 2x200 mL of water. The combined aqueous layers were extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was further azeotroped with MTBE (2x200 mL) and ethyl acetate (70 mL). The residue was diluted with 70 mL of EtOAc. A precipitate appeared and the solid was collected by filtration and washed with ~20 mL of EtOAc until the pink-red color of the solid faded to give a first crop of product (32 g). The filtrate was concentrated in rotary evaporator and dried under high vacuum to a weight of ~110 g. More precipitate appeared after the concentrated filtrate sat for 1 hour. Approximately 50 mL of Et_2O was added and the mixture was allowed to sit overnight. The resulting precipitate was collected by filtration and washed with Et_2O to afford a second crop of solid product (20.59 g). The filtrate was concentrated in a rotary evaporator to give an oily residue. Chromatography on a silica column using EtOAc/hexane (short gradient from 0/100 to 50/50 then stayed on 50/50 for 100 min, with 120 mL/min flow rate) afforded a third crop of pure product (39.3 g, yield for all crops was 72.5%). LCMS: (FA) ES- 178. ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.57 (s, br, 1H), 6.33 (s, br, 1H),4.24-4.30 (q, 2H), 3.63 (s, 2H), 1.31-1.35 (t, 3H).

[00674] **Step 2:** Ethyl 3,5-diamino-4-cyanothiophene-2-carboxylate

[00675] The mixture of ethyl 3-amino-4,4-dicyano-3-butenoate (91.9 g, 513 mmol) and sulfur (16.4 g, 513 mmol) in dry N,N-dimethylformamide (200 mL, 3000 mmol) was coooled in a water bath. Diethylamine (106 mL, 1020 mmol) was slowly added during which time the internal reaction temperature increased to 43°C. The dark-brown solution was then cooled in ice bath to rt (22°C) then the ice bath was removed. The mixture was stirred at rt for 3 hours. The mixture was poured into ice water (~1.4 L) and the resulting suspension was allowed to sit overnight.. The solid was collected by filtration and washed with 200 mL of water thoroughly to give a wet solid. The solid was stirred with 1.5 L of EtOAc at rt overnight, then filtered. The filtrate (EtOAc-water bilayer) was separated. The solid cake was dissolved in 1.2 L of EtOAc. The combined EtOAc solutions were washed with brine, dried over anhydrous Na_2SO_4, filtered, rotavaped and dried under high-vacuum overnight to give a dry powder product (102.6 g, yield 94.7%). LCMS: (FA) ES+ 212, ES- 210. ^{1}H NMR (400MHz, $CDCl_3$ and *d4*-methanol) δ: 4.14 (m, 2H), 1.21-1.25 (t, 3H).

[00676] **Step 3:** Ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate

[00677] Ethyl 3,5-diamino-4-cyanothiophene-2-carboxylate (25.0 g, 118 mmol) was dissolved in acetonitrile (500 mL, 10000 mmol). Copper(II) Bromide (105.7 g, 473.4 mmol) was added, followed by phosphorus pentoxide (6.72 g, 23.7 mmol). The mixture was stired at room temperature for 30 min, then cooled to 0°C. Butyl nitrite (56.4 mL, 473.4 mmol) was slowly added. After the completion of the

addition the mixture was heated to reflux for 1 h then cooled to room temperature. The reaction mixture was poured into 500 mL 4N HCl solution, then extracted with 500 mL DCM twice. The insoluble material was filtered off from the organic layer. The organic filtrate was dried over MgSO4, and filtered. The filtate was concentrated and purified by column chromatograph in silica gel, using the eluent of 0-6% ethyl acetate in hexane. The fractions containing product were collected and concentrated to give a suspension. The solid was collected by filtration to afford a pure product (14.45 g, yield 36.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.37-4.42 (q, 2H), 1.38-1.41 (t, 3H).

[00678] **Step 4:** 3,5-dibromo-4-cyanothiophene-2-carboxylic acid

[00679] Ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate (6.54 g, 0.0193 mol) was dissolved in a mixture of tetrahydrofuran (40.0 mL, 0.493 mol) and methanol (20.0 mL, 0.494 mol), then sodium hydroxide in water (1.0 M, 60.0 mL, 0.0600 mol) was added at 0°C. The resulting solution was warmed to rt and stirred for 20 min. The mixure was neuturalized with hydrochloric acid in water (4.0 M, 20 mL, 0.080 mol) and extracted with 80 mL DCM twice. The combined organic layesr were washed with 30 mL water, evaporated in vacuo to yield a white solid product (5.96 g, yield 99.4%). LCMS: (FA) ES-, 307, 309, 311.

[00680] **Step 5:** 3,5-Dibromo-4-cyanothiophene-2-carboxamide

[00681] 3,5-Dibromo-4-cyanothiophene-2-carboxylic acid (5.90 g, 18.6 mmol) was added to a solution of thionyl chloride (27.1 mL, 371 mmol) in acetonitrile (40.0 mL, 766 mmol). The mixture was refluxed for 30 min then cooled to rt. The solvent was evaporated in vacuo to dryness to yield a lightly yellow solid. Methylene chloride (100 mL, 2000 mmol) was added to dissolve the solid, then the solution was cooled to 0°C. Under a nitrogen atmosphere, a solution of 0.500 M ammonia in 1,4-dioxane(111.5 mL, 55.7 mmol) was slowly added, and the mixture was brought to room temperature for 1 h. The mixture was evaporated in vacuo to give a solid residue. 100 mL of 1N HCl was added and the suspension was stirred for 1 h at room temperature. The solid product was collected by filtration and dried under high vacuum to give product (5.64 g, yield 98%). LCMS: (FA) ES-, 308, 310, 312.

[00682] **Step 6:** 2,4-Dibromo-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile

[00683] 3,5-Dibromo-4-cyanothiophene-2-carboxamide (5.90 g, 19.0 mmol) was suspended in dry Toluene (250 mL, 2300 mmol). 1,1-Dimethoxy-N,N-dimethylmethanamine (10.1 mL, 76.1 mmol) was added and the mixture ws heated to 90°C for 1 hour. The mixture was cooled to rt then rotavaped to dryness to give a crude intermediate. The intermediate was suspended in acetic acid (150 mL, 2600 mmol). Hydrazine hydrate (5.78 mL, 76.1 mmol) was added dropwise and the temperature was raised to 55°C. The mixture was stirred at the same temperature for 2 hours. The suspension was then evaporated to remove most of acetic acid. The resulting solid was collected by filtration and dried under vaccumn to

give a product (5.54 g, yield 87.2%). LCMS: (FA) ES-, 331, 333, 335. ^{1}H NMR (300 MHz, *d6*-dmso) δ: 14.2 (s, br, 1H), 8.65 (s, 1H).

[00684] **Step 7:** 2,4-Dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile

[00685] 2,4-Dibromo-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (0.80 g, 2.4 mmol) was placed in a 500 mL round bottom flask and tetrahydrofuran (50 mL, 600 mmol) was added. To the resulting solution were added dihydropyran (1.31 mL, 14.4 mmol) and p-toluenesulfonic acid monohydrate (0.683 g, 3.59 mmol). The mixture was stirred for 3h at rt. The solution was then poured into 20 mL water and extracted with 40 mL ethyl acetate twice. The combined organic layers were evaporated in vacuo. The residue was purified by column chromtagraphy using 0-35% EtOAc in hexane to afford a solid product (0.842 g, yield 84%). LCMS: (AA) ES+, 417, 419, 421. ^{1}H NMR (300MHz, $CDCl_3$) δ: 8.38 (s, 1H), 5.55-5.60 (m, 1H), 4.06-4.10 (m, 1H), 3.68-3.78 (m, 1H), 2.15-2.28 (m, 1H), 2.01-2.13 (m, 2H), 1.66-1.80 (m, 3H).

[00686] **Step 8:** 4-Bromo-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile

[00687] A mixture of 2,4-dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (0.248 g, 0.594 mmol), 4-(tributylstannyl)pyridazine (2.30 mg, 0.624 mmol), copper(I) iodide (34.0 mg, 0.178 mmol), lithium chloride (75.6 mg, 1.78 mmol) and tetrakis(triphenylphosphine)palladium(0) (34.3 mg, 0.0297 mmol) in dry 1,4-dioxane (5.0 mL, 64 mmol) was sonicated under a nitrogen atmosphere for 2 min then heated in a capped vial to 130°C in microwave machine for 20 mins. The suspension was cooled to rt, diluted with 20% MeOH/DCM (~100 mL), treated with 12 g of silica gel then rotavaped and dried under high vacuum. The coated silica gel was chromatographed on a silica column eluting with MeOH/DCM (0/100 to 5/95) to afford a solid product (0.143 g, yield 57.7%). LCMS: (AA) ES+, 417, 419. ^{1}H NMR (300MHz, $CDCl_3$) δ: 9.55 (s, 1H), 9.37-9.39 (m, 1H), 8.40 (s, 1H), 7.69-8.00 (m, 1H), 5.55-5.60 (m, 1H), 4.08-4.13 (m, 1H), 3.73-3.81 (m, 1H), 2.18-2.30 (m, 1H), 2.03-2.16 (m, 2H), 1.68-1.82 (m, 3H).

[00688] **Step 9:** 4-(2-Naphthylmethyl)-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile.

[00689] Bis(tri-t-butylphosphine)palladium(0) (4.92 mg, 0.00963 mmol), 4-bromo-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (0.0402 g, 0.0963 mmol), 2-naphthylmethylzinc bromide in tetrahydrofuran (0.50M, 0.578 mL, 0.289 mmol) and tetrahydrofuran (4.0 mL, 49 mmol) were added to a microwave tube. The tube was sealed under a nitrogen atmosphere and heated at 70°C for 2 h then cooled to rt. The mixture was concentrated in vacuo and the residue was

purified by chromatography on a silica gel column eluting with 0-100% EtOAc in hexane to afford a solid product (0.0332 g, yield 72 %). LCMS: (AA) ES+, 479. ^{1}H NMR (300MHz, *d4*-methanol) δ: 9.63 (s, 1H), 9.28-9.35 (m, 1H), 8.68 (s, 1H), 8.13-8.15 (m, 1H), 7.69-8.00 (m, 4H), 7.37-7.48 (m, 3H), 5.62-5.66 (m, 1H), 3.94-4.08 (m, 1H), 3.69-3.80 (m, 1H), 3.30 (s, 2H), 2.07-2.22 (m, 1H), 1.95-2.07 (m, 2H), 1.61-1.79 (m, 3H).

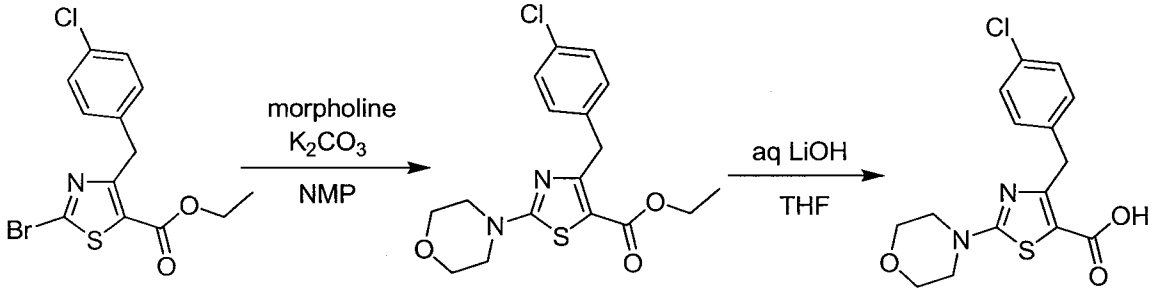
[00690] **Step 10:** 4-(2-naphthylmethyl)-2-pyridazin-4-yl-5-(4H-1,2,4-triazol-3-yl)thiophene-3-carbonitrile (Compound **88**)

[00691] 4-(2-Naphthylmethyl)-2-pyridazin-4-yl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (0.03178 g, 0.06641 mmol) was dissolved in methanol (3.00 mL, 74.0 mmol). HCl in water (12 M, 3.00mL, 36.0 mmol) was added. The solution was heated at 50°C for 60 min then cooled to rt. The mixture was evaporated in vacuo to remove the most of methanol. To the residue was added 30 mL saturated sodium bicarbonate solution, extracted with 40 mL ethyl acetate twice. The combined EtOAc layers were washed with 20 mL water then concentrated in vacuo. The resulting crystalline solid was collected by filtration to afford a pure product (0.0158 g, yield 60.3%). LCMS: (AA) ES+ 395. ^{1}H NMR (300MHz, *d4*-methanol) δ: 9.60 (s, 1H), 9.27-9.29 (m, 1H), 8.47 (s, 1H), 8.09-8.11 (m, 1H), 7.69-7.77 (m, 4H), 7.37-7.47 (m, 3H), 3.30 (s, 2H).

[00692] The compound in the following table was prepared from the appropriate starting materials in a method analogous to that of Example 27:

89	LCMS: (FA) ES+ 379, 381.

[00693] **Example 28: Synthesis of 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylic acid (Compound 91)**



[00694] **Step 1, Preparation of ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate.**

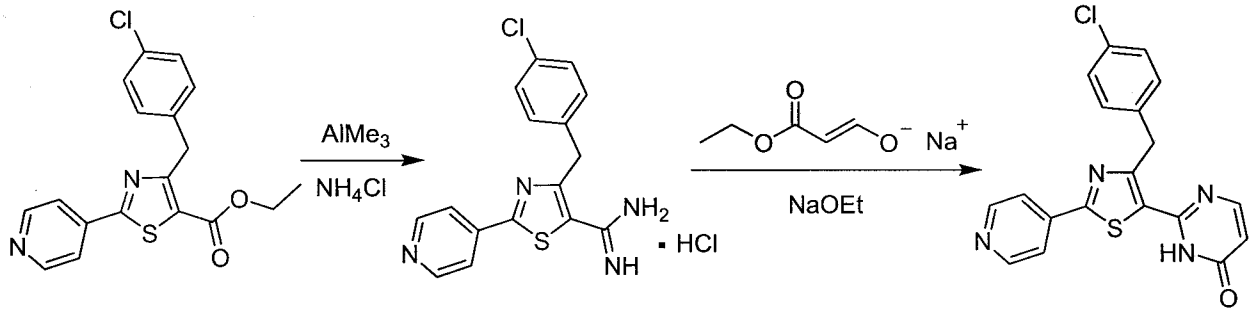
[00695] To a solution of ethyl 2-bromo-4-(4-chlorobenzyl)thiazole-5-carboxylate (4.19 g, 11.6 mmol, prepared as described in Example 10) in N-methylpyrrolidinone (12.2 mL) was added potassium carbonate (3.21 g, 23.2 mmol) and morpholine (1.52 mL, 17.4 mmol) and the resulting mixture was heated to 130 degrees for 90 minutes. The reaction was cooled and the volatiles were removed by

concentration at 65 degrees under oil pump vacuum. The residue was taken up in DCM (100 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with DCM (50 mL). The combined DCM layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→35/65) to give 3.44 g of the title compound as a white solid. (80 % yield). LC/MS (FA) ES+ 367. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.27 (m, 2H), 7.24-7.20 (m, 2H), 4.28 (s, 2H), 4.27 (q, 2H, J = 7.2 Hz), 3.80-3.76 (m, 4H), 3.53-3.48 (m, 4H), 1.32 (t, 3H, J = 7.2 Hz).

[00696] Step 2, Preparation of 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylic acid. (Compound 91)

[00697] To a solution of ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate (3.44 g, 9.38 mmol) in THF (53 mL) was added water (26 mL) and 1 N LiOH (28.2 mL, 28.2 mmol) and the resulting mixture was heated to 40 degrees overnight. The reaction was cooled, acidified with 1 N HCl, and extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by silica gel chromatography (methanol/DCM = 0/100→20/80). Recrystallization from ethyl acetate/hexanes gave 1.3 g of the title compound as a white solid. (41 % yield). LC/MS (FA) ES+ 339. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.74 (s, 1H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 2H), 4.21 (s, 2H), 3.67-3.64 (m, 4H), 3.42-3.40 (m, 4H).

[00698] Example 29: Synthesis of 2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-4(3H)-one (Compound 92)



[00699] Step 1, Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride

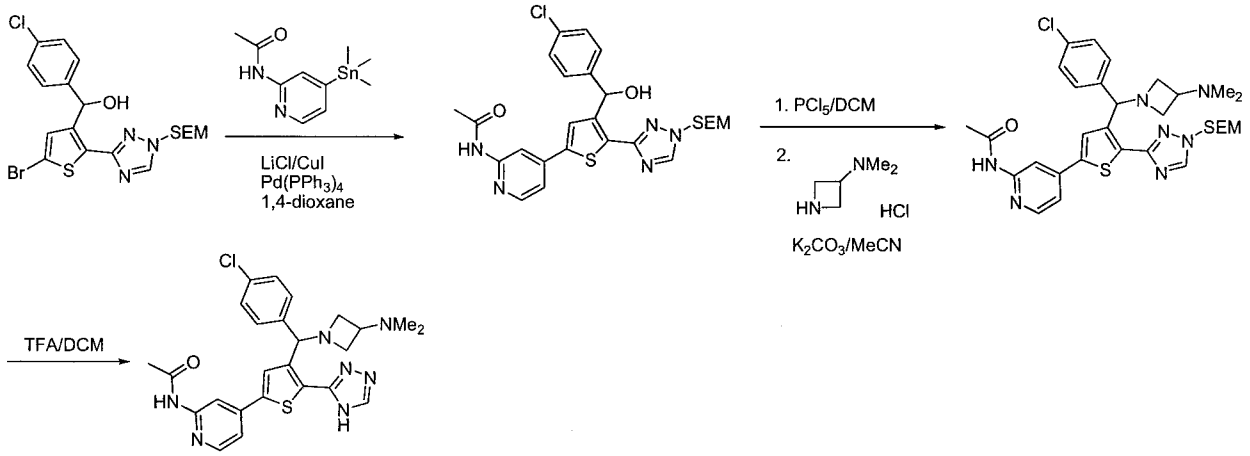
[00700] To a suspension of ammonium chloride (2.25 g, 42.1 mmol) in toluene (21.0 mL) in an ice bath was added 2.0 M trimethylaluminum in toluene (21.1 mL, 42.2 mmol) dropwise (gas evolution). The mixture was then stirred at room temperature for 30 minutes, during which time the solids dissolved. Ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate (4.11 g, 11.4 mmol) was added in one portion and the resulting solution was heated slowly to 110 °C over 1 hour, then kept at 110 °C for 2.5 hours. The reaction was allowed to cool to room temperature overnight. The reaction was poured into a

slurry of silica gel (10 grams) in chloroform (100 mL) and stirred 10 minutes. Methanol (20 mL) was added (bubbling occurs), and the mixture was filtered through a short silica gel bed in a sintered glass funnel, eluting with 1:1 methanol/chloroform to remove product. The filtrate was concentrated to give the crude product, which was purified by silica gel chromatography (methanol/chloroform = 50/50) to give 1.9 g of the title compound as a light yellow solid, which is the HCl salt. (45 % yield). (1.6 grams (45%) of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbonitrile was also recovered) LC/MS (FA) ES+ 329. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73, (bs, 4H), 8.76-8.74 (m, 2H), 7.90-7.88 (m, 2H), 7.39-7.35 (m, 2H), 7.31-7.27 (m, 2H), 4.30 (s, 2H).

[00701] Step 2, Preparation of 2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-4(3H)-one (Compound 92)

[00702] To a solution of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride (188 mg, 0.515 mmol) in ethanol (8.0 mL) was added 21% sodium ethoxide in ethanol (0.192 mL, 0.515 mmol) and sodium 2-ethoxycarbonyl ethenolate (284 mg, 2.06 mmol) (prepared as in J. Med. Chem., (2001), 44(17), 2695-2700), and the reaction was heated to reflux overnight. The reaction was cooled and concentrated. The residue was slurried DCM (15 mL) and water (15 mL) for 20 minutes. The solids were filtered, dried and purified by silica gel chromatography (methanol/DCM = 0/100→15/85) to give the product. HPLC gave 23 mg of the title compound as a yellow solid. (12 % yield). LC/MS (FA) ES+ 381. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.72-8.60 (m, 2H), 8.41 (d, 1 H, J = 5.7 Hz), 7.88-7.85 (m, 2H), 7.40-7.36 (m, 2H), 7.32-7.28 (m, 2H), 6.58 (d, 1H, J = 5.7 Hz), 4.80 (s, 2H).

[00703] Example 30: Synthesis of N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 181)



[00704] Step 1: Preparation of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamid

[00705] A mixture of [5-bromo-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-3-thienyl](4-chlorophenyl)methanol (3.07 g, 5.52 mmol)) (synthesized in an analogous way as described in Example 2), N-[4-(trimethylstannyl)pyridin-2-yl]acetamide (1.81 g, 6.07 mmol), tetrakis(triphenylphosphine)palladium(0) (319 mg, 0.28 mmol), copper(I) iodide (315 mg, 1.65 mmol) and lithium chloride (702 mg, 16.5 mmol) in 1,4-dioxane (25.0 mL) was stirred at 100 °C for 2 hours under an atmosphere of nitrogen. The reaction was cooled to room temperature and concentrated with Celite. The crude mixture was purified by column chromatography (SiO_2, eluent with methanol in dichloromethane, 0-5% gradient) to afford a yellow solid (2.48 g, 80%). LCMS: (AA) ES+ 556, 558; 1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (br s, 1H), 8.43 (br s, 1H), 8.25 (s, 1H), 8.19 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.33-7.24 (m, 2H), 7.19 (s, 1H), 7.16 (dd, J = 1.2, 5.6 Hz, 1H), 6.22 (s, 1H), 6.05 (br s, 1 H), 5.51 (s, 2H), 3.66 (t, J = 8.4 Hz, 2H), 2.22 (s, 3H), 0.94 (t, J = 8.4 Hz, 2H), -0.01 (s, 9H).

[00706] **Step 2: Preparation of N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide**

[00707] To a solution of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (100 mg, 0.18 mmol) in dichloromethane (2.00 mL) was added phosphorus pentachloride (112 mg, 0.54 mmol) at room temperature. The mixture was stirred for 15 min and then water (10 mL) was added. The mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with dichloromethane twice. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo to give an intermediate as a yellow solid. This intermediate was dissolved in acetonitrile (1.66 mL) and potassium carbonate (124 mg, 0.90 mmol) and 1-azetidin-3-yl-dimethylamine hydrochloride (130 mg, 0.54 mmol) were added. The mixture was stirred at 80 °C for 5 hours. After cooling to room temperature, the mixture was diluted with dichloromethane and filtered through a glass filter. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, elution with methanol in dichloromethane, 0-10% gradient) to afford a solid product (103 mg, 52.3%). LCMS: (AA) ES+ 638, 640; 1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (s, 1H), 8.26 (s, 1H), 8.22 (d, J = 5.2 Hz, 1H), 8.10 (s, 1H), 7.80 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.25-7.21 (m 3H), 5.61 (s, 1H), 5.56 (s, 2H), 3.72 (dd, J = 8.8, 7.6 Hz, 2H), 3.43-3.32 (m, 2H), 2.93-2.80 (m, 3H), 2.24 (s, 3H), 2.06 (s, 6H), 0.99 (dd, J = 8.8, 7.6 Hz, 2H), 0.02 (s, 9H).

[00708] **Step 3: Preparation of N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 181)**

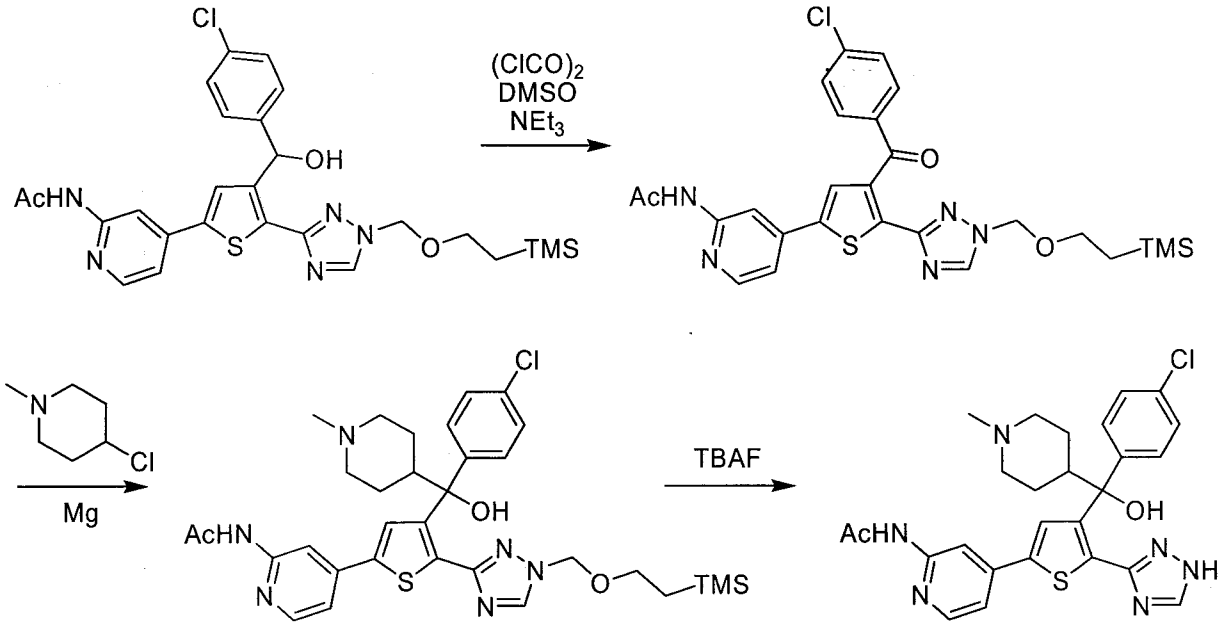
[00709] N-{4-[4-{(4-chlorophenyl)[3-(dimethylamino)azetidin-1-yl]methyl}-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (60 mg, 0.094 mmol) was dissolved in dichloromethane (1.19 mL) and trifluoroacetic acid (0.30 mL, 3.85 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo and distributed between EtOAc and saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, elution with methanol in dichloromethane, 0-20% gradient) to afford the title compound as a white solid (34.2 mg, 71.6%). LCMS: (AA) ES+ 508, 510; 1H NMR (400 MHz, d_4-methanol): 8.51 (s, 1H), 8.39 (s, 1H), 8.24 (br s, 1H), 7.78 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.32 (br s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 5.71 (s, 1H), 3.45-3.36 (m, 2H), 3.00-2.83 (m, 3H), 2.19 (s, 3H), 2.06 (s, 6H).

[00710] The compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 30:

129	LCMS: (AA) ES+ 494, 496.
144	LCMS: (AA) ES+ 508, 510.
157	LCMS: (AA) ES+ 576, 578.
160	LCMS: (AA) ES+ 508, 510.
170	LCMS: (AA) ES+ 494, 496.
172	LCMS: (AA) ES+ 479.
189	LCMS: (AA) ES+ 450, 452.
211	LCMS: (AA) ES+ 451, 453.
218	LCMS: (AA) ES+ 519, 521.
222	LCMS: (AA) ES+ 522, 524.
223	LCMS: (AA) ES+ 509, 511.
226	LCMS: (AA) ES+ 469, 471.
227	LCMS: (AA) ES+ 463, 465.
230	LCMS: (AA) ES+ 479, 481.
244	LCMS: (FA) ES+ 467, 469.

245	LCMS: (AA) ES+ 536, 538.
250	LCMS: (AA) ES+ 408, 410.
269	LCMS: (AA) ES+ 509, 511.
274	LCMS: (AA) ES+ 494, 496.
277	LCMS: (AA) ES+ 494, 496.

[00711] Example 31: Synthesis of N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide (Compound 237)



[00712] Step1: A solution of oxalyl chloride (63.1 uL, 0.746 mmol) in methylene chloride (1.50 mL, 23.4 mmol) was cooled to -78 °C. To this solution was added dimethyl sulfoxide (65.1 uL, 0.918 mmol) in methylene chloride (1.00 mL) dropwise. The reaction was stirred for 10min under an atmosphere of Nitrogen. To this mixture was added a solution of N-{4-[4-[(4-chlorophenyl)(hydroxy)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (319 mg, 0.574 mmol) in methylene chloride (1.50 mL) dropwise. In 1 hr, triethylamine (0.400 mL, 2.87 mmol) was added dropwise to the reaction and the resulting mixture was warmed to rt. In 1 hr, the solution was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2(x2). The combined org layer was washed with $NaHCO_3$(aq) saturated solution, dried, and concentrated to provide N-{4-[4-(4-

chlorobenzoyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1, 2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide as a yellow solid (325 mg, quantative). LCMS: (AA) 554, 556; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.47 (s, 1H), 8.32 – 8.24 (m, 1H), 8.11 – 8.03 (s, 1H), 8.03 – 7.92 (s, 1H), 7.87 – 7.77 (m, 2H), 7.63 – 7.57 (s, 1H), 7.42 – 7.32 (m, 3H), 5.37 – 5.32 (s, 2H), 3.53 – 3.40 (t, J = 8.1 Hz, 2H), 2.27 – 2.19 (s, 3H), 0.94 – 0.80 (t, J = 8.1 Hz, 2H), 0.02 – -0.04 (s, 9H).

[00713] **Step2**: A 25 mL round bottom flask charged with magnesium turnings (23.0 mg, 0.947 mmol) was flame-dried. To the flask was added tetrahydrofuran (1.00 mL) and a drop of 1,2-dibromoethane. The mixture was heated to 45 °C for 10 min and cooled to rt. To the mixture was added 4-chloro-N-methylpiperidine (126 mg, 0.947 mmol). The reaction was stirred at 35 °C under an atmosphere of nitrogen for 12 hrs. The mixture turned cloudy, and magnesium turnings eventually disappeared, as the reaction progressed. To a solution of N-{4-[4-(4-chlorobenzoyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (113 mg, 0.204 mmol) in tetrahydrofuran (1.00 mL) was added the pre-prepared Grignard reagent solution dropwise at 0 °C. In 3 hrs, the reaction was warmed to rt. In another 3 hrs, the reaction was quenched with water and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was dried and concentrated. Purification on a silica gel column (gradient elution, 1-20% MeOH) provided N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide as a yellow solid (59.0 mg, 44.3% yield). LCMS: (AA) ES+ 653, 655; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.66 (s, 1H), 8.60 – 8.49 (s, 1H), 8.31 – 8.23 (d, J = 5.3 Hz, 1H), 8.15 – 8.08 (m, 2H), 7.66 – 7.60 (s, 1H), 7.34 – 7.23 (m, 3H), 7.17 – 7.08 (d, J = 8.7 Hz, 2H), 5.45 – 5.38 (s, 2H), 3.63 – 3.51 (m, 2H), 3.49 – 3.44 (s, 3H), 3.02 – 2.90 (d, J = 10.8 Hz, 1H), 2.90 – 2.78 (d, J = 11.2 Hz, 1H), 2.28 – 2.20 (m, 4H), 2.20 – 2.09 (m, 1H), 2.07 – 1.95 (m, 1H), 1.96 – 1.78 (m, 2H), 1.76 – 1.58 (qd, J = 12.7, 3.8 Hz, 1H), 1.16 – 1.07 (d, J = 12.5 Hz, 1H), 0.99 – 0.85 (m, 2H), 0.02 – -0.04 (s, 9H).

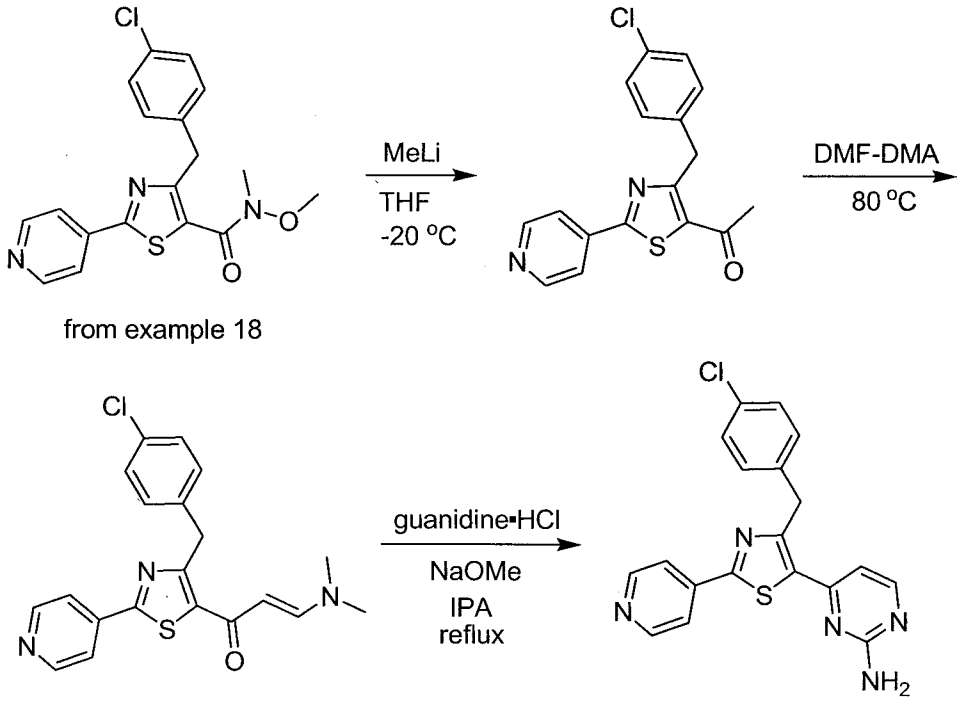
[00714] **Step3**: A 5 mL microwave tube was charged with N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide (10.0 mg, 0.0153 mmol) and tetrahydrofuran (0.500 mL, 6.16 mmol). To the solution was added 1.00

M of tetra-n-butylammonium fluoride in tetrahydrofuran(61.2 uL). The tube was sealed and heated to 80 °C in an oil bath for 4 hrs. The resulting mixture was cooled to rt and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined org layer was dried and concentrated. Purification on HPLC (reverse phase, AA) provided N-(4-{4-[(4-chlorophenyl)(hydroxy)(1-methylpiperidin-4-yl)methyl]-5-(4H-1,2,4-triazol-3-yl)-2-thienyl}pyridin-2-yl)acetamide as a white solid. (2.0mg, 25% yield) LCMS (AA) ES+ 523, 525; ^{1}H NMR (400 MHz, MeOD) δ 8.50 – 8.42 (s, 1H), 8.41 – 8.36 (s, 1H), 8.36 – 8.29 (d, J = 5.3 Hz, 1H), 7.92 – 7.83 (s, 1H), 7.50 – 7.43 (m, 1H), 7.43 – 7.34 (d, J = 8.6 Hz, 2H), 7.25 – 7.14 (d, J = 8.6 Hz, 2H), 2.91 – 2.76 (m, 1H), 2.65-2.55 (m, 4H), 2.26 – 2.15 (s, 3H), 2.11 – 2.01 (m, 2H), 1.88 – 1.72 (m, 2H), 1.70 – 1.57 (s, 1H), 1.47 – 1.35 (dd, J = 15.0, 7.4 Hz, 1H), 1.31 – 1.20 (m, 2H).

[00715] The compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 31:

145	LCMS: (AA) ES+ 511, 513
225	LCMS: (AA) ES+ 493, 495.
273	LCMS: (AA) ES+ 508, 510.

[00716] Example 32: Synthesis of 4-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-2-amine (Compound 150)



[00717] Step 1, Preparation of 1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)ethanone

[00718] To a solution of 4-(4-chlorobenzyl)-N-methoxy-N-methyl-2-(pyridin-4-yl)thiazole-5-carboxamide (1.79 g, 4.79 mmol) in THF (97 mL) at -20 °C was added a 1.60 M solution of MeLi in ether (4.19 mL, 6.70 mmol). The reaction was stirred for 30 minutes at -20 °C. An additional portion of a 1.60 M solution of MeLi in ether (0.838 mL, 1.34 mmol) was added and the reaction was stirred for 30 more minutes at -20 °C. The reaction was quenched by adding saturated ammonium chloride (25 mL) followed by water (35 mL). The mixture was extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→80/20) to give 1.27 g (81 % yield) of the title compound.as a light yellow solid. LC/MS (FA) ES+ 329, 331. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.75-8.73 (m, 2H), 7.83-7.81 (m, 2H), 7.34-7.31 (m, 2H). 7.26-7.23 (m, 2H), 4.53 (s, 2H), 2.59 (s, 3H).

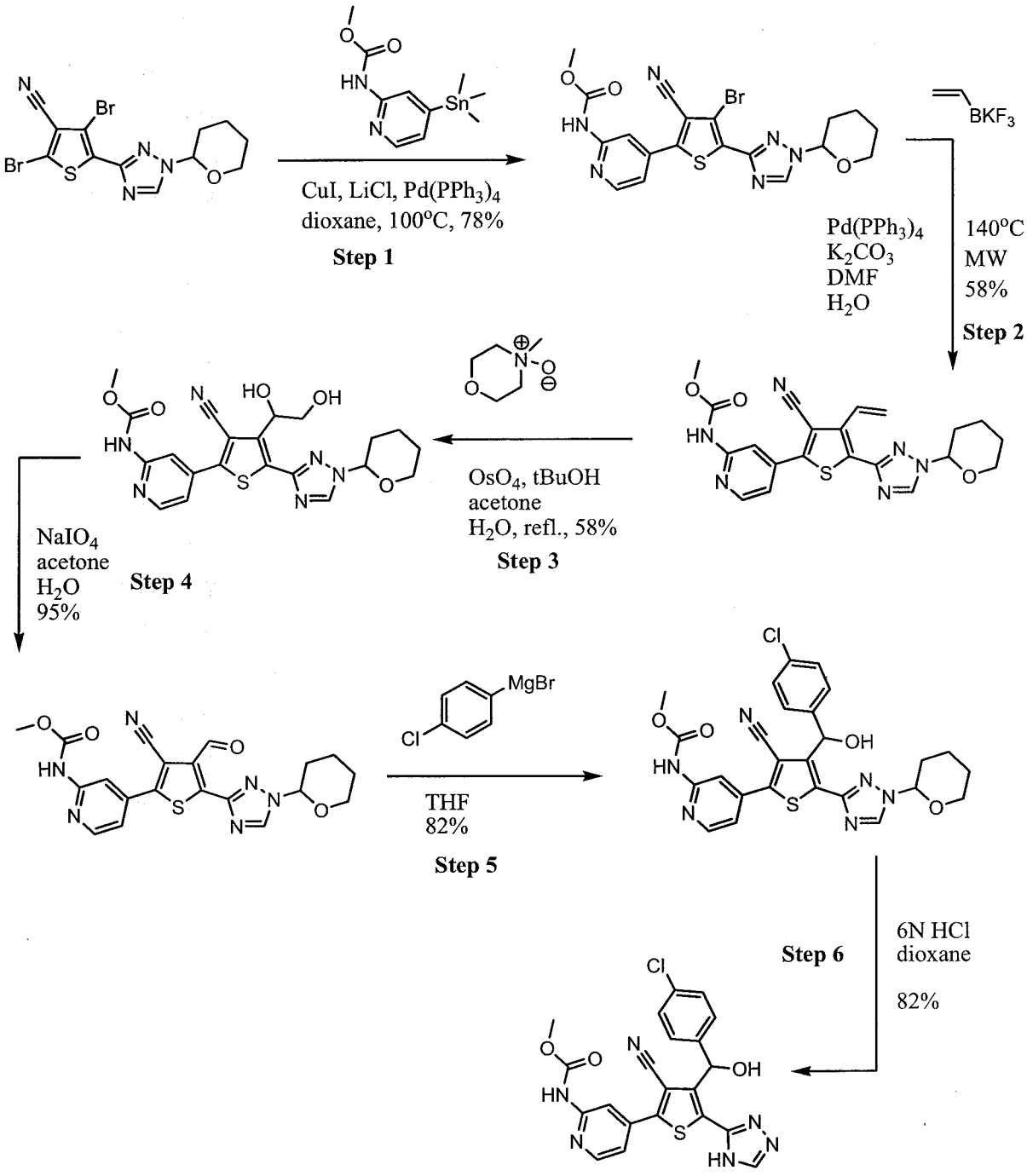
[00719] Step 2, Preparation of (E)-1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-(dimethylamino)prop-2-en-1-one

[00720] A solution of 1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)ethanone (370 mg, 1.12 mmol) in 1,1-dimethoxy-N,N-dimethylmethanamine (10.0 mL, 75.3 mmol) was heated to 80 degrees for 6 hours. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→100/0) to give 389 mg (90 % yield) of the title compound.as a yellow solid. LC/MS (FA) ES+ 384, 386. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70-8.68 (m, 2H), 7.81-7.75 (m, 3H), 7.36-7.33 (m, 2H), 7.26-7.24 (m, 2H), 5.41 (d, 1H, J = 12.3 Hz), 4.55 (s, 2H), 3.16 (s, 3H), 2.88 (s, 3H).

[00721] Step 3, Preparation of 4-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)pyrimidin-2-amine

[00722] To a solution of (E)-1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-(dimethylamino)prop-2-en-1-one (93.0 mg, 0.242 mmol) in isopropyl alcohol (1.0 mL) was added guanidine hydrochloride (34.7 mg, 0.363 mmol) and sodium ethoxide (65.4 mg, 1.21 mmol) and the resulting mixture was heated to reflux for 3 days. The reaction was cooled and concentrated in vacuo. The residue was slurried in DCM (10 mL) and water (10 mL). The undissolved solids were filtered. This material was purified by preparative reverse phase chromatography to give 57 mg (62 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 380, 382. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73-8.71 (m, 2H), 8.31 (d, 1H, J = 5.1 Hz), 7.88-7.86 (m, 2H), 7.36-7.30 (m, 4H), 6.86 (bs, 2H), 6.84 (d, 1H, J = 5.1 Hz), 4.56 (s, 2H).

[00723] Example 33: Synthesis of Methyl {4-[4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-(4H-1,2,4-triazol- 3-yl)-2-thienyl]pyridin-2-yl}carbamate (Compound 195)



[00724] Step 1: Methyl (4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00725] A mixture of 2,4-dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (1.27 g, 3.05 mmol), methyl [4-(trimethylstannyl)pyridin-2-yl]carbamate (0.960 g, 3.05 mmol), lithium chloride (0.388 g, 9.14 mmol), copper(I) iodide (0.174 g, 0.914 mmol) and tetrakis(triphenylphosphine)platinum (0) (0.190 g, 0.152 mmol) in anhydrous 1,4-dioxane (45 mL) was

degassed by evacuation in vacuum and backfilling with N_2 4 times, then heated to 100°C under N_2 for 8 hours, then cooled to room temperature. The suspension was filtered and washed with dioxane. The solid was suspensded in 20% MeOH in DCM (300 mL), and washed with water (2X). The organic suspension was concentrated in a rotavapor to give a solid residue. The residue was stirred in DMF/DCM (10 mL / 10 mL) at room temperature for 20 min, filtered and washed with DCM to give a solid product (1.16 g, yield 77.8%). LC/MS: (FA) ES+ 489, 491. ^{1}H NMR (400MHz, d_4-MeOH /*d*-chloroform) δ 8.26-8.35 (m, 3H), 7.34 (m, 1H), 5.48 (m, 1H), 4.00 (m, 1H), 3.73 (s, 3H), 3.64-3.69 (m, 1H), 1.97-2.14 (m, 3H), 1.58-1.68 (m, 3H).

[00726] Step 2: Methyl (4-{3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-4-vinyl-2-thienyl}pyridin-2-yl)carbamate

[00727] A mixture of methyl (4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (1.14 g, 2.33 mmol) , potassium vinyltrifluoroborate (0.624 g, 4.66 mmol), tetrakis(triphenylphosphine)platinum (0) (0.145 g, 0.116 mmol) and potassium carbonate (0.967 g, 7.00 mmol) in N,N-dimethylformamide (14.0 mL) and water (5.0 mL) in a microwave vial was heated under nitrogen atmosphere at 140°C in a microwave for 15 min. The mixture was cooled to room temperature, quenched with water, extracted with DCM, washed with water then brine, dried over Na_2SO_4, filtered and rotavaped to give a crude product. Purification on a silica gel column using MeOH/DCM (0/100 to 5/95) afforded the desired product (1.16 g, with PPh3 and O=PPh3 contaminated) with Rf on TLC (MeOH/DCM 5/95) of 0.4, and de-carbamide product (0.627 g, yield 58%). LC/MS: (FA) ES+ 437. ^{1}H NMR (400MHz, *d*-chloroform) δ 8.52 (s, 1H), 8.45 (s, 1H), 8.41 (m, 1H), 8.33 (s, 1H), 7.51-7.59 (m, 1H), 7.46 – 7.49 (m, 1H), 6.28-6.33 (m, 1H), 5.66-5.69 (m, 1H), 5.51-5.54 (m, 1H), 4.09-4.12 (m, 1H), 3.86 (s, 3H), 3.75-3.78 (m, 1H), 2.00-2.20 (m, 3H), 1.68-1.77 (m, 3H).

[00728] Step 3: Methyl (4-{3-cyano-4-(1,2-dihydroxyethyl)-5-[1-(tetrahydro-2H-pyran-2-yl)- 1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00729] To the suspension of methyl (4-{3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-4-vinyl-2-thienyl}pyridin-2-yl)carbamate (0.625 g, 1.34 mmol) in tert-butyl alcohol (3.0 mL) and acetone (30 mL) was added N-methylmorpholine N-oxide (0.315 g, 2.69 mmol), followed by water (1.0 mL) then 0.157 M of osmium tetraoxide in Water(0.257 mL, 0.0404 mmol). The pale yellow suspension was stirred at room temperature for 17 hours. N-Methylmorpholine N-oxide (0.315 g, 2.69 mmol) was added and the suspension was stirred for 3 more hours, then heated to reflux for 7 hours. The mixture was cooled to room temperature, rotavaped and azeotroped with MeOH to give a solid crude residue. The crude solid was partially dissolved in DCM-MeOH, coated on silica gel, evaporated in rotavapor and chromatographed in a silica gel column using an elution of MeOH/DCM (0/100 to 5/95) to afford a solid product (0.365 g, yield 57.6 %). LC/MS: (FA) ES+ 471; ES- 469, . ^{1}H NMR (400MHz, *d*-

chloroform/*d4*-methanol) δ 8.35 (m, 2H), 8.30 (m, 1H), 7.40 (m, 1H), 5.47-5.49 (m, 1H), 5.31-5.33 (m, 1H), 4.03-4.07 (m, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.71-3.81 (m, 2H), 2.13 (m, 1H), 2.00-2.02 (m, 2H), 1.65-1.70 (m, 3H).

[00730] Step 4: Methyl (4-{3-cyano-4-formyl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00731] Methyl (4-{3-cyano-4-(1,2-dihydroxyethyl)-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (0.362 g, 0.769 mmol) was dissolved in acetone (40 mL) and water (10 mL). Sodium metaperiodate (0.494 g, 2.31 mmol) was added and the mixture was stirred at room temperature for 6 hours. Sodium metaperiodate (0.329 g, 1.54 mmol) was added and the mixture was stirred for 16 more hours. The mixture was concentrated in rotavapor. The residue was triturated with water, filtered and washed throughly with water, then dried in lyophilizer to give a dry solid product (0.320 g, yield 94.8%). LC/MS: (FA) ES+ 439. ^{1}H NMR (400MHz, *d6*-dmso) δ 10.67 (s, 1H), 10.57 (s, 1H), 9.05 (s, 1H), 8.49 (m, 1H), 8.28 (s, 1H), 7.50 (m, 1H), 5.69-5.73 (m, 1H), 3.94-3.98 (m, 1H), 3.73 (s, 3H), 3.66-3.71 (m, 1H), 1.93-2.12 (m, 3H), 1.58-1.71 (m, 3H).

[00732] Step 5: Methyl (4-{4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-[1-(tetrahydro- 2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate

[00733] To a suspension of methyl (4-{3-cyano-4-formyl-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (0.1077 g, 0.2456 mmol) in anhydrous Tetrahydrofuran (6.0 mL) cooled with ice bath was added slowly 1.0 M of 4-chlorophenylmagnesium bromide in ether(2.50 mL, 2.50 mmol). The resulting clear solution was stirred with cooling for 30 min, then the mixture was quenched with methanol (0.5 mL), then with acetic acid (148 mg, 2.46 mmol) . The mixture was warmed to room temperature, then rotavaped to give crude product, which was chromatograph in a silica gel column using MeOH/DCM (0/100 to 3/97) to afford a solid product (0.116 g, yield 82%). LC/MS: (FA) ES+ 551; ES- 549, . ^{1}H NMR (400MHz, *d*-chloroform/*d4*-methanol) δ 8.36 (s, 1H), 8.29 (m, 2H), 7.43 (m, 1H), 7.34 (m, 2H), 7.19 (m, 2H), 6.37 (s, 1H), 5.41-5.46 (m, 1H), 3.99-4.04 (m, 1H), 3.79 (s, 3H), 3.68-3.72 (m, 1H), 2.13 (m, 1H), 1.97-2.00 (m, 2H), 1.55-1.70 (m, br, 3H).

[00734] Step 6: Methyl {4-[4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-(4H-1,2,4-triazol- 3-yl)-2-thienyl]pyridin-2-yl}carbamate

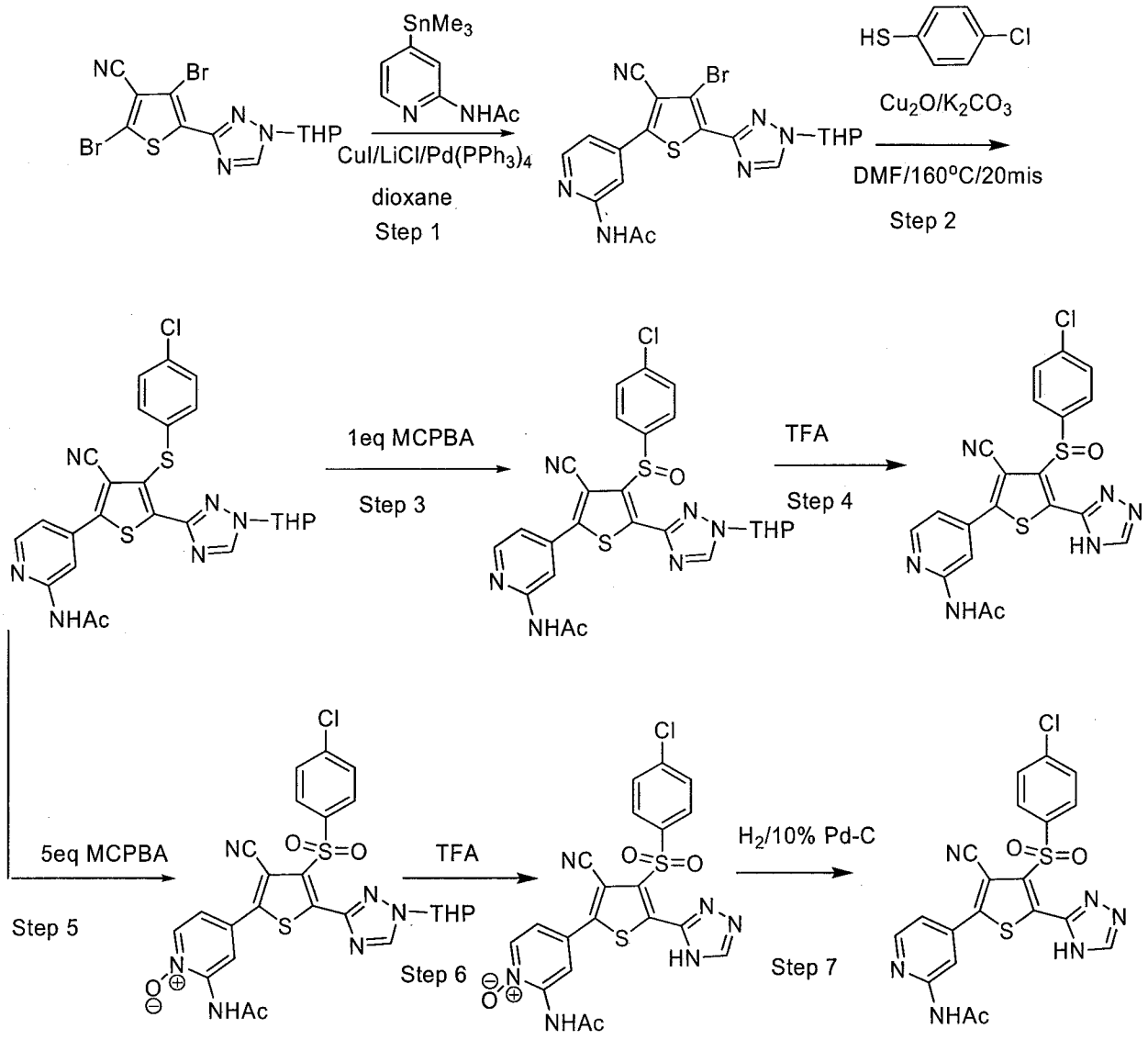
[00735] To a suspension of methyl (4-{4-[(4-chlorophenyl)(hydroxy)methyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)carbamate (0.0450 g, 0.0817 mmol) in 1,4-dioxane (4.0 mL, 51 mmol) and cooled in an ice bath was added 6.0 M hydrochloric acid in water (4.0 mL, 24 mmol). The resulting solution was brought to room temperature. Hexane (5.0 mL) was added and the bi layer mixture was stirred for 4 hours. The hexane was separated and the aqueous layer

was washed with hexane twice. The aqueous layer was concentrated on a rotavapor to ~ half volume, diluted with ice and water, basified with saturated aqueous $NaHCO_3$ to pH ~ 7.5, extracted with EtOAc (4 x). The combined EtOAc solutions were washed with brine, dried over Na_2SO_4, filtered, and rotavaped to give a crude solid. The crude solid was chromatographed on a silica gel column using MeOH/DCM (0/100 to 5/95) to afford a solid product (33 mg, yield 82 %). LC/MS: (FA) ES+ 467, 469. ^{1}H NMR (400MHz, *d6*-dmso) δ 10.50 (s, 1H), 8.82 (s, 1H), 8.41 (m, 1H), 8.20 (s, 1H), 7.57 (m, 2H), 7.39 (m, 3H), 7.06 (s, 1H), 6.59 (s, br, 1H), 3.69 (s, 3H).

[00736] The compounds in the following table were prepared from the appropriate starting materials in a method analogous to that of Example 33:

153	LCMS: (AA) ES+ 468.
165	LCMS: (AA) ES+ 451, 453.

[00737] Example 34: Synthesis of N-{4-[4-[(4-chlorophenyl)sulfinyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 131) and N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound 140)



[00738] Step 1: N-(4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide

[00739] A mixture of 2,4-dibromo-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]thiophene-3-carbonitrile (1.3809 g, 3.3027 mmol), [B] N-[4-(trimethylstannyl)-pyridin-2-yl]acetamide (987.38 mg, 3.3028 mmol), copper(I) iodide (188.70 mg, 0.99082 mmol), lithium chloride (420.04 mg, 9.9082 mmol) and tetrakis(triphenylphosphine)-palladium(0) (190.82 mg, 0.16514 mmol) in dry 1,4-Dioxane (20.0 mL) was sonicated under N_2 for 2 min, then heated in a capped vial to 130°C in microwave machine for 20 mins. The suspension was cooled to room temperature, and the resudue was purified using silica gel chromatography. The eluent was 40-100% ethyl acetate in hexane, affording a solid product (0.8802g, yield 56.3%) LCMS: (AA) ES+ 473, 475. 1H NMR (300MHz, CDCl3) δ: 8.61

(s, 1H), 8.41 (d, 1H), 8.39 (s, 1H), 8.10 (s, 1H), 7.53 (d, 1H), 5.55-5.60 (dd, 1H), 4.06-4.10 (m, 1H), 3.68-3.78 (m, 1H), 2.35 (s, 3H), 2.15-2.28 (m, 1H), 2.01-2.13 (m, 2H), 1.66-1.80 (m, 3H).

[00740] **Step 2**: N-(4-{4-[(4-chlorophenyl)sulfanyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide

[00741] N-(4-{4-bromo-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide (0.2601 g, 0.5495 mmol), copper(I) oxide (0.1572 g, 1.099 mmol), 4-chlorobenzenethiol (0.3179 g, 2.198 mmol) and potassium carbonate (0.2278 g, 1.648 mmol) were added to a microwave vial followed by DMF (15.00 mL). The reaction was irradiated at 150 °C for 15 mins. The solid was filtered and washed with DCM. The solution was diluted with 80 ml water, and extracted with 100 ml DCM for two times. The organic layer was concentrated, and purified by column. The eluent was 50-100% ethyl acetate in hexane to yield a solid product (0.224g, yield 76.0%) LCMS: (AA) ES+ 537, 539. 1H NMR (300MHz, CDCl3) δ: 8.59 (s, 1H), 8.37 (d, 1H), 8.36 (s, 1H), 8.03 (s, 1H), 7.53 (d, 1H), 7.32 (d, 2H), 7.22 (d, 2H), 5.50-5.55 (dd, 1H), 4.02-4.08 (m, 1H), 3.68-3.78 (m, 1H), 2.25 (s, 3H), 2.10-2.18 (m, 1H), 2.00-2.07 (m, 2H), 1.66-1.80 (m, 3H).

[00742] **Step 3**: N-(4-(4-(4-chlorophenylsulfinyl)-3-cyano-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)pyridin-2-yl)acetamide

[00743] N-(4-{4-[(4-chlorophenyl)sulfanyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide (0.0575 g, 0.107 mmol) was dissolved in methylene chloride (5.00 mL), followed by addition of m-chloroperbenzoic acid (0.0194 g, 0.112 mmol). The reaction mixture was stirred at room temperature for 1 hr. The solution was concentrated, and purified by column chromatography. The eluent was 50-100% ethyl acetate in hexane to yield a solid product (0.0324g, 54.7%) LCMS: (AA) ES+ 553, 555. 1H NMR (300MHz, CDCl3) δ: 8.47 (m, 2H), 8.41 (s, 1H), 8.36 (d, 1H), 8.06 (dd, 2H), 7.46 (dd, 2H), 7.45 (d, 1H), 5.53-5.59 (dd, 1H), 4.08-4.16 (m, 1H), 3.73-3.81 (m, 1H), 2.25 (s, 3H), 2.10-2.18 (m, 1H), 2.00-2.07 (m, 2H), 1.69-1.80 (m, 3H).

[00744] **Step 4**: N-{4-[4-[(4-chlorophenyl)sulfinyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound **131**)

[00745] N-(4-(4-(4-chlorophenylsulfinyl)-3-cyano-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)thiophen-2-yl)pyridin-2-yl)acetamide (0.0315 g, 0.0570 mmol) was dissolved in TFA (5.00 mL, 64.9 mmol). The mixture was stirred at room temperature for 1 hr, and the solvent was evaporated. 10 ml DCM was added to redissolve the material followed by the addition of triethylamine (1 mL). The solvent was evaporated off, and the mixture was purified by silica gel column. The eleuent was 0-6% methanol in hexane to yield a solid product (0.0112g, yield 41.9%) LCMS: (AA) ES+ 469, 471.

1H NMR (300MHz, MeOD) δ: 8.65 (s, 1H), 8.51 (s, 1H), 8.42 (d, 1H), 8.06 (d, 2H), 7.58 (d, 2H), 7.44 (dd, 1H), 2.25 (s, 3H).

[00746] **Step 5:** N-(4-{4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}-1-oxidopyridin-2-yl)acetamide

[00747] N-(4-{4-[(4-chlorophenyl)sulfanyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}pyridin-2-yl)acetamide (0.0698 g, 0.130 mmol) was dissolved in methylene chloride (6.00 mL) followed by addition of m-Chloroperbenzoic acid (0.08971 g, 0.5199 mmol). The mixture was stirred for 30 mins at room temperature. The solvent was evaporated, and the residue was purified by column chromatography. The eluent was 0-7% methanol in ethyl acetate to yield a solid product (0.0654g, yield 86.0%) LCMS: (AA) ES+ 585, 587. 1H NMR (300MHz, CDCl3) δ: 8.76 (s, 1H), 8.41 (s, 1H), 8.37 (d, 2H), 8.26 (d, 1H), 7.50 (d, 2H), 7.43 (d, 1H), 5.50-5.57 (dd, 1H), 4.03-4.10 (m, 1H), 3.70-3.78 (m, 1H), 2.25 (s, 3H), 2.10-2.18 (m, 1H), 2.00-2.07 (m, 2H), 1.69-1.80 (m, 3H).

[00748] **Step 6:** N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]-1-oxidopyridin-2-yl}acetamide

[00749] N-(4-{4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-[1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl]-2-thienyl}-1-oxidopyridin-2-yl)acetamide (0.0742 g, 0.127 mmol) was dissolved in trifluoroacetic acid (4.00 mL, 51.9 mmol). The mixture was stirred at room temperature for 4 hrs, solvent was evaporated and the residue was purified by HPLC to yield a solid product (0.0421g, yield 66.3%) LCMS: (AA) ES+ 501, 503. 1H NMR (300MHz, MeOD) δ: 8.90 (s, 1H), 8.60 (s, 1H), 8.43 (d, 1H), 8.35 (d, 2H), 7.67 (d, 2H), 7.59 (d, 1H), 2.28 (s, 3H).

[00750] **Step 7:** N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]pyridin-2-yl}acetamide (Compound **140**)

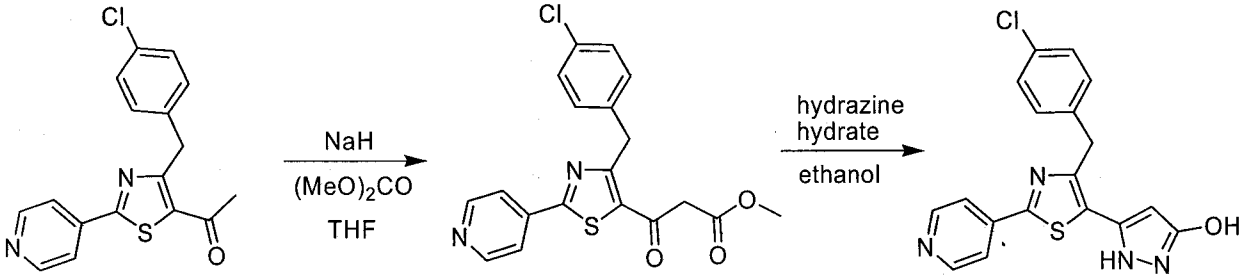
[00751] N-{4-[4-[(4-chlorophenyl)sulfonyl]-3-cyano-5-(4H-1,2,4-triazol-3-yl)-2-thienyl]-1-oxidopyridin-2-yl}acetamide (0.0229 g, 0.0457 mmol) was dissolved in methanol (3.00 mL), followed by the addition of 10% Pd-C (5 mg). The flask was filled with hydrogen at 40 psi, and the suspension was stirred at room temperature for overnight. The solid was filtered off, and the residue was concentrated followed by purification by column chromatography. The eluent was 0-8% methanol in ethyl acetate to yield a solid product (0.0142g, yield 64.0%). LCMS: (AA) ES+ 485, 487. 1H NMR (300MHz, MeOD) δ: 8.60 (s, 1H), 8.53 (s, 1H), 8.45 (d, 1H), 8.35 (d, 2H), 7.66 (d, 2H), 7.48 (d, 1H), 2.20 (s, 3H).

[00752] The compound in the following table was prepared from the appropriate starting materials in a method analogous to that of Example 34:

166	LCMS: (AA) ES+ 454

[00753]

[00754] Example 35: Synthesis of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazol-3-ol (Compound 178)



from example 32

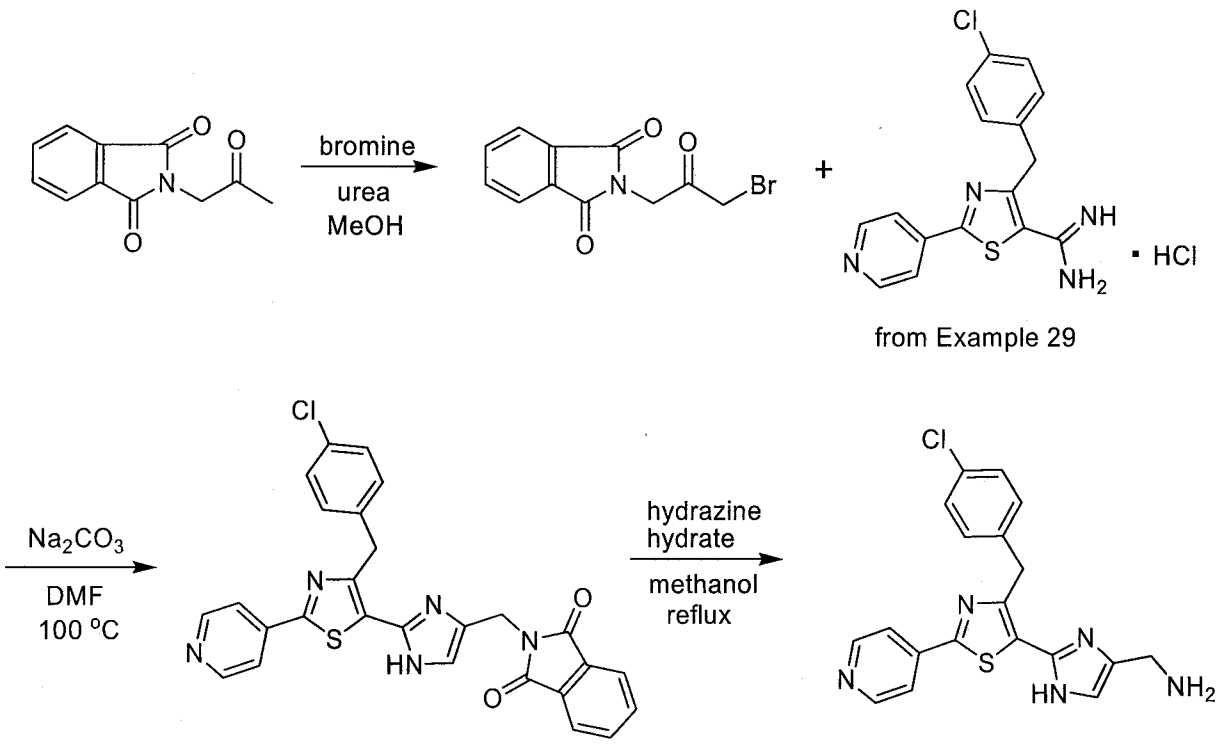
[00755] Step 1, Preparation of ethyl 3-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-oxopropanoate

[00756] To a flask containing 60% NaH in mineral oil (213 mg, 5.32 mmol) under nitrogen was added THF (31.7 mL) and carbonic acid, dimethyl ester (0.448 mL, 5.32 mmol). The mixture was heated to 60 degrees and a solution of 1-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)ethanone (875 mg, 2.66 mmol) in THF (12.7 mL) was then added. The mixture was heated at 60 degrees for 1 hour. The reaction was cooled and quenched with methanol (5 mL), then saturated NH_4Cl (10 mL). The organic solvents were concentrated in vacuo, and the aqueous residue was diluted with water (10 mL) and exctracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→40/60) to give 253 mg (25 % yield) of the title compound.as an oil. LC/MS (FA) ES+ 387, 389. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76-8.74 (m, 2H), 7.83-7.81 (m, 2H), 7.35-7.32 (m, 2H), 7.26-7.23 (m, 2H), 4.53 (s, 2H), 3.89 (s, 2H), 3.77 (s, 3H).

[00757] Step 2, Preparation of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazol-3-ol

[00758] To a solution of ethyl 3-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-3-oxopropanoate (253 mg, 0.631 mmol) in ethanol (16 mL) was added hydrazine hydrate (0.123 mL, 2.52 mmol) and the resulting solution was heated to 80 degrees for 3 hours. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→10/90) to give 118 mg of the product. This material was purified by preparative reverse phase chromatography to give 63 mg (27 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 369, 371. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.44 (bs, 1H), 8.68 (bs, 2H), 7.83-7.81 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.24 (m, 2H), 5.60 (s, 1H), 4.34 (s, 2H).

[00759] Example 36: Synthesis of (2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methanamine (Compound 255)



[00760] Step 1, Preparation of 2-(3-bromo-2-oxopropyl)isoindoline-1,3-dione

[00761] To a solution of phthalimidoacetone (4.04 g, 19.9 mmol) in methanol (100 mL) was added urea (1.19 g, 19.9 mmol) and bromine (3.18 g, 19.9 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue taken up in DCM (150 mL) and water (50 mL). The layers were separated and the organic layer was dried, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/hexanes = 0/100→50/50) to give 159 mg (3% yield) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90-7.86 (m, 2H), 7.79-7.73 (m, 2H), 4.78 (s, 2H), 4.01 (s, 2H).

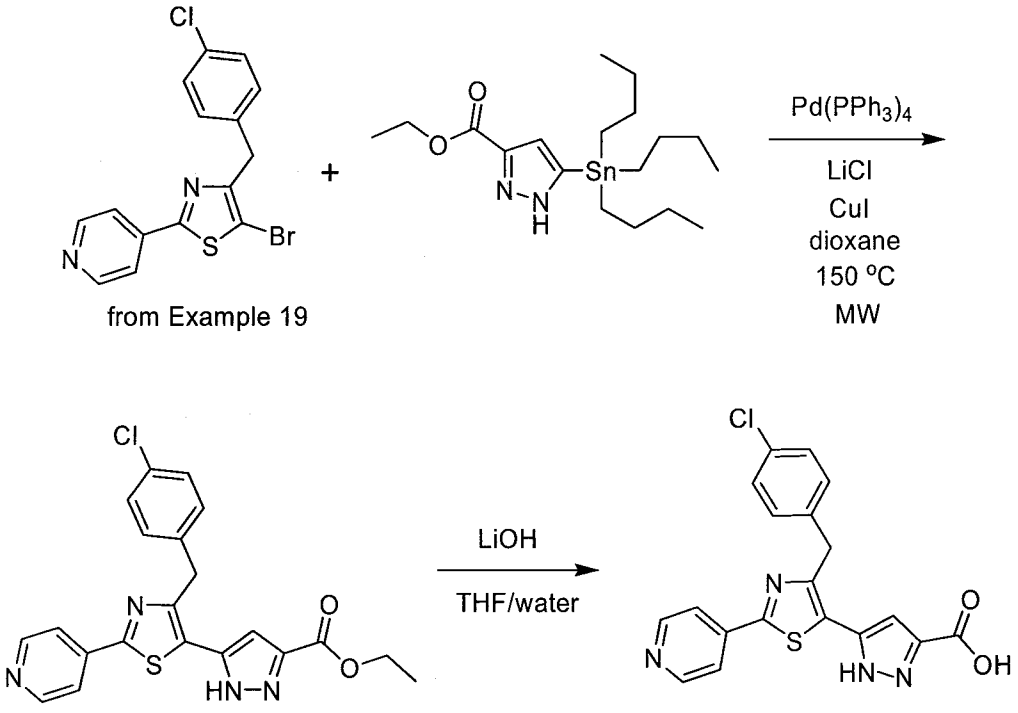
[00762] Step 2, Preparation of 2-((2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methyl)isoindoline-1,3-dione

[00763] To a mixture of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride (112 mg, 0.306 mmol) in DMF (2.96 mL) was added sodium carbonate (162 mg, 1.53 mmol) and 2-(3-bromo-2-oxopropyl)isoindoline-1,3-dione (95.0 mg, 0.337 mmol) and the resulting mixture was heated at 100 degrees for 4 hours. The reaction was cooled and taken up in ethyl acetate (30 mL) and water (5 mL). The layers were separated and the organic layer was washed with water (3 x 5 mL). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→10/90) to give 47 mg (30% yield) of the title compound. LC/MS (FA) ES+ 512. 514. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.67 (bs, 1H), 8.69-8.67 (m, 2H), 7.91-7.79 (m, 6H), 7.27-7.24 (m, 3H), 7.11-7.08 (m, 2H), 4.77 (s, 2H), 4.45 (s, 2H).

[00764] Step 3, Preparation of (2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methanamine

[00765] To a solution of 2-((2-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-imidazol-4-yl)methyl)isoindoline-1,3-dione (45 mg, 0.0879 mmol) in methanol (2.0 mL) was added hydrazine hydrate (.0086 mL, 0.176 mmol) and the resulting solution was heated to reflux for 1 hour. The reaction was cooled and concentrated in vacuo. The residue wsa taken up in ethyl acetate and water. The layers were separated and the organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→40/60) to give 13 mg (39% yield) of the title compound. LC/MS (FA) ES+ 382, 384. ^{1}H NMR (300 MHz, MeOH-d_4) δ: 8.71-8.68 (m, 2H), 7.82-7.80 (m, 2H), 7.35 -7.29 (m, 4H), 7.22 (s, 1H), 4.53 (s, 2H), 3.86 (s, 2H).

[00766] Example 37: Synthesis of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylic acid (Compound 262)



[00767] Step 1, Preparation of ethyl 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylate

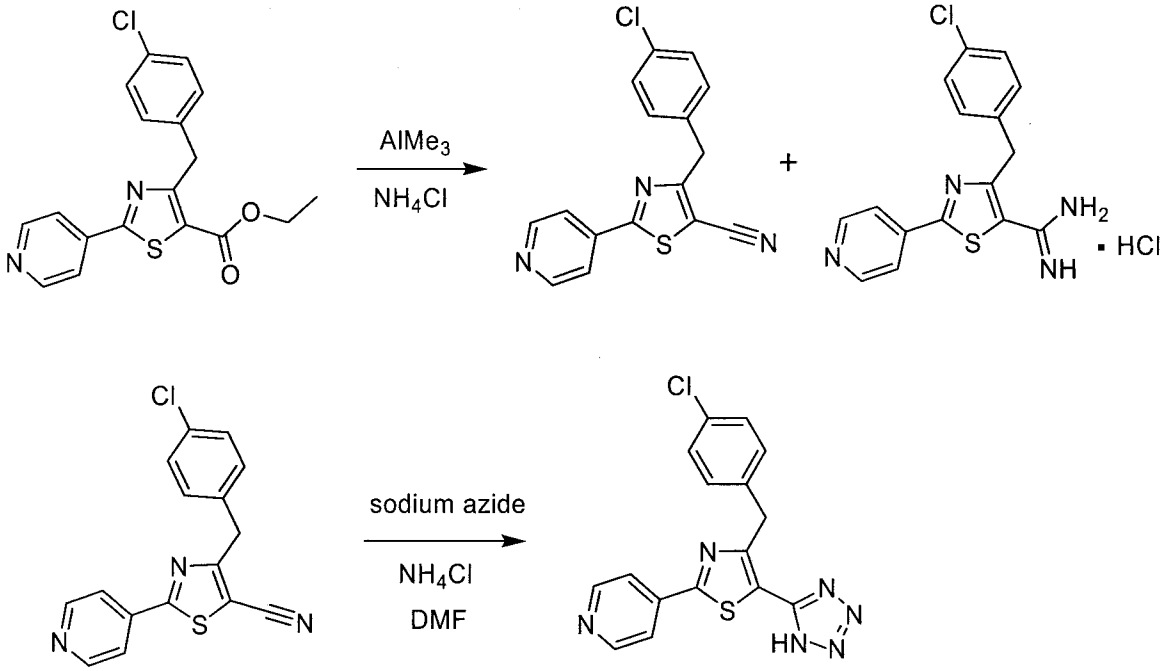
[00768] An argon degassed mixture of 5-bromo-4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole (583 mg, 1.59 mmol), ethyl 5-(tributylstannyl)-1H-pyrazole-3-carboxylate (456 mg, 1.06 mmol), tetrakis(triphenylphosphine)palladium(0) (61.4 mg, 0.0531 mmol), copper(I) iodide (60.7 mg, 0.319 mmol), and lithium chloride (135 mg, 3.19 mmol) in dioxane (7.46 mL) was heated in a microwave at 150 degrees for 30 minutes. The reaction mixture was slurried in ethyl acetate (100 mL) and water (2 mL)

and the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EA/DCM = 0/100→100/0) to give the crude product. This material was purified by preparative reverse phase chromatography to give 55 mg (12 % yield) of the title compound as a white solid.LC/MS (FA) ES+ 425, 427. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.71-8.69 (m, 2H), 7.85-7.83 (m, 2H), 7.36-7.33 (m, 2H), 7.28-7.25 (m, 2H), 7.09 (s, 1H), 4.41 (s, 2H), 4.34 (q, 1H, J = 7.2 Hz), 1.31 (t, 1H, J = 7.2 Hz).

[00769] Step 2, Preparation of 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylic acid

[00770] A solution of ethyl 5-(4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazol-5-yl)-1H-pyrazole-3-carboxylate (16.1 mg, 0.0379 mmol) in THF (0.50 mL) was treated with 1.0 M aqueous LiOH (0.0568 mL, 0568 mmol) and the solution was stirred at 40 degrees for 3 days. The reaction was then heated at 65 degrees for 6 hours. The reaction mixture was cooled and acidified with 1N HCl. The solution was extracted with EA (3 x 25 mL) and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by preparative reverse phase chromatography to give 1 mg (7 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 397, 399.

[00771] Example 38: Synthesis of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-tetrazol-5-yl)thiazole (Compound 190)



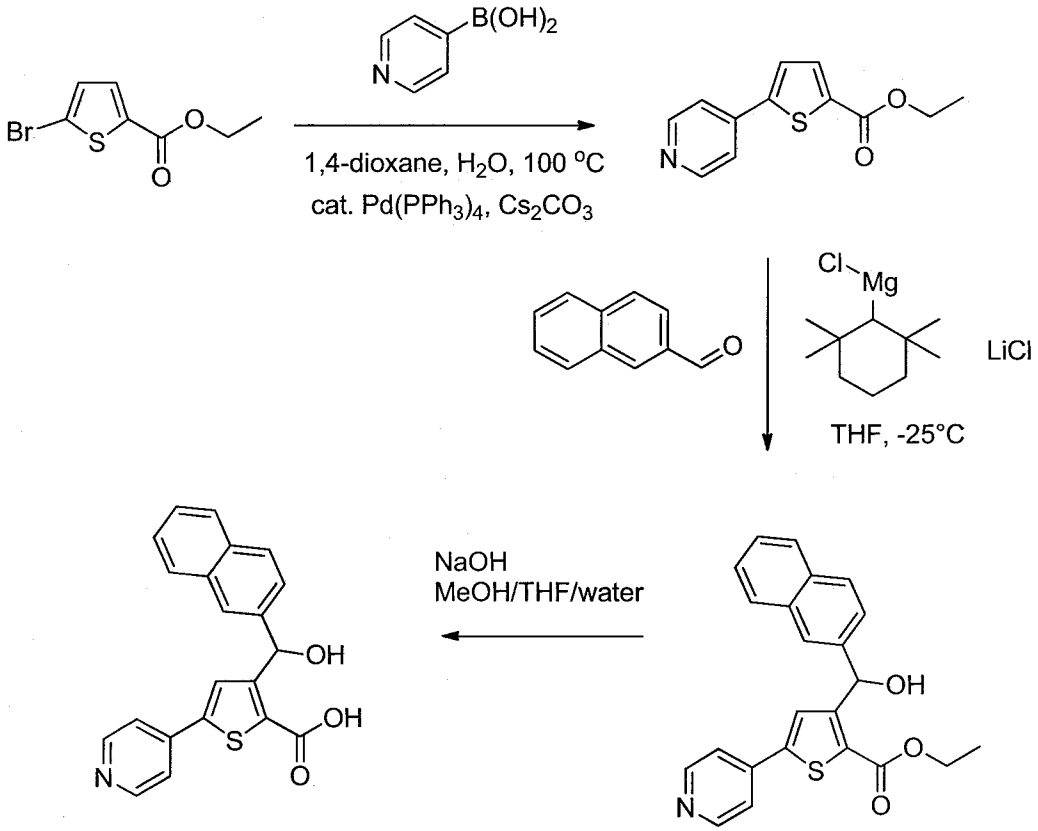
[00772] Step 1, Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carboximidamide hydrochloride and 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbonitrile

[00773] To a suspension of ammonium chloride (2.25 g, 42.1 mmol) in toluene (21.0 mL) in an ice bath was added 2.0 M trimethylaluminum in toluene (21.1 mL, 42.2 mmol) dropwise (gas evolution was observed). The mixture was then stirred at room temperature for 30 minutes, during which time the solids dissolved. Ethyl 4-(4-chlorobenzyl)-2-morpholinothiazole-5-carboxylate (4.11 g, 11.4 mmol) was added in one portion and the resulting solution was heated slowly to 110 °C over 1 hour, then kept at 110 °C for 2.5 hours. The reaction was allowed to cool to room temperature overnight. The reaction was poured into a slurry of silica gel (10 grams) in chloroform (100 mL) and stirred 10 minutes. Methanol (20 mL) was added (bubbling occured), and the mixture was filtered through a short silica gel bed in a sintered glass funnel, eluting with 1:1 methanol/chloroform to remove product. The filtrate was concentrated to give the crude product, which was purified by silica gel chromatography (MeOH/DCM = 0/100→50/0) to give 1.6 grams (45% yield) of the nitrile, which eluted first, and 1.9 g (45% yield) of the guanidine, which is the HCl salt. Guanidine: LC/MS (FA) ES+ 329. 331. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73, (bs, 4H), 8.76-8.74 (m, 2H), 7.90-7.88 (m, 2H), 7.39-7.35 (m, 2H), 7.31-7.27 (m, 2H), 4.30 (s, 2H). Nitrile: LC/MS (FA) ES+ 312, 314. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.77-8.75 (m, 2H), 7.78-7.76 (m, 2H), 7.34-7.29 (m, 4H), 4.29 (s, 2H).

[00774] **Step 2, Preparation of 4-(4-chlorobenzyl)-2-(pyridin-4-yl)-5-(1H-tetrazol-5-yl)thiazole**

[00775] To a solution 4-(4-chlorobenzyl)-2-(pyridin-4-yl)thiazole-5-carbonitrile (167 mg, 0.536 mmol) in DMF (3.5 mL) was added sodium azide (104 mg, 1.61 mmol) and ammonium chloride (86 mg, 1.61 mmol) and the resulting mixture was heated at 100 degrees overnight. The reaction was cooled and taken up in ethyl acetate and water. The aqueous layer was concentrated in vacuo, and the residue was purified by silica gel chromatography (MeOH/DCM = 0/100→10/90) to give 9 mg (5% yield) of the title compound. LC/MS (FA) ES+ 355, 357. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74-8.73 (m, 2H), 7.93-7.92 (m, 2H), 7.38-7.32 (m, 4H), 4.62 (s, 2H).

[00776] **Example 39: Preparation of 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 205)**



[00777] **Step 1:** Ethyl 5-pyridin-4-ylthiophene-2-carboxylate

[00778] A mixture of ethyl 5-bromothiophene-2-carboxylate (1.560 g, 6.65 mmol), pyridine-4-boronic acid (0.98 g, 7.98 mmol), tetrakis(triphenylphosphine)palladium(0) (768 mg, 0.665 mmol) and cesium carbonate (6.50 g, 19.9 mmol) in 1,4-dioxane (20 mL) and water (3.35 mL) was stirred and heated at 100° C under an atmosphere of nitrogen overnight.The reaction was a clear light orange with a small amount of a second liquid phase on the bottom of the flask. An aliquot was taken, quenched into water, and extracted with ethyl acetate. A TLC on silica gel (1:1 DCM:hexane) indicated that all of the starting material had been consumed. A major new product with Rf ~0.4 was seen. The reaction was cooled to room temperature then was quenched into stirring water and extracted with ethyl acetate. The ethyl acetate extracts were washed with saline, dried over sodium sulfate, filtered, and evaporated to leave crude product as an off-white solid. The crude product was dissolved in minimal DCM then was purified by column chromatography on silica gel (gradient 100% DCM to 50% ethyl acetate) to afford product 1.02g (66% yield) as white solid. LC/MS (FA) ES+ 234. ^{1}H NMR (400 MHz, DMSO) δ 8.68 – 8.60 (m, 2H), 7.91 – 7.83 (m, 2H), 7.78 – 7.71 (m, 2H), 4.37 – 4.27 (d, J = 7.1 Hz, 2H), 1.35 – 1.27 (t, J = 7.1 Hz, 3H).

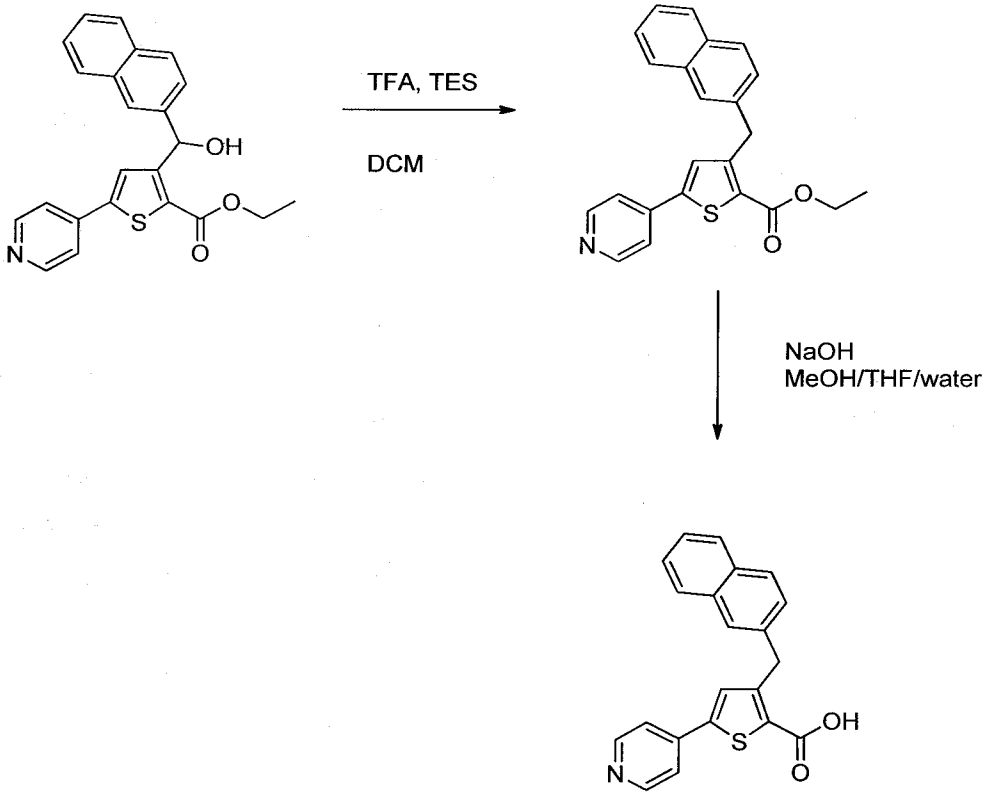
[00779] **Step 2:** Ethyl 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylate

[00780] A dry, nitrogen flushed flask, equipped with a stirbar and septum, was charged with 2,2,6,6-tetramethylpiperidinylmagnesium chloride•lithium chloride in tetrahydrofuran (1.0M, 1.21 mL, 1.21 mmol). The flask was cooled to -25° C and a solution of ethyl 5-pyridin-4-ylthiophene-2-carboxylate (0.257 g, 1.10 mmol) in tetrahydrofuran (1.0 mL, 12 mmol) was added dropwise with stirring. The resulting dark reddish orange solution was stirred at -25° C for 30 minutes. 2-Naphthalenecarboxaldehyde (0.172 g, 1.10 mmol) was then added dropwise (as a solution in 1.5 ml THF) - the reaction mixture became purple. The reaction was stirred at -25° for 5 minutes, then the cooling bath was removed and the reaction was allowed to warm to room temperature with stirring. An aliquot was removed from the reaction and quenched into sat. NH4Cl solution, then extracted with ethyl acetate. A LCMS of this extract indicated that all starting material had been consumed and that the major peak had correct mass for the desired product. The reaction was quenched by the slow dropwise addition of a saturated ammonium chloride solution (5 ml). The resulting yellow-orange mixture was transferred to a separatory funnel and diluted further with water and ethyl acetate. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate. The extracts were combined, washed with saline, dried, and evaporated to leave crude product as an orange oil which was dissolved in minimal dichloromethane then was purified by column chromatography on silica gel (gradient 100% DCM to 5% MeOH in ethyl acetate) to afford product 210 mg (49% yield) as a white foam. LC/MS (FA) ES+ 390. ^{1}H NMR (400 MHz, DMSO) δ 8.63 – 8.58 (dd, J = 4.6, 1.6 Hz, 2H), 8.04 – 8.00 (s, 1H), 8.00 – 7.96 (s, 1H), 7.87 – 7.81 (d, J = 8.7 Hz, 3H), 7.76 – 7.71 (dd, J = 4.6, 1.7 Hz, 2H), 7.62 – 7.58 (d, J = 1.6 Hz, 1H), 7.50 – 7.45 (t, J = 3.0 Hz, 2H), 6.74 – 6.69 (d, J = 4.2 Hz, 1H), 6.33 – 6.28 (d, J = 4.2 Hz, 1H), 4.37 – 4.31 (dd, J = 7.1, 4.3 Hz, 2H), 1.35 – 1.27 (t, J = 7.1 Hz, 3H).

[00781] **Step 3:** 3-[Hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 205)

[00782] Ethyl 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylate (70.0 mg, 0.180 mmol) was placed in a round bottomed flask equipped with a stirbar. Tetrahydrofuran (2.00 mL), methanol (1.00 mL), and water (1.50 mL) were added with stirring - all solids dissolved. Sodium hydroxide (1.0 M, 1.50 mL, 1.50 mmol) was added in a single portion and the resulting solution was stirred under an atmosphere of nitrogen overnight, resulting in a clear light yellow solution. The reaction was quenched into water and the pH of the mixture was adjusted the pH to ~6-6.5 with sodium bicarbonate solution. The mixture was extracted with ethyl acetate, the extracts were combined and then rotovapped to leave crude product as a light yellow solid. The crude product was purified by HPLC to yield 9 mg (14% yield) product as a pale yellow powder. LC/MS (FA) ES+ 362. ^{1}H NMR (400 MHz, DMSO) δ 8.60 – 8.51 (d, J = 6.1 Hz, 2H), 7.98 – 7.94 (s, 2H), 7.91 – 7.75 (m, 4H), 7.68 – 7.58 (m, 3H), 7.53 – 7.37 (m, 2H), 6.64 – 6.36 (s, 1H).

[00783] Example 40: Preparation of 3-(2-naphthylmethyl)-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 210)



[00784] **Step 1:** Ethyl 5-pyridin-4-ylthiophene-2-carboxylate

[00785] Ethyl 3-[hydroxy(2-naphthyl)methyl]-5-pyridin-4-ylthiophene-2-carboxylate (118.0 mg, 0.3030 mmol), methylene chloride (2.4 mL), trifluoroacetic acid (140.0 uL, 1.818 mmol), and triethylsilane (84.7 uL, 0.530 mmol) were combined in a round bottomed flask equipped with a stirbar. The reaction was stirred overnight at room temperature under an atmosphere of nitrogen. An aliquot was taken from the reaction, quenched into water, basified with sodium carbonate, and extracted with ethyl acetate. TLC analysis (2:1 ethyl acetate:DCM) indicated that the starting ester was ~50% converted to a slightly higher Rf product. Additional trifluoroacetic acid (300 uL, 4 mmol) and triethylsilane (200 uL, 1 mmol) were added and the reaction was stirred at room temperature under an atmosphere of nitrogen for another 4 hours. LCMS analysis showed one major peak with correct ES+ for product with a small amount of SM remaining. The reaction was quenched into water, basified, and extracted into ethyl acetate. The extract was washed with saline, dried over sodium sulfate, filtered, and evaporated to leave crude product as an oil. The crude product was dissolved in minimal DCM then was purified by column chromatography on silica gel (gradient 100% DCM to 50% ethyl acetate) to afford product 86 mg (76% yield) as a white solid. LC/MS (FA) ES+ 374. ^{1}H NMR (400 MHz, DMSO) δ 8.64 – 8.55 (m, 2H), 7.90

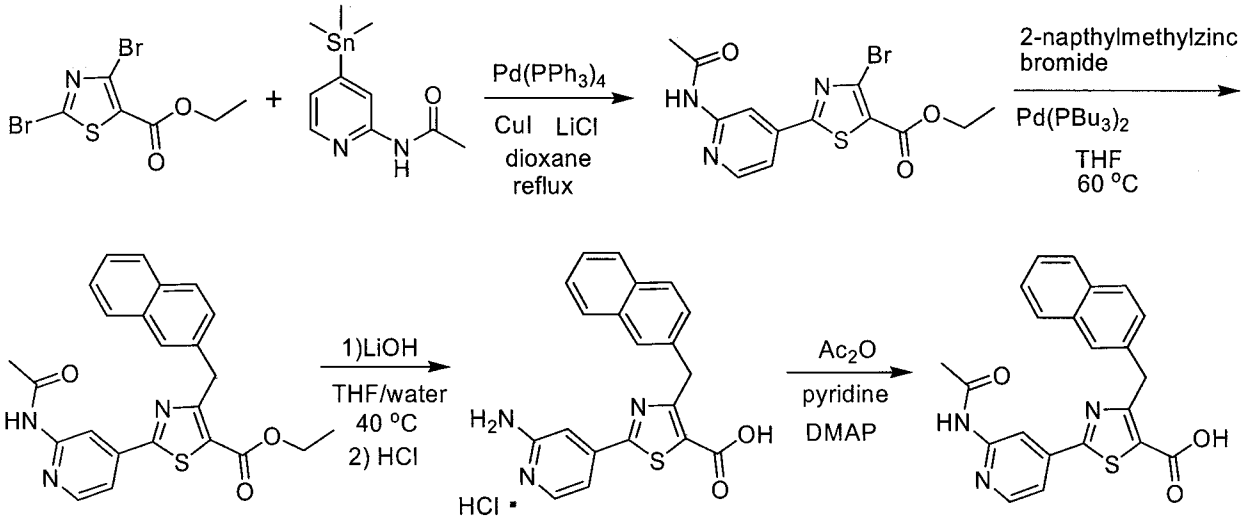
– 7.80 (m, 4H), 7.80 – 7.75 (s, 1H), 7.73 – 7.66 (m, 2H), 7.52 – 7.40 (m, 3H), 4.57 – 4.49 (s, 2H), 4.39 – 4.27 (q, J = 7.1 Hz, 2H), 1.35 – 1.25 (t, J = 7.1 Hz, 3H).

[00786] Step 2: 3-(2-naphthylmethyl)-5-pyridin-4-ylthiophene-2-carboxylic acid (Compound 210)

[00787] Ethyl 3-(2-naphthylmethyl)-5-pyridin-4-ylthiophene-2-carboxylate (80.0 mg, 0.214 mmol) was placed in a round bottomed flask equipped with a stirbar. Methanol (3 mL, 70 mmol) and tetrahydrofuran (3 mL, 40 mmol) were added followed by water (2 mL, 100 mmol). The resulting solution was stirred and lithium hydroxide in water (1.0 M, 0.643 mL, 0.643 mmol) was added. The flask was sealed and stirred overnight at RT. LCMS of an aliquot indicated that all starting material had been consumed to give a single product with the correct mass for the desired product. To the stirring reaction was added ~30 mL water and a few mL saline. The mixture was stirred and acidified to ~pH 1 with 1N HCl - a gelatinous precipitate formed. The mixture was stirred rapidly and diethyl ether (10 mL) was added – the precipitate became more granular and became suspended mostly in the organic layer. The quench mixture was stirred at room temperature for ~30 minutes then the solid was collected on a fritted funnel, washed well with water then diethyl ether, then dried in vacuo to yield product 60 mg (81% yield) as a white powder. LC/MS (FA) ES+ 346. ^{1}H NMR (400 MHz, DMSO) δ 13.62 – 13.20 (s, 1H), 8.63 – 8.52 (dd, J = 4.7, 1.5 Hz, 2H), 7.91 – 7.80 (m, 3H), 7.80 – 7.72 (d, J = 3.0 Hz, 2H), 7.70 – 7.63 (dd, J = 4.6, 1.5 Hz, 2H), 7.53 – 7.40 (m, 3H), 4.57 – 4.48 (s, 2H).

[00788] Example 41: Synthesis of 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid (Compound 177)

[00789]



[00790] Step 1, Preparation of ethyl 2-(2-acetamidopyridin-4-yl)-4-bromothiazole-5-carboxylate

[00791] A mixture of ethyl 2,4-dibromothiazole-5-carboxylate (0.500 g, 1.59 mmol), N-(4-(trimethylstannyl)pyridin-2-yl)acetamide (0.569 g, 1.90 mmol), tetrakis(triphenylphosphine)palladium(0) (91.7 mg, 0.0794 mmol), copper(I) iodide (90.7 mg, 0.476 mmol), and lithium chloride (202 mg, 4.76 mmol) in dioxane (29.1 mL) was degassed with nitrogen and heated at reflux for 1 hr. The reaction was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→50/50) to give 312 mg of the title compound. (44 % yield). LC/MS (FA) ES+ 370, 372. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 8.39 (d, 1H, J = 5.2 Hz), 8.25 (bs, 1H), 7.68 (dd, 1H, J = 5.2, 1.6 Hz), 4.41 (q, 2H, J = 7.2 Hz), 2.26 (s, 3H), 1.41 (t, 3H, J = 7.2 Hz).

[00792] Step 2, Preparation of ethyl 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylate

[00793] To a mixture of ethyl 2-(2-acetamidopyridin-4-yl)-4-bromothiazole-5-carboxylate (190 mg, 0.510 mmol) and bis(tri-t-butylphosphine)palladium(0) (65.6 mg, 0.128 mmol) under nitrogen was added a 0.500 M solution of 2-napthylmethylzinc bromide in THF (3.60 mL, 1.80 mmol). The reaction was stirred at room temperature for 5 minutes, then at 60 degrees for 1 hour. Another portion of bis(tri-t-butylphosphine)palladium(0) (60.0 mg, 0.117 mmol) was added, followed by another portion of 0.500 M solution of 2-napthylmethylzinc bromide in THF (3.00 mL, 1.50 mmol), and the reaction was heated at 60 degrees for an additional 45 minutes. The reaction was cooled to room temperature and quenched with saturated ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→100/0) to give 100 mg of the title compound. (40 % yield). LC/MS (FA) ES+ 432.

[00794] Step 3, Preparation of 2-(2-aminopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid, HCl salt

[00795] To a mixture of ethyl 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylate (100 mg, 0.232 mmol) in THF (2.00 mL) was added 1.0 M aqueous LiOH (2.32 mL, 2.32 mmol) and the resulting mixture was heated at 40 degrees for 3 days. The mixture was acidified with 1N HCl and the resulting precipitate was filtered and dried to give the 85 mg of the crude HCl salt (100% yield) which was used as is in the next step. LC/MS (FA) ES+ 362.\

Step 4, Preparation of 2-(2-acetamidopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid

a solution of (2-aminopyridin-4-yl)-4-(naphthalen-2-ylmethyl)thiazole-5-carboxylic acid, HCl salt (85.0 mg, 0.214 mmol) in acetic anhydride (1.15 mL, 12.2 mmol) and pyridine (0.300 mL, 3.71 mmol) was added DMAP (0.30 mg, 0.0024 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue was purified by silica gel

chromatography (MeOH/DCM = 0/100→40/60) to give 20 mg of the title compound (23 % yield). LC/MS (FA) ES+ 404. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.84 (bs, 1H), 10.7 1 (s, 1H), 8.63 (s, 1H), 8.41 (d, 1H, J = 5.2 Hz), 7.86-7.82 (m, 3H), 7.76 (s, 1H), 7.57 (dd, 1H, J = 5.2, 1.2 Hz), 7.49-7.42 (m, 3H), 4.70 (s, 2H), 2.10 (s, 3H).

[00796] The following analytical methods were used for examples below:

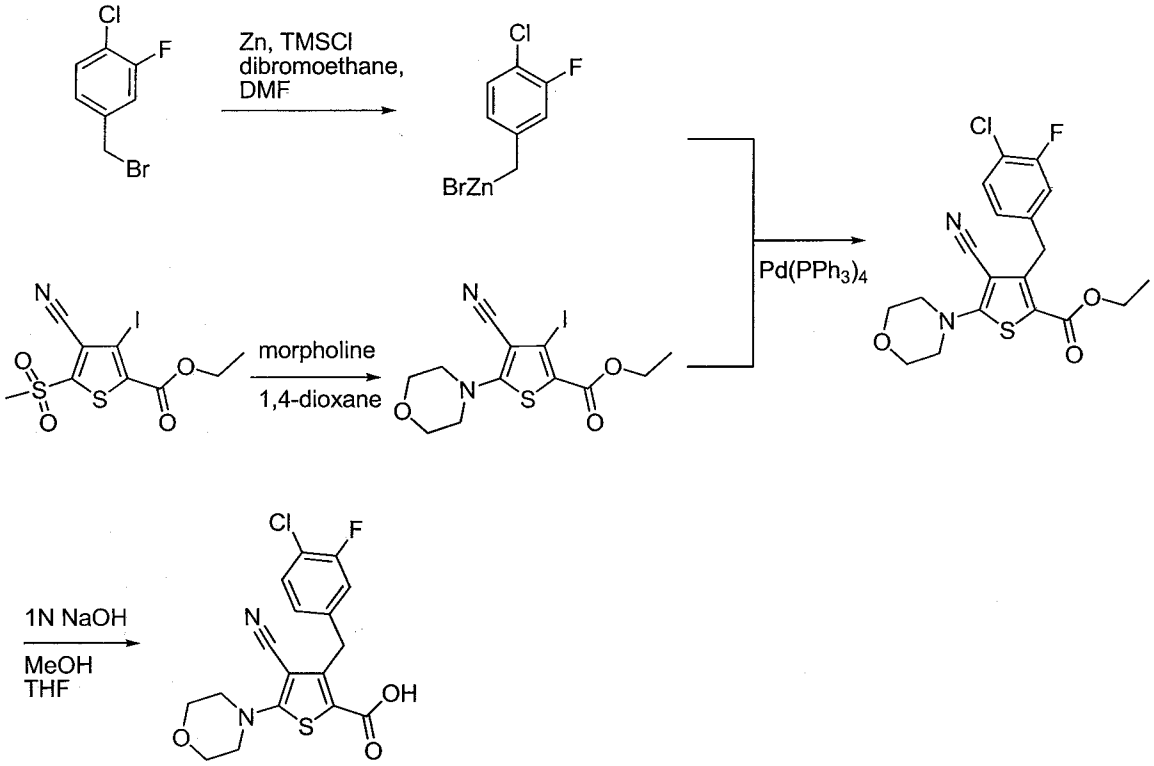
[00797] LCMS sectra were run on a Phenominex Luna 5μm C18 50 × 4.6 mm column on a Hewlett-Packard HP1100 using the following gradients:

- Method Formic Acid (FA): Acetonitrile containing 0 to 100 percent 0.1 % formic acid in water (2.5 ml/min for a 3 minute run).
- Method Ammonium Acetate (AA): Acetonitrile containing 0 to 100 percent 10 mM ammonium acetate in water (2.5 ml/min for a 3 minute run).

[00798] Chiral isomers were separated using chiral HPLC on a Chiralpak IC 250x25 mm 5 micron column using hexane/ethanol/diethylamine or hexane/isopropylalcohol/ethanol/diethylamine as mobil phase. Absolute configurations of the separated isomers were unknown, structures were assigned arbitrarily.

[00799] NMR spectrum is shown by proton NMR, with tetramethylsilane as the internal standard and using 300MHz Bruker Avance spectrometer equipped with a 5mm QNP probe and 400MHz Bruker Avance II spectrometer equipped with a 5mm QNP probe for the measurement; δ values are expressed in ppm.

[00800] Example 42: Synthesis of 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylic acid (Compound 94).



[00801] **Step 1:** Ethyl 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylate.

[00802] To a 500 mL RBF containing ethyl 4-cyano-3-iodo-5-(methylsulfonyl)thiophene-2-carboxylate (17.20 g, 44.65 mmol, prepared as in WO 2009154741) was added anhydrous 1,4-dioxane (172.0 mL, 2204 mmol). To the resulting suspension was added morpholine (8.177 mL, 93.77 mmol). A reflux condenser was attached and the pink/orange heterogeneous suspension was heated to bath temp 90 °C and allowed to stir. Shortly after heating began, reaction mixture became a cherry red, homogenous solution. Reaction was stirred for 16 hours at 90 °C. The reaction was then cooled to room temperature and diluted with water (100 mL). Mixture was filtered, and the solid was dried for in vacuo at 40 °C for 5 days to afford ethyl 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylate (14.3 grams, 82% yield). LCMS: (FA) ES+ 393; ^{1}H NMR (400 MHz, DMSO) δ 4.24 (q, J = 7.1, 2H), 3.78 – 3.70 (m, 4H), 3.63 – 3.57 (m, 4H), 1.26 (t, J = 7.1, 3H).

[00803] **Step 2:** Ethyl 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylate.

[00804] In a flame-dried scintillation vial, to a suspension of zinc (0.0998 g, 1.53 mmol) in N,N-dimethylformamide (1.36 mL, 17.6 mmol) were added 1,2-dibromoethane (0.003279 mL, 0.03805 mmol) and chlorotrimethylsilane (0.004830 mL, 0.03805 mmol). Stirred at room temperature for 15 min, at

which point a solution of 3-fluoro-4-chlorobenzylbromide (0.341 g, 1.53 mmol) in N,N-dimethylformamide (1.36 mL, 17.6 mmol) was added. The resulting suspension was stirred at room temperature for 16 hours. A scintillation vial containing ethyl 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylate (199 mg, 0.507 mmol and bis(tri-t-butylphosphine)palladium(0) (12.96 mg, 0.02537 mmol) was purged via vacuum/backfilling with argon. To this was added the organozinc solution from above, and the resulting solution was stirred at 45 °C for 6 hours, at which point LC/MS showed complete conversion to a single new peak with mass representing desired product. The reaction mixture was transferred to a separatory funnel containing saturated $NaHCO_3$ (aq., 10 mL) and water (10 mL), and then diluted with EtOAc (40 mL). The layers were separated, and the aqueous layer was extracted 2 x 30 mL with EtOAc. The combined organic layers were washed 1 x brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude ethyl 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylate as a brown oil that was used without further purification. LCMS: (FA) ES+ 409, 411

[00805] **Step 3:** 3-(4-Chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylic acid (Compound **94**).

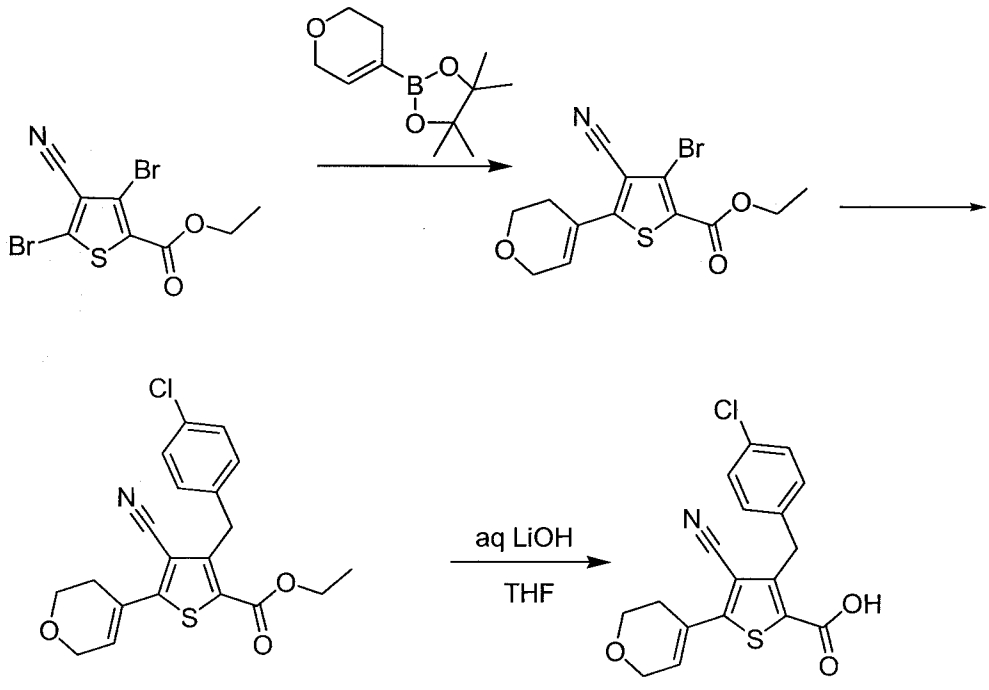
[00806] To a solution of ethyl 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylate in tetrahydrofuran (5.64 mL, 69.6 mmol) was added methanol (2.5 mL, 62 mmol) and 1 M sodium hydroxide in water (4.23 mL, 4.23 mmol) and the resulting suspension was stirred at room temp. The reaction was stirred for 16 hours at room temperature. Volatiles were then removed in vacuo, and the residue diluted with EtOAc (30 mL). Mixture was then transferred to a separatory funnel containing 1N HCl (5.0 mL) and water (10 mL), at which time the pH of aqueous layer was measured at ~2.0. Layers were separated, and the aqueous layer was extracted 3 x 20 mL with EtOAc. Combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo. Resulting residue was adsorbed to celite, and the resulting solid was placed into a dryload cartridge and purified via column chromatography (gradient elution, 0-5% MeOH:CH_2Cl_2) to afford 3-(4-chloro-3-fluorobenzyl)-4-cyano-5-morpholin-4-ylthiophene-2-carboxylic acid (**94**) as a white solid (0.128 g, yield 66.3%). LCMS: (FA) ES+ 381, 383; ^{1}H NMR (400 MHz, DMSO) δ 13.25 (s, 1H), 7.52 (dd, J = 8.1, 8.1, 1H), 7.22 (dd, J = 1.9, 10.5, 1H), 7.05 (dd, J = 1.5, 8.3, 1H), 4.31 (s, 2H), 3.80 – 3.65 (dd, J = 4.5, 5.2, 4H), 3.59 – 3.47 (dd, J = 4.5, 5.2, 4H).

[00807] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 42.

96	LC/MS: (FA) ES- 395, 397

97	LC/MS: (AA) ES+ 347
102	LC/MS: (FA) ES- 411
105	LC/MS: (AA) ES+ 359
106	LC/MS: (FA) ES- 405, 407
107	LC/MS: (FA) ES- 381
108	LC/MS: (FA) ES+ 393, 395
112	LC/MS: (FA) ES+ 379
115	LC/MS: (FA) ES+ 354
116	LC/MS: (FA) ES+ 363
117	LC/MS: (FA) ES- 391, 393
122	LC/MS: (FA) ES- 391, 393
123	LC/MS: (FA) ES+ 381
124	LC/MS: (FA) ES- 395, 397
125	LC/MS: (FA) ES+ 393, 395
126	LC/MS: (FA) ES- 397, 399
127	LC/MS: (FA) ES- 409, 411
300	LC/MS: (FA) ES- 397

[00808] Example 43: Synthesis of 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylic acid (Compound 95).



[00809] **Step 1:** Ethyl-3-bromo-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate.

[00810] To a microwave vial containing a suspension of ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate (300.0 mg, 0.8849 mmol, prepared as in MPI10-008P1M) and 3,6-dihydro-2h-pyran-4-boronic acid pinacol ester (204 mg, 0.973 mmol) in 1,4-dioxane (8.98 mL, 115 mmol) and water (0.925 mL, 51.3 mmol) were added tetrakis(triphenylphosphine)palladium(0) (102 mg, 0.0885 mmol) and cesium carbonate (865 mg, 2.65 mmol). The vial was sealed, degassed by bubbling argon through for 10 minutes, and then heated at 100 °C with stirring for 24 h. The reaction was then cooled to room temperature and partitioned between EtOAc and water. Layers were separated, and the aqueous layer was extracted 2x with EtOAc. Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Residue was subjected to column chromatography as a solution in DCM (40 g column, gradient elution 0 to 25% EtOAc/hexanes) to afford ethyl 3-bromo-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate as a white solid (183 mg, yield 63%). LCMS: (FA) ES+ 342, 344; ^{1}H NMR (400 MHz, DMSO) δ 6.86 – 6.79 (m, 1H), 4.36 – 4.27 (m, 4H), 3.82 (dd, J = 5.4, 5.4, 2H), 2.53 (ddd, J = 2.1, 4.9, 10.0, 2H), 1.30 (dd, J = 7.1, 7.1, 3H).

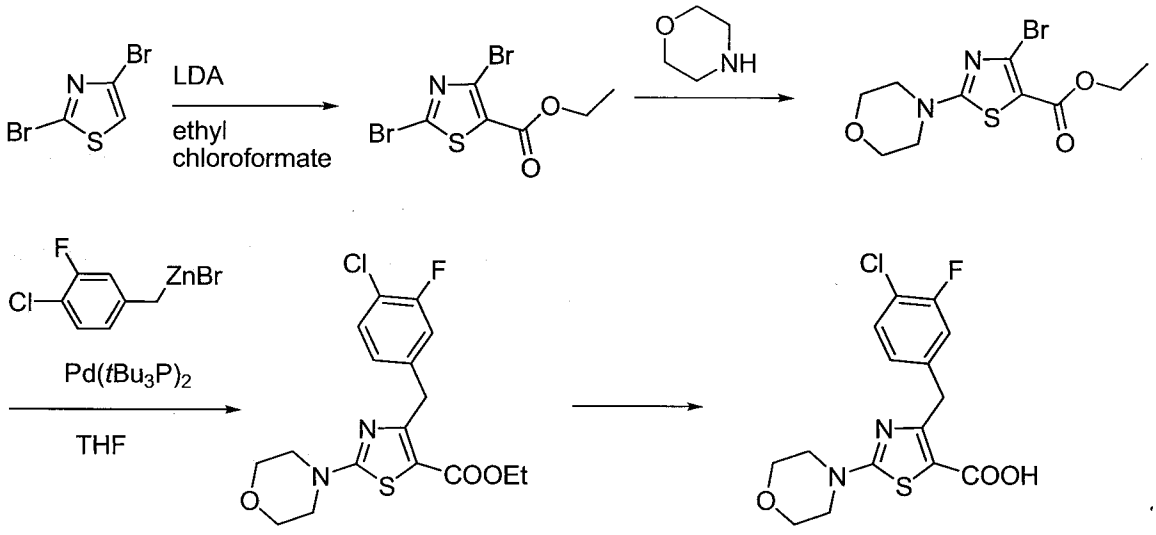
[00811] **Step 2:** Ethyl 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate.

[00812] In a sealable reaction vial, ethyl 3-bromo-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate (180.0 mg, 0.5260 mmol) and a stir pea were azeotroped with toluene 3x and dried under high vacuum overnight. To the vial was added bis(tri-t-butylphosphine)palladium(0) (26.88 mg, 0.05260 mmol). Vial was evacuated and then back-filled with argon 2X, at which time was added via syringe 4-chlorobenzylzinc chloride as a 0.50 M solution in tetrahydrofuran (3.682 mL, 1.841 mmol). The reaction was heated with stirring at 60° C for 2h. Reaction was cooled to room temperature and then diluted with EtOAc and sat. aq. NH_4Cl. Mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer extracted 2x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered through a pad of Celite, and concentrated in vacuo to afford a yellow oil. The residue was dissolved in DCM and loaded onto 40 g ISCO column (gradient elution: 0-25% EtOAc/hexanes) to afford ethyl 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate (92 mg, 43.6%) as a yellow solid. LC/MS: (AA) ES- 386, 388; ^{1}H NMR (400 MHz, DMSO) δ 7.38 – 7.33 (m, 2H), 7.22 (m, 2H), 6.80 – 6.76 (m, 1H), 4.40 (s, 2H), 4.34 – 4.24 (m, 4H), 3.80 (dd, J = 5.4, 5.4, 2H), 2.52 (dd, J = 2.2, 5.0, 2H), 1.26 (dd, J = 7.1, 7.1, 3H).

[00813] **Step 3:** 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylic acid (Compound **95**).

[00814] To a round bottom flask containing ethyl 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylate (43.0 mg, 0.111 mmol) were added tetrahydrofuran (1.23 mL, 15.2 mmol), sodium hydroxide (1.0N in water, 0.925 mL, 0.925 mmol), and methanol (0.617 mL, 15.2 mmol). The mixture was stirred at room temperature overnight. Reaction was quenched via addition of 1N HCl in water (2 mL), then diluted with EtOAc and transferred to separatory funnel. The layers were separated, and the aqueous layer was extracted 2x with EtOAc. Combined organics were washed with brine, dried over Na_2SO_4, and filtered, at adsorbed to Celite (10 mL). Column chromatography (40 g ISCO column, gradient elution 0-8% MeOH/DCM afforded 3-(4-chlorobenzyl)-4-cyano-5-(3,6-dihydro-2H-pyran-4-yl)thiophene-2-carboxylic acid (**95**) (25 mg, 63%) as a white solid. LC/MS: (FA) ES- 358, 360; ^{1}H NMR (400 MHz, DMSO) δ 14.04 (br s, 1H), 7.33 (d, J = 8.5, 2H), 7.26 (d, J = 8.5, 2H), 6.64 (s, 1H), 4.43 (s, 2H), 4.24 (d, J = 2.9, 2H), 3.79 (dd, J = 5.4, 5.4, 2H), 3.32 (br s, 2H).

[00815] **Example 44: Synthesis of 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid (Compound 118).**



[00816] **Step 1:** Ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate.

[00817] In a 50mL 2-neck RBF equipped with septa, a solution of N,N-Diisopropylamine (0.04374 g, 0.4322 mmol) in tetrahydrofuran (1.33 mL, 16.4 mmol) under atmosphere of argon was cooled at -78 °C, at which point n-butyllithium (2.50 M in hexane, 0.1647 mL, 0.4116 mmol) was added dropwise and the resulting solution was stirred for 30 minutes at -78 °C. To the above solution was added dropwise a solution of 2,4-dibromothiazole (0.100 g, 0.412 mmol) in tetrahydrofuran (1.33 mL, 16.4 mmol) at -78

°C, and this solution was stirred for 30 min -78 °C . Next, ethyl chloroformate (0.07872 mL, 0.8233 mmol) was added dropwise at -78 °C and the mixture was stirred for 30 minutes. The reaction was quenched by addition of water (20 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via silica gel column chromatography (12g Analogix column, gradient elution 5% to 10% EtOAc in hexane) to afford ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate (60 mg, yield 46%). LC/MS: (FA) ES+ 314, 316, 318; ^{1}H NMR (400 MHz, CDCl3) δ 4.37 (q, J = 7.1, 2H), 1.44 – 1.33 (m, 3H).

[00818] **Step 2:** Ethyl 4-bromo-2-morpholin-4-yl-1,3-thiazole-5-carboxylate.

[00819] In a sealable reaction vessel, to a suspension of ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate (2.90 g, 9.21 mmol, prepared as in WO 2005026149) and cesium carbonate (9.00 g, 27.6 mmol) in tetrahydrofuran (24.3 mL, 299 mmol) was added morpholine (0.883 mL, 10.1 mmol), at which point the vessel was sealed and the mixture was heated with stirring at 90 °C for 4 hours. Reaction mixture was diluted with EtOAc and water and transferred to a separatory funnel. Layers were separated, and the organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. Residue was subjected to column chromatography (gradient elution, 0 to 50% EA in hexanes) to afford ethyl 4-bromo-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (2.4 g, yield 81%) as a white solid. LC/MS: (FA) ES+ 321, 323; ^{1}H NMR (300 MHz, CDCl3) δ 4.30 (dd, J = 7.1, 7.1, 2H), 3.82 – 3.75 (m, 4H), 3.58 – 3.50 (m, 4H), 1.34 (dd, J = 7.1, 7.1, 3H).

[00820] **Step 3:** Ethyl-4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylate.

[00821] In a 50ml flame-dried round bottom flask, a suspension of zinc (0.183 g, 0.00280 mol), chlorotrimethylsilane (8.9 uL, 0.000070 mol) and 1,2-dibromoethane (6.0 uL, 0.000070 mol) in N,N-dimethylformamide (2.4 mL, 0.031 mol) was stirred for 15 minutes. To this was added a solution of 3-fluoro-4-chlorobenzylbromide (0.626 g, 0.00280 mol) in N,N-dimethylformamide (4.8 mL, 0.062 mol), and the resulting suspension was stirred overnight at room temperature. To a flame-dried 50 ml round bottom flask containing ethyl 4-bromo-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (0.300 g, 0.000934 mol) and bis(tri-t-butylphosphine)palladium(0) (36 mg, 0.000070 mol) was added the organozinc solution from above, and the reaction was heated with stirring at 60 °C for 60 min. Reaction was quenched with saturated ammonium chloride, and then transferred to a separatory funnel containing water (10 mL) and EtOAc (40 mL). The layers were separated, and the aqueous layer was extracted 2 x 30 mL with EtOAc. The combined organic layers were washed 1 x brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was dissolved in DCM, adsorbed onto silica gel and purified via column

chromotography (24 gram Isco column, gradient elution, 0-50% EtOAc / hexanes) to afford ethyl 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (245 mg, yield 68.2%).

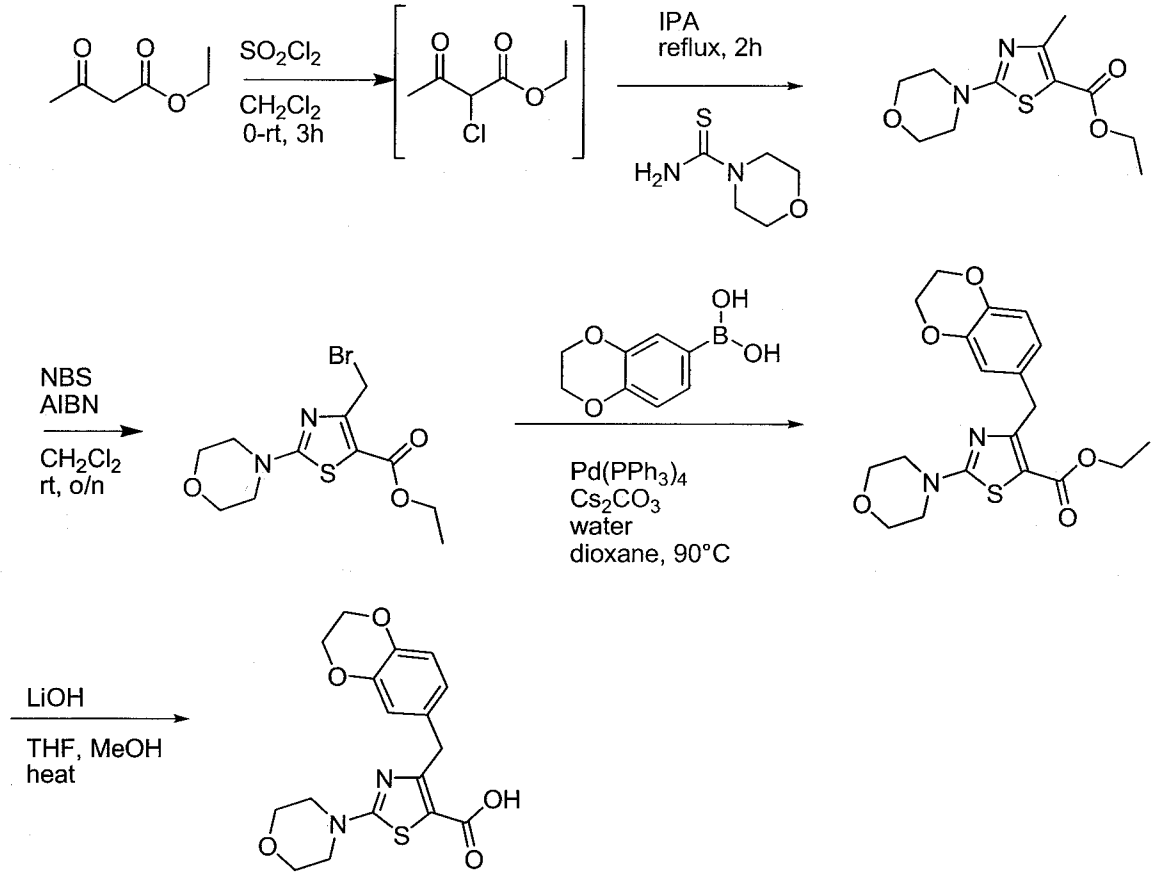
[00822] **Step 4:** 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid (Compound **118**).

[00823] In a 50 mL round bottom flask were combined ethyl 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylate (0.245 g, 0.000637 mol), tetrahydrofuran (5.49 mL, 0.0677 mol) and a solution of lithium hydroxide (2.0 M in water, 3.18 mL, 0.00637 mol). The mixture was heated at 80 °C with stirring for 2 days, and then cooled to room temperature and diluted with water. Reaction mixture was then carefully adjusted to pH 5 via addition of 1N HCl and transferred to a separatory funnel containing EtOAc (40 mL). Layers were separated, and the aqueous layer was extracted 2 x 30 mL with EtOAc. The combined organic layers were washed 1 x brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a white solid, which was dissolved in DCM and adsorbed onto silica gel. Column chromatography (4 g column, gradient elution 0-20% MeOH in DCM) then afforded 4-(4-chloro-3-fluorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid (**118**) (31 mg, 14%). LC/MS: (FA) ES+ 357, 359; ^{1}H NMR (400 MHz, DMSO) δ 12.79 (s, 1H), 7.48 (t, J = 8.1, 1H), 7.24 (dd, J = 1.9, 10.5, 1H), 7.08 (dd, J = 1.5, 8.3, 1H), 4.24 (s, 2H), 3.71 – 3.62 (m, 4H), 3.46 – 3.38 (m, 4H).

[00824] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 44

91	LC/MS: (FA) ES+ 339
93	LC/MS: (FA) ES+ 330
98	LC/MS: (FA) ES+ 355
101	LC/MS: (FA) ES+ 357, 359
103	LC/MS: (FA) ES+ 335
104	LC/MS: (FA) ES+ 373, 375, 377
109	LC/MS: (FA) ES+ 389
111	LC/MS: (FA) ES+ 373
114	LC/MS: (FA) ES+ 373, 375, 377
119	LC/MS: (FA) ES+ 323
120	LC/MS: (FA) ES+ 369, 371

[00825] Example 45: Synthesis of 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound 110).



[00826] **Step 1**: Butanoic acid, 2-chloro-3-oxo-, ethyl ester.

[00827] In a 500 mL round bottomed flask, to a solution of 3-oxobutanoic acid ethyl ester (7.69 mL, 60.3 mmol) in methylene chloride (150 mL, 2300 mmol) at 0 °C was slowly added sulfuryl chloride (6.30 mL, 77.8 mmol). The mixture was stirred for 3 hours, and then quenched with saturated $NaHCO_3$. Mixture was transferred to a separatory funnel the layers were separated. The organic layer was washed 1 x brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford butanoic acid, 2-chloro-3-oxo-, ethyl ester which was immediately used without further purification.

[00828] **Step 2:** Ethyl 4-methyl-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00829] In a 100 mL round bottomed flask, to a solution of butanoic acid, 2-chloro-3-oxo-, ethyl ester (11.2 g, 68.4 mmol) in isopropyl alcohol (250 mL, 3300 mmol) was added morpholine-4-carbothioicacidamide (10.0 g, 68.4 mmol). The mixture was stirred at reflux for 1 hour, and then stirred at room temperature for 3 days. Volatiles were removed in vacuo, and the resulting residue was dissolved in ethyl acetate and diluted with saturated, aqueous sodium bicarbonate. The mixture was transferred to a

separatory funnel, the layers were separated, and the organic layer dried with Na2SO4, filtered and concentrated in vacuo. The crude product was dissolved in DCM, adsorbed onto silica gel, and purified via column chromatography (120 g Isco column, gradient elution, 0-100% EtOAc/hexanes) to afford ethyl 4-methyl-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (14.51 g, yield for 2 steps, 82%). LC/MS: (FA) ES+ 257, 259; ^{1}H NMR (400 MHz, CDCl3) δ 4.26 (dd, J = 7.1, 7.1, 2H), 3.87 – 3.67 (m, 4H), 3.59 – 3.42 (m, 4H), 2.55 (s, 3H), 1.33 (dd, J = 7.1, 7.1, 3H).

[00830] **Step 3:** Ethyl 4-(bromomethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00831] To a round bottom flask containing a solution of ethyl-4-methyl-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (14.50 g, 56.57 mmol) in methylene chloride (400 mL, 6000 mmol) were added N-bromosuccinimide (10.07 g, 56.57 mmol) and 2,2'-azo-bis-isobutyronitrile (464 mg, 2.83 mmol). The mixture was stirred at reflux overnight. Reaction was quenched via addition of 10% aqueous sodium bisulfite (20 g in 200 ml water) and stirred for 20 minutes. Mixture was transferred to a separatory funnel, the layers separated, and the aqueous layer was extracted 2 x DCM. Combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was dissolved in DCM and adsorbed onto silica gel. Purification via column chromatography (220 g Isco column, gradient elution 0-10% EtOAc in 1:1 DCM:hexanes) afforded ethyl 4-(bromomethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (13.5 g, yield 71.1%). LC/MS: (FA) ES+ 335, 337; ^{1}H NMR (300 MHz, CDCl3) δ 4.76 (s, 2H), 4.30 (dd, J = 7.1, 7.1, 2H), 3.88 – 3.72 (m, 4H), 3.62 – 3.49 (m, 4H), 1.35 (dd, J = 7.1, 7.1, 3H).

[00832] **Step 4:** Ethyl 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00833] Ethyl 4-(bromomethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (109.4 mg, 0.326 mmol), 1,4-benzodioxane-6-boronic acid (91.0 mg, 0.506 mmol), tetrakis(triphenylphosphine)palladium(0) (43.0 mg, 0.0372 mmol), cesium carbonate (430 mg, 1.3 mmol), 1,4-dioxane (2.19 mL, 28.0 mmol) and water (43.8 uL, 2.43 mmol) were combined in a vial equipped with a stirbar. The vial was sealed and the atmosphere was replaced with nitrogen. The vial was sonicated for 1 minute then heated at 90°C (heating block temperature) with stirring for 1 hour. The reaction was cooled to room temperature, the vial was opened and the contents were quenched into stirring saline. The quench mixture was transferred to a separatory funnel and extracted twice with ethyl acetate. The extracts were combined, washed with saline, dried over sodium sulfate, filtered, and concentrated in vacuo to leave an orange oil. The crude residue was purified by silica gel chromatography (gradient elution: ethyl acetate/hexane from 0/100 to 100/0) to give ethyl 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (60 mg, 47% yield)

as a white powder. LC/MS (FA) ES+ 391; ^{1}H NMR (300 MHz, DMSO-d6) δ: 6.67-6.74 (m, 3H), 4.20 (q, 2H, J = 7.1 Hz), 4.17 (s, 4H), 4.07 (s, 2H), 3.69-3.65 (m, 4H), 3.46-3.43 (m, 4H), 1.24 (t, 3H, J = 7.1 Hz).

[00834] **Step 5:** 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound **110**).

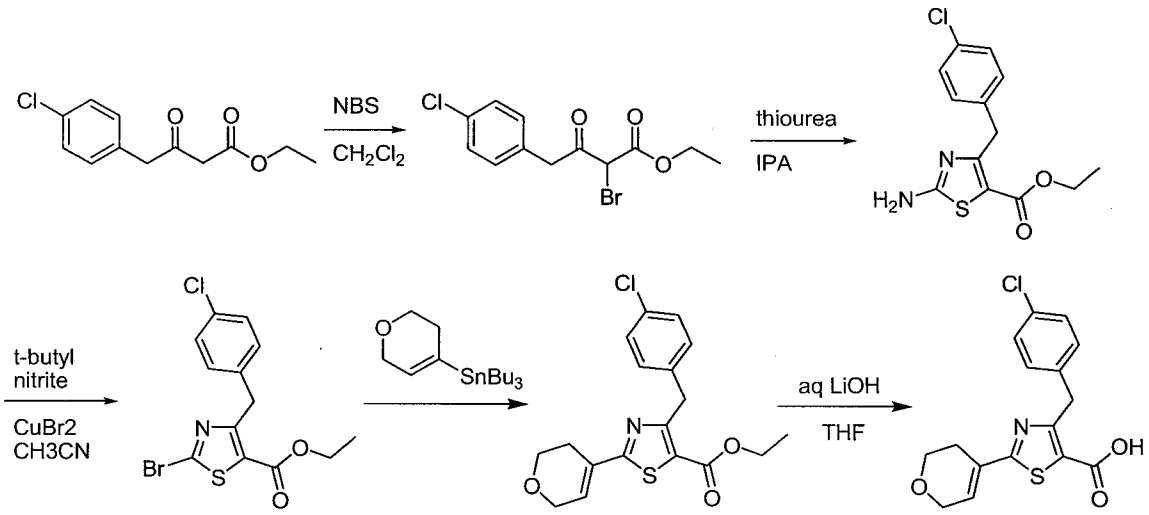
[00835] Ethyl 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (58.0 mg, 0.000148 mol) was placed in a 50 ml round bottom flask equipped with a stirbar. Tetrahydrofuran (2.25 mL, 0.0277 mol) and methanol (0.50 mL, 0.012 mol) were added and the mixture was stirred to give a clear solution. A solution of lithium hydroxide in water (2.0M, 0.750 mL, 0.00150 mol) was added in a single portion, resulting in a pale yellow solution which was stirred at room temperature under an atmosphere of nitrogen for 15 minutes. The reaction was then heated at reflux for 2.5 hours, cooled to rt, and diluted with water (~25 ml) to give a clear slightly gray solution, which was allowed to stir at room temperature overnight under an atmosphere of nitrogen. 1 N HCl (~1.8ml) was slowly added to the stirring solution to lower the pH to ~3 (pH paper) whereupon a white precipitate formed. The mixture was stirred for ~15 minutes, at which point the solid was collected on a fritted funnel, washed with water, and dried on the funnel with house vacuum under a stream of nitrogen for several hours to yield 4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (**110**) (45 mg, 84% yield) as a slightly gray powder. LC/MS (FA) ES+ 363; ^{1}H NMR (300 MHz, DMSO) δ 12.65 (s, 1H), 6.76 – 6.64 (m, 3H), 4.17 (s, 4H), 4.08 (s, 2H), 3.77 – 3.61 (m, 4H), 3.51 – 3.34 (m, 4H).

[00836] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 45.

99	LC/MS: (FA) ES+ 357, 359
128	LC/MS: (AA) ES+ 373
286	LC/MS: (FA) ES+ 361
288	LC/MS: (AA) ES+ 385
289	LC/MS: (FA) ES+ 376
290	LC/MS: (FA) ES+ 391, 393, 395
292	LC/MS: (AA) ES+ 356
299	LC/MS: (AA) ES+ 373
302	LC/MS: (FA) ES+ 358

303	LC/MS: (FA) ES+ 439, 441
310	LC/MS: (AA) ES+ 373
314	LC/MS: (AA) ES+ 373
318	LC/MS: (FA) ES+ 398
319	LC/MS: (AA) ES+ 373
325	LC/MS: (FA) ES+ 380
328	LC/MS: (FA) ES+ 344
335	LC/MS: (AA) ES+ 385
338	LC/MS: (AA) ES+ 373
339	LC/MS: (FA) ES+ 365
340	LC/MS: (AA) ES+ 373
341	LC/MS: (AA) ES+ 345
344	LC/MS: (AA) ES+ 356

[00837] Example 46: Synthesis of 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylic acid (Compound 100).



[00838] Step 1: Ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate.

[00839] In a 250 mL round bottomed flask, to a solution of ethyl 4-(4-chlorophenyl)-3-oxobutanoate (4.04 g, 16.8 mmol) in methylene chloride (100 mL, 2000 mmol) was added N-bromosuccinimide (3.13 g, 17.6 mmol) and the mixture was stirred for 3 h at room temperature. Reaction was quenched via addition of a 10% aqueous solution of $NaHSO_3$ (50 mL), and the resulting biphasic mixture was vigorously stirred for 15 minutes. The reaction mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers

were washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate (5.23 g, yield 97.5%) as a yellow oil that was used without further purification. LC/MS (FA) ES- 317, 319, 321.

[00840] **Step 2:** Ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate.

[00841] In a 100 mL round bottomed flask, to a solution of ethyl 2-bromo-4-(4-chlorophenyl)-3-oxobutanoate (990 mg, 3.1 mmol) in isopropyl alcohol (20 mL, 300 mmol) was added thiourea (590 mg, 7.8 mmol) and the resulting mixture was stirred at reflux for 16 hours. The mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was suspended in EtOAc (50 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), brine (50 mL). The resulting organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (900 mg, yield >99%) as a yellowish solid that was used without further purification. LC/MS (FA) ES+ 297, 299.

[00842] **Step 3:** Ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate.

[00843] In a 250 mL round bottomed flask, to a solution of ethyl 2-amino-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (786 mg, 2.65 mmol) in acetonitrile (75 mL, 1400 mmol) was added copper(II) bromide (963 mg, 4.31 mmol). The suspension was stirred at room temperature for 15 minutes to afford a green solution. To the mixture was added tert-butyl nitrite (0.630 mL, 5.30 mmol) and the reaction was then heated with stirring at 70 °C for 1.5 hours. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (80 gram column, gradient elution 10% to 50% EtOAc/hexanes) to afford ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (820 mg; yield 86%) as a yellow syrup. LC/MS (FA) ES+ 360, 362, 364; ^{1}H NMR (400 MHz, CDCl3) δ 7.33 – 7.20 (m, 4H), 4.44 (s, 2H), 4.34 (dd, J = 7.1, 7.1, 2H), 1.36 (dd, J = 7.1, 7.1, 3H).

[00844] **Step 4:** Ethyl-4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylate.

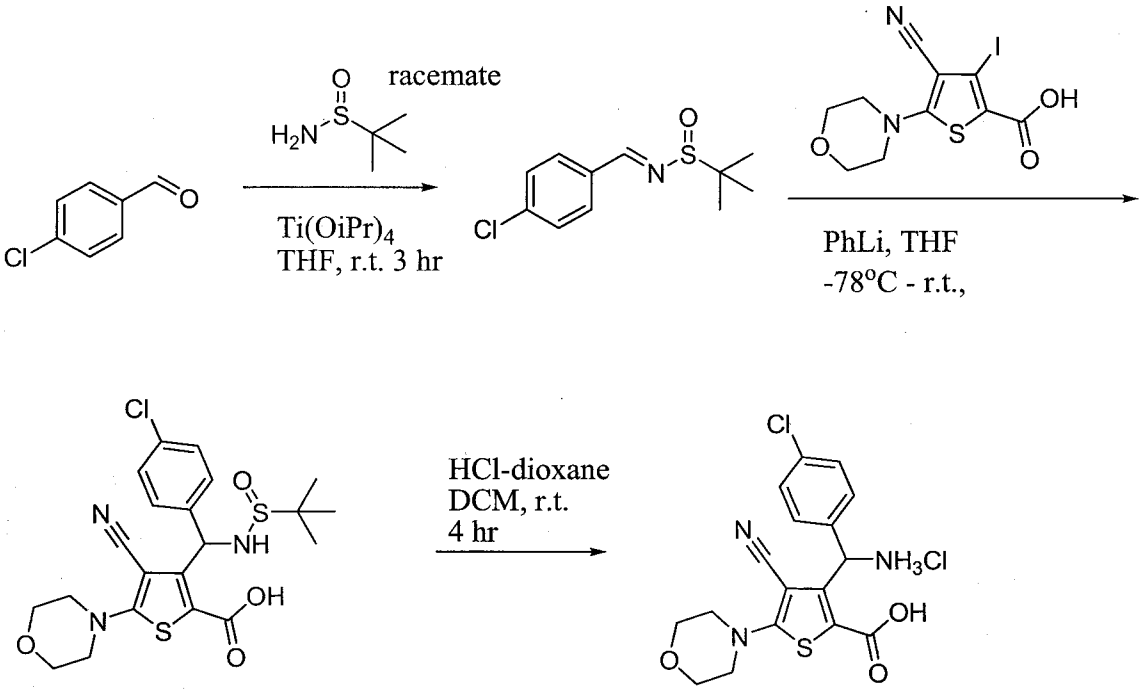
[00845] A mixture of ethyl 2-bromo-4-(4-chlorobenzyl)-1,3-thiazole-5-carboxylate (289 mg, 0.802 mmol), tributyl(3,6-dihydro-2H-pyran-4-yl)stannane (332 mg, 0.890 mmol), tetrakis(triphenylphosphine)palladium(0) (46.4 mg, 0.0401 mmol), lithium chloride (1.20E2 mg, 2.82 mmol) and copper(I) iodide (45.8 mg, 0.241 mmol) in dry 1,4-dioxane (6.26 mL, 80.2 mmol) was degassed by vacuum and backfilling with argon four times, and then heated under argon at reflux for 3 hours. The mixture was filtered thru Celite, washing with 10% MeOH in DCM. Volatiles were removed in vacuo, and the residue was adsorbed to silica gel by concentrating a DCM solution to which silica gel

had been added. Column chromatography (gradient elution, 0 to 20% EA in hexanes) afforded ethyl-4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylate (113 mg, 38.9%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.35 - 7.31 (m, 2H), 7.27 - 7.23 (m, 2H), 6.86 - 6.83 (m, 1H), 4.40 (s, 2H), 4.29 (q, J = 6.9, 2H), 4.25 – 4.22 (m, 2H), 3.78 (t, J = 5.4, 2H), 2.51 – 2.46 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H).

[00846] **Step 5:** 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylic acid (Compound **100**).

[00847] In a round bottom flask equipped with a stir bar, a solution of ethyl 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylate (109 mg, 0.300 mmol) in tetrahydrofuran (3.33 mL, 41.1 mmol) and methanol (1.67 mL, 41.1 mmol) was treated with lithium hydroxide (1.0M in water, 2.40 mL, 2.40 mmol). The mixture was stirred at room temperature overnight. pH was adjusted to ~3 via addition of 1N aqueous HCl solution, and the reaction was then diluted with EtOAc and transferred to separatory funnel. The layers were separated, and the aqueous layer was extracted 2x with EtOAc. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (gradient elution, 0 to 10 % MeOH in DCM) afforded 4-(4-chlorobenzyl)-2-(3,6-dihydro-2H-pyran-4-yl)-1,3-thiazole-5-carboxylic acid (**100**) (53 mg, yield 53% as a white powder. LCMS: (FA) ES+ 336; ^{1}H NMR (400 MHz, DMSO) δ 13.52 (bs, 1H), 7.35 – 7.31 (m, 2H), 7.27-7.23 (m, 2H), 6.82 – 6.79 (m, 1H), 4.40 (s, 2H), 4.24 – 4.22 (m, 2H), 3.77 (t, J = 5.4, 2H), 2.50 – 2.45 (m, 2H).

[00848] **Example 47: Synthesis of 3-[amino(4-chlorophenyl) methyl]-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid hydrochloride (Compound 113).**



[00849] **Step 1:** N-[(E)-(4-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide.

[00850] To a solution of 4-chlorobenzaldehyde (2.88 g, 20.5 mmol), (S)-(-)-2-methyl-2-propanesulfinamide (1.40 g, 11.6 mmol), and (R)-(+)-2-methyl-2-propanesulfinamide (1.40 g, 11.6 mmol) in anhydrous tetrahydrofuran (30.0 mL) under nitrogen atmosphere was added titanium tetraisopropoxide (6.00 mL, 20.3 mmol) dropwise. The clear solution was stirred at room temperature for 3 hours. Methylene chloride (200 mL) and water (2.0 mL) were added and the mixture was stirred at room temperature for 1 hour. The suspension was filtered through Celite and washed with DCM. The filtrate was concentrated in vacuo and purified by column chromatography (gradient elution: 0-20% EtOAc/hexane) to afford N-[(E)-(4-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide (3.93 g, yield 78.7%). LCMS: (FA) ES+ 244; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.78-7.80 (d, 2H, J = 8.53 Hz), 7.44-7.47(d, 2H, J = 8.53 Hz), 1.26 (s, 9H).

[00851] **Step 2:** 3-{[(tert-butylsulfinyl)amino](4-chlorophenyl)methyl}-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid.

[00852] 4-cyano-3-iodo-5-morpholin-4-ylthiophene-2-carboxylic acid (1.44 g, 3.96 mmol, prepared as in WO2009/154741) was suspended in anhydrous tetrahydrofuran (80.0 mL, 986 mmol), sonicated under nitrogen atmosphere for 10 min, and cooled in an acetone-dry ice bath for 10 minutes. Phenyllithium (1.8M in n-butyl ether, 8.81 mL, 15.9 mmol) was added dropwise over 7 minutes. The suspension was stirred with cooling for 5 minutes, at which point the cooling bath was removed and the

suspension was stirred without cooling for 7 minutes. Reaction mixture was recooled in an acetone-dry ice bath for 10 minutes, at which point a solution of N-[(E)-(4-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide (2.91 g, 11.9 mmol) in anhydrous tetrahydrofuran (20.0 mL, 246 mmol) was added dropwise over 8 minutes, and the mixture was stirred with cooling for 30 minutes. The mixture was quenched with methanol (5.0 mL, 120 mmol) and then acetic acid (1.0 mL, 18 mmol), and allowed to warm to room temperature. The volatiles were removed in vacuo, and the residue was diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with 2 x EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via column chromatography (gradient elution: AcOH/MeOH/DCM, 0/0/100 to 0.5/4.5/95) afforded 3-{[(tert-butylsulfinyl)amino](4-chlorophenyl)methyl}-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid as a mixture of diastereomers. Major diastereomer: 1.19 g, yield 62.2%. (FA) ES+ 482; ES- 480; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.33 (m, 2H), 7.15-7.17(m, 2H), 6.14 (br s, 2H), 3.87-3.89 (m, 4H), 3.60-3.63 (m, 4H), 1.21 (s, 9H). Minor diastereomer: (0.292 g, yield 15.3%). (FA) ES+ 482; ES- 480; ^{1}H NMR (400 MHz, CDCl3) δ 7.26-7.34 (m, 4H), 6.29-6.38 (m, br, 2H), 3.84-3.86 (m, 4H), 3.56-3.60 (m, 4H), 1.35 (s, 9H).

[00853] **Step 3:** 3-[amino(4-chlorophenyl) methyl]-4-cyano-5-(morpholin-4- yl)thiophene-2-carboxylic acid hydrochloride (Compound **113**).

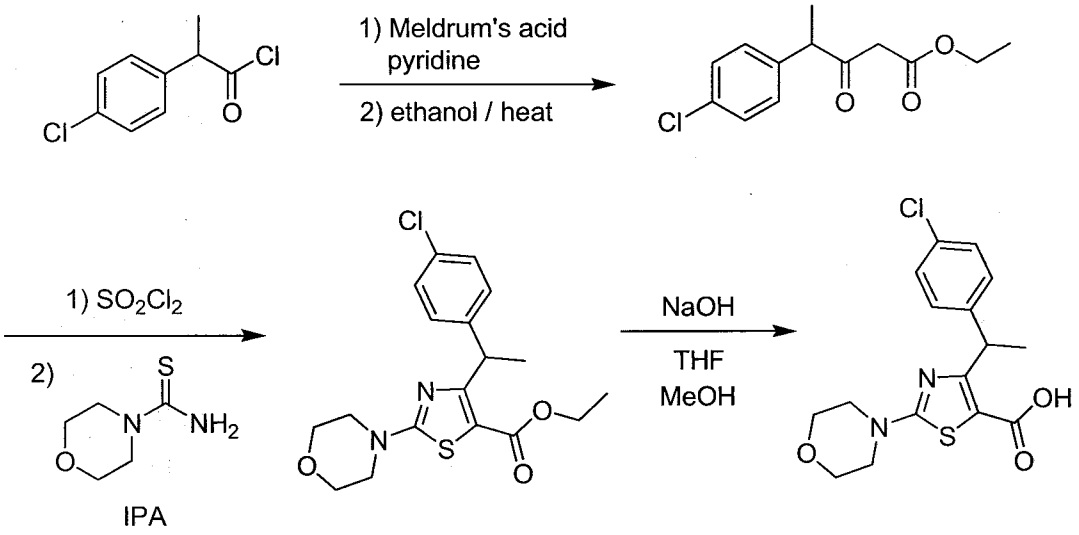
[00854] To a solution of 3-{[(tert-butylsulfinyl)amino](4-chlorophenyl)methyl}-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid (1.46 g, 3.03 mmol) in methylene chloride (25.0 mL) was slowly added hydrochloric acid (4M in 1,4-dioxane, 15.0 mL), and the resultant suspension was stirred at room temperature for 1 hour. The suspension was filtered through a fine frit funnel. The collected solid was washed with DCM and dried in vacuo to afford 3-[amino(4-chlorophenyl) methyl]-4-cyano-5-(morpholin-4- yl)thiophene-2-carboxylic acid hydrochloride (**113**) (1.10 g, yield 86.5%) as a white powder . LCMS: (FA) ES+ 378; ES- 376; ^{1}H NMR (400 MHz, CD3OD) δ 7.44-7.90 (m, 4H), 5.84 (s, 1H), 3.81-3.84 (m, 4H), 3.64-3.67 (m, 4H).

[00855] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 47.

291	LC/MS: (FA) ES+ 412, 413; ES- 410, 412
317	LC/MS: (FA) ES- 454, 456
323	LCMS: (FA) ES+ 498; ES- 496
342	LC/MS: (FA) ES+ 516, 518; ES- 514, 516
353	LC/MS: (FA) ES+ 420

354	LC/MS: (FA) ES+ 452
357	LC/MS: (FA) ES+ 394; ES- 392

[00856] Example 48: Synthesis of 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound 121).



[00857] Step 1: Ethyl 4-(4-chlorophenyl)-3-oxopentanoate.

[00858] In a round bottomed flask, to a suspension of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, 2.91 g, 20.2 mmol) in methylene chloride (11.3 mL, 177 mmol) at -10 °C (internal temp) was added pyridine (4.00 mL, 49.5 mmol) over 10 minutes. To the resulting clear solution at -10 °C, was added dropwise a solution of 2-(4-chlorophenyl)propanoyl chloride (4.10 g, 20.2 mmol) in methylene chloride (7.93 mL, 124 mmol) over 1 h. The reaction mixture was then stirred for 1h at -10 °C, and then for 1 hour at room temperature. The mixture was poured into hydrochloric acid (2.00M in water, 45.3 mL, 90.6 mmol) and ice, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with 1N HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. To the crude residue was added ethanol (39.6 mL, 679 mmol) and the mixture was heated at reflux (89 degree bath temp) for 3 hours. After cooling to room temp, the volatiles were removed in vacuo. Residue was adsorbed onto silica using DCM and purified via column chromatography (gradient elution: 0 to 20% EtOAc/hexanes to afford ethyl 4-(4-chlorophenyl)-3-oxopentanoate (2.94g, 92%) as a yellow oil. LCMS: (FA) ES+ 255; ^{1}H NMR (400 MHz, DMSO) δ 7.34 - 7.30 (m, 2H), 7.17 – 7.13 (m, 2H), 4.16 – 4.09 (m, 2H), 3.90 (q, J = 7.2, 1H), 3.40 (d, J = 15.6, 1H), 3.30 (d, J = 15.6, 1H), 1.40 (d, J = 6.8, 3H), 1.23 (t, J = 7.2, 3H).

[00859] Step 2: Ethyl 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate.

[00860] To a solution of ethyl 4-(4-chlorophenyl)-3-oxopentanoate (1.78 g, 6.99 mmol) in methylene chloride (22.4 mL, 349 mmol) at 0 °C was added sulfuryl chloride (566 uL, 6.99 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and transferred to a separatory funnel. The layers were separated and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was used immediately without further purification.

In a round bottomed flask, to a solution of the crude residue from above in isopropyl alcohol (50.3 mL, 657 mmol) was added morpholine-4-carbothioicacidamide (1.44 g, 9.86 mmol). The reaction mixture was heated with stirring at 90 °C for 90 minutes. Volatiles were removed in vacuo and the residue was redissolved in DCM and treated with saturated aqueous $NaHCO_3$ with stirring for 30 minutes. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (gradient elution: 0 to 25% EtOAc in hexanes) afforded ethyl 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (1.45 g, 57.9%) as a white solid. LCMS: (FA) ES+ 381; ^{1}H NMR (400 MHz, DMSO) δ 7.41 – 7.37 (m, 2H), 7.24 – 7.21 (m, 2H), 5.12 (q, J = 7.2 , 1H), 4.33 – 4.20 (m, 2H), 3.81 – 3.78 (m, 4H), 3.57 – 3.48 (m, 4H), 1.57 (d, J = 6.8, 3H), 1.33 (t, J = 7.2, 3H).

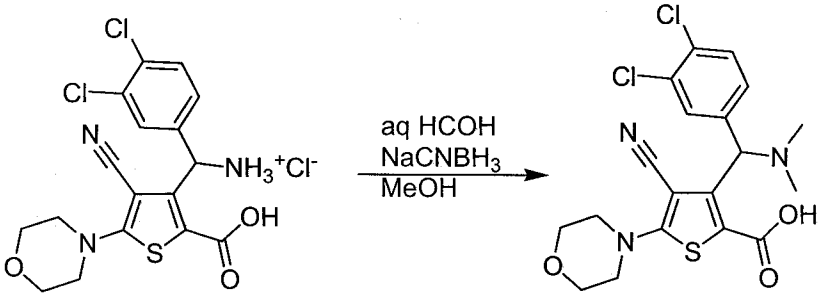
[00861] **Step 3:** 4-[1-(4-Chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (Compound **121**). To a solution of ethyl 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylate (1.42 g, 0.00373 mol) in tetrahydrofuran (30.2 mL, 0.373 mol) and methanol (6.04 mL, 0.149 mol) was added sodium hydroxide (1.0N in water, 29.8 mL, 0.0298 mol), and the resulting cloudy mixture was heated at 65 °C for 5 hours. The reaction was cooled to room temperature, diluted with water, and adjusted to pH 3.0 via addition of 1N aqueous HCl. The mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 4-[1-(4-chlorophenyl)ethyl]-2-(morpholin-4-yl)-1,3-thiazole-5-carboxylic acid (**121**) (1.21 g, yield 92%) as a white solid. LCMS: (FA) ES+ 353; ^{1}H NMR (400 MHz, DMSO) δ 12.70 (bs, 1H), 7.37 – 7.34 (m, 2H), 7.33 – 7.30 (m, 2H), 5.09 (q, J = 7.2, 1H), 3.69 – 3.76 (m, 4H), 3.48 – 3.39 (m, 4H), 1.49 (d, J = 6.8, 3H).

[00862] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 48.

304	LC/MS: (AA) ES+ 381, 383
332	LC/MS: (AA) ES+ 387, 389

[00863]

[00864] Example 49: Synthesis of 4-cyano-3-[(3,4-dichlorophenyl)(dimethylamino)methyl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid (Compound 362)



[00865] Step 1: 4-cyano-3-[(3,4-dichlorophenyl)(dimethylamino)methyl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid.

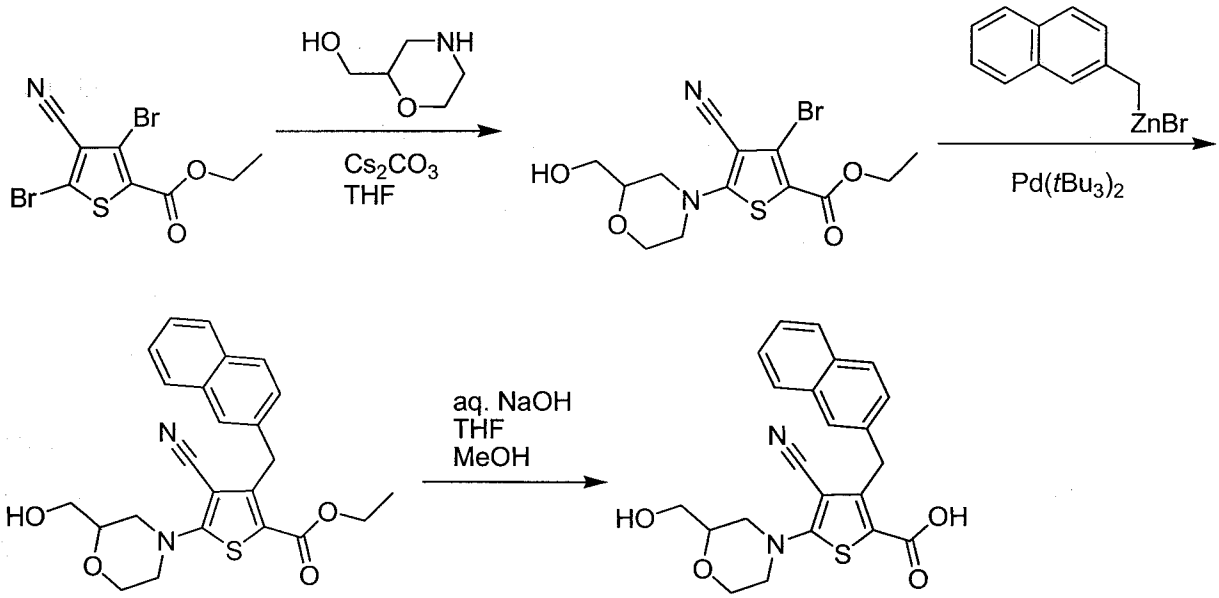
[00866] To a suspension of 3-[amino(3,4-dichlorophenyl)methyl]-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylic acid•HCl (186.0 mg, 0.4145 mmol, prepared according to Example 6) in methanol (8.09 mL, 0.101 mol) was added 10 M of formaldehyde in water (74.00 uL, 0.9119 mmol), and sodium cyanoborohydride (130 mg, 2.07 mmol) . Stirred at rt under argon for 16 hours. Added 10 M of formaldehyde in water soln (74.00 uL, 0.919 mmol) and sodium cyanoborohydride (0.130 g, 2.07 mmol) and stirred at rt for 72 hours. Quenched reaction with saturated aqueous sodium bicarbonate solution, added EtOAc, separated layers, extracted again w/EtOAc, combined organics, washed organics with saturated sodium bicarbonate, brine, dried over Na_2SO_4, filtered, added Celite to filtrate, and concentrated *in vacuo*. Purification of dry load via silica gel column chromatography (gradient elution: 100% DCM to 8% MeOH in DCM) afforded racemic 4-cyano-3-[(3,4-dichlorophenyl)(dimethylamino)methyl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid (134 mg, 68%) as an off-white solid. LC/MS: (FA) 440, 442, 444; ^{1}H NMR (400 MHz, DMSO) δ 7.80-7.76 (m, 2 H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.26 (s, 1H), 3.74 – 3.64 (m, 4H), 3.53 – 3.38 (m, 4H), 2.76 (s, 3H), 2.42 (s, 3H). Combined with another batch of 134 mg racemate for chiral HPLC to obtain pure enantiomers. Purified on IC 4.6X250 mm with 90/10/0.1 HEX/ETOH/DEA 10 uL Injection at 1.0 mL/min for 70 min. CD AT 254 nm to obtain separated enantiomers as the diethylamine salts. Each compound Peak1 and Peak2 were separately dissolved in water, acidified to pH of 2 with aqueous 1N HCl solution, extracted w/EtOAc, 3x, combined organics and washed w/brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, added water, freeze-dried, lyophilized overnight to recover parent compound. Peak 1 (103 mg, tan solid, overall 27% yield) LC/MS: (FA) 440, 442, 444; ^{1}H NMR (400 MHz, DMSO) δ 7.80-7.76 (m, 2 H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.26 (s, 1H), 3.74 – 3.64 (m, 4H), 3.53 – 3.38 (m, 4H), 2.76 (s, 3H), 2.42 (s, 3H). Peak 2 (80 mg, beige solid, overall 20% yield) LC/MS: (FA) 440, 442, 444; ^{1}H NMR (400 MHz, DMSO) δ 7.80-7.76 (m, 2

H),, 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.26 (s, 1H), 3.74 – 3.64 (m, 4H), 3.53 – 3.38 (m, 4H), 2.76 (s, 3H), 2.42 (s, 3H).

[00867] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 49.

336	LC/MS: (FA) ES+ 440, 442, 444
351	LC/MS: (FA) ES+ 406, 408

[00868] Example 50: Synthesis of 4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene-2-carboxylic acid (Compound 297).



[00869] Step 1: ethyl 3-bromo-4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]thiophene-2-carboxylate

[00870] Ethyl 3,5-dibromo-4-cyanothiophene-2-carboxylate (0.360 g, 1.06 mmol), cesium carbonate (1.05 g, 3.21 mmol), 2-hydroxymethylmorpholine (137 mg, 1.17 mmol), and tetrahydrofuran (4.5 mL, 36 mmol) were combined in a 15 mL pressure vessel equipped with a stir bar. The vessel was sealed, and the rxn was heated @ 90° C with stirring for 4 hours. The reaction was cooled to rt. The rxn was poured into water/saline. The reaction vessel was washed out with additional water, then ethyl acetate, and these were added to the quench which was then transferred to a separatory funnel. The aqueous layer was extracted 3X with EtOAc. The extracts were combined, washed with saline, dried over Na_2SO_4, filtered, added Celite, concentrated *in vacuo*, and dried on high vac 30 min. Purified dry load via silica gel chromatography (gradient elution: 0-60% EtOAc/hexanes) to give 163 mg solid (41% yield). ^{1}H NMR

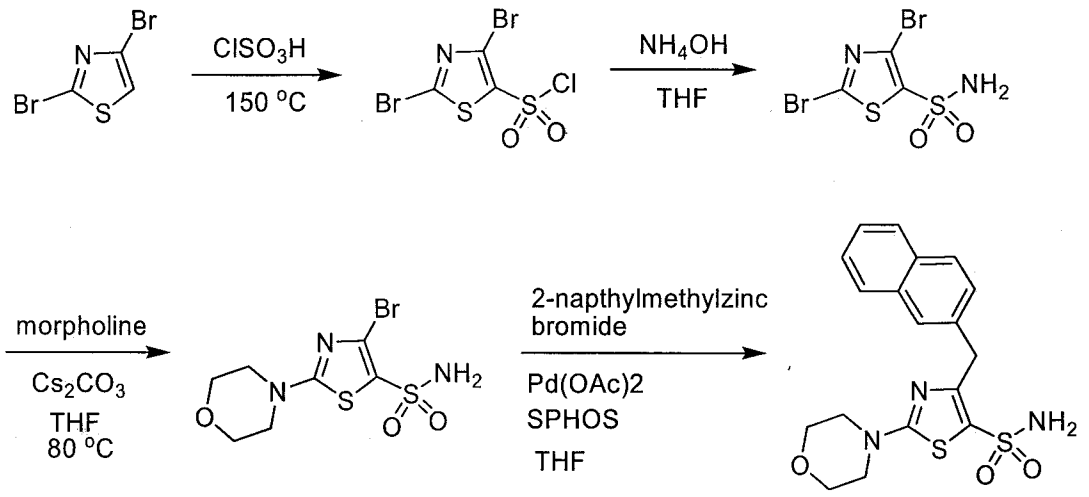
(400 MHz, DMSO) δ 4.91 (t, *J* = 5.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.99-3.92 (m, 3 H), 3.69-3.58 (m, 2 H), 3.50 (dt, *J* = 10.5, 5.2 Hz, 1H), 3.41 (dt, *J* = 11.5, 5.8 Hz, 1H), 3.37 – 3.27 (m, 1H, under H2O peak),3.15 – 3.08 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

[00871] Step 2: ethyl 4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene- 2-carboxylate and 4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene- 2-carboxylic acid

[00872] Bis(tri-t-butylphosphine)palladium(0) (16.44 mg, 0.03218 mmol) and ethyl 3-bromo-4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]thiophene-2-carboxylate (161.0 mg, 0.4290 mmol) were combined in a dry round bottom flask equipped with a stirbar and septum. Evacuated/refilled with argon 3X, then added 0.50 M solution of 2-naphthylmethylzinc bromide in tetrahydrofuran(1.72 mL, 0.858 mmol) via a syringe to give a brown soln. The reaction was stirred at rt for 5 minutes, then at 60° C for 1.5 h. Bis(tri-t-butylphosphine)palladium(0) (38.4 mg, 0.0751 mmol) and 0.50 M solution of 2-naphthylmethylzinc bromide in tetrahydrofuran (1.29 mL, 0.644 mmol) was added, degassed 2x and flushed w/argon, heated at 60 °C 1h. The reaction was cooled to rt, diluted with EtOAc, and then quenched with sat. NH4Cl solution. Transferred quenched mixture to a separatory funnel, separated layers, and extracted the aqueous layer once more with EtOAc, combined organics, washed w/brine, dried over Na2SO4, filtered, and concentrated *in vacuo*. Added EtOAc and Celite, rotovapped, dried on high vac 30 min. Purified dry load onto 40 g ISCO column (gradient elution: 0-55% EtOAc/hexanes) to obtain 119 mg yellow oil (64% yield). LC/MS (AA) ES+437.

[00873] To ethyl-4-cyano-5-[2-(hydroxymethyl)morpholin-4-yl]-3-(2-naphthylmethyl)thiophene-2-carboxylate (0.116 g, 0.266 mmol) in a rbf equipped with a stirbar was added tetrahydrofuran (2.96 mL, 36.4 mmol) and 1.000 M of sodium hydroxide in water (2.22 mL, 2.22 mmol) and methanol (1.48 mL, 36.5 mmol). The resulting yellow mixture was stirred at rt for 16 h. The reaction was quenched with the addition of 2.5 mL of 1N HCl in water to pH of 2, and added EtOAc Transferred to separatory funnel, separated layers, extracted aquoeous 2x w/EtOAc, combined organics, washed w/brine, dried over Na2SO4, filtered, added Celite, and concentrate *in vacuo*. Purified dry load *via* silica gel chromatography on 40 g ISCO column (gradient elution 0-20% MeOH/DCM) to give 66 mg white solid (61% yield). LC/MS (FA) ES+409; ES-407; ^{1}H NMR (400 MHz, DMSO) δ 13.45 (br s, 1H), 7.88-7.77 (m, 3 H), 4.7 Hz, 3H), 7.69 (s, 1H), 7.51 – 7.42 (m, 3H), 4.87 (s, 1H), 4.57 – 4.47 (m, 2H), 3.94-3.77 (m, 3 H), 3.65-3.53 (m, 2 H), 3.60 – 3.52 (m, 1H), 3.47 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.37 (dd, *J* = 11.3, 5.8 Hz, 1H, overlaps with H_2O peak), 3.15 (td, *J* = 12.1, 3.4 Hz, 1H), 2.99 – 2.89 (m, 1H).

[00874] Example 10: Synthesis of 2-morpholino-4-(naphthalen-2-ylmethyl)thiazole-5-sulfonamide (Compound 329)



[00875] **Step 1, Preparation of 2,4-dibromothiazole-5-sulfonyl chloride**

[00876] To a flask containing chlorosulfonic acid (51.0 mL, 767 mmol) was added 2,4-dibromothiazole (10.2 g, 42.0 mmol) with stirring over 15 minutes. The resulting solution was heated to 150 degrees overnight. The reaction was quenched by carefully and slowly pouring onto ice (500 mL). The resulting precipitate was extracted with ethyl acetate (2 x 200 mL) and the combined organic layers were washed with water, dried, and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/hexane = 0/100→15/85) to give 8.1 g (56 % yield) of the title compound as a yellow oil which partially solidified. ^{13}C NMR (400 MHz, $CDCl_3$) δ: 145.04, 138.78, 131.81.

[00877] **Step 2, Preparation of 2,4-dibromothiazole-5-sulfonamide**

[00878] To a mixture of 2,4-dibromothiazole-5-sulfonyl chloride (3.17 g, 9.28 mmol) in THF (51.4 mL) was added 33% aqueous NH_4OH (24.1 mL, 278 mmol) and the reaction was stirred at room temperature for 30 minutes. The reaction was concentrated in vacuo and the residue was taken up in ethyl acetate (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL), then dried and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→20/80) to give 1.7 g (57 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 321, 323, 325. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.33 (s, 2H).

[00879] **Step 3, Preparation of 4-bromo-2-morpholinothiazole-5-sulfonamide**

[00880] A mixture of 2,4-dibromothiazole-5-sulfonamide (0.515 g, 1.60 mmol), morpholine (0.153 mL, 1.76 mmol), THF (4.22 mL) and cesium carbonate (1.56 g, 4.80 mmol) in a sealed tube was heated to 80 degrees for 4 hours. The cooled reaction was concentrated in vacuo and the residue was taken up in ethyl acetate (50 mL) and water (25 mL). The layers were separated and the organic layer was washed with water (15 mL), dried and concentrated in vacuo. The residue was purified by silica gel

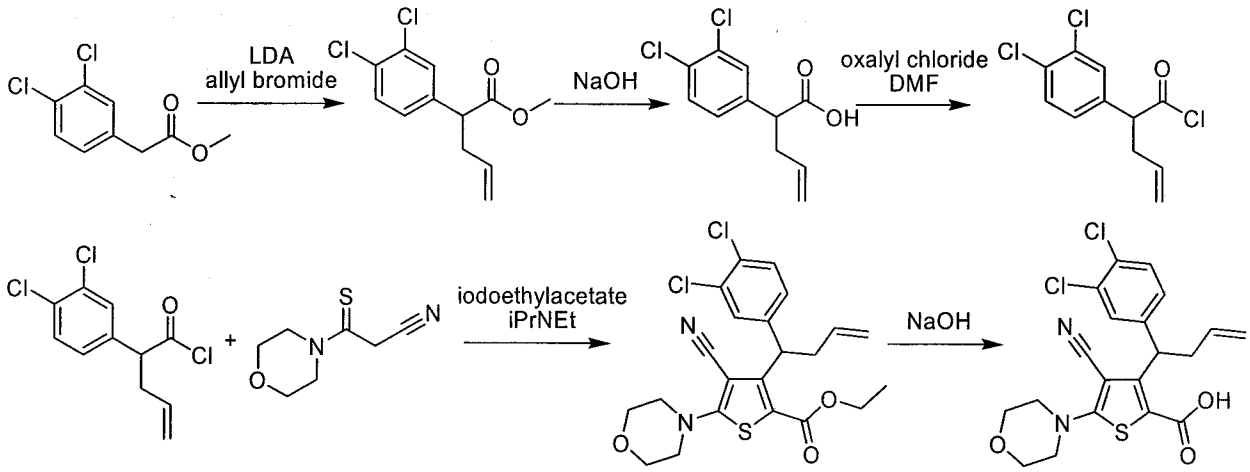
chromatography (ethyl acetate/DCM = 0/100→50/50) to give 230 mg (44 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 328, 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.76 (s, 2H), 3.69-3.66 (m, 4H), 3.43-3.40 (m, 4H).

[00881] Step 4, Preparation of 2-morpholino-4-(naphthalen-2-ylmethyl)thiazole-5-sulfonamide

[00882] To a dried flask was added 4-bromo-2-morpholinothiazole-5-sulfonamide (194 mg, 0.591 mmol), THF (4.79 mL), palladium(II) acetate (1.33 mg, 0.00591 mmol) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (4.85 mg, 0.0118 mmol). The mixture was stirred for 5 minutes, and a 0.500 M solution of 2-napthylmethylzinc bromide in THF (4.14 mL, 2.04 mmol) was then added dropwise over 30 minutes. The reaction was stirred at room temperature for 1 hour and quenched with saturated ammonium chloride (10 mL). The reaction was extracted with ethyl acetate (2 x 25 mL) and the combined organic layers were washed with water (15 mL), dried and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→40/60) which gave a mixture of the desired product with residual 4-bromo-2-morpholinothiazole-5-sulfonamide. This material was purified by preparative reverse phase chromatography to give 51 mg (22 % yield) of the title compound as a white solid. LC/MS (FA) ES+ 390. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.85-7.77 (m, 4H), 7.71 (bs, 2H), 7.50-7.42 (m, 3H), 4.25 (s, 2H), 3.64-3.61 (m, 4H), 3.35-3.32 (m, 4H).

[00883]

[00884] Example 51: Synthesis of 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene-2-carboxylate (Compound 355)



[00885] Step 1: To a solution of N,N-diisopropylamine (1.79 mL, 12.8 mmol) in tetrahydrofuran (10.0 mL, 123 mmol) was added 2.50 M of n-butyllithium in hexane(4.68 mL, 11.7 mmol) dropwise at 0 °C. The solution was stirred under an atmosphere of Nitrogen for 10 min, and then cooled to -78 °C. A solution of methyl 3,4-dichlorophenylacetate (2.27 g, 10.4

mmol) in tetrahydrofuran (10.0 mL) was added to the LDA solution dropwise via cannula. After 10min of stirring, the reaction was warmed to 0 °C for 1 hr. The solution was cooled back to -78 °C, and allyl bromide (2.24 mL, 25.9 mmol) was added in one portion. In 10 min, the reaction was warmed back to 0 °C. After 1 hr of stirring, the reaction was quenched with NH_4Cl sat soln and extracted with EtOAc(x3). The combined organic layer was dried and concentrated to provide an orange oil. Further purification on a silica gel column (gradient elution, 0-10% EtOAc/hexanes) provided methyl 2-(3,4-dichlorophenyl)pent-4-enoate as a colorless oil (2.47 g, 92.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.18 – 7.12 (dd, J = 8.3, 2.1 Hz, 1H), 5.73 – 5.60 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.70 – 3.64 (s, 3H), 3.63 – 3.55 (t, J = 7.8 Hz, 1H), 2.85 – 2.71 (m, 1H), 2.55 – 2.43 (m, 1H).

[00886] **Step2**: To a solution of methyl 2-(3,4-dichlorophenyl)pent-4-enoate (2.47 g, 9.53 mmol) in tetrahydrofuran (15.0 mL) was added a solution of lithium hydroxide monohydrate (2.00 g, 47.6 mmol) in water (15.0 mL). The mixture was vigorously stirred at rt for 12 hrs. The resulting mixture was acidified by addition of 12.0 M of hydrochloric acid in water (3.97 mL, 47.6 mmol) at 0 °C, and extracted with EtOAc(x3). The combined organic layer was dried and concentrated to provide 2-(3,4-dichlorophenyl)pent-4-enoic acid as a yellow syrup (2.65 g, quantative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.21 – 7.11 (dd, J = 8.3, 2.1 Hz, 1H), 5.76 – 5.59 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.14 – 4.99 (m, 2H), 3.65 – 3.56 (t, J = 7.7 Hz, 1H), 2.88 – 2.74 (dt, J = 14.8, 7.5 Hz, 1H), 2.58 – 2.43 (dt, J = 14.3, 6.9 Hz, 1H).

[00887] **Step3**: To a soln of 2-(3,4-dichlorophenyl)pent-4-enoic acid (2.34 g, 9.53 mmol) in methylene chloride (25.0 mL) was added oxalyl chloride (1.61 mL, 19.0 mmol) followed by N,N-dimethylformamide (73.8 uL, 0.953 mmol) After 1 hr of stirring at rt, the solution was concentrated to provide 2-(3,4-dichlorophenyl)pent-4-enoyl chloride as a yellow oil (2.70 g, quantative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (d, J = 8.3 Hz, 1H), 7.40 – 7.36 (d, J = 2.2 Hz, 1H), 7.17 – 7.10 (dd, J = 8.3, 2.2 Hz, 1H), 5.73 – 5.57 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.15 – 5.06 (m, 2H), 4.06 – 3.97 (t, J = 7.6 Hz, 1H), 2.97 – 2.83 (m, 1H), 2.61 – 2.49 (m, 1H).

[00888] **Step4**: To a solution of 2-(3,4-dichlorophenyl)pent-4-enoyl chloride (2.51 g, 9.53 mmol) and 3-morpholin-4-yl-3-thioxopropanenitrile (1.62 g, 9.53 mmol) in acetonitrile (40.0 mL) in a 100 mL round bottom flask was added N,N-diisopropylethylamine (1.82 mL, 10.5 mmol), and the resulting deep orange/red solution was stirred at room temp for 1 hr. To the resulting mixture was added N,N-diisopropylethylamine (4.15 mL, 23.8 mmol) and then ethyl

iodoacetate (1.24 mL, 10.5 mmol). The flask was fitted with a reflux condenser and the reaction was heated to reflux over 48 hrs. The mixture was concentrated and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined org layer was washed with brine, dried, and concentrated to provide a dark syrup. Purification on a silica gel column (gradient elution 3-30% EtOAc/hexanes) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene- 2-carboxylate (704 mg, 15.9% yield). LCMS: (AA) ES+ 465, 467, 469; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 1H), 7.41 – 7.33 (m, 1H), 7.31 – 7.27 (m, 1H), 5.82 – 5.66 (ddt, J = 17.2, 10.1, 6.8 Hz, 1H), 5.62 – 5.50 (t, J = 8.2 Hz, 1H), 5.16 – 5.08 (dd, J = 17.1, 1.6 Hz, 1H), 5.04 – 4.94 (dd, J = 10.2, 1.5 Hz, 1H), 4.35 – 4.27 (q, J = 7.1 Hz, 2H), 3.86 – 3.78 (m, 4H), 3.59 – 3.48 (m, 4H), 3.10 – 2.99 (h, J = 6.9 Hz, 2H), 1.40 – 1.31 (m, 3H).

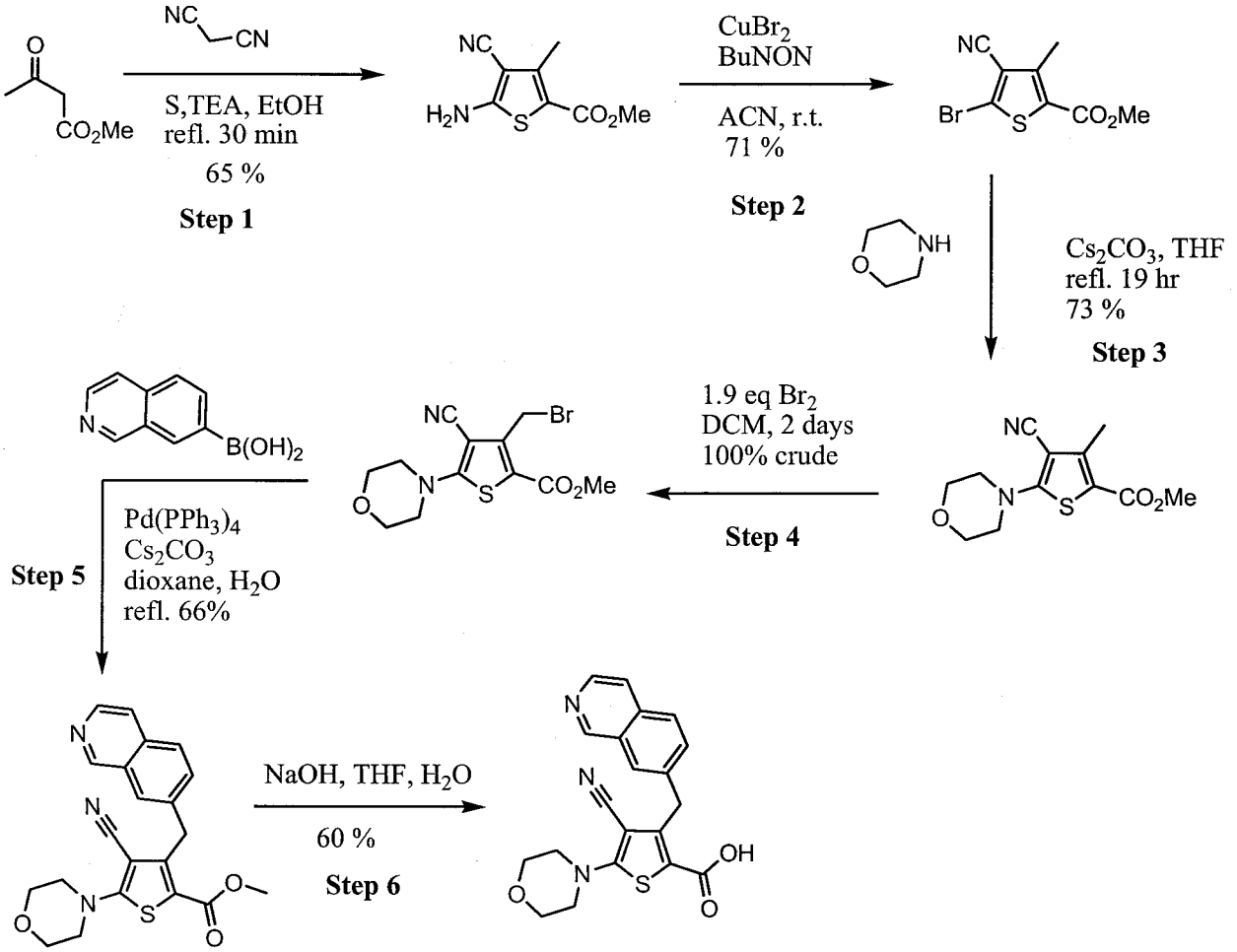
[00889] **Step5**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene-2-carboxylate (0.211 g, 0.453 mmol) in tetrahydrofuran (8.00 mL) was added 1.000 M of sodium hydroxide in water(10.0 mL) and methanol (4.00 mL). The resulting mixture was stirred at room temp over 3 hrs. The volatiles were removed under reduced pressure, and the resulting mixture was acidified with conc. HCl soln to pH~2, and extracted with EtOAc(x3). The combined org layer was dried and concentrated to provide a purple syrup. Purification of the crude mixture on HPLC (AA, reverse phase) provided 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene- 2-carboxylic acid as a white solid (63 mg, 31.8% yield). LCMS: (AA) ES- 391, 393, 395; ^{1}H NMR (400 MHz, MeOD) δ 7.54 – 7.46 (d, J = 1.6 Hz, 1H), 7.45 – 7.35 (d, J = 8.4 Hz, 1H), 7.34 – 7.24 (dd, J = 8.4, 1.6 Hz, 1H), 5.88 – 5.68 (m, 2H), 5.16 – 5.05 (dd, J = 17.1, 1.7 Hz, 1H), 5.00 – 4.92 (m, 1H), 3.82 – 3.71 (t, J = 4.8 Hz, 4H), 3.51 – 3.40 (t, J = 4.8 Hz, 4H), 3.05 – 2.95 (m, 2H).

[00890] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 51.

307	LC/MS: (FA) ES- 412
308	LC/MS: (FA) ES- 413
321	LC/MS: (AA) ES+ 411, 413
326	LC/MS: (AA) ES+ 411
345	LC/MS: (FA) ES- 395
349	LC/MS: (FA) ES- 437

358	LC/MS: (FA) ES+ 399, 401
364	LC/MS: (FA) ES- 395
369	LC/MS: (AA) ES+ 411

[00891] Example 52: **Synthesis of 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylic acid (Compound 309)**



[00892] **Step 1: 5-Amino-4-cyano-3-methyl-thiophene-2-carboxylic acid ethyl ester:**

[00893] To a solution of 3-oxobutanoic acid, methyl ester (8.25 mL, 76.4 mmol), malononitrile (5.05 g, 76.4 mmol) and sulfur (2.45 g, 76.4 mmol) in anhydrous ethanol (100 mL, 2000 mmol) was added triethylamine (10.7 mL, 76.8 mmol). The mixture was heated to reflux for 30 min. The mixture was cooled to room temperature. The resulted crystal was collected by filtration and washed with MeOH, dried in vacuum to afford the product (9.25 g, yield 61.7%). LC/MS: (FA) ES- 195. ^{1}H NMR (400MHz, *d*-chloroform) δ 5.13 (s, br, 2H), 3.82 (s, 3H), 2.52 (s, 3H).

[00894] **Step 2 Methyl 5-bromo-4-cyano-3-methylthiophene-2-carboxylate:**

[00895] To a dark solution of Methyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (6.65 g, 33.9 mmol) and copper(II) bromide (15.1 g, 67.8 mmol) in anhydrous acetonitrile (260 mL) was added slowly butyl nitrite (7.26 mL, 61.0 mmol) over 8 min. The mixture was stirred at room temperature for 70 min. The mixture was concentrated in rotavapor to give a black residue. The residue was dissolved in DCM, filtered through Celite. The filtrate was rotavaped with Celite. The Celite coated residue was dry loaded into a silica gel column and chromatographed using EtOAc/hexane (0/100 to 10/90) to give a white solid product (6.29 g, yield 71.4%). ^{1}H NMR (400MHz, *d*-chloroform) δ 3.89 (s, 3H), 2.67 (s, 3H)

[00896] **Step 3: Methyl 4-cyano-3-methyl-5-(morpholin-4-yl)thiophene-2-carboxylate:**

[00897] A mixture of methyl 5-bromo-4-cyano-3-methylthiophene-2-carboxylate (6.29 g, 24.2 mmol), morpholine (2.53 g, 29.0 mmol) and cesium carbonate (15.8 g, 48.4 mmol) in anhydrous Tetrahydrofuran (110 mL) was heated to reflux for 19 hours, and then cooled to room temperature. The mixture was filtered and washed with DCM. The filtrate was rotavaped with Celite. The coated Celite was dry loaded in a silica gel cartridge and chromatographed using MeOH/DCM (1/99) to give a white solid product (4.70 g, yield 73 %). LC/MS: (FA) ES$^+$ 267. ^{1}H NMR (400MHz, *d*-chloroform) δ 3.85 (m, 4H), 3.82 (s, 3H), 3.58 (m, 4H), 2.56 (s, 3H).

[00898] **Step 4: Methyl 3-(bromomethyl)-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylate:**

[00899] To the solution of methyl 4-cyano-3-methyl-5-(morpholin-4-yl)thiophene-2-carboxylate (0.500 g, 1.88 mmol) in anhydrous methylene chloride (15 mL, 230 mmol) was added a solution of bromine (0.409 g, 2.56 mmol) in anhydrous methylene chloride (5.0 mL, 78 mmol). The mixture was stirred at room temperature for 4 days. The mixture was evaporated under reduced pressure and dried in vacuum to give a crude product that was used without further purification (0.658g, contained 3.4% starting material, yield 96.6%). LC/MS: (FA) ES$^+$ 345, 347. ^{1}H NMR (400MHz, *d*-chloroform) δ 4.83 (s, 2H), 3.87 (s, 3H), 3.85 (m, 4H), 3.62 (m, 4H).

[00900] **Step 5: Methyl 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylate**

[00901] A mixture of methyl 3-(bromomethyl)-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylate (0.128 g, 0.371 mmol), isoquinoline-7-boronic acid (101 mg, 0.584 mmol), tetrakis(triphenylphosphine)palladium(0) (21.4 mg, 0.0185 mmol) and cesium carbonate (0.242 g, 0.742 mmol) was suspended in 1,4-dioxane (8.0 mL, 100 mmol) and Water (0.60 mL, 33 mmol) under N_2 atmosphere in a 20 mL vial. The vial was capped and heated to 90°C for 1 hour. The mixture was cooled to room temperature and concentrated in vacuum. The residue was suspended in DCM and filtered over a celite pad. The filtrate was chromatographed in a silica gel column using MeOH/DCM (0/100 to 3/97) to afford a solid product (103 mg, 66.4 %). LC/MS: (FA) ES$^+$ 394. ^{1}H NMR (400MHz, *d*-chloroform) δ

9.20 (s, 1H), 8.47 (d, J = 5.77 Hz, 1H), 7.87 (s, 1H), 7.73 (d, J = 5.77 Hz, 1H), 7.60 (d, J = 5.77 Hz, 1H), 7.44-7.48 (m, 1H), 4.60 (s, 2H), 3.86 (s, 3H), 3.84 (m, 4H), 3.59 (m, 4H).

[00902] Step 6: 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylic acid

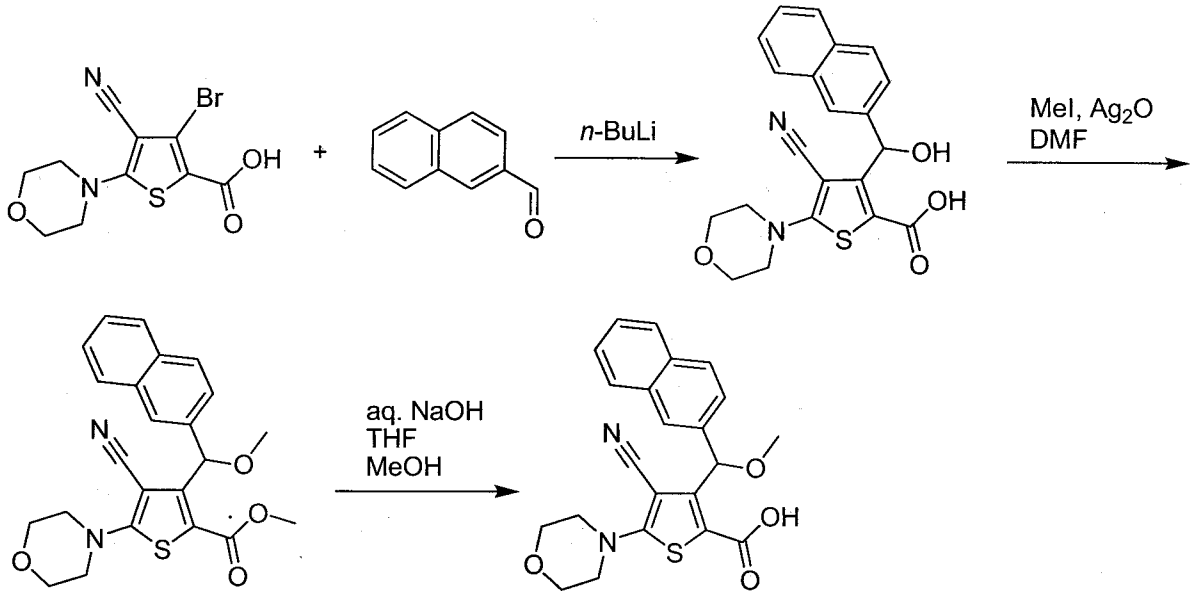
[00903] To the solution of methyl 4-cyano-3-(isoquinolin-7-ylmethyl)-5-(morpholin-4-yl)thiophene-2-carboxylate (0.103 g, 0.246 mmol) in tetrahydrofuran (15.0 mL, 185 mmol) was added 1.00 M of sodium hydroxide in water (3.80 mL, 3.80 mmol) , followed by water (4.0 mL, 220 mmol) and methanol (4.0 mL, 99 mmol). The homogeneous solution was stirred at room temperature for 18 hours. Acetic acid (270 mg, 4.5 mmol) was added and the mixture was concentrated in rotavapor. The residue was dissloved in DCM-MeOH and then concentrated with celite. The mixture was loaded in a cartridge and chromatographed in a silica gel column using AcOH/MeOH/DCM (0/0/100 to 0.5/4.5/95) to afford a white solid product (56.5 mg, yield 60.3%). LC/MS: (FA) ES^+ 380; ES^- 378. ^1H NMR (400MHz, *d*-chloroform) δ 9.23 (s, 1H), 8.45 (d, J = 5.77 Hz, 1H), 7.90 (d, J = 8.53 Hz, 1H), 7.84 (s, 1H), 7.76 (d, J = 5.77 Hz, 1H), 7.65 (dd, J = 8.53, 1.76 Hz, 1H), 4.53 (s, 2H), 3.72 (m, 4H), 3.52 (m, 4H).

[00904] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 52.

287	LC/MS: (AA) ES- 395
293	LC/MS: (AA) ES- 395
295	LC/MS: (AA) ES- 395
301	LC/MS: (AA) ES+ 409
305	LC/MS: (FA) ES- 381
311	LCMS: (FA) ES+ 385; ES- 383
312	LC/MS: (FA) ES+ 386, 388; ES- 384, 386
315	LC/MS: (FA) ES+ 397
324	LC/MS: (AA) ES- 395
330	LC/MS: (FA) ES+ 382; ES- 380
343	LC/MS: (AA) ES- 395
359	LC/MS: (FA) ES+ 402, 404 ; ES- 401, 403
361	LC/MS: (AA) ES+ 409

[00905] Example 53: Synthesis Example 3: Synthesis of 4-cyano-3-[methoxy(2-naphthyl)methyl]- 5-(morpholin-4- yl)thiophene-2- carboxylic acid (Compound

368).



[00906] Step 1: 4-cyano-3-[hydroxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid

A solution of 3-bromo-4-cyano-5-morpholinothiophene-2-carboxylic acid (5.50 g, 17.3 mmol) and 2-naphthalenecarboxaldehyde (8.12 g, 52.0 mmol) in tetrahydrofuran (550 mL) was cooled at -78 °C for 10 min, resulting in a white suspension. 2.5 M of n-butyllithium in hexane (27.7 mL, 69.4 mmol) was added dropwise, resulting in an orange solution. The solution was stirred at -78 °C for 10 min, then the cold bath was removed and the orange solution was stirred at ambient temperature for 40 minutes. The solution was quenched by the addition of methanol (21 mL) and acetic acid (3.9 mL), and the resulting mixture was let to warm up to rt O/N. The mixture was combined with a previous run on 2.86 g scale of the carboxylic acid, concentrated *in vacuo*, and azeotroped with toluene (2x50 mL). The crude solid was dissolved in MeOH, added Celite, rotavapped, dried on high vac O/N. The crude product was purified using dry load *via* silica gel chromatography on 330 g ISCO column (gradient elution 0-20% of (10%AcOH in MeOH) in DCM) to give 15.2 g solid containing 37wt% AcOH, for overall 92% yield. LC/MS (AA) ES-393; ^{1}H NMR (400 MHz, DMSO) δ 10.86 (d, J = 9.9 Hz, 1H), 7.86-7.81 (m, 4H), 7.70 (dd, J = 8.6, 1.6 Hz, 1H), 7.51 – 7.42 (m, 2H), 5.69 (d, J = 9.4 Hz, 1H), 3.73 – 3.68 (m, 4H), 3.39 – 3.33 (m, 4H).

[00907] Step 2: methyl 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylate

[00908] To a round bottom flask was added silver(I) oxide (56.15 g, 0.2423 mol), 4-cyano-3-[hydroxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid (15.17 g, 0.02423 mol), and N,N-dimethylformamide (66.2 mL), followed by methyl iodide (53.7 mL, 0.863 mol). Added another 10

mL DMF, sonicated to suspend/mix all solid. The reaction mixture was stirred at room temperature for 26 hours, then was diluted with EtOAc, filtered through a pad of Celite, concentrated filtrate *in vacuo*, azeotroped w/toluene (10x 10 mL), DCM (20 mL), dried on high vacuum pump. The rude material was used directly in the next step. LC/MS (AA) ES+423, ES+Na+445; ^{1}H NMR (400 MHz, DMSO) δ 7.97 (s, 1H), 7.91-7.86 (m, 3H), 7.53 – 7.48 (m, 3H), 6.62 (s, 1H), 3.85 (s, 3H), 3.72 – 3.69 (m, 4H), 3.52-3.50 (m, 4 H), 3.43 (s, 3H).

[00909] Step 3: 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid

[00910] To methyl 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (10.56 g, 25 mmol) in a round bottom flask equipped with a stirbar was added tetrahydrofuran (278 mL) and 1.000 M of sodium hydroxide in water (208 mL, 208 mmol). Methanol (139 mL) was added to the mixture, and the resulting yellow mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by the addition of 1N HCl aqueous solution to adjust the pH to 2 and EtOAc was added. The mixture was transferred to a separatory funnel, separated layers, extracted aqueous 2x w/EtOAc, combined organics, washed w/brine, dried over Na_2SO_4, filtered, added celite, rotavapped, dried on high vacuum for 45 min. The crude material was purified using a dry load on 330 g silica gel ISCO column (gradient elution: 0-20% MeOH/DCM) to obtain the product as an impure beige solid (9.8g). Took 2 g, redissolved in DCM, added Celite, rotovapped, dried on high vac 45 min. Repurified this portion of product on 120 g ISCO silica gel column (gradient elution: 0-12% MeOH/DCM) to obtain 2.0 g beige foam product (racemate). LC/MS (FA) ES-407; ^{1}H NMR (400 MHz, DMSO) δ 13.57 (s, 1H), 7.96 (s, 1H), 7.89-7.86 (m, 3H), 7.53 – 7.46 (m, 3H), 6.68 (s, 1H), 3.73 – 3.67 (m, 4H), 3.50 – 3.45 (m, 4H), 3.43 (s, 3H). Enantiomeric separation of the enantiomers was performed by chiral HPLC on CHIRALPAK IC 4.6X250 mm with 85/5/10/0.1% HEX/IPA/ETOH/DEA 10 uL Injection at 1.0 mL/min for 50 min.

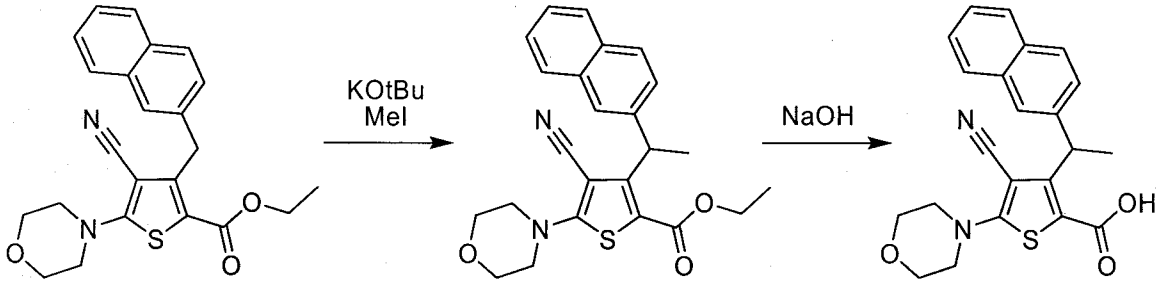
[00911] Step 4: 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid •Na

[00912] 4-cyano-3-[methoxy(2-naphthyl)methyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid (313.0 mg, 0.7663 mmol) was suspended in ethanol (7.159 mL, 122.6 mmol) and water (2.071 mL, 114.9 mmol) at room temperature. 1.030 M of sodium hydroxide in water (744.0 uL, 0.7663 mmol) was added slowly and the resulting solution was stirred for 10 min. The organic solvent was removed *in vacuo*. Added 40 ml water, freeze-dried, and lyophilized over night to give 322 mg amber solid (98% yield). LC/MS (FA) ES-407.5; ^{1}H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.88 – 7.76 (m, 3H), 7.61 (dd, J = 8.6, 1.3 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.24 (s, 1H), 3.68 – 3.65 (m, 4H), 3.37 (s, 3H), 3.26-3.33 (m, 4H).

[00913] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 53.

337	LC/MS: (FA) ES- 407

[00914] Example 54: Synthesis of Ethyl 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylate (Compound 367)



[00915] **Step 1**: A 1 L flask was charged with a big egg-shape stirring bar and ethyl 4-cyano-5-morpholin-4-yl-3-(2-naphthylmethyl)thiophene-2-carboxylate (14.5 g, 35.7 mmol). To the flask was added N,N-dimethylformamide (240 mL) and the mixture was evacuated and purged with nitrogen (x3). To the flask was added tetrahydrofuran (60 mL), and the mixture was stirred until it became a clear yellow solution. The solution was cooled to ~-25 °C in a dry ice-acetone bath (the temperature was actively controlled by slow addition of dry ice between -30~-40 °C). 1 M of Potassium tert-butoxide in tetrahydrofuran (42.8 mL) was added dropwise over 3 min. The mixture turned deep purple immediately. After the addition the mixture was stirred for 10 min at this temperature. Methyl iodide (11.1 mL, 178 mmol) was added over 1 min. By the end of addition the mixture turned light red. After stirring the resulting mixture at 0 °C for 10 min, the reaction was quenched by addition of 10 mL of water. All volatiles were removed under reduced pressure and the resulting mixture was distributed between brine and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layers were washed with 10% LiCl(aq) soln(x3), then brine, dried, and concentrated to provide a yellow syrup. Purification on a silica gel column (gradient elution 5-20% EtOAc/hexanes) provided Ethyl 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylate as a white solid (11.8g, 78.7% yield). LCMS: (AA) ES+ 421; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.82 – 7.70 (dd, J = 15.4, 8.1 Hz, 2H), 7.50 – 7.37 (m, 3H), 5.82 – 5.67 (q, J = 7.3 Hz, 1H), 4.40 – 4.25 (qd, J = 6.1, 5.0, 3.1 Hz, 2H), 3.86 – 3.72 (t, J = 4.8 Hz, 4H), 3.54 – 3.44 (t, J = 4.8 Hz, 4H), 1.95 – 1.85 (d, J = 7.3 Hz, 3H), 1.42 – 1.31 (t, J = 7.1 Hz, 3H).

[00916] **Step2**: Ethyl 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylate (13.3 g, 31.6 mmol) in tetrahydrofuran (200mL) and methanol (150mL) was stirred until the mixture turned into a clear solution. To the solution was added 1.000 M sodium hydroxide in water (158 mL). The resulting turbid mixture was vigorously stirred at rt for 12h. The volatiles were removed under reduced pressure, and the resulting aqueous solution was acidified by addition of 12.0 M of hydrochloric acid in water (15.9 mL, 191 mmol) at 0 °C, and then extracted with EtOAc(x3). The combined organic layers were washed with 1M HCl soln, dried, and concentrated to provide 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylic acid as a white solid (12.1g, 97.5% yield). 250 mg of the racemic mixture was purified on chiral prep HPLC to provide each enantiomer (115 mg each, >95% ee) (OJ column, elution with 85/5/10/0.1% hexane/iPrOH/EtOH/Et_2NH). LCMS: (AA) ES+ 393; ^1H NMR (400 MHz, MeOD) δ 7.85 – 7.76 (m, 3H), 7.76 – 7.71 (d, J = 8.6 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.38 – 7.29 (dd, J = 8.5, 1.7 Hz, 1H), 5.90 – 5.74 (q, J = 7.3 Hz, 1H), 3.82 – 3.69 (m, 4H), 3.52 – 3.43 (dd, J = 5.8, 4.0 Hz, 4H), 1.91 – 1.80 (d, J = 7.3 Hz, 3H).

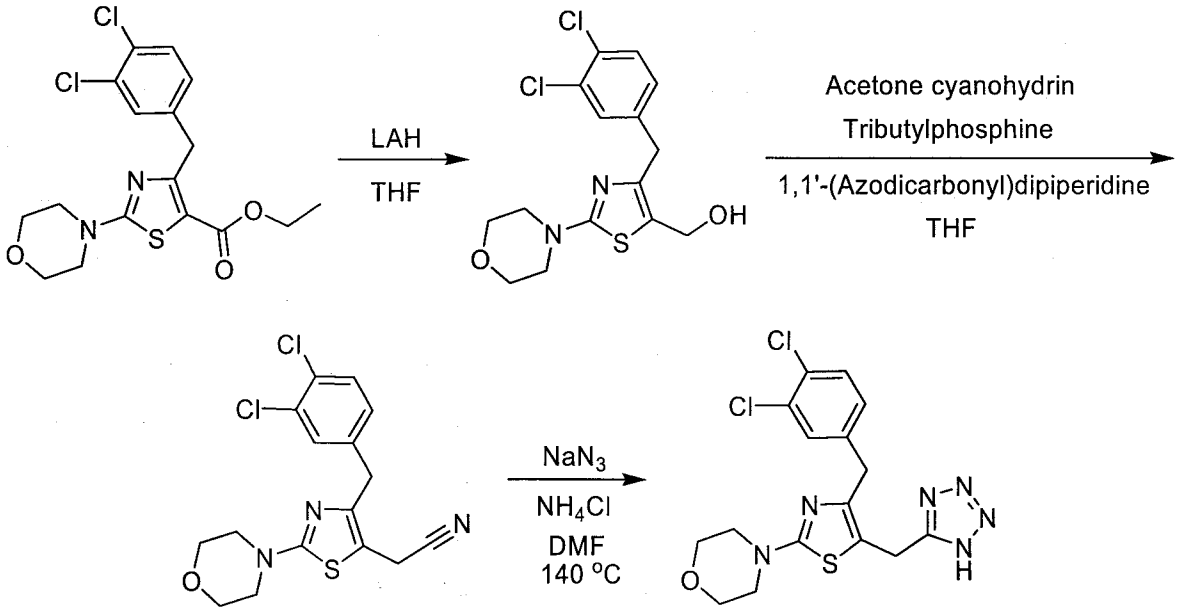
Step3: The active enantiomer 4-cyano-5-(morpholin-4-yl)-3-[1-(2-naphthyl)ethyl]thiophene-2-carboxylic acid (780 mg, 1.99 mmol) was suspended in ethanol (10.0 mL, 171 mmol). To the mixture was added 1.030 M of sodium hydroxide in water (2.00 mL, 2.06 mmol). The mixture was swirled and sonicated until it turned homogeneous. The solution was concentrated to provide 4-cyano-5-(morpholin- 4-yl)-3-[1-(2-naphthyl) ethyl]thiophene-2-carboxylic acid•Na as a yellow solid (785 mg, 95% yield). LCMS: (AA) ES+ 393; ^1H NMR (400 MHz, MeOD) δ 7.85 – 7.72 (m, 3H), 7.72 – 7.66 (d, J = 8.6 Hz, 1H), 7.45 – 7.30 (ddd, J = 12.6, 4.9, 2.2 Hz, 3H), 6.20 – 6.06 (q, J = 7.0 Hz, 1H), 3.81 – 3.70 (t, J = 4.8 Hz, 4H), 3.40 – 3.32 (t, J = 4.8 Hz, 4H), 1.88 – 1.78 (d, J = 7.4 Hz, 3H).

[00917] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 54.

306	LC/MS: (FA) ES+ 423
313	LC/MS: (FA) ES+ 423
322	LC/MS: (FA) ES+ 425
333	LC/MS: (AA) ES+ 393
346	LC/MS: (FA) ES+ 369
363	LC/MS: (FA) ES+ 423

365	LC/MS: (FA) ES+ 425
366	LC/MS: (AA) ES- 409, 411, 413

[00918] Example 55: Synthesis of 4-(5-((1H-tetrazol-5-yl)methyl)-4-(3,4-dichlorobenzyl)thiazol-2-yl)morpholine (Compound 350)



[00919] Step 1, Preparation of (4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)methanol

[00920] To a solution of ethyl 4-(3,4-dichlorobenzyl)-2-morpholinothiazole-5-carboxylate (4.92 g, 12.2 mmol) in THF (100 mL) was added a 2.00 M solution of LAH in THF (12.9 mL, 25.8 mmol) and the resulting solution was stirred for 2 hours at room temperature. The reaction was quenched by adding saturated NH_4Cl (26 mL) followed by 1M HCl (26 mL). Water (100 mL) and ethyl acetate (200 mL) were then added. The layers were separated and the organic layer was washed with brine (50 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→100/0) to give 2.87 g (65 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 359, 361. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.31 (m, 2H), 7.09 (dd, 1H, J = 6.0, 2.0 Hz), 4.66 (d, 2H, J = 1.2 Hz), 3.84 (s, 2H), 3.79-3.77 (m, 4H), 3.42-3.39 (m, 4H).

[00921] Step 2, Preparation of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetonitrile

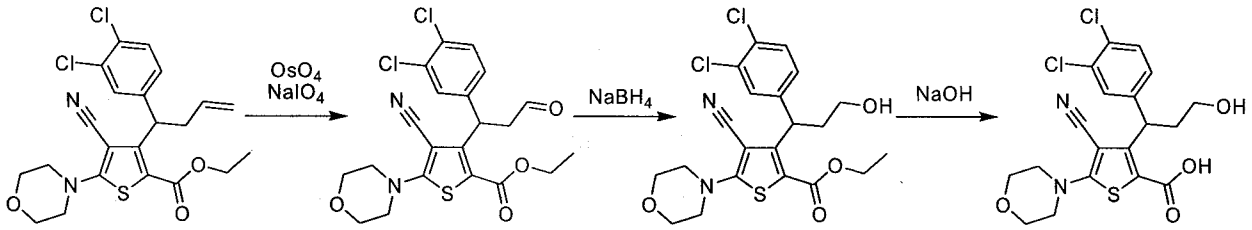
[00922] To a solution of (4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)methanol (1.19 g, 3.31 mmol) in THF (58.6 mL) was added acetone cyanohydrin (0.454 mL, 4.97 mmol), 1,1'-(azodicarbonyl)dipiperidine (1.67 g, 6.62 mmol) and tributylphosphine (1.65 mL, 6.62 mmol) and the reaction was stirred for 3 hours at room temperature. The reaction was concentrated in vacuo. The residue was purified by silica gel chromatography (ethyl acetate/DCM = 0/100→20/80) to give 551 mg (45 %

yield) of the title compound as a beige solid. LC/MS (FA) ES+ 368, 370. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, 1H, J = 6.0 Hz), 7.32 (d, 1H, J = 2.0 Hz), 7.07 (dd, 1H, J = 6.0, 2.0 Hz), 3.82 (s, 2H), 3.80-3.77 (m, 4H), 3.66 (s, 2H), 3.42-3.40 (m, 4H).

[00923] Step 3, Preparation of 4-(5-((1H-tetrazol-5-yl)methyl)-4-(3,4-dichlorobenzyl)thiazol-2-yl)morpholine

[00924] To a solution of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetonitrile (87.0 mg, 0.236 mmol) in DMF (0.74 mL) was added sodium azide (21.6 mg, 0.332 mmol) and NH_4Cl (17.8 mg, 9.53 mmol) and the resulting mixture was heated to 140 degrees overnight. More sodium azide (43 mg, 0.66 mmol) and NH_4Cl (36 mg, 19 mmol) were added and the reaction was heated to 120 degrees overnight. The reaction was cooled and taken up in ethyl acetate (25 mL) and water (5 ml). The layers were separated and the organic layer was washed with water (3 x 5 mL).). The organic layer was dried and concentrated in vacuo. The residue was purified by preparative reverse phase chromatography to give 5 mg (5 % yield) of the title compound.as a white solid.LC/MS (FA) ES+ 411. 413. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.50 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 2.0 Hz), 7.20 (dd, 1H, J = 8.0, 2.0 Hz), 4.41 (s, 2H), 3.88 (s, 2H), 3.65-3.62 (m, 4H), 3.32 (bs, 1H), 3.26-3.24 (m, 4H).

[00925] Example 56: Synthesis of 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid (Compound 347)



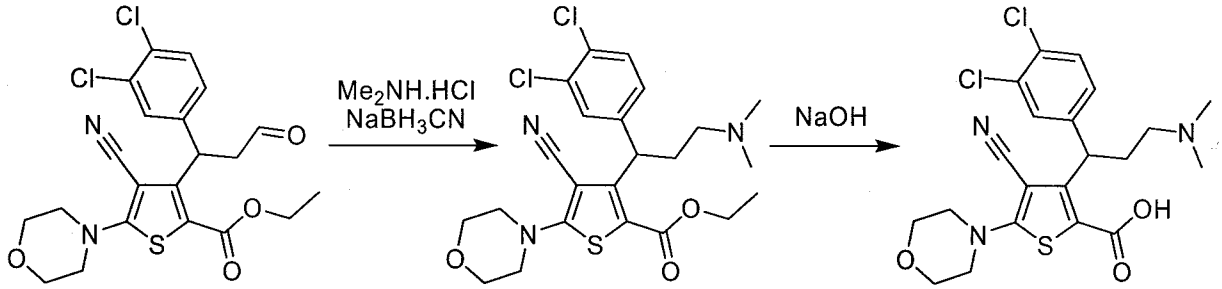
[00926] Step1: To a suspension of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)but-3-en-1-yl]-5-(morpholin-4-yl)thiophene-2-carboxylate (247 mg, 0.531 mmol) in 1,4-dioxane (6.00 mL) and water (2.00 mL) was added sodium metaperiodate (454 mg, 2.12 mmol), 2,6-lutidine (246 uL, 2.12 mmol), and 4% osmium tetroxide in water (4:96, osmium tetraoxide:water, 64.9 uL, 0.0106 mmol). The reaction was vigorously stirred at rt for 5 hrs. The mixture was filtered over a celite pad and the filtered solid was rinsed with EtOAc. The filtrate was washed with $NaHCO_3$(aq) saturated solution and the aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with 1N HCl soln and brine, dried, and concentrated. Purification on a silica gel column (gradient elution 5-50% EtOAc/hexanes) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-oxopropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate as a yellow syrup (108 mg, 43.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 – 9.73 (d, J = 1.3 Hz, 1H), 7.48 –

7.42 (d, J = 2.1 Hz, 1H), 7.42 – 7.32 (d, J = 8.4 Hz, 1H), 7.30 – 7.18 (m, 1H), 6.06 – 5.94 (t, J = 7.7 Hz, 1H), 4.38 – 4.26 (q, J = 7.1 Hz, 2H), 3.86 – 3.77 (t, J = 4.9 Hz, 4H), 3.62 – 3.51 (dd, J = 5.7, 4.0 Hz, 4H), 3.50 – 3.42 (m, 2H), 1.41 – 1.29 (m, 3H).

[00927] **Step2**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-oxopropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (50.0 mg, 0.107 mmol) in ethanol (1.00 mL) was added sodium tetrahydroborate (4.05 mg, 0.107 mmol). The mixture was stirred at rt for 1 hr. The reaction was quenched with 1.00 M of hydrochloric acid in water (0.428 mL) and distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was dried and concentrated to provide a white solid. Purification on a silica gel column (gradient elution 0-5% MeOH) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate as a colorless syrup (38 mg, 75.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.30 – 7.19 (m, 1H), 5.65 – 5.52 (t, *J* = 8.0 Hz, 1H), 4.42 – 4.26 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.77 (t, *J* = 4.9 Hz, 4H), 3.76 – 3.65 (ddt, *J* = 13.0, 9.0, 4.6 Hz, 1H), 3.57 – 3.44 (t, *J* = 4.8 Hz, 5H), 2.69 – 2.58 (dd, *J* = 8.4, 4.1 Hz, 1H), 2.56 – 2.43 (dt, *J* = 8.1, 4.9 Hz, 2H), 1.44 – 1.32 (t, *J* = 7.1 Hz, 3H).

[00928] **Step3**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (38.0 mg, 0.0810 mmol) in tetrahydrofuran (1.00 mL) was added NaH 60% in mineral oil (60:40, Sodium hydride:mineral Oil, 3.56 mg, 0.0890 mmol). The mixture was heated to 60 °C for 3 hrs. The reaction was cooled to rt and distributed between brine and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with brine, dried, and concentrated to provide a yellow solid. Purification on HPLC (reverse phase, AA) provided 4-cyano-3-[1-(3,4-dichlorophenyl)-3-hydroxypropyl]-5-(morpholin-4-yl)thiophene-2-carboxylic acid as a white solid (6.5mg, 18.2% yield). LCMS: (AA) ES+ 441, 443, 445; ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.45 (s, 1H), 7.45 – 7.37 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.22 (m, 1H), 5.79 – 5.63 (m, 1H), 3.83 – 3.71 (t, *J* = 4.8 Hz, 4H), 3.60 – 3.50 (q, *J* = 6.9, 6.0 Hz, 2H), 3.50 – 3.41 (d, *J* = 3.2 Hz, 4H), 2.52 – 2.37 (m, 2H).

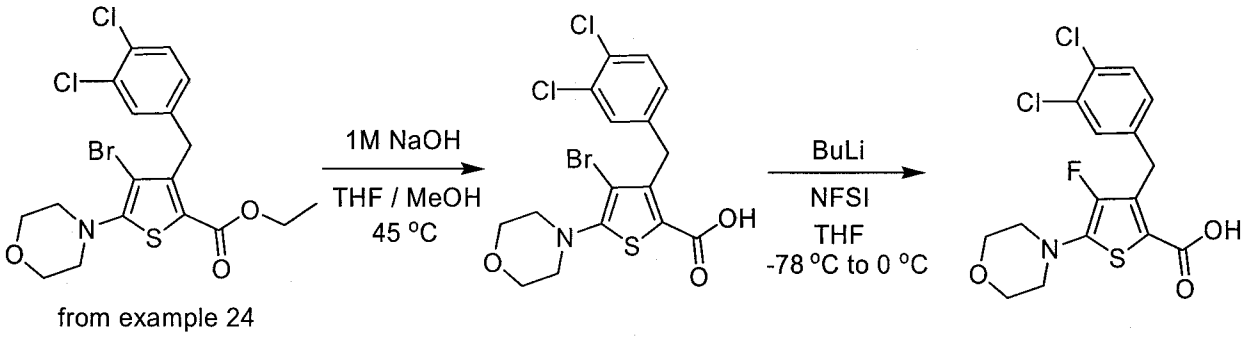
[00929] Example 57: Synthesis of 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin- 4-yl)thiophene-2-carboxylic acid (Compound 331)



[00930] **Step1**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-oxopropyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (38.0 mg, 0.0813 mmol) (from example 56, step 1) in methanol (1.00 mL) was added dimethylamine hydrochloride (9.94 mg, 0.122 mmol), sodium acetate (8.00 mg, 0.0976 mmol), and sodium cyanoborohydride (6.13 mg, 0.0976 mmol). The reaction was stirred at rt for 2h. The mixture was distributed between $NaHCO_3$(aq) saturated solution and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was dried and concentrated. Purification on a silica gel column (gradient elution, 0-15% MeOH/CH_2Cl_2) provided ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin- 4-yl)thiophene-2-carboxylate as a yellow syrup (29.0 mg, 71.8% yield). LCMS: (AA) ES+ 496, 498, 500; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.44 (d, J = 1.9 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 5.54 – 5.40 (t, J = 7.7 Hz, 1H), 4.38 – 4.27 (q, J = 7.1 Hz, 2H), 3.88 – 3.76 (t, J = 4.9 Hz, 4H), 3.58 – 3.49 (dd, J = 5.7, 4.0 Hz, 4H), 2.57 – 2.31 (m, 3H), 2.29 – 2.24 (s, 6H), 2.24 – 2.16 (m, 1H), 1.41 – 1.30 (t, J = 7.1 Hz, 3H).

[00931] **Step2**: To a solution of ethyl 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin-4-yl)thiophene-2-carboxylate (29.0 mg, 0.0584 mmol) in methanol (0.500 mL) was added 1.030 M of sodium hydroxide in water (284 uL, 0.284 mmol). The reaction was stirred at rt over 2 days. The mixture was neutralized with 1.00 M of hydrochloric acid in water(0.292 mL), diluted with 5 mL of water and extracted with 10% MeOH/$CHCl_3$ (x5). The combined organic layer was dried and concentrated, and the resulting white syrup/solid was lyophilized to provide 4-cyano-3-[1-(3,4-dichlorophenyl)-3-(dimethylamino)propyl]-5-(morpholin- 4-yl)thiophene-2-carboxylic acid as a white solid (26 mg, 95% yield). LCMS: (AA) ES+ 468, 470, 472; ^{1}H NMR (400 MHz, DMSO) δ 7.63 – 7.52 (d, J = 8.4 Hz, 1H), 7.44 – 7.37 (s, 1H), 7.15 – 7.02 (d, J = 8.1 Hz, 1H), 5.49 – 5.34 (d, J = 9.4 Hz, 1H), 3.73 – 3.63 (t, J = 4.8 Hz, 4H), 3.38 – 3.31 (dd, J = 6.2, 4.0 Hz, 4H), 3.13 – 2.97 (s, 1H), 2.85 – 2.73 (s, 1H), 2.72 – 2.60 (s, 6H), 2.56 – 2.52 (m, 1H).

[00932] Example 58: Synthesis of 3-(3,4-dichlorobenzyl)-4-fluoro-5-morpholinothiophene-2-carboxylic acid (Compound 320)



[00933] Step 1, Preparation of 4-bromo-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylic acid

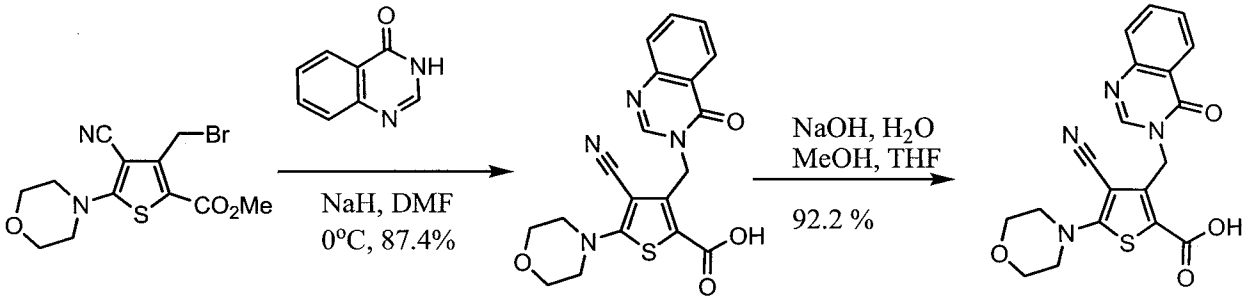
[00934] To a solution of ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylate (109 mg, 0.227 mmol) in THF (1.8 mL) and MeOH (0.37 mL) was added 1.00 M aqueous NaOH (1.82 mL, 1.82 mmol) and the resulting mixture was stirred at 45 °C overnight. The reaction was diluted with water (5 mL) and acidified to pH = 3 with 1 N HCl. The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried, filtered and concentrated in vacuo to give 92 mg (90% yield) of a white solid which was used as is in the next step. LC/MS (AA) ES+ 450, 452, 454. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.21 (bs, 1H), 7.52 (d, 1H, J = 8.0 Hz), 7.39 (d, 1H, 2.0 Hz), 7.09 (dd, 1H, J = 8.0, 2.0 Hz), 4.36 (s, 2H), 3.74-3.71 (m, 4H), 3.13-3.11 (m, 4H).

[00935] Step 2, Preparation of 3-(3,4-dichlorobenzyl)-4-fluoro-5-morpholinothiophene-2-carboxylic acid

[00936] To a solution of 4-bromo-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylic acid (89.0 mg, 0.197 mmol) in THF (3.00 mL) in a dry-ice/acetone bath was added 1.60 M BuLi in hexanes (0.271 mL, 0.434 mmol) and the resulting solution was stirred for 10 minutes at -78 °C. A solution of N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (93.3 mg, 0.296 mmol) in THF (0.70 mL) was then added and the reaction was allowed to warm to 0 °C. The reaction was quenched with saturated NH_4Cl (5 mL) and ethyl acetate (15 mL) was then added. The layers were separated and the aqueous layer was acidified to pH = 3 with 1N HCl. The acidic aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→15/85) to give 31 mg of product. This material was purified by preparative reverse phase chromatography to give 9 mg (10 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 390, 392. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.04 (bs, 1H), 7.54 (d, 1H, J = 8.0

Hz), 7.44 (d, 1H, J = 1.6 Hz), 7.16 (dd, 1H, J = 8.0, 1.6 Hz), 4.21 (s, 2H), 3.71-3.68 (m, 4H), 3.14-3.12 (m, 4H).

[00937] Example 59: Synthesis of 4-cyano-5-(morpholin-4-yl)-3-[(4-oxoquinazolin-3(4H)-yl)methyl]thiophene-2-carboxylic acid (Compound 294)



[00938] Step 1: Methyl 4-cyano-5-(morpholin-4-yl)-3-[(4-oxoquinazolin-3(4H)-yl)methyl]thiophene-2-carboxylate

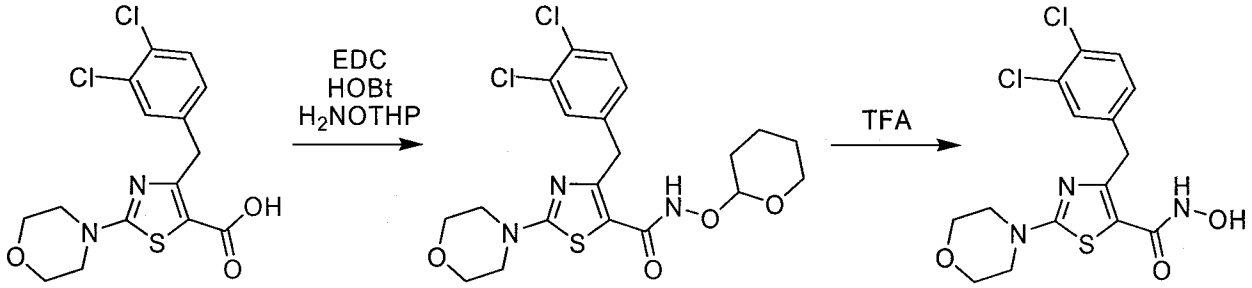
[00939] Under N_2 atmosphere Sodium hydride (23.0 mg, 0.910 mmol) was suspended in anhydrous N,N-Dimethylformamide (3.0 mL, 39 mmol), cooled with ice bath and stirred for 10 min. 4-hydroxyquinazoline (0.120 g, 0.821 mmol) was added and the clear solution was stirred at r.t. for 10 min, cooled with ice bath. Mmethyl 3-(bromomethyl)-4-cyano-5-(morpholin-4-yl)thiophene-2-carboxylate (0.203 g, 0.588 mmol) was added and the reddish-brown solution was stirred with cooling for 40 min. The mixture was quenched with saturated NH4Cl aqueous solution, extracted with EtOAc. The EtOAc solution was washed with water (3x) then brine, dried over Na_2SO_4, filtered, rotavaped to give a crude solid. Chromatograph in a silica gel column using MeOH/DCM (0/100 to 5/95) afforded a solid product (0.211 g, yield 87.4%). LC/MS: (FA) ES^+ 411. ^1H NMR (400MHz, *d*-chloroform) δ 8.30 (m, 1H), 8.26 (s, 1H),7.68-7.76 (m, 2H), 7.45-7.49 (m, 1H), 5.43 (s, 2H), 3.83-3.85 (m, 4H), 3.82 (s, 3H), 3.59-3.62 (m, 4H).

[00940] Step 2: 4-Cyano-5-(morpholin- 4-yl)-3-[(4-oxoquinazolin- 3(4H)-yl)methyl]thiophene- 2-carboxylic acid sodium salt

[00941] Methyl 4-cyano-5-(morpholin-4-yl)-3-[(4-oxoquinazolin-3(4H)-yl)methyl]thiophene-2-carboxylate (0.139 g, 0.339 mmol) was disolved in Tetrahydrofuran (15.0 mL), Water (2.0 mL) and Methanol (5.0 mL). 1.00 M of Sodium hydroxide in Water (1.0 mL, 1.0 mmol) was added and the homogeneous solution was stirred at room temperature for 24 hours. The solution was concentrated in rotavapor to give a white crude solid, dissolved in H2O/MEOH (1/10, ~ 20 mL) and concentrated in rotavapor until a white suspension (~ 2 mL volumn). The suspension was filtered to collect the solid, dried in lyopholizer to give a white solid product (0.132 g, yield 92.2 %). LC/MS: (FA) ES^+ 397; ES^- 395.

^{1}H NMR (400MHz, *d4*-methanol) δ 8.37 (s, 1H), 8.22 (d, J = 8.03 Hz, 1H),7.78-7.82 (m, 1H), 7.65 (d, J = 7.28 Hz, 1H), 7.51-7.55 (m, 1H), 5.99 (s, 2H), 3.78-3.81 (m, 4H), 3.47-3.50 (m, 4H).

[00942] Example 60: Synthesis of 4-(3,4-dichlorobenzyl)-N-hydroxy-2-(morpholin-4-yl)-1,3-thiazole-5-carboxamide (Compound 298)



[00943] Step1: To a suspension of 4-(3,4-dichlorobenzyl)-2-morpholin-4-yl-1,3-thiazole-5-carboxylic acid•Na(125 mg, 0.316 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (72.8 mg, 0.380 mmol), and 1-hydroxybenzotriazole (51.3 mg, 0.380 mmol) in N,N-dimethylformamide (1.50 mL) was added O-(tetrahydropyran-2-yl)hydroxylamine (55.6 mg, 0.474 mmol). The reaction was stirred at rt for 15 hrs. The mixture was distributed between water and EtOAc, and the aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with $NaHCO_3$(aq) saturated solution and 10% LiCl(aq) soln(x2), dried over Na_2SO_4, and concentrated to provide 4-(3,4-dichlorobenzyl)-2-(morpholin-4-yl)-N-(tetrahydro-2H-pyran-2-yloxy)-1,3-thiazole-5-carboxamide as a white solid (153 mg, quantitative). LCMS: (AA) ES+ 472, 474, 476; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (d, *J* = 1.9 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.26 – 7.17 (m, 1H), 5.01 – 4.89 (d, *J* = 2.8 Hz, 1H), 4.31 – 4.21 (m, 2H), 3.96 – 3.86 (td, *J* = 10.4, 9.1, 2.8 Hz, 1H), 3.80 – 3.70 (t, *J* = 4.9 Hz, 4H), 3.66 – 3.56 (m, 1H), 3.51 – 3.42 (t, *J* = 4.9 Hz, 4H), 1.90 – 1.73 (m, 3H), 1.69 – 1.49 (m, 3H).

[00944] Step2: To a solution of 4-(3,4-dichlorobenzyl)-2-(morpholin-4-yl)-N-(tetrahydro-2H-pyran-2-yloxy)-1,3-thiazole-5-carboxamide (153 mg, 0.324 mmol) in methylene chloride (1.50 mL) was added trifluoroacetic Acid (1.50 mL, 19.5 mmol). The reaction was stirred at rt for 12 hrs. The resulting solution was concentrated and distributed between $NaHCO_3$(aq) saturated solution and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2(x2). The combined org layer was washed with water, dried, and concentrated. Purification on a silica gel column (gradient elution, 0-8% MeOH/CH_2Cl_2) provided 4-(3,4-dichlorobenzyl)-N-hydroxy-2-(morpholin-4-yl)-1,3-thiazole-5-carboxamide as a yellow solid (53 mg, 42.1% yield). LCMS: (AA) ES+ 388, 390,

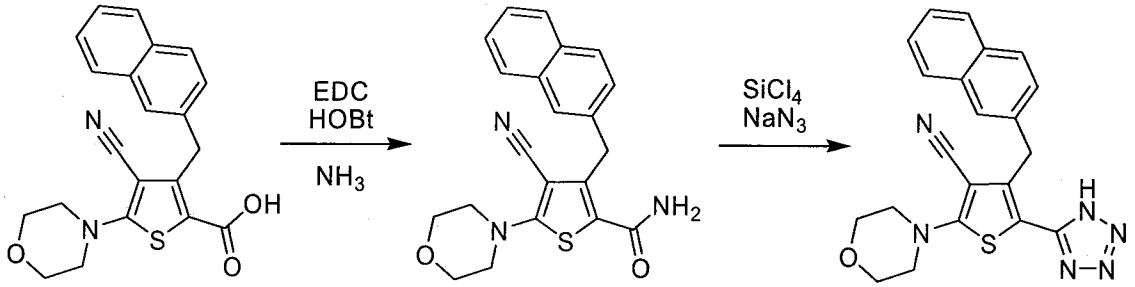
392; ^{1}H NMR (400 MHz, MeOD) δ 7.47 – 7.41 (d, J = 1.8 Hz, 1H), 7.38 – 7.29 (d, J = 8.3 Hz, 1H), 7.25 – 7.14 (dd, J = 8.3, 1.9 Hz, 1H), 4.28 – 4.21 (s, 2H), 3.79 – 3.71 (t, J = 4.9 Hz, 4H), 3.50 – 3.43 (t, J = 4.9 Hz, 4H), 3.33 – 3.27 (t, J = 1.6 Hz, 1H).

[00945] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 60.

334	LC/MS: (AA) ES+ 354

[00946]

[00947] Example 61: Synthesis of 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)thiophene-3-carbonitrile (Compound 316)

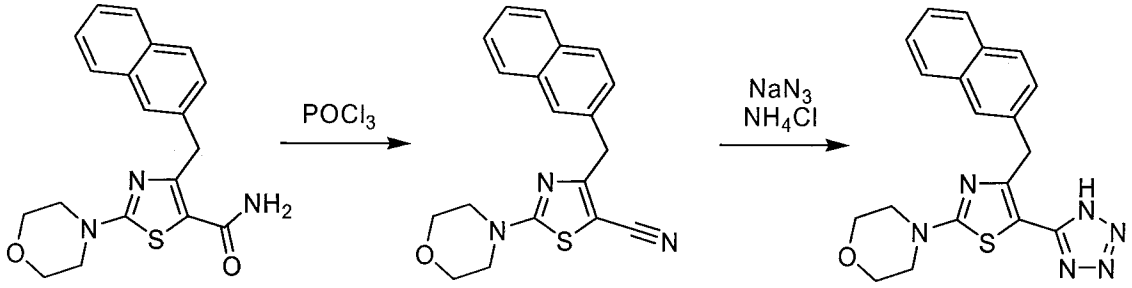


[00948] **Step1**: To a mixture of 4-cyano-5-morpholin-4-yl-3-(2-naphthylmethyl)thiophene-2-carboxylic acid•Na(255 mg, 0.637 mmol) in N,N-dimethylformamide (6.00 mL) was added 1-hydroxybenzotriazole hydrate (117 mg, 0.764 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (146 mg, 0.764 mmol), and 0.500 M of ammonia in 1,4-dioxane(3.18 mL, 1.59 mmol). The reaction was vigorously stirred at rt for 5 hrs. The mixture was distributed between brine and EtOAc, and the aqueous layer was extracted with EtOAc(x2). The combined organic layers were washed with 10% LiCl(aq) solution (x2), dried, and concentrated to provide 4-cyano-5-(morpholin-4-yl)-3-(2-naphthylmethyl)thiophene-2-carboxamide (Compound 327) as a white solid (224 mg, 93.2% yield). LCMS: (AA) ES+ 378; ^{1}H NMR (400 MHz, DMSO) δ 7.89 – 7.76 (td, J = 11.0, 6.6 Hz, 3H), 7.68 – 7.62 (s, 1H), 7.51 – 7.44 (td, J = 6.8, 6.0, 3.7 Hz, 3H), 7.43 – 7.34 (m, 1H), 4.50 – 4.42 (s, 2H), 3.78 – 3.69 (t, J = 4.9 Hz, 4H), 3.50 – 3.40 (t, J = 4.9 Hz, 4H).

[00949] **Step2**: To a mixture of sodium azide (153 mg, 2.35 mmol) in acetonitrile (2.50 mL) in a 20 mL microwave tube was added silicon(IV) chloride (89.9 uL, 0.783 mmol). The mixture was stirred at rt under an atmosphere of Nitrogen for 20 min, then 4-cyano-5-(morpholin-4-yl)-3-(2-naphthylmethyl)thiophene-2-carboxamide (197 mg, 0.522 mmol) was added. The tube was sealed and the reaction was heated to 90 °C for 12 hrs. The mixture was cooled and distributed

between water and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with brine, dried, and concentrated to provide a purple syrup. Purification on HPLC (reverse phase, AA) provided 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)thiophene-3-carbonitrile as a yellow solid (44 mg, 20.9% yield). LCMS: (AA) ES+ 403; ^{1}H NMR (400 MHz, MeOD) δ 7.78 – 7.73 (m, 1H), 7.73 – 7.67 (d, J = 7.8 Hz, 2H), 7.67 – 7.61 (s, 1H), 7.42 – 7.36 (m, 2H), 7.36 – 7.30 (m, 1H), 4.63 – 4.57 (s, 2H), 3.85 – 3.76 (t, J = 4.9 Hz, 4H), 3.57 – 3.48 (t, J = 4.8 Hz, 4H).

[00950] Example 62: Synthesis of 4-[4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)-1,3-thiazol-2-yl]morpholine (Compound 360)



[00951] Step1: A mixture of 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-1,3-thiazole-5-carboxamide (229 mg, 0.648 mmol) (for amide coupling, see example 61 – step 1) and phosphoryl chloride (4.00 mL, 42.9 mmol) was stirred at 80 °C for 30 min. The reaction slowly turned homogeneous. The resulting solution was concentrated under reduced pressure and carefully quenched with 1N NaOH solution at 0 °C. The resulting mixture was distributed between 1N NaOH solution and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was dried and concentrated to provide 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-1,3-thiazole-5-carbonitrile as a yellow solid (213 mg, 98.0% yield). LCMS: (AA) ES+ 336; ^{1}H NMR (400 MHz, DMSO) δ 7.90 – 7.83 (dd, J = 9.0, 1.9 Hz, 3H), 7.80 – 7.72 (s, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.38 (m, 1H), 4.18 – 4.09 (s, 2H), 3.70 – 3.60 (t, J = 4.9 Hz, 4H), 3.51 – 3.41 (t, J = 4.9 Hz, 4H).

[00952] Step2: To a solution of 2-(morpholin-4-yl)-4-(2-naphthylmethyl)-1,3-thiazole-5-carbonitrile (213 mg, 0.635 mmol) in N,N-dimethylformamide (3.00 mL) was added sodium azide (61.9 mg, 0.952 mmol) and ammonium chloride (102 mg, 1.90 mmol). The mixture was heated to 100 °C and stirred for 24 hrs. The resulting mixture was cooled to rt and distributed between water and EtOAc. The aqueous layer was extracted with EtOAc(x2). The combined organic layer was washed with 10% LiCl(aq) solution (x2), dried, and concentrated. Purification

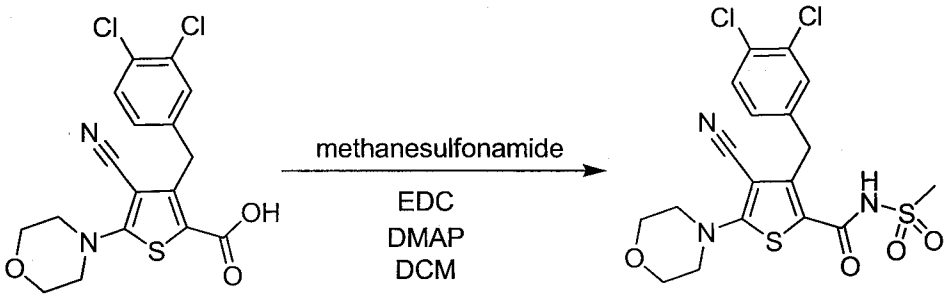
on HPLC (reverse phase, AA) provided 4-[4-(2-naphthylmethyl)-5-(1H-tetrazol-5-yl)-1,3-thiazol-2-yl]morpholine as a yellow solid (105 mg, 43.7% yield). LCMS: (AA) ES+ 379; ^{1}H NMR (400 MHz, MeOD) δ 7.79 – 7.61 (m, 4H), 7.43 – 7.31 (m, 3H), 4.57 – 4.45 (s, 2H), 3.82 – 3.68 (t, J = 4.9 Hz, 4H), 3.53 – 3.43 (t, J = 4.9 Hz, 4H).

[00953] Compounds in the following table are prepared from appropriate starting materials in a method analogous to that of Example 62.

356	LC/MS: (AA) ES+ 378

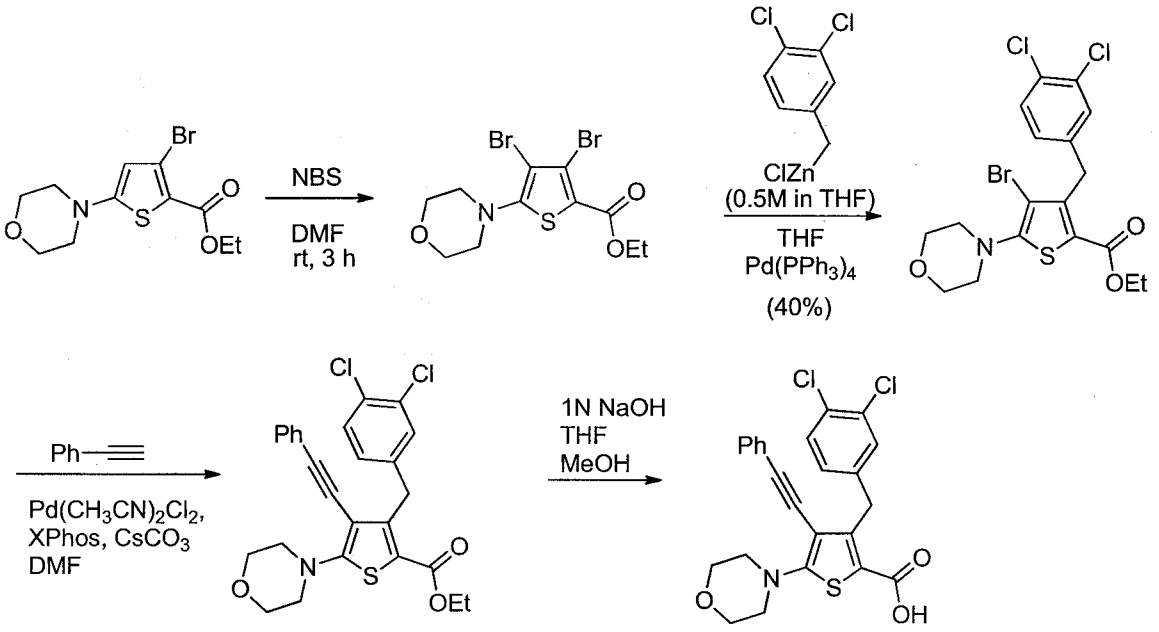
[00954]

[00955] Example 63: Synthesis of 4-cyano-3-(3,4-dichlorobenzyl)-N-(methylsulfonyl)-5-morpholinothiophene-2-carboxamide (Compound 352)



[00956] To a mixture of 4-cyano-3-(3,4-dichlorobenzyl)-5-morpholinothiophene-2-carboxylic acid (291 mg, 0.732 mmol), in DCM (5.0 mL) was added methanesulfonamide (87.1 mg, 0.916 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (176 mg, 0.916 mmol), and *N,N*-dimethylaminopyridine (103 mg, 0.842 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was diluted with DCM (10 mL), 1N HCl (3 mL) and with water (3 mL). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→20/80) to give 250 mg of crude product. This material was purified by preparative reverse phase chromatography to give 70 mg (20 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 474, 476. ^{1}H NMR (400 MHz, MeOH-d_4) δ: 7.45 (d, 1H, J = 2.0 Hz)), 7.38 (d, 1H, J = 8.4 Hz), 7.25 (dd, 1H, J = 8.0, 2.0 Hz), 4.38 (s, 2H), 3.82-3.80 (m, 4H), 3.57-3.55 (m, 4H), 3.18 (s, 3H).

[00957] Example 64: Synthesis of 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2- carboxylic acid (Compound 296).



[00958] **Step 1:** Ethyl 3,4-dibromo-5-(morpholin-4-yl)thiophene-2-carboxylate.

[00959] To a degassed solution of ethyl 3-bromo-5-morpholin-4-ylthiophene-2-carboxylate (0.688 g, 2.15 mmol) in DMF (14 mL, 180 mmol) was added N-bromosuccinimide (0.7648 g, 4.297 mmol) dropwise as a solution in degassed DMF (4.1 mL, 52 mmol). The mixture was wrapped in foil to protect from ambient light, and the reaction was stirred under argon at room temperature for 2 hours. The reaction mixture was quenched via addition of 10% sodium thiosulfate solution (10 mL) and then diluted with EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (eluent: 0-25% EtOAc:hexane) afforded ethyl 3,4-dibromo-5-(morpholin-4-yl)thiophene-2-carboxylate (593 mg, yield 69%). LCMS: (FA) ES+ 398, 400, 402; ^{1}H NMR (400 MHz, DMSO) δ 4.26 (q, J = 7.1 Hz, 2H), 3.75 (dd, J = 5.5, 3.8 Hz, 4H), 3.24 – 3.10 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H).

[00960] **Step 2:** Ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)thiophene-2-carboxylate.

[00961] A sealable reaction vessel containing a suspension of ethyl 3,4-dibromo-5-(morpholin-4-yl)thiophene-2-carboxylate (0.560 g, 1.40 mmol), 0.500 M 3,4-dichlorobenzylzinc chloride in THF (3.368 mL, 1.684 mmol) and THF (2.06 mL, 25.4 mmol) was purged via vacuum/backfilling with argon. To this suspension was added tetrakis(triphenylphosphine)palladium(0) (81.07 mg, 0.07016 mmol), the vial was capped, and the resulting black suspension was stirred at 95 °C overnight. The reaction mixture was adsorbed to celite in vacuo, and the solid thus obtained was purified via column chromatography (eluent: 0-15% EtOAc:hexane) to afford ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-(morpholin-4-

yl)thiophene-2-carboxylate (323 mg, 50%). LCMS: (FA) ES+ 478, 480, 482; ^{1}H NMR (400 MHz, DMSO) δ 7.53 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 4.36 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.75 – 3.70 (m, 4H), 3.17 – 3.12 (m, 4H), 1.22 (t, J = 7.1 Hz, 3H).

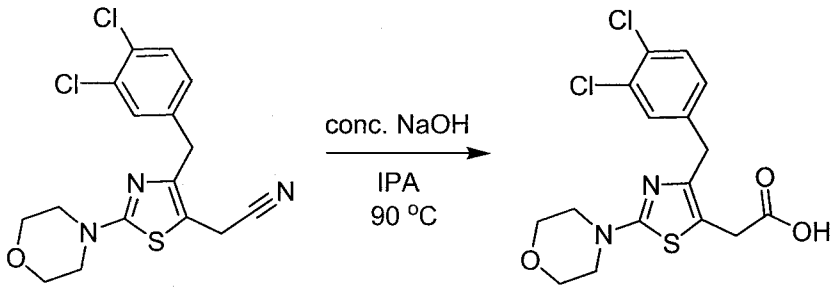
[00962] Step 3: Ethyl 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)-thiophene-2-carboxylate.

[00963] To a suspension of ethyl 4-bromo-3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)thiophene-2-carboxylate (0.125 g, 0.000222 mol), XPhos (0.0172 g, 0.0000362 mol), CsCO3 (0.199 g, 0.000612 mol) and phenylacetylene (0.146 mL, 0.00133 mol) in DMF (1.2 mL, 0.015 mol) was added bis(acetonitrile)palladium(II) chloride (0.00288 g, 0.0000111 mol) and the mixture was heated at 50 °C overnight. The reaction mixture was diluted with EtOAc (30 mL) and water (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified using a dry load on a silica gel column (eluent: 0-30% EtOAc:hexane), affording ethyl 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2-carboxylate (45 mg, 40% yield). LCMS: (FA) ES+ 500, 501, 502; ^{1}H NMR (400 MHz, DMSO) δ 7.55 – 7.51 (m, 2H), 7.43 – 7.37 (m, 5H), 7.20 (dd, J = 8.3, 2.0 Hz, 1H), 4.38 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.79 – 3.74 (m, 4H), 3.57 – 3.52 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H).

[00964] Step 4: 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)-thiophene-2-carboxylic acid.

[00965] To a suspension of ethyl 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2-carboxylate (0.041 g, 0.082 mmol in THF (2.00 mL, 24.6 mmol) and methanol (0.37 mL, 9.1 mmol) was added 1.000 M of sodium hydroxide in water (1.684 mL, 1.684 mmol) and the resulting biphasic mixture was stirred at room temp for 2 days. The pH was carefully adjusted to 3.0 via addition of 1N HCl (monitored in real time with a pH meter), and the reaction mixture was transferred to a separatory funnel. The mixture was diluted with EtOAc (40 mL) and water (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, then dried over Na_2SO_4, filtered, and concentrated. Column chromatography (eluent: 0-5% MeOH:DCM) afforded 3-(3,4-dichlorobenzyl)-5-(morpholin-4-yl)-4-(phenylethynyl)thiophene-2-carboxylic acid (30 mg, 78% yield). LCMS: (FA) ES+ 472, 473, 474; ^{1}H NMR (400 MHz, DMSO) δ 12.92 (s, 1H), 7.55 – 7.50 (m, 2H), 7.43 – 7.34 (m, 5H), 7.21 (dd, J = 8.3, 2.0 Hz, 1H), 4.39 (s, 2H), 3.81 – 3.68 (m, 4H), 3.56 – 3.42 (m, 4H).

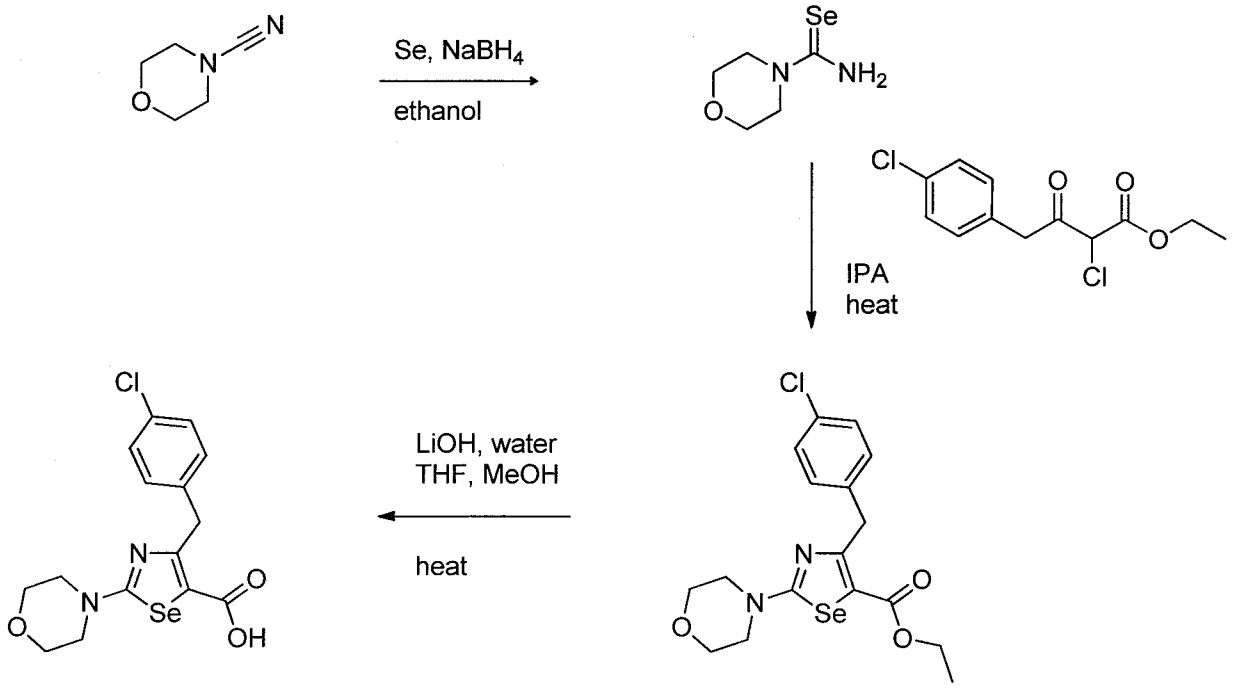
[00966] Example 65: Synthesis of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetic acid (Compound 348)



from example 65 above

[00967] To a solution of 2-(4-(3,4-dichlorobenzyl)-2-morpholinothiazol-5-yl)acetonitrile (165 mg, 0.448 mmol) in IPA (4.88 mL) was added 50% aqueous NaOH (1.68 mL, 44.8 mmol) and the resulting solution was heated to 90 degrees for 3 hours.The reaction was cooled and concentrated in vacuo. The residue was acidified with 1 N HCl and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM = 0/100→20/80) to give 120 mg of product. This material was purified by preparative reverse phase chromatography to give 16 mg (9 % yield) of the title compound.as a white solid. LC/MS (FA) ES+ 387, 389. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.49 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 2.0 Hz), 7.21 (dd, 1H, J = 8.0, 2.0 Hz), 3.78 (s, 2H), 3.67 (s, 2H), 3.66-3.63 (m, 4H), 3.26-3.24 (m, 4H).

[00968] Example 66: Synthesis of 4-(4-chlorobenzyl)-2-morpholino-1,3-selenazole-5-carboxylic acid (Compound 370)



[00969] Step 1: Morpholine-4-carboselenoamide

[00970] In a round bottomed flask equipped with a stir bar were added selenium metal (4.00 g, 49.4 mmol) and ethanol (50 mL). The mixture was cooled in an ice bath and stirred under a nitrogen atmosphere while sodium tetrahydroborate (2.01 g, 53.1 mmol) was slowly added. Gas was evolved and the selenium slowly dissolved. After gas evolution had ceased, 4-morpholinecarbonitrile (2.77 g, 24.7 mmol) was slowly added followed by pyridine hydrochloride (11.4 g, 98.7 mmol). The resulting dark mixture was stirred overnight at room temperature.The grayish reaction mixture was quenched with water (~250 mL) and the mixture was stirred briefly then transferred to a separatory funnel. The mixture was extracted with dichloromethane (3X). The extracts were combined and dried over sodium sulfate. The insolubles were filtered off and the filtrate was evaporated to leave a light pink solid which was stirred with water then filtered. The collected solid was washed with ethyl acetate and the washings were combined then evaporated to leave 80 mg (2% yield) product as a light pink solid. LC/MS (FA) ES+ 195. ^{1}H NMR (400 MHz, DMSO) δ 8.15 - 7.71 (br s, 2H), 3.94 - 3.61 (br s, 4H), 3.60 - 3.51 (t, J = 4.9 Hz, 4H).

[00971] Step 2: Ethyl 4-(4-chlorobenzyl)-2-morpholino-1,3-selenazole-5-carboxylate

[00972] In a round bottomed flask were placed ethyl 2-chloro-4-(4-chlorophenyl)-3-oxobutanoate (84.4 mg, 0.3069 mmol), isopropyl alcohol (5 mL), and morpholine-4-carboselenoamide (80.0 mg, 0.414 mmol). The resulting mixture was brought to reflux under an atmosphere of nitrogen (all solids dissolved to give a clear pale pink solution). After ~1 hour reflux, TLC analysis indicated that all starting materials had been consumed with the production of one major product. The reaction was allowed to cool to room temperature and stir overnight. The solvent was removed on the rotovap then the residue was dissolved in minimal dichloromethane and purified by column chromatography on silica gel (gradient 100% hexane to 35% ethyl acetate) to afford 35 mg (28% yield) product as a white solid. LC/MS (FA) ES+ 413/415/417. ^{1}H NMR (400 MHz, DMSO) δ 7.37 - 7.23 (m, 4H), 4.25 - 4.14 (m, 4H), 3.72 - 3.62 (t, J = 4.9 Hz, 4H), 3.50 - 3.41 (t, J = 4.8 Hz, 4H), 1.27 - 1.20 (t, J = 7.1 Hz, 3H).

[00973] Step 3: 4-(4-chlorobenzyl)-2-morpholino-1,3-selenazole-5-carboxylic acid

[00974] The ethyl 4-(4-chlorobenzyl)-2-(morpholin-4-yl)-1,3-selenazole-5-carboxylate (35.0 mg, 0.0846 mmol) was placed in a round bottomed flask equipped with a stirbar. Tetrahydrofuran (1.00 mL) and methanol (0.1 mL) were added and the mixture was stirred to give a light yellow solution. A solution of lithium hydroxide in water (2.0 M, 0.423 mL, 0.846 mmol) was added in a single portion, and the resulting mixture was stirred under an atmosphere of nitrogen at room temperature overnight. LCMS analysis of the reaction indicated that starting material still remained; only a small amount of it had been hydrolyzed to the product. Additional tetrahydrofuran (2 mL) and lithium hydroxide in water (2.0 M, 0.423 mL, 0.846 mmol) were added and the reaction was heated overnight at 50°C under an atmosphere of nitrogen. LCMS analysis indicated that the reaction was 90% complete. The reaction was heated at

60° C for a further 8 hours. LCMS analysis indicated complete hydrolysis. The reaction was cooled to room temperature, diluted with 10 ml saline, and acidified with dilute acetic acid with good stirring. A white precipitate formed which became granular with stirring. The product was isolated on a fritted funnel, washed with water, and dried at 40° C overnight to yield 29.2 mg (89% yield) product as a white powder. LC/MS (FA) ES+ 385/387/389. ^{1}H NMR (400 MHz, DMSO) δ 12.73 – 12.44 (br s, 1H), 7.36 – 7.24 (m, 4H), 4.26 – 4.18 (s, 2H), 3.74 – 3.63 (t, J = 4.8 Hz, 4H), 3.49 – 3.39 (t, J = 4.7 Hz, 4H).

[00975] Formulation Example 1 (amount per tablet)

(1) Compound obtained in Example 1	10.0 mg
(2) Lactose	60.0 mg
(3) Corn starch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

[00976] A mixture of 10.0 mg of the compound obtained in Example 1, 60.0 mg of lactose and 35.0 mg of corn starch is granulated through a 1 mm-mesh sieve using 0.03 ml of a 10% by weight aqueous solution of gelatin (3.0 mg of gelatin), after which the granules are dried at 40°C and filtered again. The granules obtained are mixed with 2.0 mg of magnesium stearate and compressed. The core tablets obtained are coated with a sugar coat comprising a suspension of sucrose, titanium dioxide, talc and gum arabic and polished with beeswax to yield sugar-coated tablets.

[00977] Formulation Example 2 (dose per tablet)

(1) Compound obtained in Example 1	10.0 mg
(2) Lactose	70.0 mg
(3) Corn starch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

[00978] 10.0 mg of the compound obtained in Example 1 and 3.0 mg of magnesium stearate are granulated using 0.07 ml of an aqueous solution of soluble starch (7.0 mg of soluble starch), after which these granules are dried and mixed with 70.0 mg of lactose and 50.0 mg of corn starch. This mixture is compressed to yield tablets.

[00979] BIOLOGICAL DATA:

[00980] PI3K and VPS34 Enzyme Assays

[00981] Cloning, expression, and purification of PI3Ks and VPS34

[00982] The catalytic subunits of PI3Ks are cloned into either pDEST8(p110 alpha) or pDEST10(p110beta, p110delta, and p110gamma) as N-terminal His tagged fusion proteins using the Gateway system (Invitrogen, catalog# 11804-010 for pDEST8 and 11806-015 for pDEST10). The sequences are verified before recombinant protein expression using the Baculovirus Expression System with Gateway® Technology. The accession numbers for the subunits are as follows:

p110 alpha (GB:U79143)

p110beta (GB:S67334)

p110delta (GB: U86453)

p110gamma (GB: X83368)

[00983] The regulatory subunits of PI3Ks are cloned into pDEST8 as un-tagged protein using the Gateway system (Catalog#11804-010). The sequences are verified before recombinant protein expression using the Baculovirus Expression System with Gateway® Technology. The accession numbers for the subunits are as following:

p85 alpha (GB: BC030815)

p101(GB: AB028925)

[00984] VPS34 (accession number GB:BC033004) is cloned into pDEST20-Thombin as N-terminal GST tagged fusion proteins using the Gateway system (Invitrogen, catalog# 11804-013). The sequences are verified before recombinant protein expression using the Baculovirus Expression System with Gateway® Technology.

[00985] For expression of the p110 complexes, the p85 (MOI of 4) is co-infected with p110 alpha, beta, and delta respectively (1MOI) in SF9 cells and harvested at 60 hours post co-infection. P110 gamma was infected at 1 MOI and harvested at 60 hours post infection.

[00986] For purification, PI3Ks are purified by Ni-NTA Agarose (Qiagen #30250) followed by Mono Q 10/100 GL (Ge Healthcare #17-5167-01). VPS34 is purified by Glutathione Sepharose 4 Fast Flow (GE Healthcare #17-5132-03) followed by HiTrap Q (GE Healthcare #17-1153-01).

[00987] For expression VPS34 was infected at 1MOI in SF9 cells and harvested 72 hours post infection.

[00988] For purification, VPS34 is purified by Glutathione Sepharose 4 Fast Flow (GE Healthcare #17-5132-03) followed by HiTrap Q (GE Healthcare #17-1153-01).

[00989] PI3K and VPS34 Assay Conditions

[00990] 1) Human PI3K alpha enzyme assay method

[00991] 0.5uL compounds in DMSO are added to wells of a 384 well microtitre plate (Corning 3575). At room temperature: 10ul PI3K reaction buffer (50 mM Hepes, 5mM DTT, 150mM NaCl, 10mM beta-glycerophosphate, 10mM MgCl2, 0.25mM sodium cholate and 0.001% CHAPS, pH 7.00) containing ATP (25uM, Promega) is added followed immediately by 10ul PI3K reaction buffer containing di-C8 PI(4,5)P2 (3.5uM, CellSignals) and PI3Kalpha (0.4875nM, Millennium Protein Sciences Group) and the mixture is incubated with shaking at room temperature for 30 minutes. Then 5ul PI3K stop mix (50mM Hepes, 5mM DTT, 150 mM NaCl, 0.01% Tween-20, 15 mM EDTA and 25nM biotin-PI(3,4,5)P3 (Echelon) is added to quench the reaction followed immediately by addition of 5ul HTRF detection mix (50mM Hepes, 5mM DTT, 150 mM NaCl, 0.01% Tween-20, 40mM KF, 10nM GST:GRP-1 PH domain (Millennium Protein Sciences Group), 15nM Streptavidin-XL (CisBio) and 0.375nM anti-GST Eu++ antibody (CisBio) at pH 7.00). The plates are then incubated for 1 hour at room temperature with shaking and then read on a BMG PheraStar Plus reader.

[00992] 2) Human PI3K beta, delta and gamma isoforms are tested using the procedure described for PI3K alpha above but with the following changes: PI3K beta (5.25nM), PI3K delta (0.75nM) and PI3K gamma (5nM). All isoforms supplied by Millennium Protein Science Group.

[00993] 3) VPS34 is assayed using Adapta ™ Universal Kinase Assay Kit (Invitrogen).

[00994] 4) Human VPS34 enzyme assay method

[00995] 100nL compounds in DMSO are added to wells of a 384 well microtitre plate (Greiner 780076). At room temperature: 5ul VPS34 reaction buffer (Invitrogen Assay Buffer Q (diluted 1 in 5 with nanopure water) plus 2mM DTT and 2mM MnCl2) containing ATP (20uM, Promega) and 200uM PI-PS substrate (Invitrogen PV5122) is added followed immediately by 5ul VPS34 reaction buffer (as above) containing VPS34 (5nM, Millennium Protein Sciences Group) and the mixture is incubated with shaking at room temperature for 1 hour. Then 5ul VPS34 stop-detect mix (as per Invitrogen Adapta Assay kit (PV5009) instructions (contains kinase quench buffer, TR-FRET buffer, Adapta Eu anti-ADP antibody and Alexa Fluor 647 ADP tracer)) is added to quench the reaction. The plates are then incubated for 30 minutes at room temperature with shaking and then read on a BMG PheraStar Plus reader.

[00996] For the assay methods described above, test compound percent inhibition, at various concentrations, is calculated relative to control (DMSO and EDTA) treated samples. Compound concentration versus percent inhibition curves are fitted to generate IC_{50} values. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[00997] PI3K Cell Assays

[00998] 1) In-Cell Western Assay

[00999] The pSer473 AKT LI-COR In-Cell Western Assay is a quantitative immunofluorescent assay that measures phosphorylation of serine 473 AKT (pSer473 AKT) in WM266.4 and SKOV3 tumor cell lines grown in cell culture.

[001000] WM266.4 cells are propagated in Minimum Essential Media (MEM) (Invitrogen) containing L-glutamine, 10% Fetal Bovine Serum, 1 mM MEM Sodium Pyruvate, and 0.1 mM MEM Non-Essential Amino Acids and SKOV3 cells are propagated in McCoy's 5A Media (modified) (Invitrogen) containing L-Glutamine and 10% Fetal Bovine Serum. Both cell lines are kept in a humidified chamber at 37°C with 5% CO_2. For the pSer473 AKT LI-COR In-Cell Western Assay, 1.5 x 10^4 WM266.4 and 1.5 x 10^4 SKOV3 cells are cultured in 100 µl of media per well in tissue culture-treated black-walled, clear bottom Optilux 96-well plates (BD Biosciences) for 16-20 hours. Prior to addition of compounds, cell media is removed and replaced with 75 µl of fresh media. Test compounds in DMSO are diluted 1:100 in media. The diluted test compounds are added to the cells (25 µl per well) in 3-fold dilutions with a final concentration range of 0.0015 to 10 µM. The cells are incubated for 2 hours in a humidified chamber at 37°C with 5% CO_2. Immediately following compound incubation, all liquid is removed from the wells and cells are fixed with 4% paraformaldehyde in PBS (150 µl per well) for 20 minutes at room temperature. The paraformaldehyde solution is removed from wells and the cells are permeabilized with 200 µl 0.1% Triton X-100 in PBS per well for 10 min x 3 at room temperature. After removal of PBS + 0.1% Triton X-100, 150 µl Odyssey blocking buffer (LI-COR Biosciences) is added to each well and plates are incubated at room temperature for 1.5 h. Blocking buffer is removed from the wells and primary antibodies (Phospho-AKT (Ser473) (D9E) XP™ Rabbit mAb and AKT (pan) (40D4) Mouse mAb, Cell Signaling Technology) diluted in Odyssey blocking buffer are added (50 µl per well). Plates are incubated at 4°C overnight. The cells are washed for 20 min x 3 with PBS + 0.1% Tween-20 (200 µl per well). Secondary antibodies (IRDye 680 Goat anti-Rabbit IgG (H+L) and IRDye 800CW Goat anti-Mouse IgG (H+L), LI-COR Biosciences) are diluted in Odyssey blocking buffer and added to wells (50 µl per well) followed by a 1 h incubation at room temperature, protected from light. Cells are washed for 20 min x 3 with PBS + 0.1% Tween-20 (200 µl per well). Wash buffer is completely removed from wells after last wash, plates are protected from light until scanned and analyzed with the Odyssey Infrared Imaging System (LI-COR Biosciences). Both pS473 AKT and AKT are simultaneously visualized with the 680 nm fluorophore indicated by a red color and the 800 nm fluorophore indicated by a green color. Relative fluorescence units derived from the scans allow for quantitative analyses of both labeled proteins and the ratio of pS473 AKT to AKT is calculated. Concentration response curves are generated by plotting the average ratios of PI3K inhibitor-treated samples relative to DMSO-treated controls to determine percent change in expression of pS473 AKT, and percentage inhibition values at a single concentration or growth inhibition (IC_{50}) values are determined from those curves. One skilled in the art

will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[001001] 2) ATPlite Viability Assay

[001002] The ATPLite™ Assay (Perkin-Elmer) measures cellular adenosine-triphosphate (ATP) through the generation of a luminescent signal formed from the ATP-dependent enzyme firefly luciferase. The luminescent signal intensity can be used as a measure of cellular proliferation, and can be used to assess the anti-proliferative effects of PI3K inhibitors.

[001003] WM266.4 cells propagated in Minimum Essential Media (MEM) (Invitrogen) containing L-Glutamine, 10% Fetal Bovine Serum, 1 mM MEM Sodium Pyruvate, and 0.1 mM MEM Non-Essential Amino Acids are cultured in 384-well tissue culture-treated Black/Clear plates (Falcon) at 1 x 10^3 cells per well in a volume of 75 µl in a humidified chamber at 37°C with 5% CO_2 for 24 h. Test compounds (2 µl in 100% DMSO) are diluted in 95 µl of cell culture media. The diluted test compounds are added (8 µl per well) to 384-well plates. Final concentration range of 3-fold serial dilution of compounds is 0.001 to 20 µM. Plates are incubated for 72 h in a humidified chamber at 37°C with 5% CO_2. One control plate without compound addition is processed at the start of the 72 h incubation as a "Time Zero" reading for quantitative evaluation of cell viability at start of assay. After 72 h, all but 25 µl of cell culture media is removed from each well, followed by the addition of 25 µl of ATPlite 1step reagent (Perkin Elmer) to each well. Luminescence is measured on a LEADSeeker Luminescence Counter (GE Healthcare Life Sciences). Concentration response curves are generated by calculating the luminescence decrease in test compound-treated samples relative to DMSO-treated controls, and percentage inhibition values at a single concentration or growth inhibition (IC_{50}) values are determined from the curves. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[001004] Vps34 Cell Assays

[001005] 1) FYVE domain redistribution assay

[001006] The FYVE domain redistribution assay monitors translocation of EGFP-2XFYVE from its initial location bound to (PtdIns(3)P) in early endosomes to the cytoplasm in response to test compounds. Recombinant U2OS cells stable expressing the FYVE finger from the human homologue of the hepatocyte growth factor-regulated tyrosine kinase substrate Hrs, duplicated in tanden (GenBank Acc. NM_004712) and fused to the C-terminus of enhanced green fluorescent protein (EGFP). U2OS cells are adherent epithelial cells derived from human osteosarcoma. Expression of EGFP-2X-FYVE is controlled by a standard CMV promoter and continous expression is maintained by addition of geneticin to the culture medium. Localization of the fusion protein within the cells is imaged on the Evotec Technologies

OPERA Confocal Imager and Integrated Spot Signal Per Cellular Signal is quantified using Acapella software. Using this information, percentage inhibition values at a single concentration or IC_{50} values for inhibitors can be determined.

[001007] U2OS EGFP-2XFYVE cells are propagated in Dulbecco's Modified Eagle Media High glucose(D-MEM) (Invitrogen cat. 11995) containing 10% Fetal Bovine Serum (HyClone cat. SH30071.02) and 0.5mg/ml Geneticin (Invitrogen) and kept in a humidified chamber at 37°C with 5% CO_2. 8 x 10^3 cells are cultured in 100 µl of media per well in tissue culture-treated black-walled, clear bottom Optilux 96-well plates (BD Biosciences) for 16-24 hours.

[001008] Prior to addition of compounds, cell media is removed and replaced with 75 µl of fresh media. Test compounds in DMSO are diluted 1:100 in media. The diluted test compounds are added to the cells (25 µl per well) in 3-fold dilutions with a final concentration range of 0.0015 to 10 µM. The cells are incubated for 30 minutes in a humidified chamber at 37°C with 5% CO_2. Immediately following compound incubation, all liquid is removed from the wells and cells are fixed with 4% paraformaldehyde in PBS (75 µl per well) for 15 minutes at room temperature. The paraformaldehyde solution is removed from wells and washed once with PBS (100 µl per well). The PBS is removed and cells are incubated with DRAQ5 Nucleur Dye (Alexis/Biostatus) (85 µl per well). The plates are covered with Flash Plate plastic adhesive foil and imaged on the Evotec Technologies OPERA Confocal Imager Opera after at least a 30 minute incubation. Concentration curves are generated by caluculating the Integrated Spot Intensity Per Cellular Signal decrease in test-compound treated samples relative to DMSO-treated controls and a 100% control inhibitor, and percentage inhibition values at a single concentration or growth inhibition (IC_{50}) values are determined from the curves. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

[001009] As detailed above, compounds of the invention inhibit PI3K and/or VPS34. Examples of class I PI3-kinase isoforms are PI3K α, β, γ and δ. In certain embodiments, the compounds of the invention inhibit one or more isoforms of PI3K. In certain other embodiments, the compounds of the invention selectively inhibit one particular isoform of PI3K. For example, in some embodiments the compounds of the invention selectively inhibit PI3Kα. In some embodiments the compounds of the invention selectively inhibit PI3Kβ.

[001010] As used herein, selective inhibitor refers to compounds that inhibit one or more of the particular PI3K isoforms with at least about >10-fold, or at least about >20-fold, or at least about >30-fold selectivity for the one or more particular PI3K isoforms relative to other class I PI3-kinase isoforms in a biochemical assay. By way of example, compounds that inhibit PI3Kβ with at least about >10-fold, or at least about >20-fold, or at least about >30-fold selectivity relative to PI3K α, γ or δ are selective inhibitors

of PI3Kβ. Alternatively, compounds that inhibit PI3K β and δ with at least about >10-fold, or at least about >20-fold, or at least about >30-fold selectivity relative to PI3K α or γ are selective inhibitors of PI3K β and δ.

[001011] As detailed above, compounds of the invention inhibit PI3K. In certain embodiments, compounds inhibit one or more isoforms of PI3K. In other embodiments, compounds of the invention inhibit PI3Kalpha and have an IC_{50} > 1.0 μM. For example, these compounds include 2, 3, 5, 6, 7, 8, 9, 11, 12, 15, 16, 17, 18, 19, 21, 22, 23, 25, 26, 27, 33, 34, 36, 37, 39, 43, 44, 45, 46, 47, 49, 51, 52, 55, 58, 59, 60, 62, 63, 65, 66, 68, 69, 70, 73, 75, 76, 77, 78, 79, 80, 81, 84, 85, 87, 88, 89, 91, 92. In other embodiments, compounds of the invention have an IC_{50} < 1.0 μM but > 0.1 μM. For example, these compounds include compounds 1, 4, 10, 14, 20, 24, 28, 30, 31, 32, 35, 38, 40, 42, 48, 53, 54, 56, 57, 61, 64, 67, 71, 72, 74, 82, 83, 86, 90. In still other embodiments, compounds of the invention have an IC_{50} < 0.1 μM. For example, these compounds include compounds 13, 29, 41, 50. In still other embodiments, compounds of the invention inhibit PI3Kbeta and have an IC_{50} > 1.0 μM. For example, these compounds include 2, 18, 22, 24, 29, 49, 55, 63, 67, 78. In other embodiments, compounds of the invention have an IC_{50} < 1.0 μM but > 0.1 μM. For example, these compounds include compounds 1, 4, 6, 8, 10, 12, 15, 17, 23, 25, 26, 27, 28, 32, 33, 34, 35, 37, 38, 39, 40, 42, 46, 47, 48, 53, 54, 56, 57, 58, 60, 61, 62, 64, 68, 69, 70, 71, 72, 73, 74, 76, 79, 82, 83, 84, 89. In still other embodiments, compounds of the invention have an IC_{50} < 0.1 μM. For example, these compounds include compounds 3, 5, 7, 9, 11, 13, 14, 16, 19, 20, 21, 30, 31, 36, 41, 43, 44, 45, 50, 51, 52, 59, 65, 66, 75, 77, 80, 81, 85, 86, 87, 88, 90, 91, 92.

[001012] In some embodiments, compounds of the invention inhibit PI3K α and β at a 1.1 μM concentration with the percent inhibition as shown in the table below.

Compound	PI3Kα Percent Inhibition	PI3Kβ Percent Inhibition	Compound	PI3Kα Percent Inhibition	PI3Kβ Percent Inhibition
91	27	105	**111**	7	77
93	9	80	**112**	95	110
94	58	97	**113**	25	100
95	68	101	**114**	40	106
96	58	109	**115**	45	97
97	53	101	**116**	46	98
98	58	111	**117**	48	94

99	12	72	**118**	28	104
100	20	98	**119**	9	88
101	30	105	**120**	18	97
102	30	78	**121**	11	59
103	2	71	**122**	49	106
104	26	109	**123**	64	105
105	21	98	**124**	79	109
106	58	103	**125**	46	99
107	49	103	**126**	42	103
108	44	100	**127**	40	110
109	6	76	**128**	46	106
110	5	41			

[001013] In some embodiments, compounds of the invention inhibit PI3K δ and γ at a 1.0 μM concentration with the percent inhibition as shown in the table below.

Compound	PI3Kδ Percent Inhibition	PI3Kγ Percent Inhibition	Compound	PI3Kδ Percent Inhibition	PI3Kγ Percent Inhibition
91	84.8	15.4	**112**	114.5	69.0
93	46.0	9.5	**113**	78.8	32.5
94	102.4	52.6	**114**	112.8	56.9
95	86.1	23.9	**115**	63.0	12.0
96	96.0	36.2	**116**	83.0	36.7
97	89.8	17.8	**117**	78.5	14.7
98	108.5	67.6	**118**	89.3	27.5
99	55.4	6.4	**119**	62.6	7.6
100	65.5	13.2	**120**	77.0	11.0
102	38.1	6.8	**121**	77.3	7.3
103	38.6	6.4	**122**	96.2	49.6
104	93.0	28.8	**123**	96.8	36.6
105	51.2	9.8	**124**	112.0	74.2
106	88.8	51.8	**125**	85.1	25.9
107	87.3	20.2	**126**	100.4	37.6
108	99.6	38.1	**127**	100.4	55.0
109	35.4	3.9	**128**	114.2	63.4
111	60.5	6.9			

[001014] In some embodiments, compounds of the invention inhibit VPS34 at a 1.0 μM concentration with the percent inhibition as shown in the tables below.

Compound	VPS34 Percent Inhibition	Compound	VPS34 Percent Inhibition	Compound	VPS34 Percent Inhibition
93	19.2	**106**	34.4	**119**	19.5
94	30.6	**107**	45.8	**120**	38.3
95	167.0	**108**	62.4	**121**	64.8
96	47.8	**109**	24.0	**122**	55.2
97	45.0	**111**	46.8	**123**	45.1
98	68.9	**112**	37.8	**124**	78.8
99	46.7	**113**	18.1	**125**	37.1
100	36.6	**114**	131.4	**126**	44.0
102	28.2	**115**	39.7	**127**	33.7
103	7.2	**116**	54.2	**128**	88.1
104	63.2	**117**	28.6		
105	22.6	**118**	68.2		

Compound	p110 alpha Percent Inhibition	p110 beta Percent Inhibition	p110 gamma Percent Inhibition	p110 delta Percent Inhibition
129	83	106	32	109
130	21	73	22	62
131	75	78	5	80
132	45	103	53	77
133	84	101	26	74
134	21	72	8	44
135	78	87	8	99
136	80	110	67	109
137	12	54	12	30

138	43	86	13	69
139	77	100	24	105
140	76	47	62	74
141	17	89	15	66
142	15	67	7	47
143	58	115	62	85
144	63	94	19	111
145	64	98	9	97
146	67	103	23	110
147	83	96	18	107
148	41	98	34	69
149	54	109	75	117
150	2	54	6	35
151	72	105	17	108
152	61	97	16	106
153	75	84	11	87
154	79	108	39	108
155	29	64	28	53
156	13	47	2	33
157	55	68	7	101
158	18	94	20	69
159	18	61	5	31
160	74	101	20	107
161	14	60	7	40
162	38	93	33	83
163	97	110	25	106
164	100	107	44	112
165	64	77	14	87
166	92	82	3	85
167	105	103	26	110
168	23	107	58	110
169	65	89	7	65
170	84	106	26	105

171	59	106	60	99
172	28	101	6	60
173	69	67	3	83
174	15	70	8	59
175	19	85	7	36
176	76	109	35	109
177	79	100	34	106
178	20	109	38	88
179	29	60	5	89
180	60	102	21	102
181	85	91	35	108
182	83	100	45	107
183	-2	16	3	9
184	76	112	16	112
185	16	97	9	50
186	68	109	65	92
187	32	95	25	77
188	47	94	36	82
189	89	96	21	106
190	3	60	7	33
191	26	97	30	90
192	48	90	12	100
193	26	69	13	46
194	17	18		
195	52	74	8	88
196	69	91	12	105
197	15	23	4	19
198	18	108	35	70
199	21	64	16	42
200	101	118	60	111
201	74	105	37	110
202	12	80	8	54
203	10	88	16	67

204	70	101	25	90
205	42	114	64	83
206	90	96	11	106
207	27	83	9	51
208	42	108	47	107
209	92	107	34	108
210	52	110	68	92
211	111	111	13	106
212	87	109	38	112
213	57	80	35	109
214	46	84	14	46
215	29	85	8	51
216	64	91	11	99
217	30	74	24	60
218	61	102	14	97
219	32	101	31	107
220	92	91	9	99
221	62	94	8	100
222	68	98	9	102
223	67	94	21	102
224	70	92	15	103
225	51	52	51	84
226	46	98	14	93
227	-2	76	3	24
228	24	94	11	57
229	62	105	16	106
230	57	93	29	102
231	34	104	47	77
232	38	105	26	67
233	61	97	28	74
234	60	100	10	104
235	65	101	17	66
236	11	53	10	48

237	61	89		
238	72	88	11	96
239	30	68	27	41
240	52	79	8	98
241	59	107	27	104
242	81	104	36	112
243	12	66	4	45
244	77	101	14	101
245	73	109	15	104
246	15	81	8	43
247	83	105	21	104
248	89	106	35	109
249	51	98	9	56
250	53	92	5	88
251	14	96	12	44
252	58	85	12	60
253	20	64	2	27
254	49	96	8	91
255	0	55	5	39
256	25	87	8	57
257	31	97	30	68
258	18	86	13	47
259	69	100	25	101
260	37	74	6	37
261	79	113	33	105
262	0	69	4	12
263	48	105	43	84
264	32	99	28	100
265	64	109	64	111
266	36	90	8	52
267	100	113	43	111
268	82	95	16	102
269	72	100	15	101

270	81	114	24	111
271	35	82	8	63
272	70	96	10	70
273	88	73	7	98
274	98	109	38	107
275	17	47	14	44
276	4	15	6	12
277	95	97	55	116
278	23	98	35	83
279	19	106	42	78
280	35	106	34	92
281	52	96	56	97
282	14	99	21	64
283	96	98	18	99
284	39	114	66	110
285	16	83	18	77
286	36	92	50	104
287	84	109	69	112
288	14	85	19	76
289	11	32	10	32
290	23	104	49	104
291	36	107	57	105
292	4	82	6	56
293	98	108	78	110
294	47	94	35	101
295	101	111	76	112
296	37	79	14	107
297	26	104	33	77
298	11	95	38	103
299	39	109	42	108
300	44	105	46	97
301	55	107	49	89
302	21	100	15	97

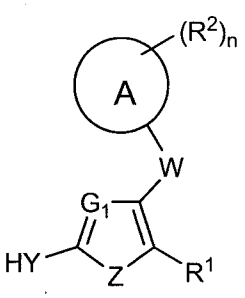
303	99	110	69	115
304	6	25	7	32
305	37	106	37	74
306	81	109	51	108
307	15	84	9	62
308	41	106	39	92
309	56	101	66	108
310	34	106	64	105
311	55	104	64	105
312	64	105	47	92
313	73	117	30	86
314	42	109	42	104
315	97	110	75	114
316	78	106	62	111
317	20	77	29	70
318	18	96	14	76
319	59	105	50	113
320	16	94	35	97
321	67	73	59	86
322	64	104	28	67
323	66	61	46	97
324	107	118	67	113
325	17	89	22	89
326	79	108	56	96
327	34	109	22	109
328	11	98	48	83
329	39	112	29	80
330	85	109	61	106
331	37	105	51	107
332	11	77	27	91
333	63	95	55	74
334	21	103	12	101
335	54	111	31	107

336	16	90	10	49
337	14	60	11	46
338	67	110	73	109
339	20	86	12	55
340	48	113	59	104
341	30	110	30	98
342	34	80	12	97
343	84	110	67	113
344	24	103	59	102
345	64	105	62	83
346	21	98	23	98
347	71	102	60	111
348	4	63	4	56
349	43	108	42	96
350	6	58	3	41
351	15	82	46	79
352	18	85	14	84
353	19	87	15	80
354	89	111	40	99
355	44	100	53	105
356	11	95	23	72
357	89	110	79	110
358	13	43	32	51
359	90	109	64	102
360	30	106	49	110
361	104	115	60	111
362	80	116	44	104
363	99	113	65	106
364	88	109	56	101
365	105	117	63	112
366	66	113	77	113
367	99	110	72	116
368	89	112	87	113

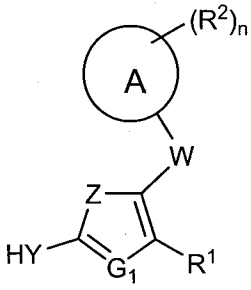
369	109	115	65	109
370	22	98	12	62

[001015] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments, which utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments, which have been represented by way of example.

1. A compound of formula **IA-a** or **IB-a**:



IA-a

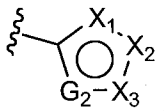


IB-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $–N(R^{3'})$ –, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $–Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-CO_2$-, $-C(O)NR^{4a}$-, $-N(R^{4a})C(O)$-, $-N(R^{4a})CO_2$-, $-S(O)_2NR^{4a}$-, $-N(R^{4a})S(O)_2$-, $-OC(O)N(R^{4a})$-, $-N(R^{4a})C(O)NR^{4a}$-, $-N(R^{4a})S(O)_2N(R^{4a})$-, or -OC(O)-;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic,

3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-

10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or $-CN$;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5

heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

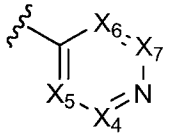
G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2$-, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

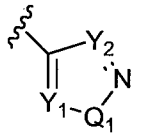
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

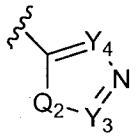
HY is an optionally substituted group selected from:



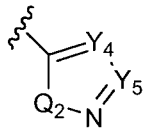
A ,



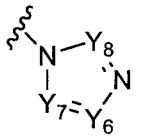
B ,



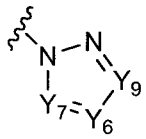
C ,



D



E ,



or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $–CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $–NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

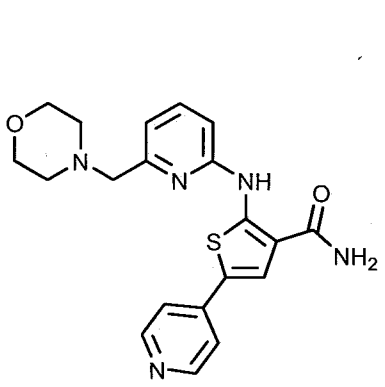
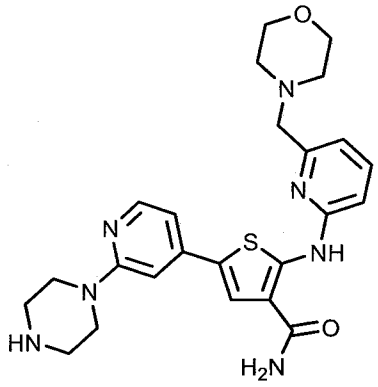
wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

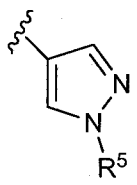
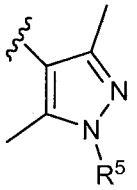
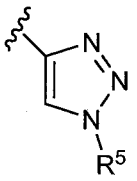
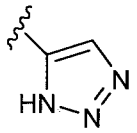
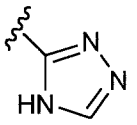
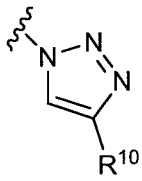
wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, provided that:

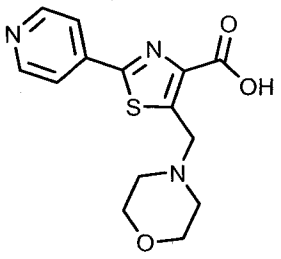
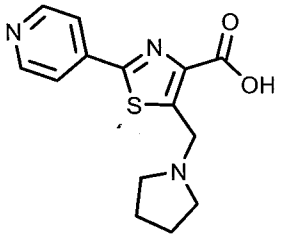
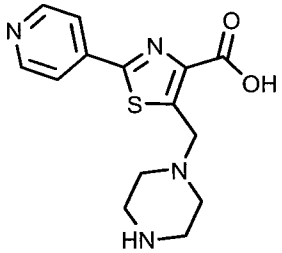
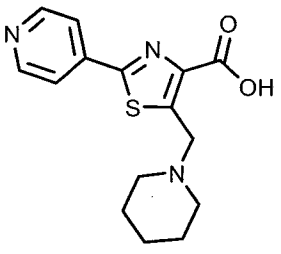
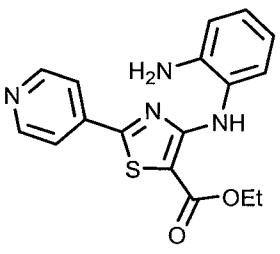
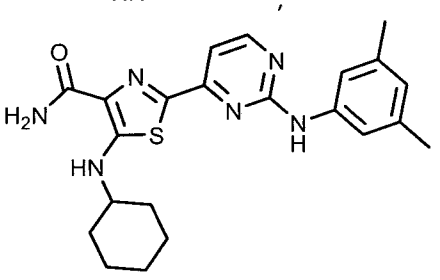
a) for compounds of formula IB-a compounds are other than:

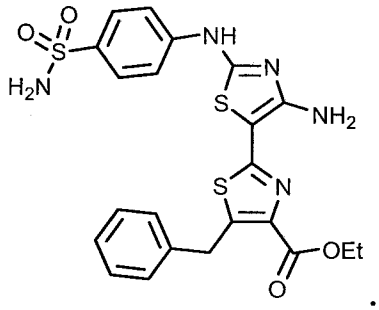

,

; and

when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than

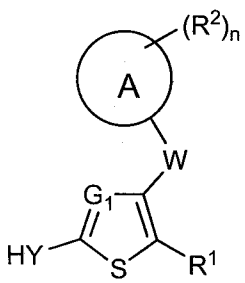

,

,

,

,

,

, or ; and

b) the compound is other than:

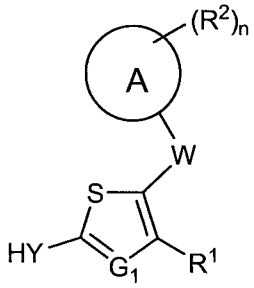

,

,

,

,

,

,



2. A compound of formula **IA** or **IB**:



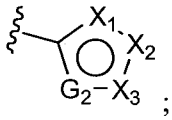
IA



IB

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, -C(O)(NH)OH, -C(=NH)NHOH, $-C(O)NR^3N(R^3)_2$, $-C(=N\text{-}NH_2)NH_2$, $-C(=N)N(R^3)_2$, wherein:

CY is  ; wherein:

G_2 is –N= , =N–, or $-N(R^{3'})$ –, wherein:

each occurrence of R^3 and $R^{3'}$ is independently hydrogen or an optionally substituted C_{1-6} aliphatic, wherein:

X_1, X_2, and X_3, are each independently N, $NR^{3'}$, O, S, or CR^4, provided that only one of X_1, X_2, or X_3 may be O, S, or $NR^{3'}$;

each occurrence of R^4 is independently hydrogen, -CN, halogen, $-Z_3\text{-}R^6$, or an optionally substituted group selected from C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_3 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{4a})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-CO_2$-, $-C(O)NR^{4a}$-, $-N(R^{4a})C(O)$-,

$-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$,
$-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, or $-OC(O)-$;

R^{4a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^6 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic,

3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein two adjacent occurrences of $R^{3'}$ or R^4, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, and:

each occurrence of R^{12a} is independently halogen, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_1-C_6 aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered

aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently -$N(R^{12e})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{12e})$-, -$S(O)_2N(R^{12e})$-, -$OC(O)N(R^{12e})$-, -$N(R^{12e})C(O)$-, -$N(R^{12e})SO_2$-, -$N(R^{12e})C(O)O$-, -$N(R^{12e})C(O)N(R^{12e})$-, -$N(R^{12e})SO_2N(R^{12e})$-, -OC(O)-, or -$C(O)N(R^{12e})$-O-; and

T_2 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by -$N(R^{13})$-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -C(O)O-, -$C(O)N(R^{13})$-, -$S(O)_2N(R^{13})$-, -$OC(O)N(R^{13})$-, -$N(R^{13})C(O)$-, -$N(R^{13})SO_2$-, -$N(R^{13})C(O)O$-, -$N(R^{13})C(O)N(R^{13})$-, -$N(R^{13})S(O)_2N(R^{13})$-, -OC(O)-, or -$C(O)N(R^{13})$-O- or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

n is 0 to 4;

W is selected from –$C(R^7)_2$-, –$C(=C(R^7)_2)$-, -$C(R^7)_2O$-, -$C(R^7)_2NR^{7a}$-, –O-, -$N(R^{7b})$-, -S-, -S(O)-, -$S(O)_2$-, -C(O)-, -$C(O)NR^{7a}$-, or -$N(R^{7a})C(O)$-, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, or –CN;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, -$C(O)R^{7a}$, -$C(O)OR^{7a}$, $S(O)R^{7a}$, or -$S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from

a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

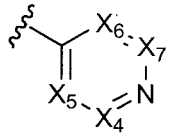
G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2–R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2$-, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

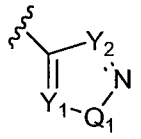
R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

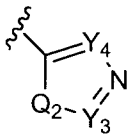
HY is an optionally substituted group selected from:



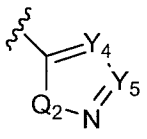
A ,



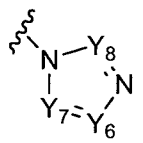
B ,



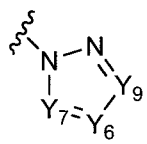
C ,



D



E ,



or **F** ;

wherein each occurrence of X_4, X_5, X_6, and X_7 is independently $–CR^{10}$ or N, provided no more than two occurrences of X_4, X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $–NR^5$;

each occurrence of Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, and Y_9 is independently $-CR^{10}$ or N, provided no more than two occurrences of Y_6, Y_7, Y_8, and Y_9 are N;

or wherein two adjacent occurrences of X_4 and X_5, X_6 and X_7, Y_1 and Q_1, Y_3 and Q_2, or Y_4 and Y_5 taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein R^{10} is $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, or $-V_1-T_1-R^{10b}$ wherein:

V_1 is $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, or $-SO_2NR^{11}-$;

each occurrence of R^{10a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

T_1 is an optionally substituted C_1-C_6 alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ or wherein T_1 forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

each occurrence of R^{10b} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{10c} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-

10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

R^{10a} and R^{10c} taken together with a nitrogen atom to which they are bound form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{11} is independently hydrogen, $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{11a} is independently hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^5 is independently hydrogen, $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

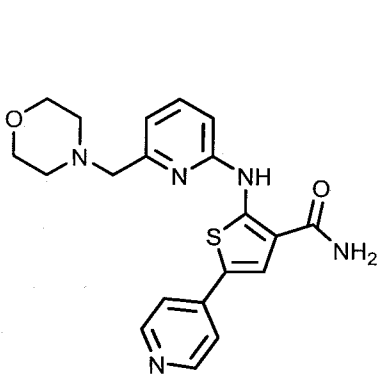
wherein each occurrence of R^{5a} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur;

wherein each occurrence of R^{5b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteratoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R^{5b} taken together with the nitrogen atom to which they are bound, form an optionally

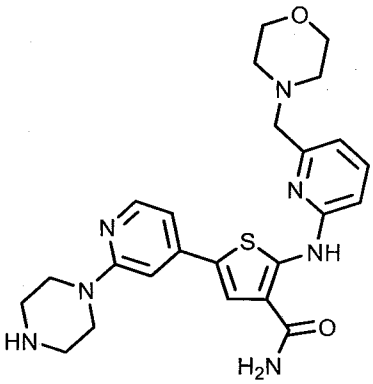
substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

a) for compounds of formula IB compounds are other than:

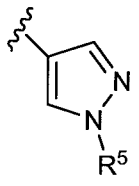


,

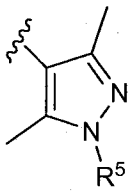


; and

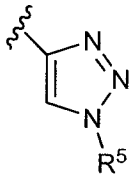
when G^1 is CR^8, R^1 is $CONH_2$, and W is NH, then HY is other than



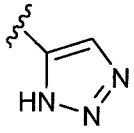
,



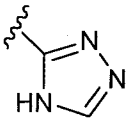
,



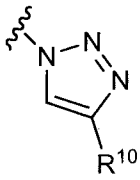
,



,

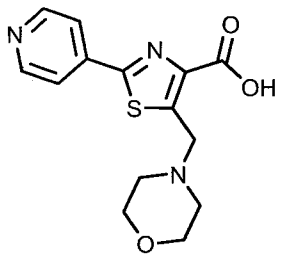
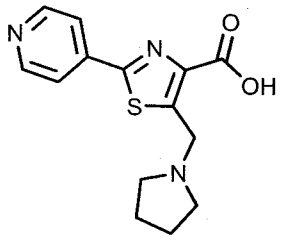
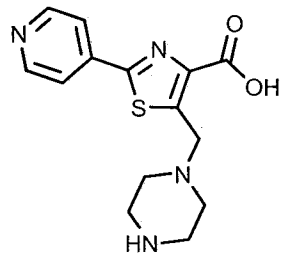
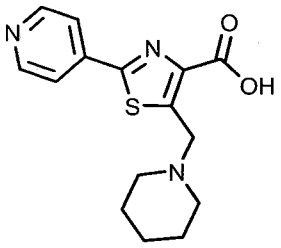
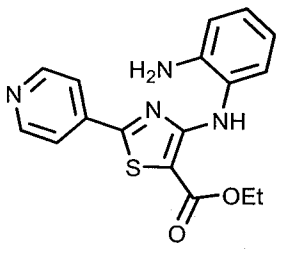
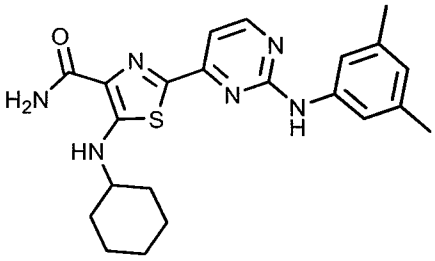
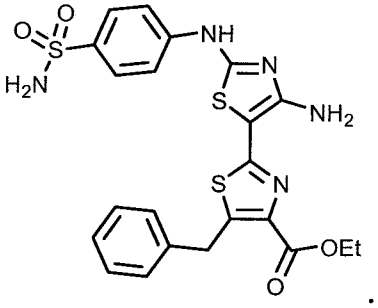


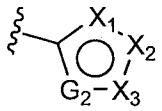
,



, or ; and

b) the compound is other than:

3. The compound of claim 1 or 2, wherein R^1 is CY, and CY is  .

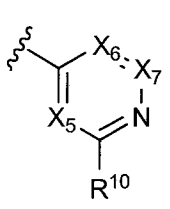
4. The compound of claim 1 or 2, wherein X_1 is N, G_2 is -N($R^{3'}$)-, and X_2 and X_3 are CH.

5. The compound of claim 1 or 2,wherein X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH.

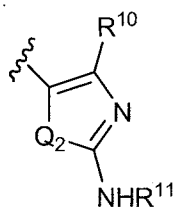
6. The compound of claim 1 or 2, wherein X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH.

7. The compound of claim 1 or 2, wherein X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

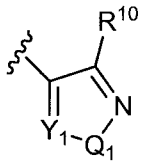
8. The compound of claim 1 or 2, wherein HY is selected from:



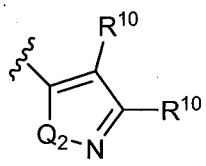
H ,



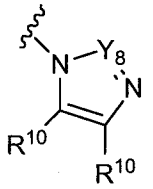
J ,



K ,



L , or



M;

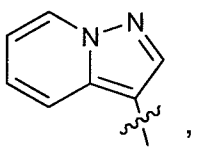
wherein each occurrence of X_5, X_6, and X_7 is independently $-CR^{10}$ or N, provided no more than two occurrences of X_5, X_6, and X_7 are N;

each occurrence of Q_1 and Q_2 is independently S, O or $-NR^5$;

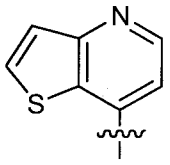
each occurrence of Y_1 and Y_7 is independently $-CR^{10}$ or N;

or wherein two adjacent occurrences of X_6 and X_7, or Y_1 and Q_1, taken together with the atom to which they are bound, form an optionally substituted fused group selected from 5-6-membered aryl, or 5-6-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

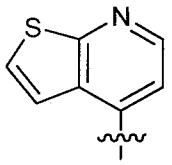
9. The compound of claim 8, wherein HY is selected from:



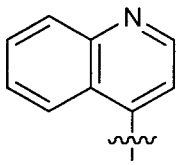
i ,



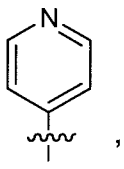
ii ,



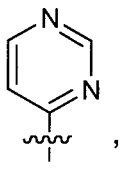
iii ,



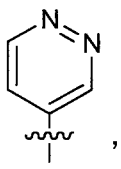
iv ,



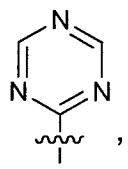
v ,



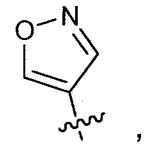
vi ,



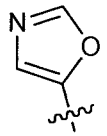
vii ,



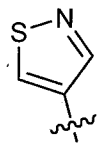
viii ,



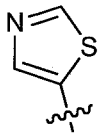
ix



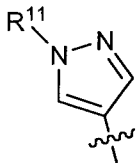
x



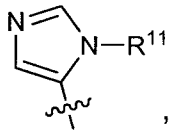
xi



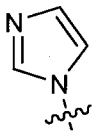
xii



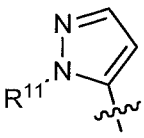
xiii



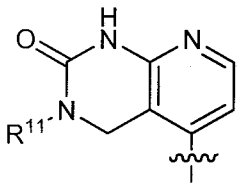
xiv



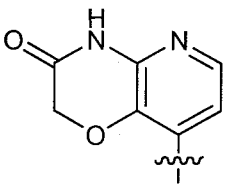
xv



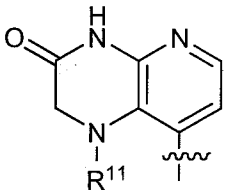
xvi



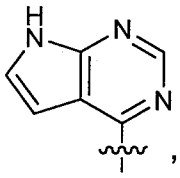
xvii



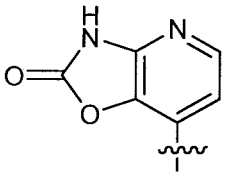
xviii



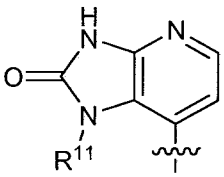
xix



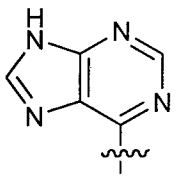
xx



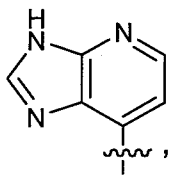
xxi



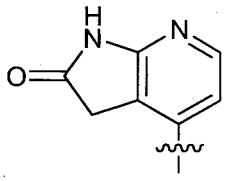
xxii



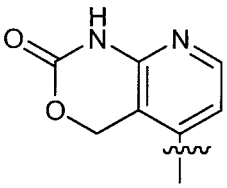
xxiii



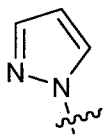
xxiv



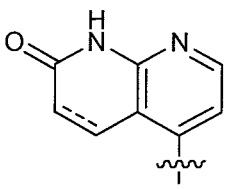
xxv



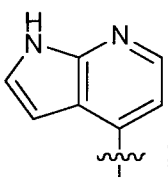
xxvi



xxvii



, or

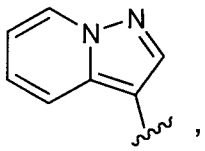


;

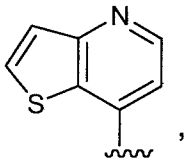
xxviii **xxix**

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

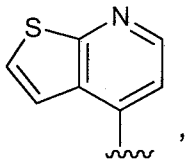
10. The compound of claim 9, wherein HY is selected from:



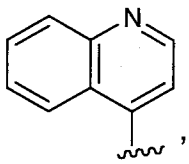
i



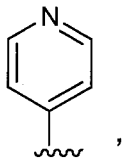
ii



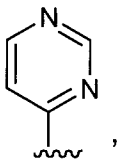
iii



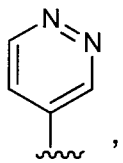
iv



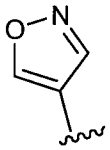
v



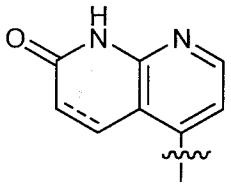
vi



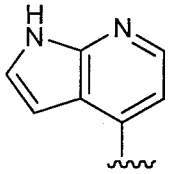
vii



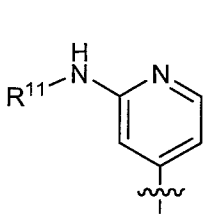
ix



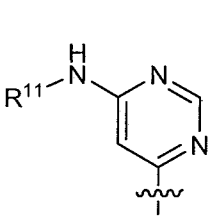
xxviii



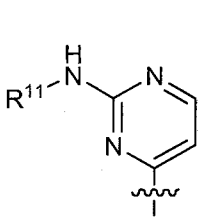
xxix



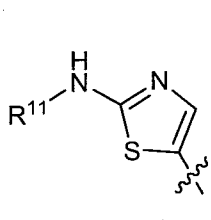
xxx



xxxi



xxxii



xxxiii

wherein each HY group is optionally additionally substituted with one or more occurrences of R^{10}, and ====== in **xviii** represents a single bond or a double bond.

11. The compound of claim 1 or 2, wherein G_1 is $C(R^8)$.

12. The compound of claim 1 or 2, wherein G_1 is CH.

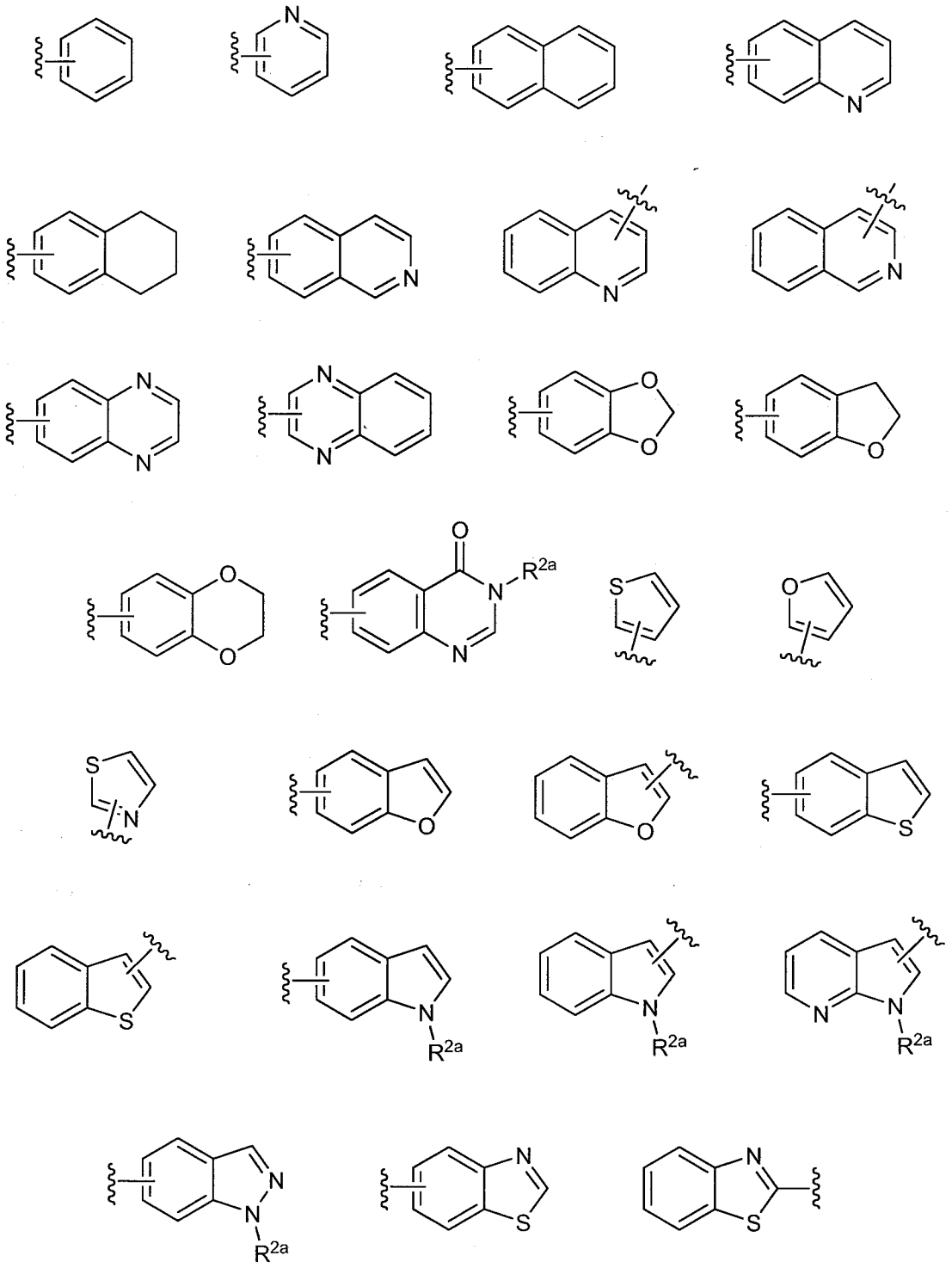
13. The compound of claim 1 or 2, wherein G_1 is N.

14. The compound of claim 1 or 2, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or –CN; and wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring.

15. The compound of claim 14, wherein W is $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

16. The compound of claim 1 or 2, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

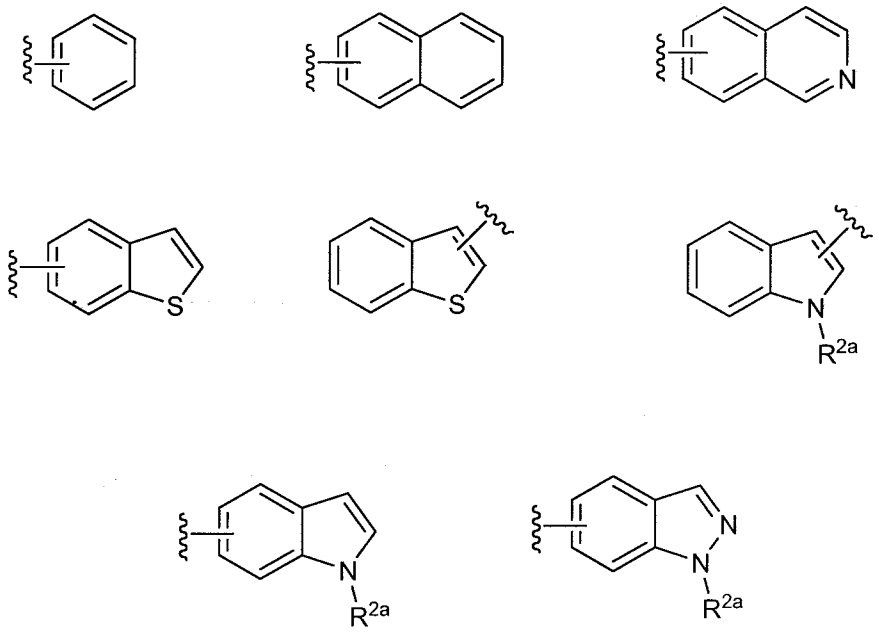
17. The compound of claim 16, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

18. The compound of claim 16, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

19. The compound of claim 16, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

20. The compound of claim 16, wherein:

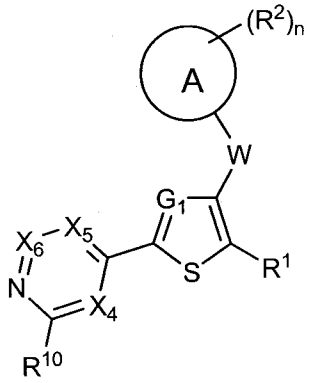
ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

21. The compound of claim 19, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

22. The compound of claim 19, wherein ring A is a naphthyl group and n is 0.

23. The compound of claim 20, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

24. A compound having the following formula **II**:



II

wherein:

X_4, X_5 and X_6 are each independently $-CR^{10}$ or N, provided no more than two occurrences of X_4, X_5 and X_6 are N;

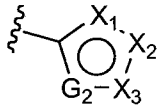
or two adjacent groups selected from R^{10}, X_4, X_5, and X_6, taken together, form an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

25. The compound of claim 24, wherein one of X^4, X^5, or X^6 is N.

26. The compound of claim 24, wherein all of X^4, X^5, or X^6 are CR^{10}.

27. The compound of claim 24, wherein each occurrence of R^{10} is independently selected from –CN, $-OR^{10a}$, $-N(R^{11})_2$, halogen, C_{1-4}alkyl, $-N(R^{11})COR^{10a}$, or wherein two occurrences of

R^{10}, taken together with the atoms to which they are bound form an optionally substituted group selected from a fused 5- or 6-membered cycloaliphatic, 4-10-membered heterocyclyl, 6-10-membered aryl or 5-10-membered heteroaryl ring, wherein the heterocyclyl and heteroaryl rings have 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

28. The compound of claim 24, wherein R^1 is CY, and CY is  .

29. The compound of claim 28, wherein X_1 is N, G_2 is -N($R^{3'}$)-, and X_2 and X_3 are CH.

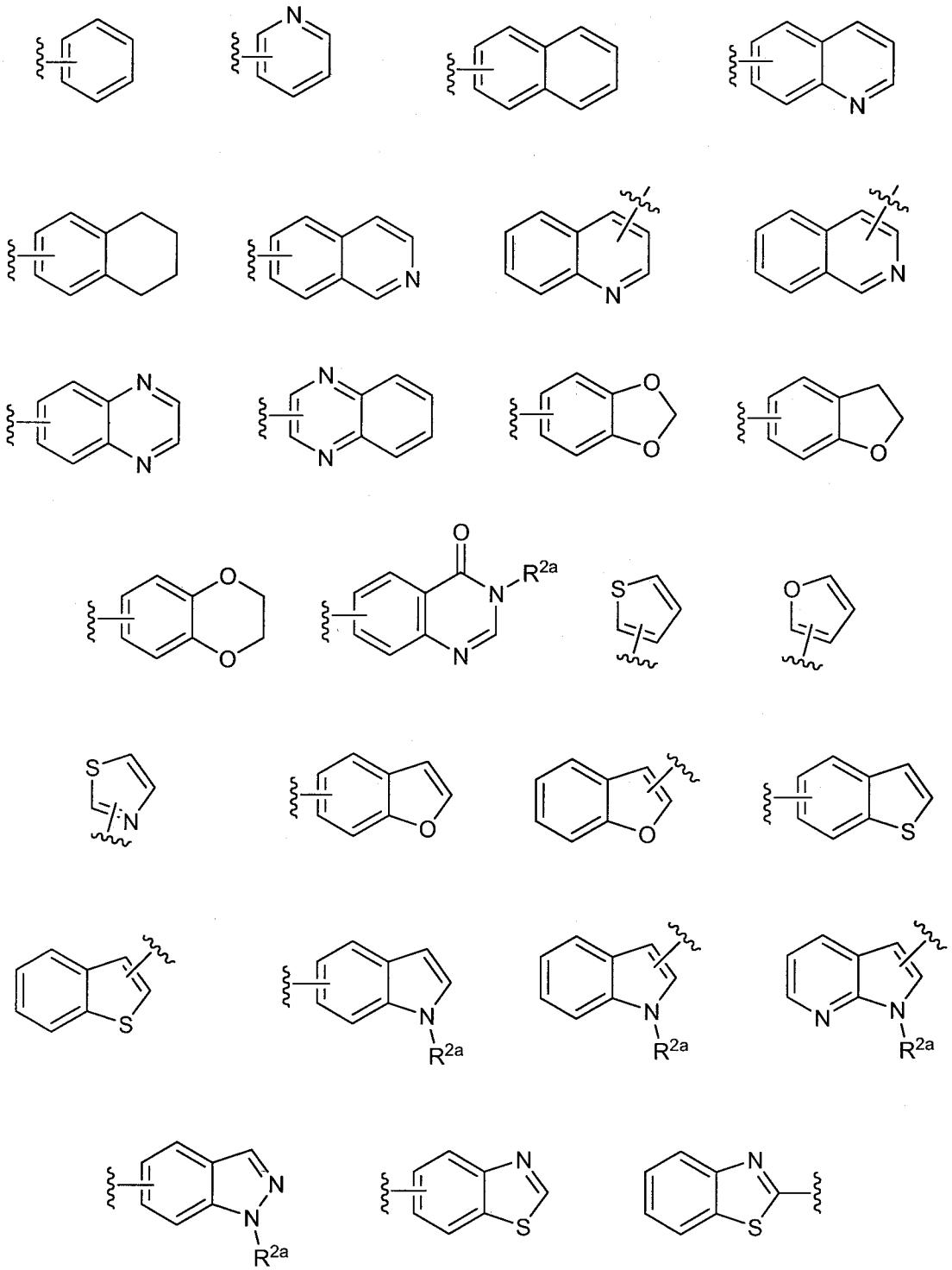
30. The compound of claim 28, wherein X_1 and X_2 are N, G_2 is -N($R^{3'}$)-, and X_3 is CH.

31. The compound of claim 28, wherein X_3 is N, G_2 is -N($R^{3'}$)-, and X_1 and X_2 are CH.

32. The compound of claim 28, wherein X_1 is N, X_2 is CH, X_3 is –N($R^{3'}$)- and G_2 is =N-.

33. The compound of claim 24, wherein Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

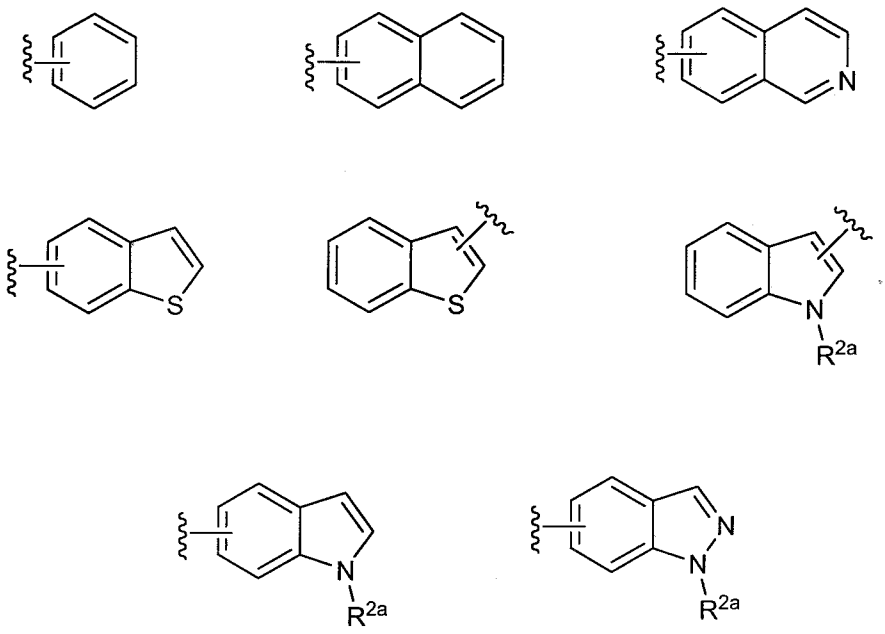
34. The compound of claim 33, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

35. The compound of claim 33, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

36. The compound of claim 33, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

37. The compound of claim 33, wherein Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, $NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

38. The compound of claim 36, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

39. The compound of claim 38, wherein ring A is a naphthyl group and n is 0.

40. The compound of claim 37, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

41. The compound of claim 24, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or –CN; and

wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

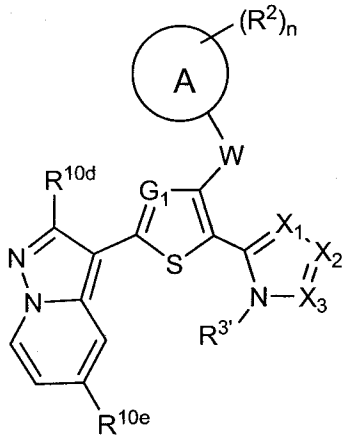
each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

42. The compound of claim 41, wherein W is $-C(H)(N(R^{7b})_2)-$,, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

43. A compound having the formula **III**:



III

wherein R^{10d} is hydrogen or optionally substituted C_{1-4}alkyl, and R^{10e} is R^{10}.

44. The compound of claim 43, wherein R^{10e} is $-T_1-R^{10b}$, or hydrogen.

45. The compound of claim 43, wherein R^{10e} is hydrogen, $-CH_2N(R^{11})_2$, or $-CH_2N(R^{11})C(=NR^{11})N(R^{11})_2$, wherein R^{11} is $-C(O)R^{11a}$, an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

46. The compound of claim 45, wherein when R^{11} is an optionally substituted C_{1-6} aliphatic group, the C_{1-6} aliphatic group is further defined as $-(CH_2)_xR^{11b}$ or $-(CH_2)_xN(R^{11b})_2$, $-(CH_2)_xN(R^{11b})C(O)R^{11b}$, or $-(CH_2)_xN(R^{11b})C(O)OR^{11b}$, wherein R^{11b} is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and x is 1 to 3.

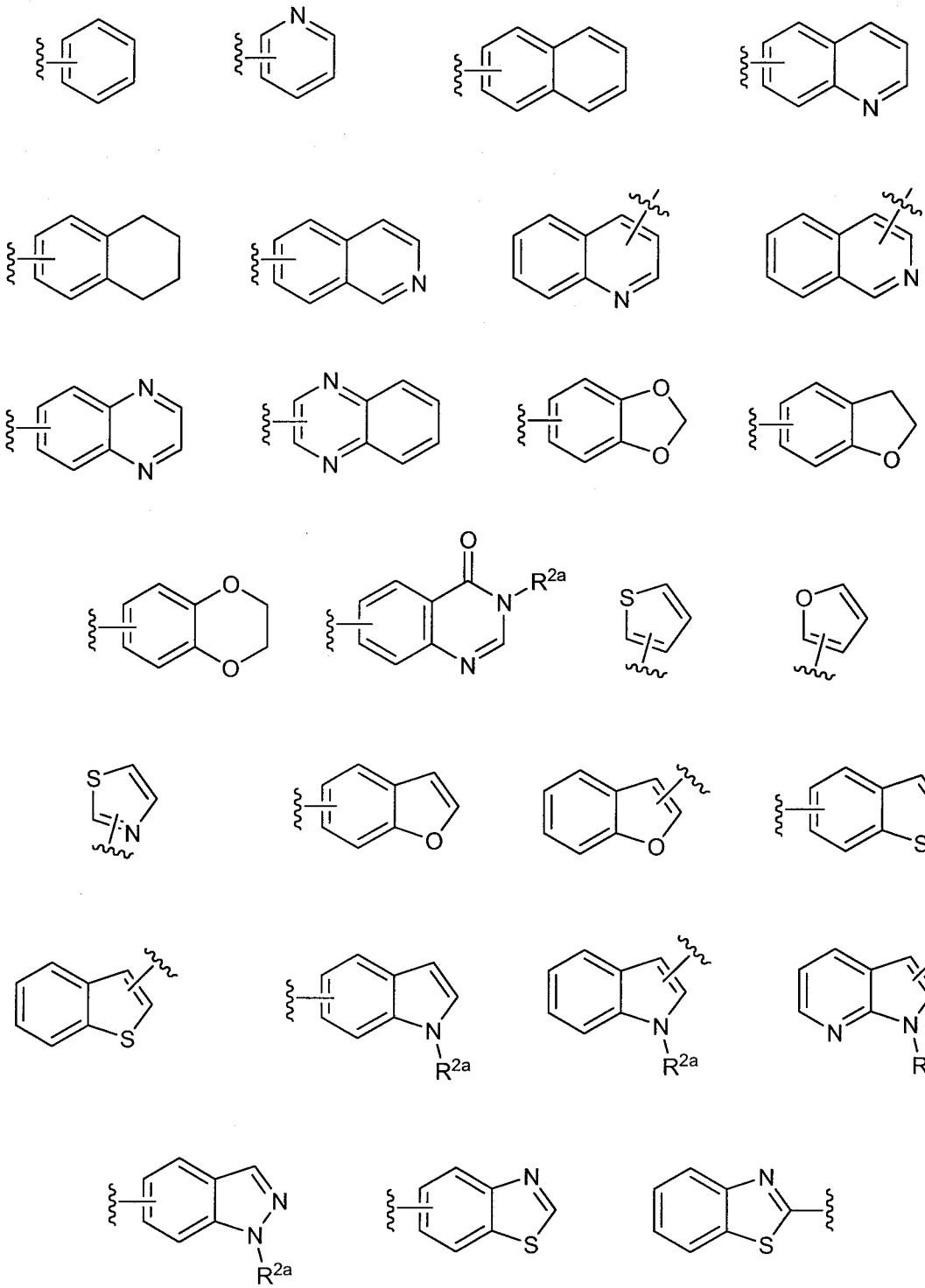
47. The compound of claim 43, wherein X_1 is N, and X_2 and X_3 are CH.

48. The compound of claim 43, wherein X_1 and X_2 are N, and X_3 is CH.

49. The compound of claim 43, wherein X_3 is N, and X_1 and X_2 are CH.

50. The compound of claim 43, wherein Ring A is an optionally substituted 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

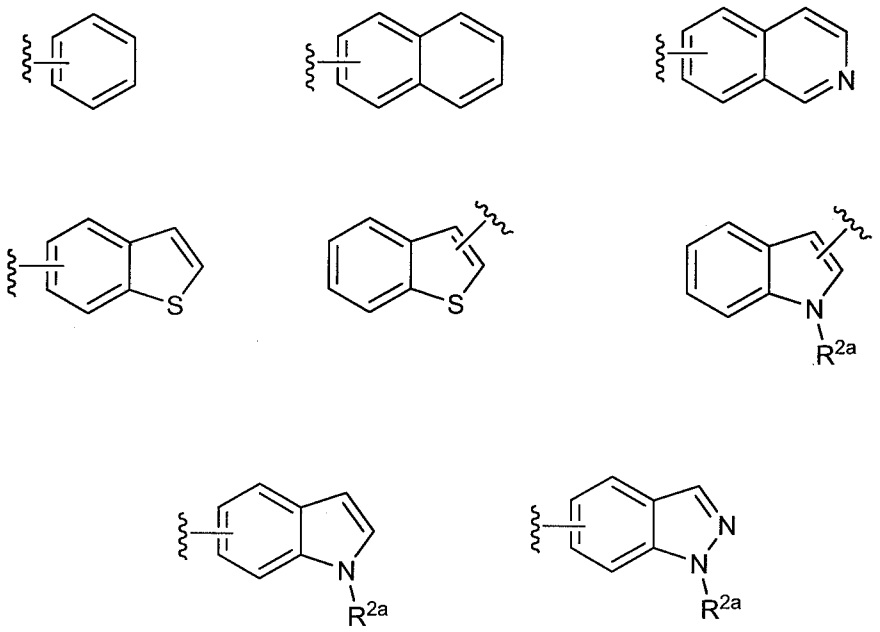
51. The compound of claim 50, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

52. The compound of claim 50, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

53. The compound of claim 50, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

54. The compound of claim 50, wherein Ring A is a phenyl group optionally substituted with 1-3 independent occurrences of halogen, C_{1-3} alkyl, -CN, C_{1-3}haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -$NHC(O)C_{1-3}$ alkyl, -$NHC(O)NHC_{1-3}$ alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

55. The compound of claim 54, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

56. The compound of claim 53, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

57. The compound of claim 56, wherein ring A is a naphthyl group and n is 0.

58. The compound of claim 43, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is selected from hydrogen, optionally substituted C_{1-4} aliphatic, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, or -CN; and

wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic;

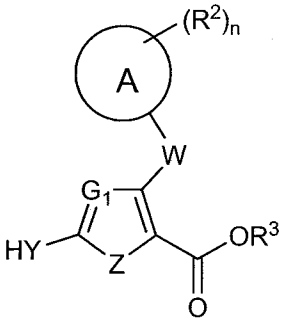
each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

wherein any two occurrences of R^7, R^{7a}, or R^{7b} taken together with the atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

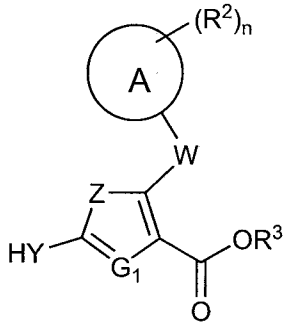
any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

59. The compound of claim 58, wherein W is $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, or $-N(R^{7a})C(O)-$, wherein each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic; and each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

60. A compound of formula **IA-i-a** or **IB-i-a**:



IA-i-a



IB-i-a

or a pharmaceutically acceptable salt thereof, wherein:

Z is S or Se;

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having

1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, -OC(O)-, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, -C(O)O-, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, -OC(O)-, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, -O-, $-N(R^{7b})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with atom to which they are bound, form an optionally substituted group selected from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

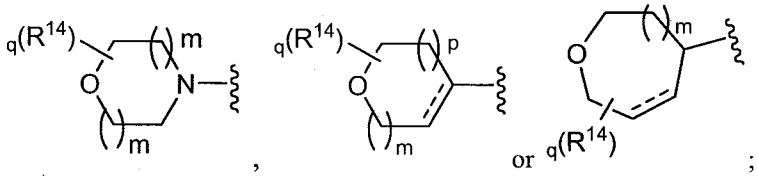
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is  , , or ;

$=\!=\!=\!=\!=\!=$ represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or $-T_1-R^{14d}$, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, or

$-N(R^{14c})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

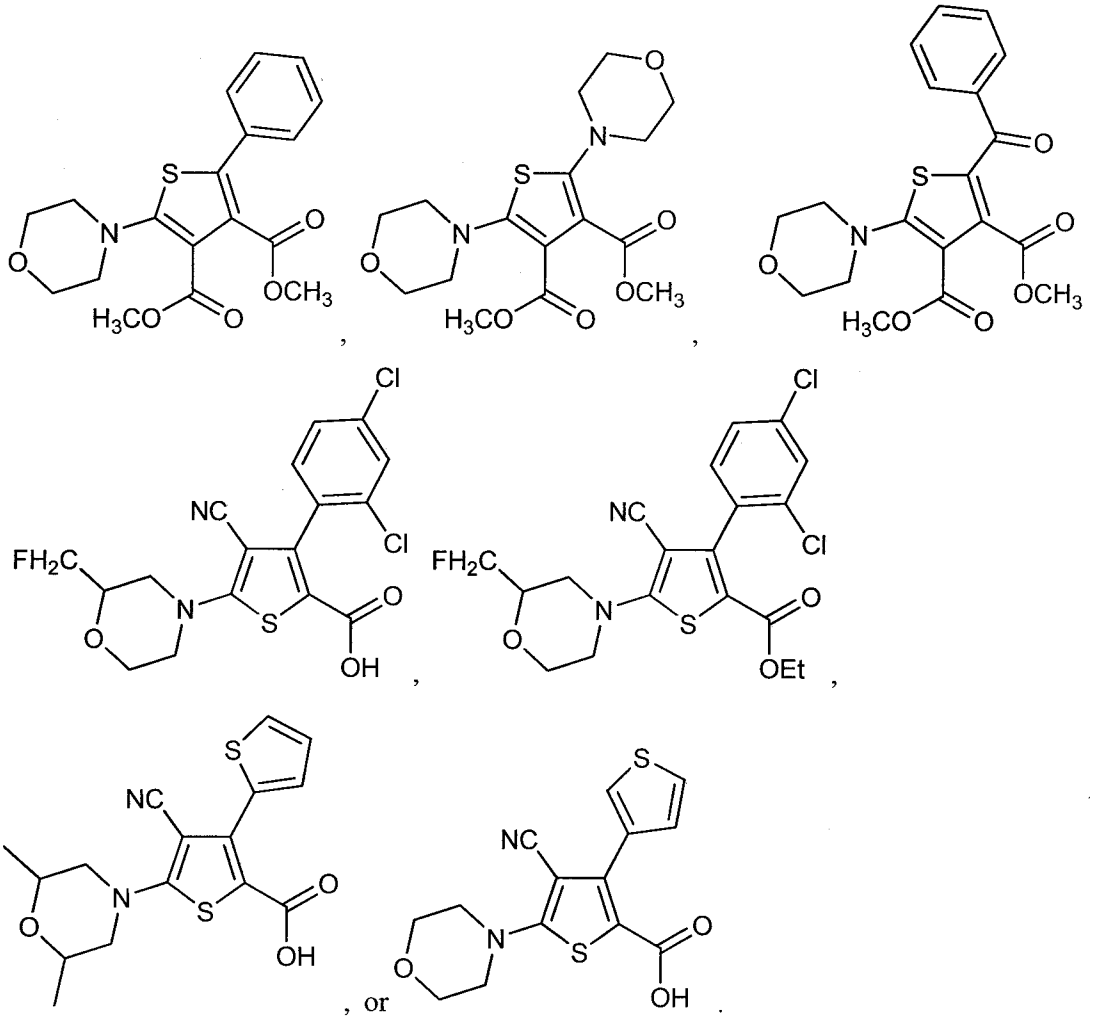
p is 0, 1, or 2;

provided that for compounds where Z is S:

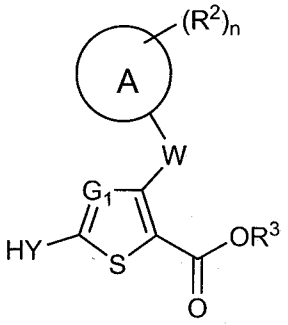
a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

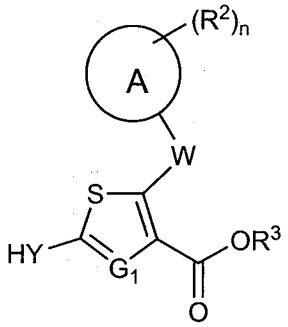
c) the compound is other than:



61. A compound of formula **IA** or **IB**:



IA-i



IB-i

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen or an optionally substituted C_{1-6} aliphatic;

Ring A is a group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^2 is independently $-R^{12a}$, $-T_2-R^{12d}$, or $-V_2-T_2-R^{12d}$, or:

two adjacent R^2 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12a} is independently halogen, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, or $-N(R^{12e})SO_2N(R^{12b})_2$;

each occurrence of R^{12b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or two occurrences of R^{12b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered

aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12d} is independently hydrogen, $-N(R^{7b})_2$, or an optionally substituted group selected from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{12e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of V_2 is independently $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, or $-C(O)N(R^{12e})-O-$; and

T_2 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, or $-C(O)N(R^{13})-O-$ or wherein T_2 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring, wherein R^{13} is hydrogen or an optionally substituted C_{1-4}aliphatic group;

W is selected from a covalent bond, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, or $-N(R^{7a})C(O)-$, wherein:

each occurrence of R^7 is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 6-10-membered aryl, 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, or F;

each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-6} cycloaliphatic;

each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-6} cycloaliphatic, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, or $-S(O)_2R^{7a}$; or

each occurrence of R^{7c} is independently an optionally substituted C_{1-6}aliphatic or an optionally substituted 3-7 membered cycloalphatic; or

wherein any two occurrences of R^7, R^{7a}, R^{7b} , or R^{7c}, taken together with the atom to which they are bound, form an optionally substituted group selected

from a 3-6-membered cycloaliphatic ring, 6-10-membered aryl, 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

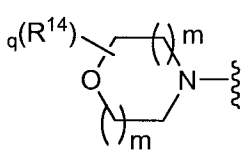
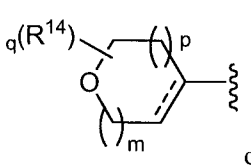
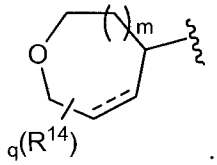
or wherein any two occurrences of R^{7a} and R^2, or R^{7b} and R^2 taken together with the nitrogen atom to which they are bound, form an optionally substituted group selected from 3-6-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

G_1 is N or $-CR^8$, wherein R^8 is H, –CN, halogen, $–Z_2-R^9$, C_{1-6} aliphatic, or 3-10-membered cycloaliphatic, wherein:

Z_2 is selected from an optionally substituted C_{1-3} alkylene chain, –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, or -OC(O)-;

R^{8a} is hydrogen or an optionally substituted C_{1-4} aliphatic, and

R^9 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

HY is  ,  , or  ;

$\cdots\cdots$ represents a single bond or a double bond;

wherein each occurrence of R^{14} is independently–R^{14a} or $-T_1-R^{14d}$, wherein:

each occurrence of R^{14a}, as valency and stability permit, is independently fluorine, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, or $–N(R^{14e})SO_2N(R^{14b})_2$, or two occurrences of R^{14b}, taken together with a nitrogen atom to which they are bound, form an optionally substituted 4-7-membered

heterocyclyl ring having 0-1 additional heteroatoms selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14b} is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14c} is independently an optionally substituted group selected from C_{1-6} aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14d} is independently hydrogen or an optionally substituted from 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each occurrence of R^{14e} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and

T_1 is an optionally substituted C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, or $-C(O)N(R^{14a})-O-$ or wherein T_1 or a portion thereof optionally forms part of an optionally substituted 3-7 membered cycloaliphatic or heterocyclyl ring;

n is 0-6;

q is 0-4;

m is 1 or 2; and

p is 0, 1, or 2;

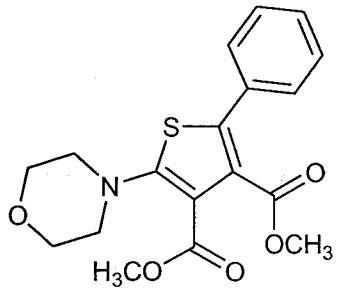
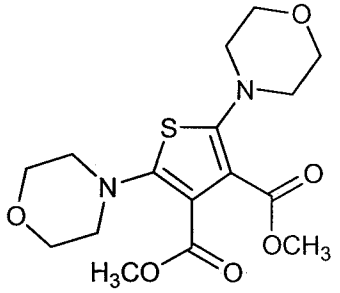
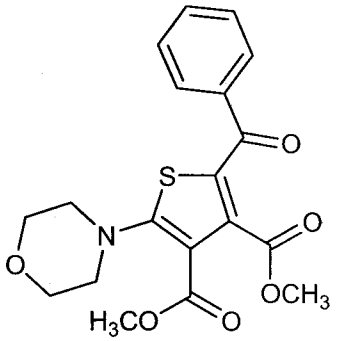
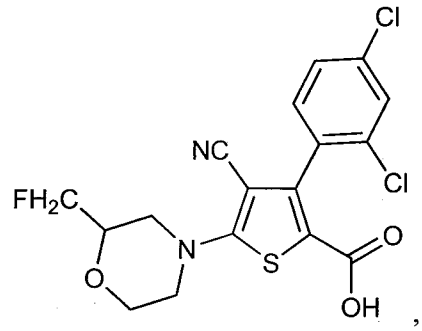
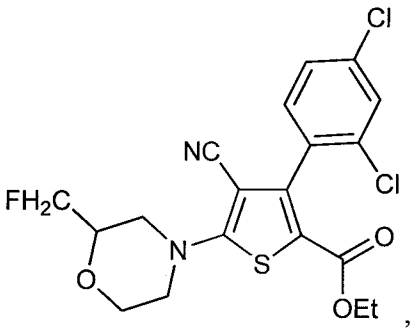
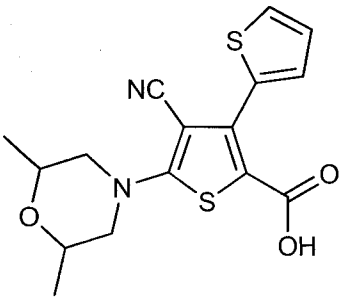
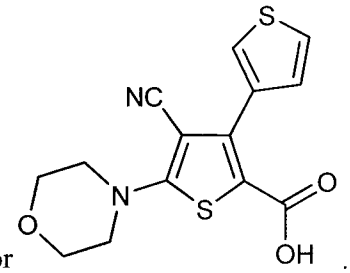
provided that:

a) when G_1 is C-CN, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl, 2-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl,

3,4-dichlorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, or 3-(acetylamino)phenyl;

b) when G_1 is N, HY is unsubstituted morpholine, R^1 is -C(O)OH, -C(O)OMe, or -C(O)OEt, and W is a covalent bond, then Ring A is other than unsubstituted phenyl or 2-chlorophenyl; and

c) the compound is other than:


,

,


,

,

, or

.

62. The compound of claim 60 or 61, wherein G_1 is N.

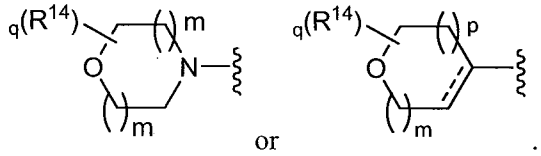
63. The compound of claim 60 or 61, wherein G_1 is $C(R^8)$.

64. The compound of claim 63, wherein R^8 is –CN, halogen, or C_{1-6} aliphatic.

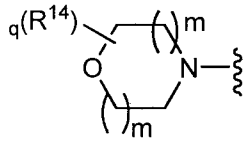
65. The compound of claim 63, wherein R^8 is C_{1-4} alkyl, C_{2-4} alkenyl, or C_{2-4} alkynyl.

66. The compound of claim 63, wherein R^8 is –CN or C_{2-4} alkynyl.

67. The compound of claim 60 or 61, wherein HY is selected from:



or .

68. The compound of claim 67, wherein HY is  .

69. The compound of claim 88, wherein both occurrences of m are 1.

70. The compound of claim 88, wherein q is 0.

71. The compound of claim 60 or 61, wherein R^3 is H.

72. The compound of claim 60 or 61, wherein R^3 is C_{1-6} aliphatic.

73. The compound of claim 62, wherein R^3 is C_{1-4} alkyl.

74. The compound of claim 63, wherein R^3 is methyl or ethyl.

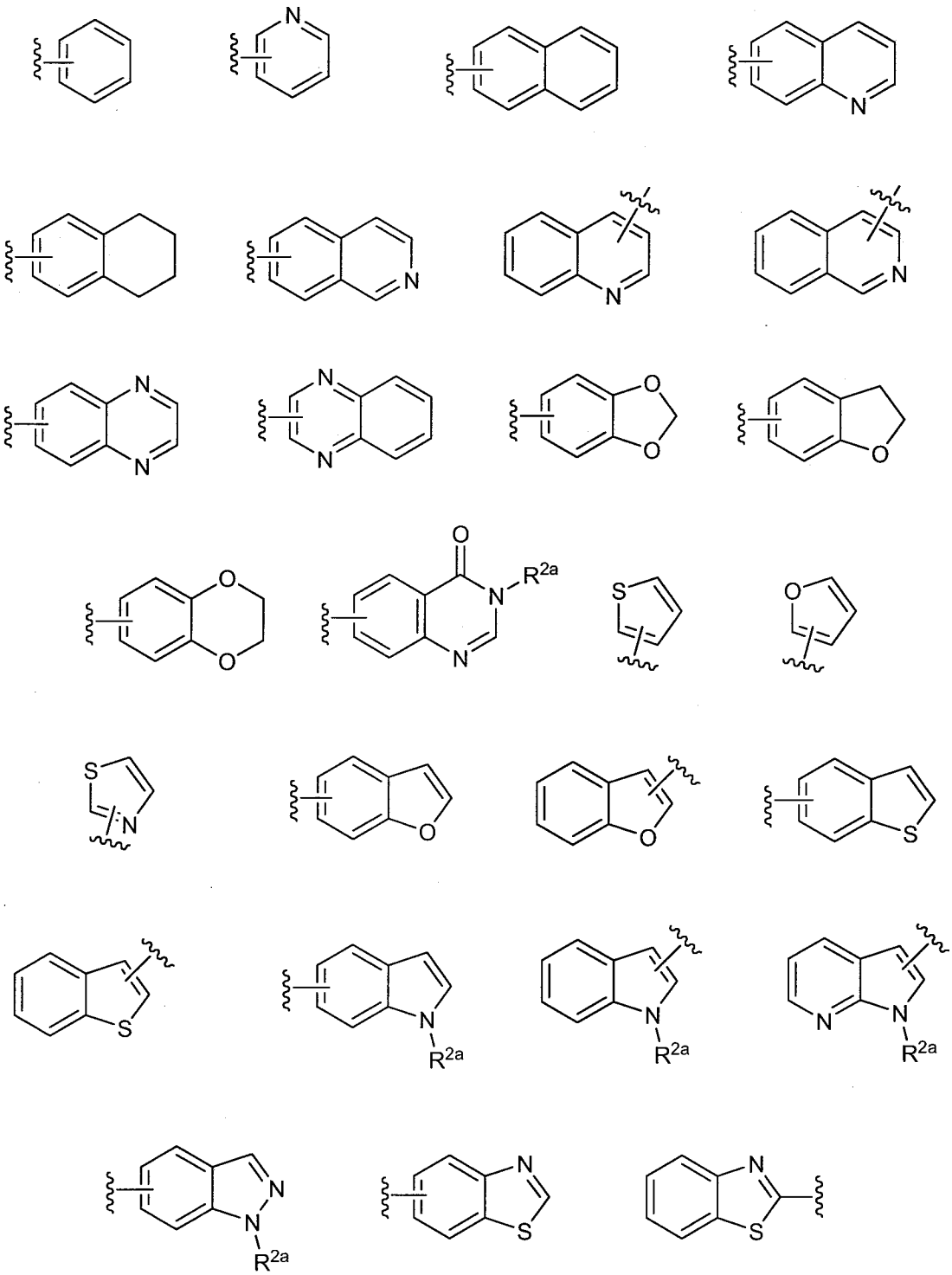
75. The compound of claim 60 or 61, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

76. The compound of any one of claims 60 or 61, wherein W is $-C(H)(N(R^{7b})_2)-$ or $-CH_2-$, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

77. The compound of any one of claims 60 or 61, wherein W is a covalent bond.

78. The compound of claim 60 or 61, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

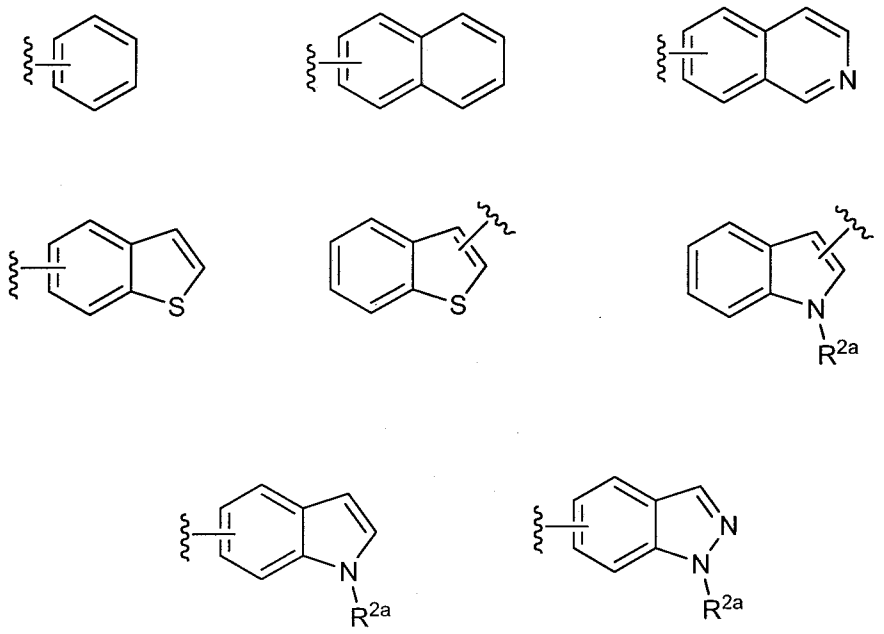
79. The compound of claim 60 or 61, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

80. The compound of claim 60 or 61wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

81. The compound of claim 80, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

82. The compound of claim 60 or 61, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is –C(H)(N(R^{7b})$_2$)- or -CH_2-, wherein each occurrence of R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

83. The compound of claim 82, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

84. The compound of claim 60 or 61, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

85. The compound of claim 84, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OC_{1-3}$ alkyl, or $-OC_{1-3}$ haloalkyl; and n is 0 to 3.

86. The compound of claim 85, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, $-OCH_3$, or $-OCF_3$; and n is 0 to 3.

87. The compound of claim 60 or 61, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

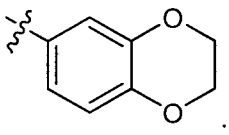
88. The compound of claim 60 or 61, wherein Ring A is a phenyl group, n is 1, and R^2 is in the para position.

89. The compound of claim 60 or 61, wherein Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions.

90. The compound of claim 60 or 61, wherein ring A is a naphthyl group, R^2 is halogen and n is 0, 1 or 2.

91. The compound of claim 60 or 61, wherein ring A is a naphthyl group and n is 0.

92. The compound of claim 90, wherein Ring A is a 2-naphthyl group.

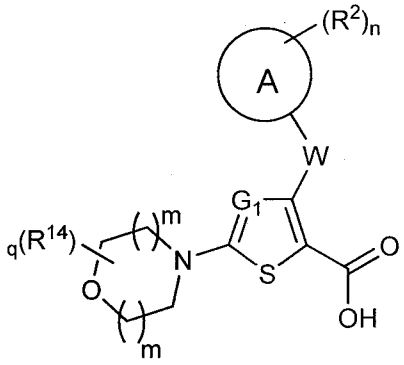
93. The compound of claim 60 or 61, wherein Ring A is  .

94. The compound of claim 60 or 61, wherein Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

95. The compound of claim 94, wherein Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring.

96. The compound of claim 95, wherein Ring A is substituted with one or more C_{1-3} alkyl groups.

97. A compound having the following formula **II-A**:



II-A.

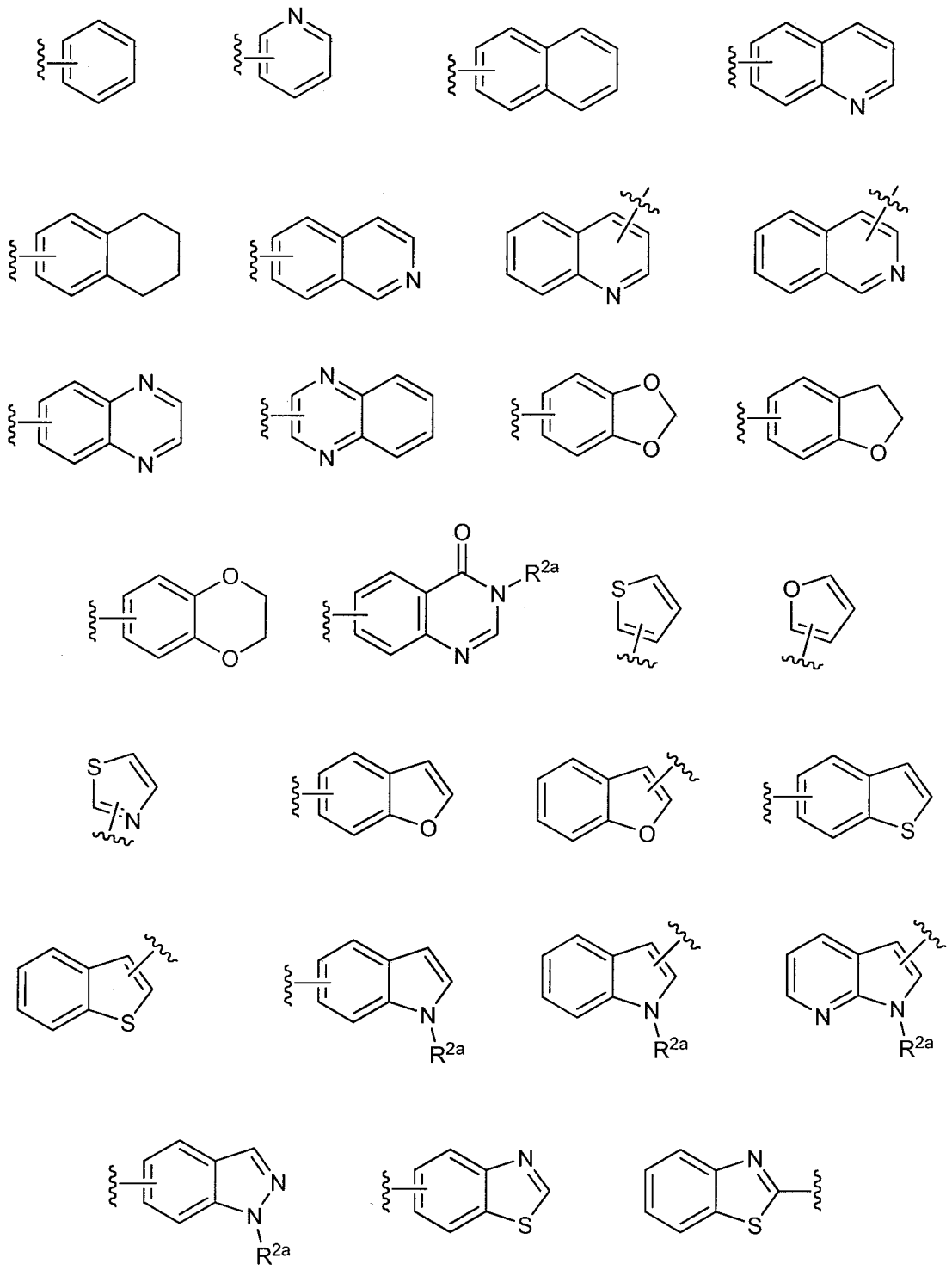
98. The compound of claim 97, wherein W is $-C(R^7)_2-$, wherein one occurrence of R^7 is hydrogen and the other occurrence of R^7 is hydrogen, optionally substituted C_{1-6} aliphatic, $-N(R^{7b})_2$, or F; and wherein each occurrence of R^{7b} is independently hydrogen, optionally substituted C_{1-6} aliphatic, $-C(O)R^{7a}$, or $-S(O)_2R^{7a}$; or wherein two occurrences of R^{7b}, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-6-membered heterocyclic ring; and each occurrence of R^{7a} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

99. The compound of claim 97, wherein W is $-C(H)(N(R^{7b})_2)-$, or $-CHR^7$, wherein each occurrence of R^7 or R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

100. The compound of claim 97, wherein W is a covalent bond and G_1 is N.

101. The compound of claim 97, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and n is 0 to 3.

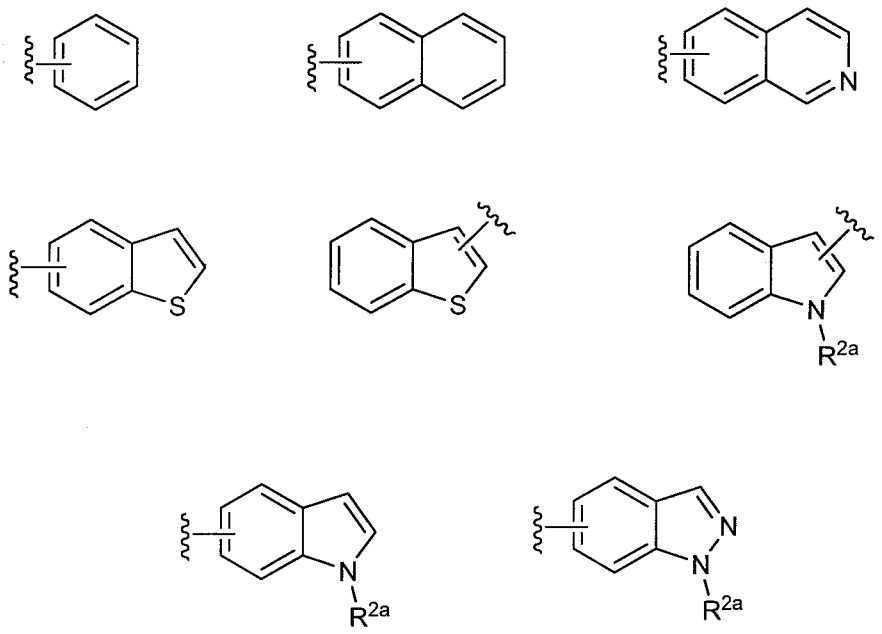
102. The compound of claim 97, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

103. The compound of claim 102, wherein ring A is a group selected from:



wherein ring A is optionally further substituted by n occurrences of R^2, and wherein R^{2a} is hydrogen or an optionally substituted group selected from C_{1-6}aliphatic, 3-10-membered cycloaliphatic, 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6-10-membered aryl, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

104. The compound of claim 97, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-C(H)(N(R^{7b})_2)-$ or $-CHR^7-$, wherein each occurrence of R^7 or R^{7b} is independently hydrogen or optionally substituted C_{1-6} aliphatic.

105. The compound of claim 104, wherein Ring A is 6-10-membered aryl or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; n is 0 to 3, and W is $-CH_2-$.

106. The compound of claim 97, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -NHS(O)$_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

107. The compound of claim 106, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, -OC_{1-3} alkyl, or –OC_{1-3} haloalkyl; and n is 0 to 3.

108. The compound of claim 107, wherein Ring A is a phenyl group; each occurrence of R^2 is independently halogen, -CN, -OCH_3, or –OCF_3; and n is 0 to 3.

109. The compound of claim 108, wherein Ring A is a phenyl group, R^2 is halogen and n is 1 to 2.

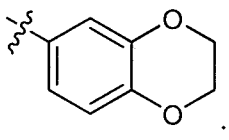
110. The compound of claim 109, wherein Ring A is a phenyl group, n is 1, and R^2 is in the para position.

111. The compound of claim 109, wherein Ring A is a phenyl group, n is 2, and the two R^2 groups are in the para and meta positions.

112. The compound of claim 101, wherein ring A is a naphthyl group, R^2 is halogen and n is 1 to 2.

113. The compound of claim 101, wherein ring A is a naphthyl group and n is 0.

114. The compound of claim 101, wherein Ring A is a 2-naphthyl group.

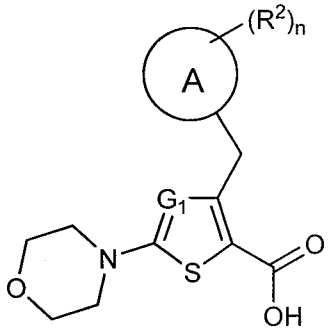
115. The compound of claim 101, wherein Ring A is  .

116. The compound of claim 101, wherein Ring A is a 3-10-membered cycloaliphatic or 4-10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

117. The compound of claim 101, wherein Ring A is an N-linked 3-, 4-, 5-, 6-, or 7-membered heterocyclyl ring.

118. The compound of claim 117, wherein Ring A is substituted with one or more C_{1-3} alkyl groups.

119. A compound having the formula **III-A**:



III-A

wherein G_1 is N or $-CR^8$, and R^8 is –CN.

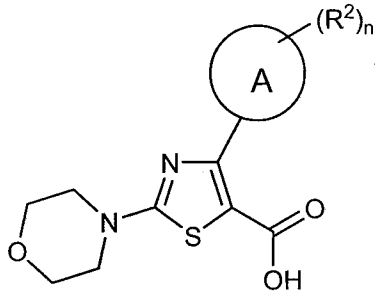
120. The compound of claim 119, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

121. The compound of claim 119, wherein:

ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, $-OC_{1-3}$ alkyl, $-OC_{1-3}$ haloalkyl, $-NHC(O)C_{1-3}$ alkyl, $-NHC(O)NHC_{1-3}$ alkyl, $-NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

122. The compound of claim 61, wherein the compound has the formula **IV-A**:



IV-A.

123. The compound of claim 122, wherein:

ring A is a naphthyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

124. The compound of claim 122, wherein:

ring A is a phenyl group; each occurrence of R^2 is independently halogen, C_{1-3} alkyl, -CN, C_{1-3} haloalkyl, -OC_{1-3} alkyl, –OC_{1-3} haloalkyl, -NHC(O)C_{1-3} alkyl, -NHC(O)NHC_{1-3} alkyl, -$NHS(O)_2C_{1-3}$ alkyl, or –C(O)H; and n is 0 to 3.

125. A composition comprising a compound of any one of claims 1, 2, 24, 43, 60, 61, 97, 119 or 122, and a pharmaceutically acceptable carrier.

126. A method of treating a proliferative disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of claim 1, 2, 24, 43, 60, 61, 97, 119 or 122,.

127. The method of claim 126, further comprising administering an additional therapeutic agent..

128. The method of claim 126, further comprising administering an additional chemotherapeutic agent.

129. The method of claim 126, wherein the proliferative disorder is breast cancer, bladder cancer, colon cancer, glioma, glioblastoma, lung cancer, hepatocellular cancer, gastric cancer,

melanoma, thyroid cancer, endometrial cancer, renal cancer, cervical cancer, pancreatic cancer, esophageal cancer, prostate cancer, brain cancer, or ovarian cancer.

130. A method of treating an inflammatory or cardiovascular disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1, 2, 24, 43, 60, 61, 97, 119 or 122,.

131. The method of claim 130, wherein the inflammatory or cardiovascular disorder is selected from allergies/anaphylaxis, acute and chronic inflammation, rheumatoid arthritis, autoimmunity disorders, thrombosis, hypertension, cardiac hypertrophy, and heart failure.

132. A method for inhibiting PI3K or VPS34 activity in a patient comprising administering a composition comprising a therapeutically effective amount of a compound of any one of claims 1, 2, 24, 43, 60, 61, 97, 119 or 122,.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/47407

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/33; A61K 31/425 (2011.01)
USPC - 514/183; 514/370-371
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)
USPC: 514/183; 514/370-371
IPC(8): A61K 31/33; A61K 31/425 (2011.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 546/270.4; 546/270.0; 546/274.1; 546/274.4; 514/300; 514/342; 514/333; 514/368 (see search words below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: PGPB, USPT, USOC, EPAB, JPAB
Google: Scholar/Patents: pI3k inhibitor breast cancer chronic inflammation heart failure thiazole pyrrolidine pyridine phenyl morpholine $dioxane$ carboxylate cardiovascular hyperension

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0075951 A1 (CARDIN et al.) 25 March 2010 (25.03.2010) para [0009]-[0027];[0052];[0054];[0056];[0058];[0061];[0079];[0087];[0091];[0104]; [0119]-[0122];[0126];[0127];[0140]; Table 1	1-132
Y	LIANG et al. 'Crystal Structure of P13K SH3 Domain at 2.0 A Resolution', Journal of Molecular Biology, 1996, 257, 632-643. pg 635, Figure2; Col 1, para 2; Col 2, para 1; pg 636, Col 1, para 1-2; pg 636, Col 2, para 1-2; pg 637, Figure 6; pg 640, Figure 8, pg 642, Figure 11	1-132

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
12 December 2011 (12.12.2011)	22 DEC 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

HETEROARILOS Y SUS USOS

Antecedentes de la invención

[0001] La fosfatidilinositol 3-quinasa (P13K) es una familia de lípido quinasas que fosforilan fosfatidilinositol en la posición 3’ del anillo inositol. La P13K está compuesta de varias clases de genes, que incluyen la Clase IA, IB, II y III y algunas de estas clases contienen varias isoformas (que se revisaron en Engelman et al., Nature Review Genetics 7:606-619 (2006)). Sumado a la complejidad de esta familia se encuentra el hecho de las P13Ks funcionan como heterodímeros, que comprenden un dominio catalítico y un dominio regulador. La familia P13K se relaciona estructuralmente con un grupo más grande lípido y serina/treonina proteína quinasas conocidas, como las fosfatidilinositol 3-quinasa del tipo quinasas (PIK Ks), que además incluyen DNA-PK, ATM, ATR, mTOR, TRRAP y SMG1.

[0002] La P13K se active corriente abajo de varias señales mitogénicas mediadas a través de las tirosina quinasas receptoras, y posteriormente estimula una variedad de resultados biológicos; que incluyen la supervivencia celular aumentada, el avance del ciclo celular, el desarrollo celular, el metabolismo celular, la migración celular y la angiogénesis (que se revisó en Cantley, Science 296:1655-57 (2002); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005); Engelman et al., Nature Review Genetics 7:606-619 (2006)). De este modo, la hiperactivación se asocial con un número de trastornos hiperproliferativos, inflamatorios, o cardiovasculares, que incluyen cáncer, inflamación, y enfermedad cardiovascular.

[0003] Existe una cantidad de aberraciones genéticas que conducen a la señalización de la P13K constitutiva, que incluyen las mutaciones de activación en la P13K misma (Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005); se revisó en Bader et

al., Nature Reviews Cancer 5:921-9 (2005)); RAS (que se revisó en Downward Nature Reviews Cancer 3:11-22 (2003)) y las tirosina quinasas receptoras corriente arriba (que se revisó en Zwick et al., Trends in Molecular Medicine 8:17-23 (2002)) como también las mutaciones de inactivación en el supresor de tumor PTEN (que se revisó en Cully et al., Nature Reviews Cancer 6:184-92 (2006)). Las mutaciones en cada una de estas clases génicas han demostrado ser oncogénicas y normalmente se hallan en una variedad de cánceres.

[0004] Las moléculas que se definen dentro de la invención inhiben la actividad de la P13K, y por lo tanto pueden ser útiles para el tratamiento de trastornos proliferativos, inflamatorios, o cardiovasculares. Los casos donde las mutaciones de la trayectoria de la P13K han sido enlazados a los trastornos proliferativas donde las moléculas que se definen dentro de esta invención pueden tener un beneficio terapéutico incluyen tumores benignos y malignos y cánceres de diverso linaje, que incluyen, pero sin limitación los que derivan del colon (Samuels et al., Science 304:554 (2004); se revisó en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), hígado (que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), intestino (que se revisa en Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), estómago (Samuels et al., Science 304:554 (2004); que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), esófago (Phillips et al., International Journal of Cancer 118:2644-6 (2006)); páncreas (que se revisa en Downward Nature Reviews Cancer 3:11-22 (2003)); piel (que se revisa en Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), próstata (que se revisa en Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), pulmón (Samuels et al., Science 304:554 (2004); que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), pecho (Samuels et

al., Science 304:554 (2004); Isakoff et al., Can Res 65:10992-1000 (2005); que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), endometrio (Oda et al., Can Res 65:10669-73 (2005); que se revisa en Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), cuello uterino (que se revisa en Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); ovario (Shayesteh et al., Nature Genetics 21:99-102 (1999); que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), testículos (Moul et al., Genes Chromosomes Cancer 5:109-18 (1992); Di Vizio et al., Oncogene 24:1882-94 (2005)), células hematológicas (que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)), páncreas (que se revisa en Downward Nature Reviews Cancer 3:11-22 (2003)), tiroides (que se revisa en Downward Nature Reviews Cancer 3:11-22 (2003); que se revisa en Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); cerebro (Samuels et al., Science 304:554 (2004); que se revisa en Karakas et al., British Journal of Cancer 94: 455-59 (2006)), vejiga (Lopez-Knowles et al., Cancer Research 66:7401-7404 (2006); Hennessy et al., Nature Reviews Drug Discovery 4:988-1004 (2005)); riñón (que se revisa en Downward Nature Reviews Cancer 3:11-22 (2003)) y cabeza y cuello (que se revisa en Engelman et al., Nature Reviews Genetics 7:606-619 (2006)).

[0005] Otras clases de trastornos con señalización de la vía de la P13K aberrante donde las moléculas que se definen dentro de la invención pueden tener un beneficio terapéutico incluyen enfermedades inflamatorias y cardiovasculares, que incluyen, pero sin limitación, alergias /anafilaxis (que se revisa en Rommel et al., Nature Reviews Immunology 7:191-201 (2007)), inflamación crónica y aguda (que se revisa en Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006); que se revisa en Rommel et al., Nature Reviews Immunology 7:191-201 (2007)), artritis reumatoide

(que se revisa en Rommel et al., Nature Reviews Immunology 7:191-201 (2007)); trastornos autoinmunes (que se revisa en Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), trombosis (Jackson et al., Nature Medicine 11:507-14 (2005); que se revisa en Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), hipertensión (que se revisa en Ruckle et al., Nature Reviews Drug Discovery 5:903-12 (2006)), hipertrofia cardiaca (que se revisa en Proud et al., Cardiovascular Research 63:403-13 (2004)), e insuficiencia cardiaca (que se revisa en Mocanu et al., British Journal of Pharmacology 150:833-8 (2007))

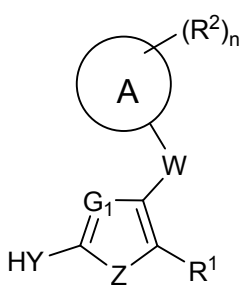
[0006] La clasificación de la proteína vacuolar 34 (VPS34) es el único miembro de la familia de la P13K Clase III. Las funciones de la VPS34 en la formación y tráfico de múltiples vesículas intracelulares, que incluyen vacuolas, endosomas, cuerpos multivesiculares, lisosomas y autofagosomas (que se revisa en Backer Biochem J 2008; Yan and Backer Biochem J 2007). La VPS34 lleva a cabo estas actividades mediante las PtdIns de fosforilación que forman las PtdIns3P, dando por resultado el reclutamiento y la localización de una variedad del dominio FYVE y PX que contiene las proteínas efectoras que facilitan la formación vesicular, la elongación y el movimiento. En un nivel celular, la inhibición de la VPS34 da por resultado los defectos en la clasificación de la proteína y la autofagia. En una definición amplia, la autofagia es un proceso regulado por el cual las células catabolizan los componentes subcelulares que focalizan la degradación al encerrarlos en vesículas de doble membrana que posteriormente se fusionan con los lisosomas. La autofagia ha sido mejor caracterizada como que se produce durante los momentos de privación de nutrientes, pero además cumple un rol en la homeostasis celular y tisular normal y en las funciones, que incluyen el desarrollo de múltiples tipos de tejidos, la respuesta inmune, la aclaración de los agregados neuronales y la supresión

del tumor. Además de funcionar en la formación de vesículas y el movimiento, la VPS34 además puede participar en varias trayectorias de transducción en Backer Biochem J 2008). Dado que la VPS34 cumple un rol importante en muchos procesos celulares críticos que incluyen la autofagia, los inhibidores de la VPS34 pueden tener aplicación terapéutica en una cantidad de enfermedades, que incluyen, pero sin limitación, cáncer, trastornos musculares, neurodegeneración, enfermedad inflamatoria, enfermedades infecciosas y otras enfermedades relacionadas con la edad (que se revisa en Shintani and Klionshy Science 2004; Kondo et al Nat Rev Cancer 2005; Delgato et al Immunol Rev 2009).

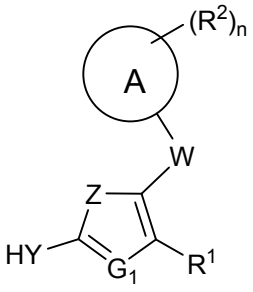
[0007] Claramente, sería beneficioso proporcionar nuevos inhibidores de la P13K que posean buenas propiedades terapéuticas, especialmente para el tratamiento de trastornos proliferativos, inflamatorios, o cardiovasculares.

[0008] *1. Descripción general de los compuestos de la invención:*

[0009] La presente invención proporciona compuestos que son inhibidores de la P13K, y en consecuencia son útiles para el tratamiento de trastornos proliferativos, inflamatorios o cardiovasculares. En una realización, los compuestos de esta invención están representados por la fórmula **IA-a** o **IB-a**:



IA-a

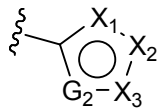


IB-a

o una sal aceptable para uso farmacéutico del mismo, donde:

Z es S o Se;

R^1 es CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$,
$-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$, donde:

CY es  ; donde:

G_2 es $-N=$, $=N-$, o $-N(R^{3'})-$, donde:

cada aparición de R^3 y $R^{3'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido, donde:

X_1, X_2, y X_3, son cada uno de ellos independientemente N, $NR^{3'}$, O, S, o CR^4, siempre que sólo uno de X_1, X_2, o X_3 pueda ser O, S, o $NR^{3'}$;

cada aparición de R^4 es independientemente hidrógeno, -CN, halógeno, $-Z_3-R^6$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, o cicloalifático de 3 a 10 miembros, donde:

Z^3 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido, $-O-$, $-N(R^{4a})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$,
$-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, o $-OC(O)-$;

R^{4a} es hidrógeno o un alifático C_{1-6} opcionalmente sustituido, y

R^6 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6},

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

o donde dos apariciones adyacentes de $R^{3'}$ o R^4, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de R^{12b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o $-CN$;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

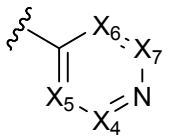
donde:

Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o -OC(O)-;

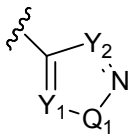
R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático $C1_{-6}$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

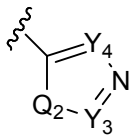
HY es un grupo opcionalmente sustituido seleccionado de:



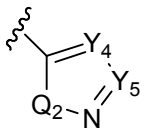
A ,



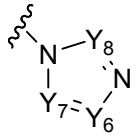
B ,



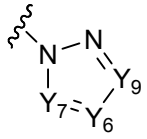
C ,



D



E ,



o **F** ;

donde cada aparición de X_4, X_5, X_6, y X_7 es independientemente

$-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o $-NR^5$;

cada aparición de Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, e Y_9 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de Y_6, Y_7, Y_8, e Y_9 sean N;

o donde dos apariciones adyacentes de X_4 y X_5, X_6 y X_7, Y_1 y Q_1, Y_3 y Q_2, o Y_4 y Y_5 tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

donde R^{10} es $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, o $-V_1-T_1-R^{10b}$ donde:

V_1 es $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, o $-SO_2NR^{11}-$;

cada aparición de R^{10b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$,

$-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, o $-C(O)N(R^{11})-O-$ o donde T_1 forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

cada aparición de R^{10b} es independientemente hidrógeno, halógeno, $-CN$, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, or $-N(R^{11})SO_2N(R^{11})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxigeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{10c} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

R^{10a} y R^{10c} tomados juntos con un átomo de nitrógeno al cual están unidos forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional independientemente seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{11} es independientemente hidrógeno o , -$C(O)R^{11a}$, -CO_2R^{11a} , -$C(O)N(R^{11a})_2$, -$C(O)N(R^{11a})$-OR^{11a}, -SO_2R^{11a}, -$SO_2N(R^{11a})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{11a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático $C1_{-6}$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^5 es independientemente hidrógeno o , -$C(O)R^{5a}$, -CO_2R^{5a}, -$C(O)N(R^{5b})_2$, -SO_2R^{5a}, -$SO_2N(R^{5b})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

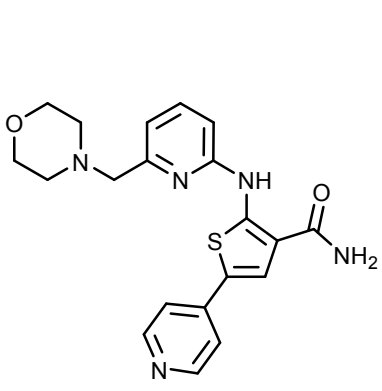
donde cada aparición de R^{5a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o

azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

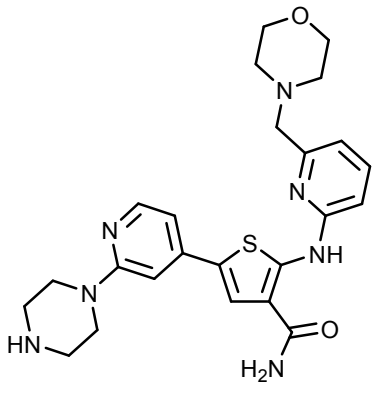
donde cada aparición de R^{5b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{5b} tomados juntos con el átomo de nitrógeno al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

siempre que:

a) para los compuestos de fórmula IB_{-a} los compuestos sean diferentes de:

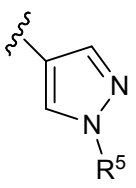
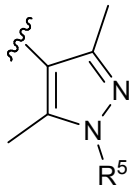
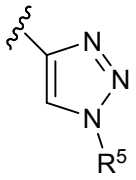


,

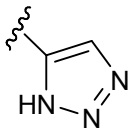
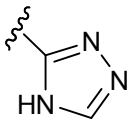
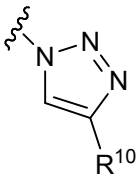


; y

cuando G^1 es CR^8, R^1 es $CONH_2$, y W es NH, entonces HY es diferente de

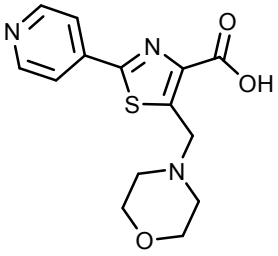
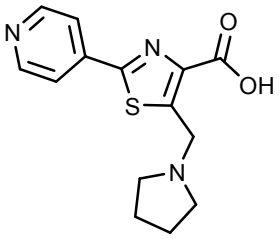




, , ,

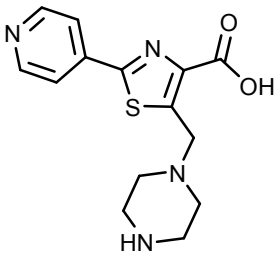
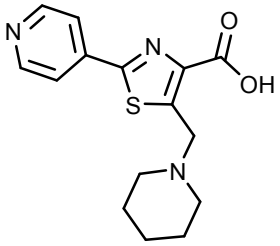
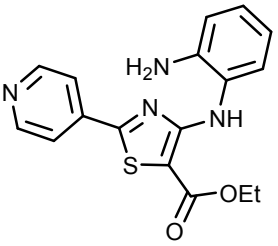




, , o ; y

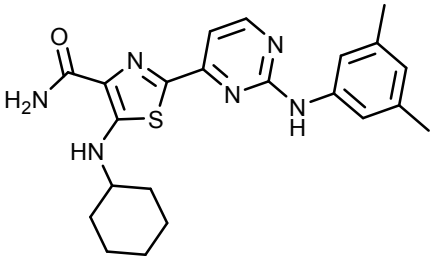
b) el compuesto es diferente de:

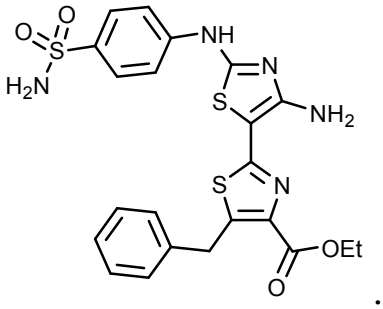
, ,

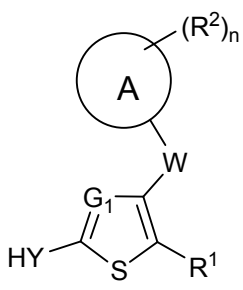
, , ,



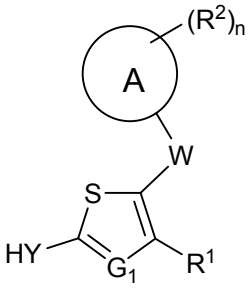
,



[0010] En otra realización, los compuestos de esta invención están representados por la fórmula **IA** o **IB**:



IA

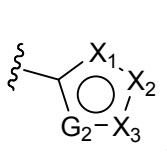


IB

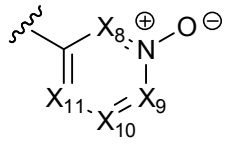
o una sal aceptable para uso farmacéutico del mismo, donde:

R^1 es CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$, donde:

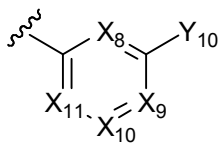
CY es un grupo opcionalmente sustituido seleccionado de:



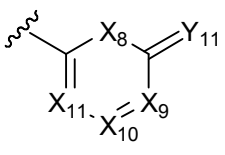
Q



R



S



T

donde:

G_2 es $-N=$, $=N-$, o $-N(R^{3'})-$, donde:

cada aparición de R^3 y $R^{3'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido, donde:

X_1, X_2, y X_3, son cada uno de ellos independientemente N, $NR^{3'}$, O, S, o CR^4, siempre que sólo uno de X_1, X_2, o X_3 pueda ser O, S, o $NR^{3'}$;

X_8, X_9, X_{10}, y X_{11} son cada uno de ellos independientemente N, o CR^4, siempre que no más de dos apariciones de X_8, X_9, X_{10}, y X_{11} sean N;

cada aparición de R^4 es independientemente hidrógeno, -CN, halógeno, $-Z_3-R^6$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, o cicloalifático de 3 a 10 miembros, donde:

Z_3 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido, $-O-$, $-N(R^{4a})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, o $-OC(O)-$;

R^{4a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^6 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6},

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

o donde dos apariciones adyacentes de $R^{3'}$ o R^4, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

Y_{10} es $-OR^{4'}$ o $-N(R^{4'})_2$;

Y_{11} es O o N-$R^{4'}$;

cada aparición de $R^{4'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de R^{12b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_3 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

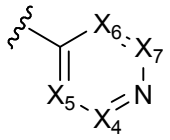
donde:

Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o -OC(O)-;

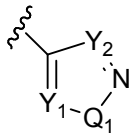
R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

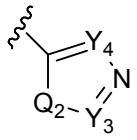
HY es un grupo opcionalmente sustituido seleccionado de:



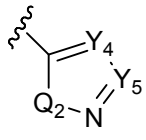
A ,



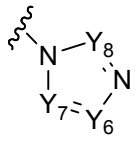
B ,



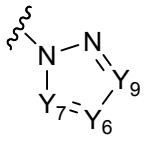
C ,



D



E , o



F ;

donde cada aparición de X_4, X_5, X_6, y X_7 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o $-NR^5$;

cada aparición de Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, e Y_9 es

independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de Y_6, Y_7, Y_8, e Y_9 sean N;

o donde dos apariciones adyacentes de X_4 y X_5, X_6 y X_7, Y_1 y Q_1, Y_3 y Q_2, o Y_4 y Y_5 tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

donde R^{10} es $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, o $-V_1-T_1-R^{10b}$ donde:

V_1 es $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, o $-SO_2NR^{11}-$;

cada aparición de R^{10a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, o $-C(O)N(R^{11})-O-$o donde T_1 forma parte de un cicloalifático

de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

cada aparición de R^{10b} es independientemente hidrógeno, halógeno, CN, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, o $-N(R^{11})SO_2N(R^{11})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{10c} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

R^{10a} y R^{10c} tomados juntos con un átomo de nitrógeno al cual están unidos forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional independientemente seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{11} es independientemente hidrógeno o , $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, o un grupo opcionalmente sustituido seleccionado de

alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{11a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático $C1_{-6}$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

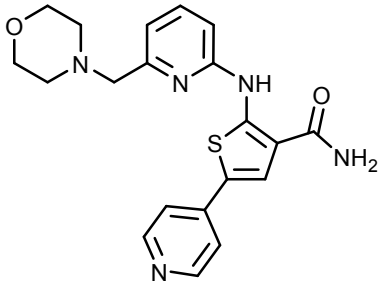
cada aparición de R^5 es independientemente hidrógeno o , $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{5a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

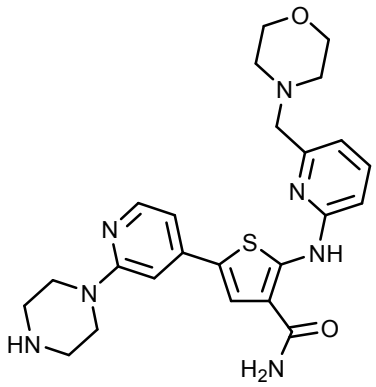
donde cada aparición de R^{5b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R5b tomados juntos con el átomo de nitrógeno al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

siempre que:

a) para los compuestos de fórmula IB los compuestos sean diferentes de:

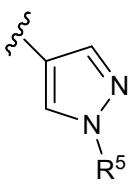
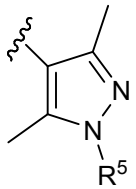
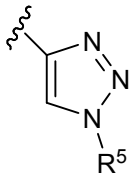


,

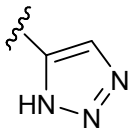
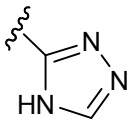
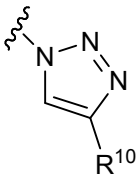


; y

cuando G^1 es CR^8, R^1 es $CONH_2$, y W es NH, entonces HY es diferente de

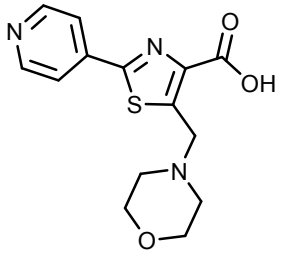
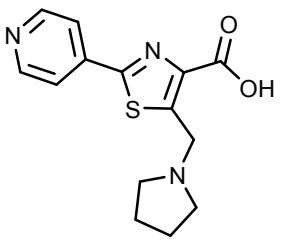
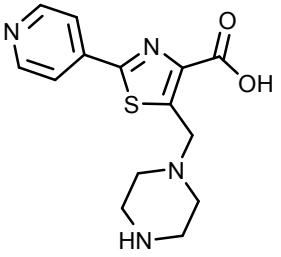




, , ,

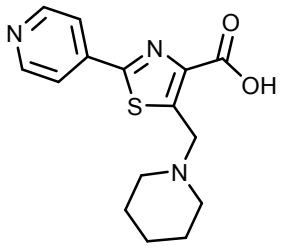
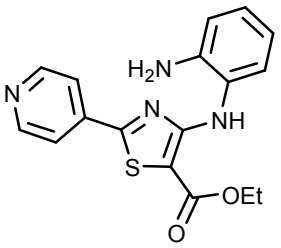
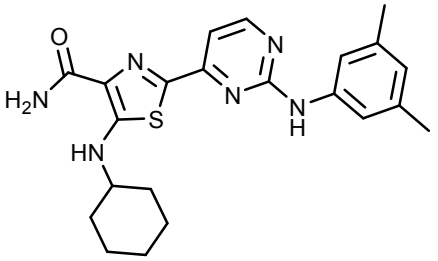




, , o ; y

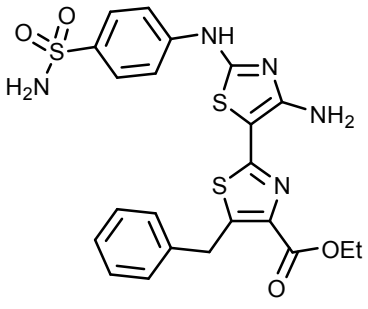
b) el compuesto es diferente de:

, , ,

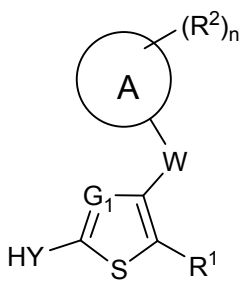




, , ,

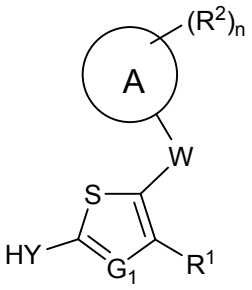


.

[0011] En otro aspecto, los compuestos de esta invención están representados por la fórmula **IA** o **IB**:



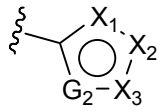
IA



IB

o una sal aceptable para uso farmacéutico del mismo, donde:

R^1 es CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$, donde:

CY es  ; donde:

G_2 es $-N=$, $=N-$, o $-N(R^{3'})-$, donde:

cada aparición de R^3 y $R^{3'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido, donde:

X_1, X_2, y X_3, son cada uno de ellos independientemente N, $NR^{3'}$, O, S, o CR^4, siempre que sólo uno de X_1, X_2, o X_3 pueda ser O, S, o $NR^{3'}$;

cada aparición de R^4 es independientemente hidrógeno, -CN, halógeno, $-Z_3-R^6$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, o cicloalifático de 3 a 10 miembros, donde:

Z^3 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido, $-O-$, $-N(R^{4a})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, u $-OC(O)-$;

R^{4a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^6 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6},

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

o donde dos apariciones adyacentes de $R^{3'}$ o R^4, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de R^{12b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros

opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$,

$-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o $-CN$;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado

del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $–Z_2–R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

donde:

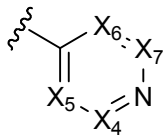
Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o -OC(O)-;

R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

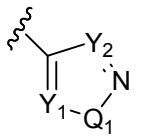
R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos

independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

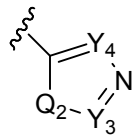
HY es un grupo opcionalmente sustituido seleccionado de:



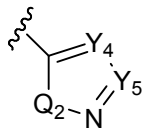
A ,



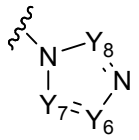
B



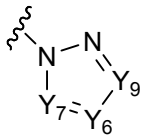
C



D



E o



F

donde cada aparición de X_4, X_5, X_6, y X_7 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o $-NR^5$;

cada aparición de Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, e Y_9 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de Y_6, Y_7, Y_8, e Y_9 sean N;

o donde dos apariciones adyacentes de X_4 y X_5, X_6 y X_7, Y_1 y Q_1, Y_3 y Q_2, o Y_4 y Y_5 tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

donde R^{10} es $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, o $-V_1-T_1-R^{10b}$ donde:

V_1 es $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, -

$NR^{11}S(O)_2NR^{11}$-, -C(O)-, $-CO_2$-, $-C(O)NR^{11}$-, $-C(O)NR^{11}O$-, $-SO_2$-, o $-SO_2NR^{11}$-;

cada aparición de R^{10a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{11})$ -, -O-, -S-, $-S(O)_2$-, -C(O) -, -C(O)O-, $-C(O)N(R^{11})$ -, $-S(O)_2N(R^{11})$-, $-OC(O)N(R^{11})$-, $-N(R^{11})C(O)$-, $-N(R^{11})SO_2$-, $-N(R^{11a})C(O)O$-, $-NR^{10a}C(O)N(R^{10a})$-, $-N(R^{10a})S(O)_2N(R^{10a})$-, -OC(O)-, o $-C(O)N(R^{11})$-O- o donde T_1 forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

cada aparición de $R10^b$ es independientemente hidrógeno, halógeno, CN, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, -S(O)2R^{10a}, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, o $-N(R^{11})SO_2N(R^{11})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5

heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{10c} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

R^{10a} y R^{10c} tomados juntos con un átomo de nitrógeno al cual están unidos forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional independientemente seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{11} es independientemente hidrógeno o , $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{11a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático $C1_{-6}$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5

heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^5 es independientemente hidrógeno o , $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

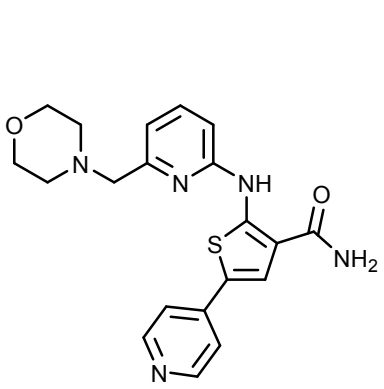
donde cada aparición de R^{5a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{5b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_1-$_6$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{5b} tomados juntos con el átomo de nitrógeno al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, heteroarilo de 5 a 10 miembros que tiene 1

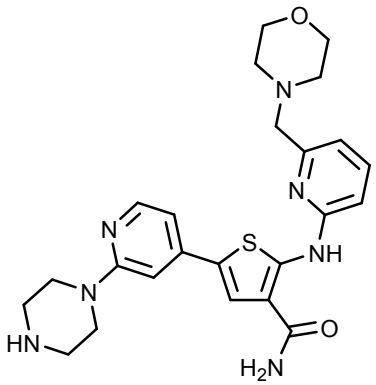
a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

siempre que:

a) para los compuestos de fórmula IB los compuestos sean diferentes de:

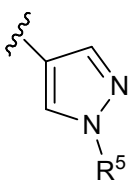


,

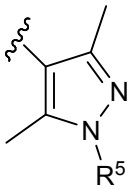


; y

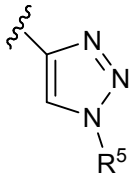
cuando G^1 es CR^8, R^1 es $CONH_2$, y W es NH, entonces HY es diferente de



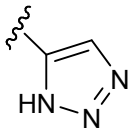
,



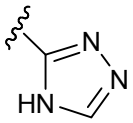
,



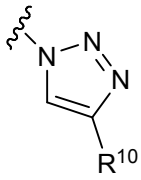
,



,

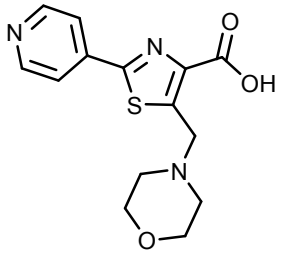
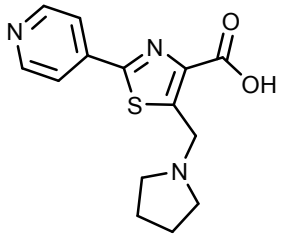
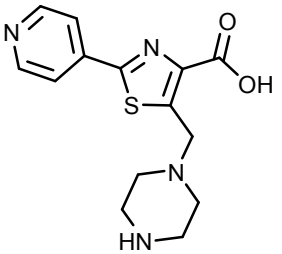
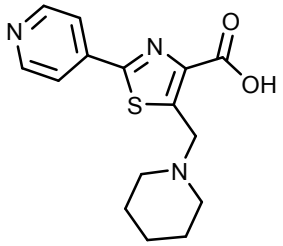
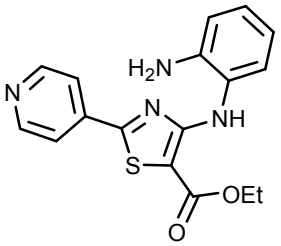
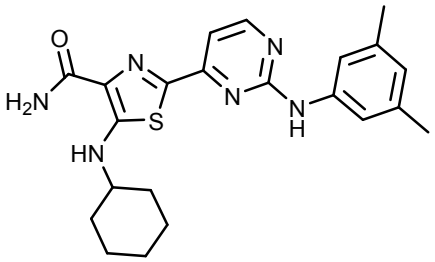
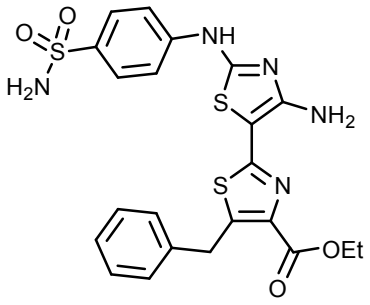
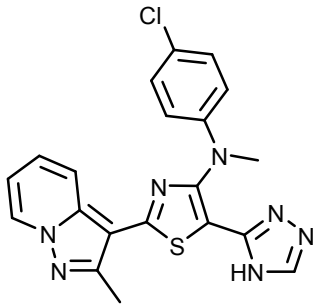


,

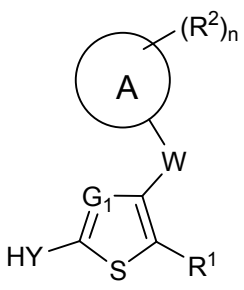


, o ; y

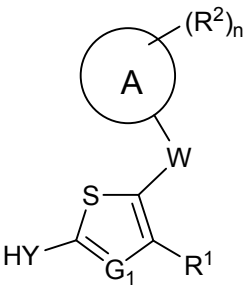
b) el compuesto es diferente de:

[0012] En otro aspecto, los compuestos de esta invención están representados por la fórmula **IA** o **IB**:



IA



IB

o una sal aceptable para uso farmacéutico del mismo, donde:

R^1 es $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$;

cada aparición de R^3 es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de R^{12b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a

10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

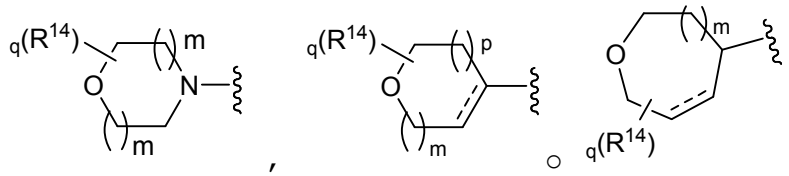
cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a

5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

G_1 es N; y

HY es  ;

donde cada aparición de R^{14} es independientemente $-R^{14a}$ o $-T_1-R^{14d}$, donde:

cada aparición de R^{14a} como permiso de valencia y estabilidad, es independientemente flúor, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, o $-N(R^{14e})SO_2N(R^{14b})_2$, o dos apariciones de R^{14b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático

C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14e} es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido; y

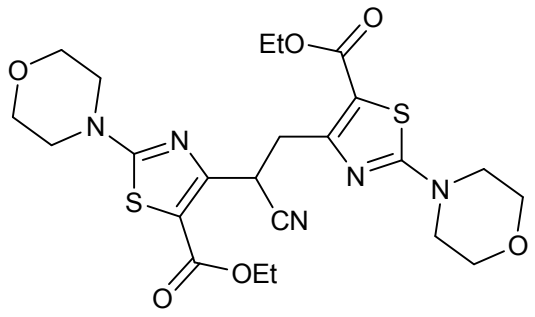
T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, o $-C(O)N(R^{14a})-O-$ o donde T_1 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

n es 0 a 6;

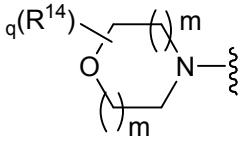
M es 1 o 2;

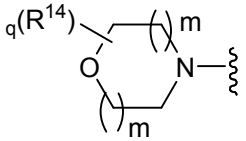
P es 0, 1, o 2;

siempre que el compuesto sea diferente de:

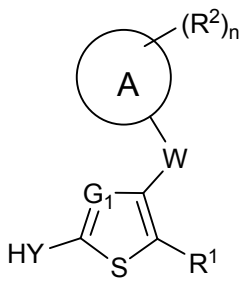


.

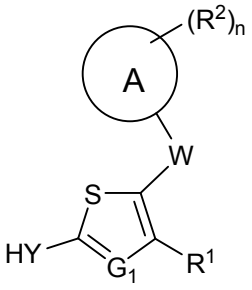
[0013] En algunas realizaciones para los compuestos que se describieron directamente más arriba, HY es  , donde ambas apariciones de m son 1.

[0014] En otras realizaciones para los compuestos que se describieron directamente más arriba, HY es  , donde ambas apariciones de m son 1, y R^1 es COOH.

[0015] Incluso en otro aspecto, los compuestos de esta invención están representados por la fórmula **IA** o **IB**:



IA

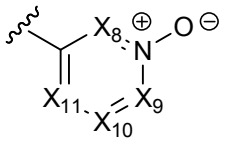
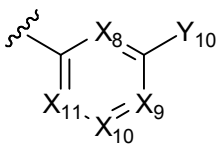
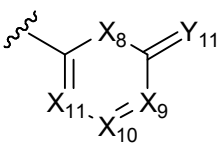


IB

o una sal aceptable para uso farmacéutico del mismo, donde:

R^1 es CY, donde:

CY es un grupo opcionalmente sustituido seleccionado de:


; 
, o 
.

R **S** **T**

donde:

cada aparición de R^3 es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido, donde:

X_8, X_9, X_{10}, y X_{11} son cada uno de ellos independientemente N, o CR^4, siempre que no más de dos apariciones de X_8, X_9, X_{10}, y X_{11} sean N;

cada aparición de R^4 es independientemente hidrógeno, -CN, halógeno, $-Z_3-R^6$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, o cicloalifático de 3 a 10 miembros, donde:

Z_3 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido, –O-, $-N(R^{4a})-$, -S-, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, o $-OC(O)-$;

R^{4a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^6 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

Y_{10} es $-OR^{4'}$ o $-N(R^{4'})_2$;

Y_{11} es O o $N-R^{4'}$;

cada aparición de $R^{4'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de R^{12b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a

10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido,o cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a

5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

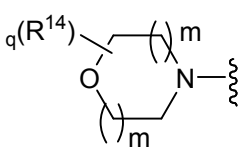
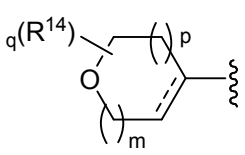
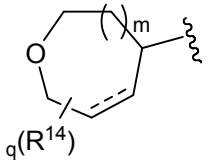
G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

donde:

Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, $-S(O)-$, $S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o $-OC(O)-$;

R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es  ,  o  ;

donde cada aparición de R^{14} es independientemente $-R^{14a}$ o $-T_1-R^{14d}$, donde:

cada aparición de R^{14a} como permiso de valencia y estabilidad, es independientemente flúor, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, -

$N(R^{14e})C(O)N(R^{14b})_2$, o $-N(R^{14e})SO_2N(R^{14b})_2$, o dos apariciones de R^{14b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14e} es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido; y

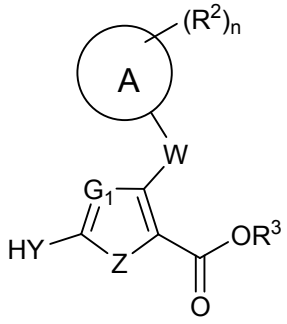
T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}$ $C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, o $-C(O)N(R^{14a})-O-$ o donde T_1 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

n es 0 a 6;

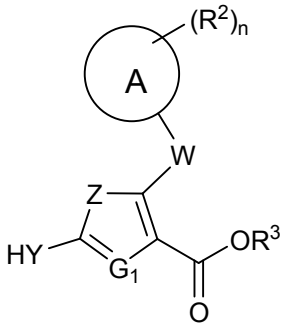
m es 1 o 2; y

p es 0, 1, o 2.

[0016] Incluso en otra realización de la invención, los compuestos de esta invención están representados por la fórmula IA-i-a o IB-i-a:



IA-i-a



IB-i-a

o una sal aceptable para uso farmacéutico del mismo, donde:

Z es S o Se;

R^3 es hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, o:

dos grupos R^2 adyacentes se toman juntos con sus átomos intervinientes para formar un anillo parcialmente insaturado, saturado de 4 a 7 miembros opcionalmente sustituido, o arilo que tiene de 0 a 4 heteroátomos seleccionados de nitrógeno, oxígeno o azufre;

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$,

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{12b} tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6},

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno, $-N(R^{7b})_2$, o un grupo opcionalmente sustituido seleccionado de cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

W se selecciona de un enlace covalente, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, o F;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$,o $-S(O)_2R^{7a}$; o

cada aparición de R^{7c} es independientemente un alifático C_{1-6} opcionalmente sustituido o un cicloalifático de 3 a 7 miembros opcionalmente sustituido; o

donde cualquiera de dos apariciones de R^7, R^{7a}, R^{7b} o R^{7c} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3

a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

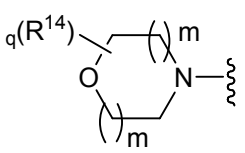
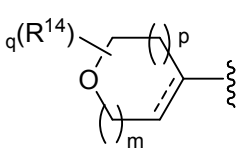
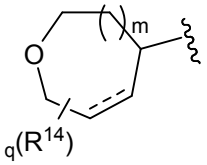
G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

donde:

Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o -OC(O)-;

R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es  ,  o  ;

------ representa un enlace simple o un enlace doble;

donde cada aparición de R^{14} es independientemente $-R^{14a}$ o $-T_1-R^{14d}$, donde:

cada aparición de R^{14a} como permiso de valencia y estabilidad, es independientemente flúor, =O, =S, -CN, -

NO_2, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, o $-N(R^{14e})SO_2N(R^{14b})_2$, o dos apariciones de R^{14b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de

6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14e} es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido; y

T_1 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, o $-C(O)N(R^{14a})-O-$ o donde T_1 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

n es 0 a 6;

q es 0 a 4;

m es 1 o 2; y

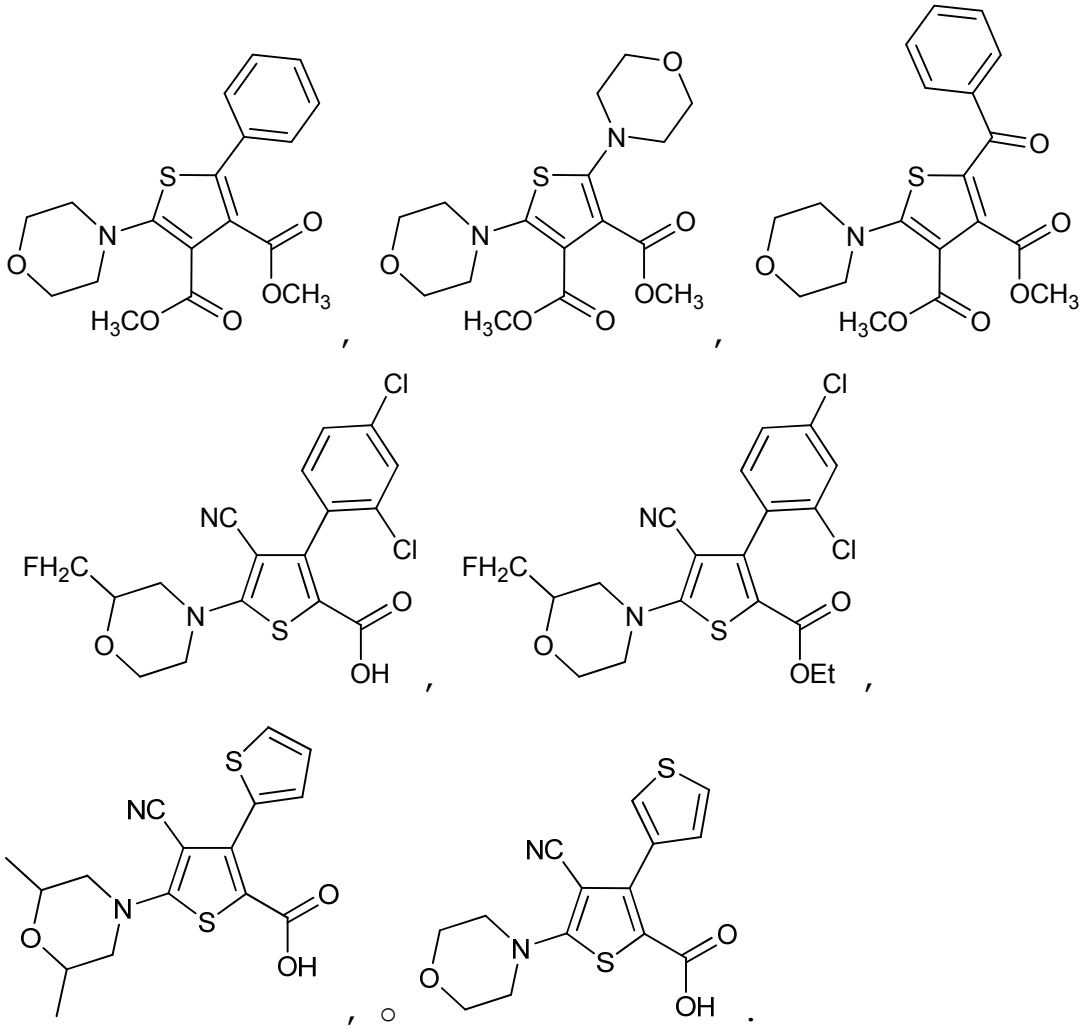
P es 0, 1, o 2;

siempre que:

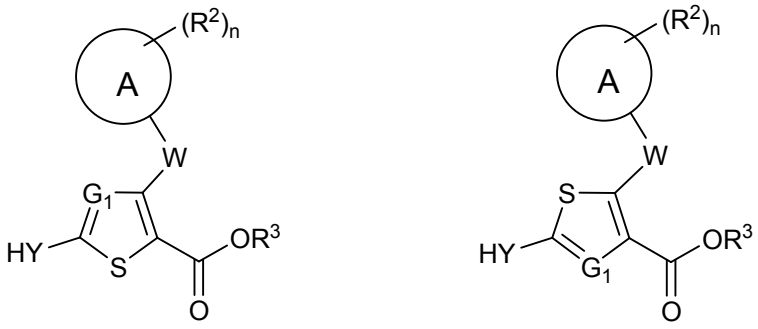
a) Cuando G_1 es C-CN, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido, 2-clorofenilo, 4-clorofenilo, 2-fluorofenilo, 4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 4-metilfenilo, 3-metoxifenilo, 4-metoxifenilo, 3,4-dimetoxifenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, o 3-(acetilamino)fenilo;

b) cuando G_1 es N, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido o 2-clorofenilo; y

c) el compuesto es diferente de:



[0017] Incluso en otra realización de la invención, los compuestos de esta invención están representados por la fórmula **IA-i o IB-i:**



IA-i **IB-i**

o una sal aceptable para uso farmacéutico del mismo, donde:

R^3 es hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, o:

dos grupos R^2 adyacentes se toman juntos con sus átomos intervinientes para formar un anillo parcialmente insaturado, saturado de 4 a 7 miembros opcionalmente sustituido, o arilo que tiene de 0 a 4 heteroátomos seleccionados de nitrógeno, oxígeno o azufre;

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{12b} tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un

anillo heterociclilo de 4 a 7 miembros que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno, $-N(R^{7b})_2$, o un grupo opcionalmente sustituido seleccionado de cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un

cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

W se selecciona de un enlace covalente, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, o F;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

cada aparición de R^{7c} es independientemente un alifático C_{1-6} opcionalmente sustituido o un cicloalifático de 3 a 7 miembros opcionalmente sustituido; o

donde cualquiera de dos apariciones de R^7, R^{7a}, R^{7b} o R^{7c} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

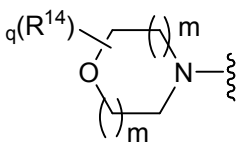
G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

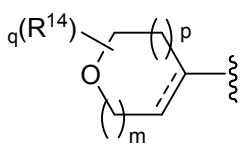
donde:

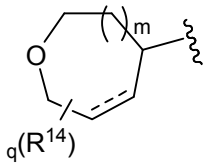
Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o -OC(O)-;

R^{8a} es hidrógeno o un alifático C_{1-6} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es 

, 

o 

;

$\underline{\underline{\text{------}}}$ representa un enlace simple o un enlace doble;

donde cada aparición de R^{14} es independientemente $-R^{14a}$ o $-T_1-R^{14d}$, donde:

cada aparición de R^{14a} como permiso de valencia y estabilidad, es independientemente flúor, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, o $-N(R^{14e})SO_2N(R^{14b})_2$, o dos apariciones de R^{14b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14e} es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido; y

T_1 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, o $-C(O)N(R^{14a})-O-$ o donde T_1 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

n es 0 a 6;

q es 0 a 4;

m es 1 o 2; y

P es 0, 1, o 2;

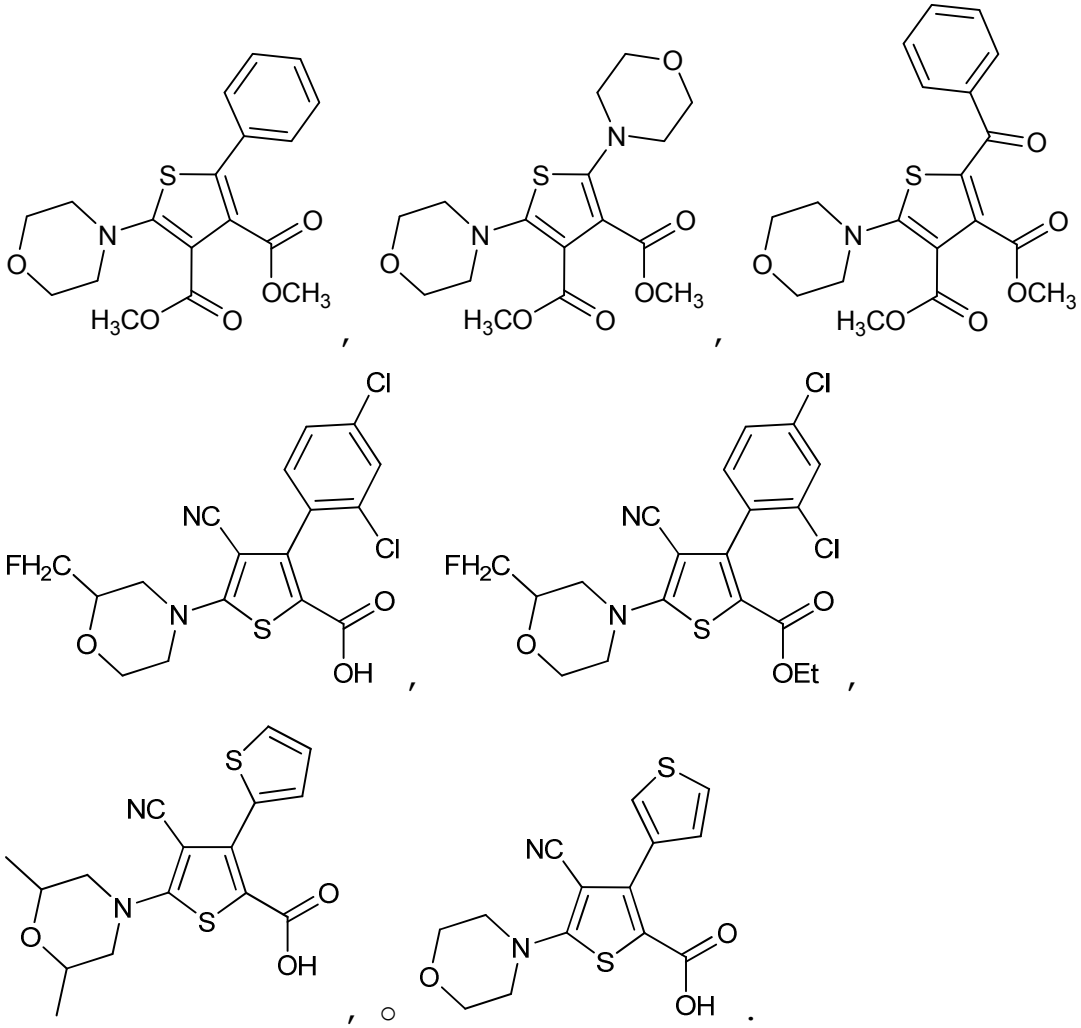
siempre que:

a) cuando G_1 es C-CN, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido, 2-clorofenilo, 4-clorofenilo, 2-fluorofenilo, 4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 4-metilfenilo, 3-metoxifenilo, 4-metoxifenilo,

3,4-dimetoxifenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, o 3-(acetilamino)fenilo;

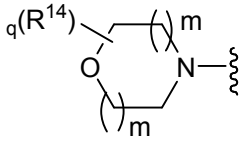
b) cuando G_1 es N, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido o 2-clorofenilo; y

c) el compuesto es diferente de:



[0018] En algunas realizaciones para los compuestos que se describieron directamente más arriba, G_1 es N.

[0019] En algunas realizaciones para los compuestos que se describieron directamente más arriba, G_1 es $C(R^8)$, en donde R^8 es –CN o alquinilo C_{2-4}.

[0020] En algunas realizaciones para los compuestos que se describieron directamente más arriba, HY es  , donde ambas apariciones de m son 1.

[0021] En algunas realizaciones para los compuestos que se describieron directamente más arriba, R^3 es H.

Descripción detallada de la invención

[0022] *2. Compuestos y definiciones:*

[0023] Los compuestos de esta invención incluyen los que se describen en general más arriba, y se ilustran además mediante las clases, subclases y especies que se divulgan en la presente. Se apreciará que los subconjuntos preferidos que se describen para cada variable en la presente se pueden utilizar para cualquiera de los subconjuntos estructurales también. Tal como se utiliza en la presente, las siguientes definiciones se aplicarán a menos que se indique lo contrario.

[0024] Como se describe en la presente, los compuestos de la invención se pueden sustituir opcionalmente con uno o más sustituyentes, tales como los que se ilustran en general anteriormente, o como se ejemplifica mediante clases, subclases y especies particulares de la invención. Se apreciará que la frase "opcionalmente sustituido" se utiliza intercambiablemente con la frase "sustituido o no sustituido". En general, el término "sustituido", sea que esté o no precedido por el término "opcionalmente", significa que un radical hidrógeno del resto

designado se reemplaza con el radical de un sustituyente específico siempre que la sustitución de por resultado un compuesto estable o químicamente factible. El término "sustituible", cuando se utiliza con referencia a un átomo designado, significa que unido al átomo es un radical hidrógeno, dicho átomo de hidrógeno puede ser reemplazado con el radical de un sustituyente adecuado. A menos que se indique los contrario, un grupo "opcionalmente sustituido" puede tener un sustituyente en cada posición sustituible del grupo, y cuando más de una posición en cualquier estructura dada puede ser sustituida con más de un sustituyente seleccionado de un grupo específico, el sustituyente puede estar o bien en la misma o en una diferente posición. Las combinaciones de sustituyentes abarcados por esta invención son aquéllos que con preferencia dan por resultado la formación de compuestos estables o químicamente factibles.

[0025] Un compuesto estable o un compuesto químicamente factible es uno en el cual la estructura química no se altera sustancialmente cuando se mantiene a una temperatura de aproximadamente -80°C hasta aproximadamente +40°C, en ausencia de humedad y otras condiciones químicamente reactivas, durante al menos una semana, o un compuesto que mantiene su integridad lo suficiente como para ser útil para la administración terapéutica o profiláctica a un paciente.

[0026] La frase "uno o más sustituyentes", tal como se utiliza en la presente, se refiere a un número de sustituyentes que es igual a uno hasta el número máximo de sustituyentes posibles basados en el número de sitios de unión disponibles, siempre que se reúnan las condiciones anteriores de estabilidad y factibilidad química.

[0027] Tal como se utiliza en la presente, "independientemente seleccionado" significa que los mismos o diferentes valores se pueden seleccionar para múltiples instancias de una variable dada en un único compuesto.

[0028] Tal como se utiliza en la presente, "un anillo monocíclico de 3 a 7 miembros saturado, parcialmente insaturado, o aromático que tiene de 0 a 3 heteroátomos independientemente seleccionado de nitrógeno, oxígeno, o azufre, o un sistema anular bicíclico de 8 a 10 miembros parcialmente insaturado, o aromático que tiene de 0 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre" incluye anillos arilo y heteroarilo cicloalifáticos, heterocíclicos.

[0029] Tal como se utiliza en la presente, el término "aromático" incluye grupos arilo y heteroarilo como se describe en general a continuación y en la presente.

[0030] El término "alifático" o "grupo alifático", tal como se utiliza en la presente, significa un hidrocarburo C_{1-12} de cadena recta o ramificada opcionalmente sustituido, o un hidrocarburo C_{1-12} cíclico que es completamente saturado o que contiene una o más unidades de insaturación, pero que no es aromático (además se denomina en la presente "carbociclo", "cicloalifático", "cicloalquilo", o "cicloalquenilo"). Por ejemplo, los grupos alifáticos adecuados incluyen grupos alquilo, alquenilo, alquinilo cíclico o ramificado, lineal opcionalmente sustituido e híbridos de los mismos, tales como (cicloalquil)alquilo, (cicloalquenil)alquilo, o (cicloalquil)alquenilo. A menos que se especifique lo contrario, en varias realizaciones, los grupos alifáticos tienen 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, o 1–2 átomos de carbono.

[0031] El término "alquilo", utilizado solo o como parte de un resto más grande, se refiere a un grupo hidrocarbonado de cadena recta o ramificada opcionalmente sustituido que tiene 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, o 1–2 átomos de carbono.

[0032] El término "alquenilo", utilizado solo o como parte de un resto más grande, se refiere a un grupo hidrocarbonado de cadena recta o ramificada opcionalmente sustituido que tiene al menos un

enlace doble y tiene 2-12, 2-10, 2-8, 2-6, 2-4, o 2-3 átomos de carbono.

[0033] El término "alquinilo", utilizado solo o como parte de un resto más grande, se refiere a un grupo hidrocarbonado de cadena recta o ramificada opcionalmente sustituido que tiene al menos un enlace triple y tiene 2-12, 2-10, 2-8, 2-6, 2-4, o 2-3 átomos de carbono.

[0034] Los términos "cicloalifático", "carbociclo", "carbociclilo", "carbociclo", o "carbocíclico", utilizados solos o como arte de un resto más grande ser refieren a un sistema anular alifático cíclico saturado o parcialmente insaturado opcionalmente sustituido que tiene desde 3 hasta aproximadamente 14 átomos de carbono del anillo. En algunas realizaciones, el grupo cicloalifático es un hidrocarburo monocíclico opcionalmente sustituido que tiene 3-8 o 3-6 átomos de carbono del anillo. Los grupos cicloalifático incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, cicloheptilo, cicloheptenilo, ciclooctilo, ciclooctenilo, o ciclooctadienilo. Los términos "cicloalifático", "carbociclo", "carbociclilo", "carbociclo", o "carbocíclico" además incluyen anillos bicíclicos fusionados o puenteados opcionalmente sustituidos que tienen 6-12, 6-10, o 6-8 átomos de carbono del anillo, donde cualquier anillo individual en el sistema bicíclico tiene 3 a 8 átomos de carbono del anillo.

[0035] El término "cicloalquilo" se refiere a un sistema anular saturado opcionalmente sustituido de aproximadamente 3 hasta aproximadamente 10 átomos de carbono del anillo. Ejemplos de anillos cicloalquilo monocíclico incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y cicloheptilo.

[0036] El término "cicloalquenilo" se refiere a un sistema anular multicíclico o monocíclico no aromático opcionalmente sustituido que contiene al menos un enlace doble carbono-carbono y tiene

aproximadamente 3 hasta aproximadamente 10 átomos de carbono. Ejemplos de anillos cicloalquenilo monocíclico incluyen ciclopentilo, ciclohexenilo, y cicloheptenilo.

[0037] Los términos "haloalifático", "haloalquilo", "haloalquenilo" y "haloalcoxi" se refieren a un grupo alifático, alquilo, alquenilo o alcoxi, según pueda ser el caso, el cual está sustituido con uno o más átomos de halógeno. Tal como se utiliza en la presente, el término "halógeno" o "halo" significa F, Cl, Br, o I. El término "fluoroalifático" se refiere a un haloalifático donde el halógeno es flúor, que incluye grupos alifáticos perfluorinados. Ejemplos de grupos fluoroalifáticos incluyen, pero sin limitación, fluorometilo, difluorometilo, trifluorometilo, 2-fluoroetilo, 2,2,2-trifluoroetilo, 1,1,2-trifluoroetilo, 1,2,2-trifluoroetilo, y pentafluoroetilo.

[0038] El término "heteroátomo" se refiere a uno o más de oxígeno, azufre, nitrógeno, fósforo, o silicio (que incluye cualquier forma oxidada de nitrógeno, azufre, fósforo, o silicio; la forma cuaternizada de cualquier anillo de nitrógeno básico, o; un nitrógeno sustituible de un anillo heterocíclico, por ejemplo N (como en 3,4-dihidro-2H-pirrolilo), NH (como en pirrolidinilo) o NR+ (como pirrolidinilo N-sustituido).

[0039] Los términos "arilo" y "ar-", utilizados solos o como parte de un resto más grande, por ej., "aralquilo", "aralcoxi", o "ariloxialquilo", se refieren a un resto hidrocarbonado aromático C_{6-14} opcionalmente sustituido que comprende uno a tres anillos aromáticos. Con preferencia, el grupo alquilo es un grupo arilo C_{6-10}. Los grupos arilo incluyen, pero sin limitación, fenilo opcionalmente sustituido, naftilo, o antracenilo. Los términos "arilo" y "ar-", como se utilizan en la presente, además incluyen grupos en los cuales un anillo arilo está fusionado a uno o más anillos cicloalifáticos para formar una estructura cíclica opcionalmente sustituida tal como un anillo tetrahidronaftilo,

indenilo, o indanilo. El término "arilo" se puede utilizar intercambiablemente con los términos "grupo arilo", "anillo arilo", y "anillo aromático".

[0040] Un grupo "aralquilo" o "arilalquilo" comprende un grupo arilo unido covalentemente a un group alquilo, cualquiera de los cuales está independientemente opcionalmente sustituido. Con preferencia, el grupo aralquilo es arilo C_{6-10}-alquilo C_{1-6}, que incluyen, pero sin limitación, bencilo, fenetilo, y naftilmetilo.

[0041] Los términos "heteroarilo" y "heteroar-", utilizado solos o como parte de un resto más grande, por ej., "heteroaralquilo", o "heteroaralcoxi", se refieren a grupos que tienen 5 a 14 átomos de anillo, con preferencia, 5, 6, 9 o 10 átomos del anillo; que tienen 6, 10 o 14 electrones compartidos en una matriz cíclica, y que tiene, además de los átomos de carbono, de uno a cinco heteroátomos. Un grupo heteroarilo puede ser mono-, bi-, tri-, o policíclico, con preferencia mono-, bi-, o tricíclico, con mayor preferencia mono- o bicíclico. El término "heteroátomo" se refiere a nitrógeno, oxígeno, o azufre, e incluye cualquier forma oxidada de nitrógeno o azufre, y cualquier forma cuaternizada de un nitrógeno básico. Por ejemplo, un átomo de nitrógeno de un heteroarilo puede ser un átomo de nitrógeno básico y además puede estar opcionalmente oxidado al correspondiente N-óxido. Cuando un heteroarilo está sustituido mediante un grupo hidroxi, además incluye su correspondiente tautómero. Los términos "heteroarilo" y "heteroar-", tal como se utilizan en la presente, además incluyen grupos en los cuales un anillo heteroaromático está fusionado a uno o más anillos arilo, cicloalifático, o hterocicloalifático. Ejemplos no limitantes de grupos heteroarilo incluyen tienilo, furanilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, indolizinilo, purinilo, naftiridinilo,

pteridinilo, indolilo, isoindolilo, benzotienilo, benzofuranilo, dibenzofuranilo, indazolilo, bencimidazolilo, benztiazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, 4H-quinolizinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo, fenoxazinilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, and pirido[2,3-b]-1,4-oxazin-3(4H)-ona. El término "heteroarilo" se puede utilizar intercambiablemente con los términos "anillo de heteroarilo", "grupo heteroarilo", o "heteroaromático", cualquiera de estos términos incluyen anillos que están opcionalmente sustituidos. El término "heteroaralquilo" se refiere a un grupo alquilo sustituido con un heteroarilo, donde las porciones de alquilo y heteroarilo independientemente están opcionalmente sustituidas.

[0042] Tal como se utiliza en la presente, los términos "heterociclo", "heterociclilo", "radical heterocíclico", y "anillo heterocíclico" se utilizan intercambiablemente y se refieren a un resto heterocíclico bicíclico de 7 a 10 miembros o monocíclico de 3 a 8 miembros que está saturado o parcialmente insaturado, y tiene, además de átomos de carbono, uno o más, con preferencia uno a cuatro heteroátomos, como se definió anteriormente. Cuando se utiliza con referencia a un átomo del anillo de un heterociclo, el término "nitrógeno" incluye un nitrógeno sustituido. Como ejemplo, en un anillo saturado o parcialmente insaturado que tiene 0 a 3 heteroátomos seleccionados de oxígeno, azufre, o nitrógeno, el nitrógeno puede ser N (como en 3,4-dihidro-2H-pirrolilo), NH (como en pirrolidinilo), o NR^+ (como en pirrolidinilo N-sustituido).

[0043] Un anillo heterocíclico puede estar unido a su grupo pendiente en cualquier heteroátomo o átomo de carbono que de por resultado una estructura estable y cualquiera de los átomos del anillo puede estar opcionalmente sustituido. Ejemplos de estos radicales heterocíclicos saturados o parcialmente insaturados incluyen, pero sin limitación, tetrahidrofuranilo,

tetrahidrotienilo, piperidinilo, decahidroquinolinilo, oxazolidinilo, piperazinilo, dioxanilo, dioxolanilo, diazepinilo, oxazepinilo, tiazepinilo, morfolinilo, y tiamorfolinilo Un grupo heterociclilo puede ser mono-, bi-, tri-, o policíclico, con preferencia mono-, bi-, o tricíclico, con mayor preferencia mono- o bicíclico. El término "heterociclilalquilo" se refiere a un grupo alquilo sustituido con un heterociclilo, donde las porciones de alquilo y heterociclilo independientemente están opcionalmente sustituidas. Además, un anillo heterocíclico además incluye grupos en los cuales el anillo heterocíclico está fusionado a uno o más anillos arilo.

[0044] Tal como se utiliza en la presente, el término "parcialmente insaturado" se refiere a un resto del anillo que incluye al menos un enlace doble o triple entre los átomos del anillo. El término "parcialmente insaturado" intenta abarcar anillos que tienen múltiples sitios de insaturación, pero no intenta incluir restos aromáticos (por ej., arilo o heteroarilo), como se define en la presente.

[0045] El término "alquileno" se refiere a un grupo alquilo bivalente. Una "cadena alquileno" es un grupo polimetileno, es decir, $-(CH_2)_n-$, donde n es un entero positivo, con preferencia de 1 a 6, de 1 a 4, de 1 a 3, de 1 a 2, o de 2 a 3. Una cadena alquileno opcionalmente sustituida es un grupo polimetileno en el cual uno o más átomos de metileno hidrógeno está opcionalmente reemplazado con un sustituyente. Los sustituyentes adecuados incluyen los que se describen a continuación para un grupo alifático sustituido y además incluyen los que se describen en la memoria descriptiva en la presente. Se apreciará que dos sustituyentes del grupo alquileno pueden tomarse juntos para formar un sistema anular. En ciertas realizaciones, dos sustituyentes pueden ser tomados juntos para formar un anillo de 3

a 7 miembros. Los sustituyentes pueden estar en los mismos o diferentes átomos.

[0046] Una cadena alquileno además puede estar opcionalmente interrumpida mediante un grupo funcional. Una cadena alquileno es "interrumpida" por un grupo funcional cuando una unidad metileno interna es interrumpida por el grupo funcional. Ejemplos de "grupos funcionales de interrupción" adecuados se describen en la memoria descriptiva y en las reivindicaciones en la presente.

[0047] A los fines de claridad, todos los grupos bivalentes que se describen en la presente, que incluyen, por ej., los conectores de la cadena alquileno que se describieron anteriormente, se leen de izquierda a derecha, con una lectura de izquierda a derecha correspondiente de la fórmula o estructura en la cual aparece la variable.

[0048] Un grupo arilo (que incluye aralquilo, aralcoxi, ariloxialquilo y similares) o heteroarilo (que incluye heteroaralquilo y heteroarilalcoxi y similares) puede contener uno o más sustituyentes y de este modo puede estar "opcionalmente sustituido". Además de los sustituyentes que se definieron anteriormente y en la presente, los sustituyentes adecuados sobre el átomo de carbono insaturado de un grupo arilo o heteroarilo incluyen y se seleccionan en general de -halo, $-NO_2$, -CN, $-R^+$, $-C(R^+)=C(R^+)_2$, $-C\equiv C-R^+$, $-OR^+$, -SR°, -S(O)R°, $-SO_2R°$, $-SO_3R^+$, $-SO_2N(R^+)_2$, $-N(R^+)_2$, $-NR^+C(O)R^+$, $-NR^+C(S)R^+$, $-NR^+C(O)N(R^+)_2$, $-NR^+C(S)N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-R°$, $-NR^+CO_2R^+$, $-NR^+SO_2R°$, $-NR^+SO_2N(R^+)_2$, $-O-C(O)R^+$, $-O-CO_2R^+$, $-OC(O)N(R^+)_2$, $-C(O)R^+$, -C(S)R°, $-CO_2R^+$, $-C(O)-C(O)R^+$, $-C(O)N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(O)N(R^+)-OR^+$, $-C(O)N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)-C(O)R^+$, $-C(=NR^+)-N(R^+)_2$, $-C(=NR^+)-OR^+$, $-N(R^+)-N(R^+)_2$, $-C(=NR^+)-N(R^+)-OR^+$, $-C(R°)=N-OR^+$, $-P(O)(R^+)_2$, $-P(O)(OR^+)_2$, $-O-P(O)-OR^+$, y $-P(O)(NR^+)-N(R^+)_2$, donde R^+, independientemente, es hidrógeno o un grupo alifático, arilo, heteroarilo, cicloalifático, o

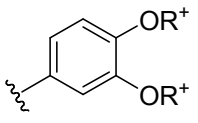
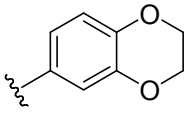
heterociclilo opcionalmente sustituido, o dos apariciones independientes de R^+ se toman juntas con sus átomos intervinientes para formar un anillo arilo de 5 a 7 miembros, heteroarilo, cicloalifático o heterociclilo. Cada R° es un grupo alifático, arilo, heteroarilo, cicloalifático o heterociclilo opcionalmente sustituido.

[0049] Un grupo alifático o heteroalifático, o un anillo carbicíclico o heterocíclico no aromático puede contener uno o más sustituyentes y de este modo puede estar "opcionalmente sustituido". A menos que se define de otro modo anteriormente y en la presente, los sustituyentes en el carbono saturado de un grupo alifático o heteroalifático, o de un anillo carbocíclico o heterocíclico no aromático se seleccionan de los que se mencionaron anteriormente para el carbono insaturado de un grupo arilo o heteroarilo y además incluyen lo siguiente: =O, =S, $=C(R^*)_2$, $=N-N(R^*)_2$, $=N-OR^*$, $=N-NHC(O)R^*$, $=N-NHCO_2R^\circ$ $=N-NHSO_2R^\circ$ o $=N-R^*$ donde R° se define anteriormente, y cada R^* se selecciona independientemente de hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido.

[0050] Además de los sustituyentes que se definieron anteriormente y en la presente, los sustituyentes opcionales en el nitrógeno de un anillo heterocíclico no aromático además incluyen y se seleccionan en general de $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-C(O)OR^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-S(O)_2R^+$, $-S(O)_2N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, o $-N(R^+)S(O)_2R^+$; donde cada R^+ se define anteriormente. Un átomo de nitrógeno del anillo de un anillo heteroarilo o heterocíclico no aromático además puede oxidarse para formar el compuesto N-hidroxi o N-óxido. Un ejemplo no limitante de este heteroarilo que tiene un átomo de nitrógeno del anillo oxidado es N-oxidopiridilo.

[0051] Como se detalló anteriormente, en algunas realizaciones, dos apariciones independientes de R^+ (o cualquier otra variable

definida de manera similar en la memoria descriptiva y en las reivindicaciones en la presente), se toman juntas con sus átomos intervinientes para formar un anillo monocíclico o bicíclico seleccionado de cicloalifático de 3 a 13 miembros, heterociclilo de 3 a 12 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

[0052] Ejemplos de anillos que se forman cuando dos apariciones independientes de R^+ (o cualquier otra variable definida de forma similar en la memoria descriptiva y en las reivindicaciones en la presente), se toman juntas con sus átomos intervinientes incluyen, pero sin limitación lo siguiente: a) dos apariciones independientes de R^+ (o cualquier otra variable que se define de manera similar en la memoria descriptiva o en la reivindicaciones en la presente) que se unen al mismo átomo y se toman juntas con ese átomo para formar un anillo, por ejemplo, $N(R^+)_2$, donde ambas apariciones de R^+ se toman juntas con el átomo de nitrógeno para formar un grupo piperidin-1-ilo, piperazin-1-ilo, o morfolin-4-ilo; y b) dos apariciones independientes de R^+ (o cualquier otra variable que se define de manera similar en la memoria descriptiva o en la reivindicaciones en la presente) que se unen a diferentes átomos y se toman juntas con ambos de esos átomos para formar un anillo, por ejemplo donde un grupo fenilo está sustituido con dos apariciones de OR^+  , estas dos apariciones de R^+ se toman juntas con los átomos de oxígeno a los cuales están unidos para formar un anillo que contiene oxígeno de 6 miembros fusionado:  . Se apreciará que una variedad de otros

anillos (por ej, anillos espiro y puenteados) se pueden formar cuando dos apariciones independientes de R^+ (o cualquier otra variable que se define de manera similar en la memoria descriptiva y en la reivindicaciones en la presente) se toman juntas con sus átomos intervinientes y que los ejemplos que se detallaron anteriormente no intentan ser limitantes.

[0053] Ejemplos de anillos que se forman cuando dos apariciones independientes de $R^{3'}$ o R^4 se toman juntas con sus átomos intervinientes incluyen, pero sin limitación los siguientes: indolizinilo, imidazopiridilo, indolilo, isoindolilo, indazolilo, bencimidazolilo, benztiazolilo, benzoxazolilo, 4H-furo[3,2-b]pirrolilo, pirazolopirimidinilo, purinilo, y pirrolizinilo.

[0054] Ejemplos de anillos que se forman cuando dos apariciones independientes de R^7, R^{7a}, o R^{7b} se toman juntas con sus átomos intervinientes incluyen, pero sin limitación los siguientes: ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidrotienilo, pirrolidinilo, pirrolidonilo, piperidinilo, pirrolinilo, oxazolidinilo, piperazinilo, dioxanilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, triazinilo, morfolinilo, y tiomorfolinilo.

[0055] Ejemplos de anillos que se forman cuando dos apariciones independientes de R^{7a} y R^2, o R^{7b} y R^2 se toman juntas con sus átomos intervinientes incluyen, pero sin limitación los siguientes: isoindolilo, indazolilo, benzotienilo, dihidrobenzotienilo, isobenzofuranilo, benzoisoxazolilo, dihidroisobenzofuranilo, pirazolopirimidinilo, pirazolopiridinilo, isoquinolilo, tetrahidroisoquinolinilo, ftalazinilo, isocromanilo, isotiocromanilo, isoindolinilo, y benzoisotiazolilo.

[0056] Ejemplos de anillos que se forman cuando dos apariciones independientes de X_4 y X_5, o X_6 y X_7; se toman juntas con sus átomos intervinientes incluyen, pero sin limitación los siguientes: pirazolopirimidinilo, purinilo, quinolilo, tetrahidroquinolinilo, quinazolinilo, naftiridinilo, piridopirimidinilo, pirazolopiridinilo, pirrolopiridinilo, pirrolopirimidinilo, imidazopiridinilo, 1H-pirrolo[2,3-b]piridinilo-2(3H)-ona, 3,4-dihidro-1,8-naftiridinil-2(1H)-ona, 1,8-naftiridinil-2(1H)-ona, 1H-piridil[2,3-d][1,3]oxazin-2(4H)-ona, 1H-imidazo[4,5-b]piridil-2(3H)-ona, oxazolo[4,5-b]piridil-2(3H)-ona, 1,2-dihidropiridil[2,3-b]pirazin-3(4H)-ona, 2H-piridil[3,2-b][1,4]oxazin-3(4H)-ona, 3,4-dihidropiridil[2,3-d]pirimidin-2(1H)-ona, imidazopiridinilo, y tetrahidroquinazolinilo.

[0057] Ejemplos de anillos que se forman cuando dos apariciones independientes de Y_1 y Q_1, Y_3 y Q_2, o Y_4 e Y_5 se toman juntas con sus átomos intervinientes incluyen, pero sin limitación los siguientes: indolilo, indazolilo, 4H-furo[3,2-b]pirrolilo, 4H-tieno[3,2-b]pirrolilo, 5H-furo[2,3-b]pirrolilo, 5H-tieno[2,3-b]pirrolilo, pirrolo[3,4-b]pirrolilo, pirrolo[3,2-b]pirrolilo, pirrolo[2,3-b]pirrolilo, dihidropirrolo[3,2-b]pirrolilo, dihidropirrolo[2,3-b]pirrolilo, 5H-pirrolo[3,2-d]oxazol, 5H-pirrolo[3,2-d]tiazol, pirrolopirimidinilo, pirrolopiridinilo, pirazolopirimidinilo y pirazolopiridinilo.

[0058] A menos que se establezca lo contrario, las estructuras que se describen en la presente incluyen todas las formas isoméricas (por ej., enantioméricas, diastereoméricas y geométricas (o conformacionales) de la estructura; por ejemplo las configuraciones R y S para cada centro asimétrico; isómeros de enlace doble (Z) y (E); e isómeros conformacionales (Z) y (E). Por lo tanto, los isómeros estereoquímicos simples como también las mezclas enantioméricas, diastereoméricas y geométricas (o conformacionales) de los presentes compuestos están dentro del

alcance de la invención. A menos que se establezca lo contrario, todas las formas tautoméricas de los compuestos de la invención están dentro del alcance de la invención. Además, a menos que se establezca lo contrario, las estructuras que se describen en la presente además incluyen los compuestos que difieren sólo en la presencia de uno o más átomos isotópicamente enriquecidos. Por ejemplo, los compuestos que tienen las presentes estructuras donde hay un reemplazo de hidrógeno por deuterio o tritio, o un reemplazo de un carbono por un carbono ^{13}C- o ^{14}C-enriquecido están dentro del alcance de esta invención. Estos compuestos son útiles, como ejemplo no limitante, en forma de herramientas o sondas analíticas en ensayos biológicos.

[0059] Se debe entender que, cuando un compuesto divulgado tiene al menos un centro quiral, la presente invención abarca un enantiómero del inhibidor libre del correspondiente isómero óptico, la mezcla racémica del inhibidor y las mezclas enriquecidas en un enantiómero relacionado con su correspondiente isómero óptico. Cuando una mezcla está enriquecida en un enantiómero con relación a sus isómeros ópticos, la mezcla contiene, por ejemplo, un exceso enantiomérico de al menos 50%, 75%, 90%, 95% 99% o 99,5%.

[0060] Los enantiómeros de la presente invención pueden resolverse mediante métodos conocidos por los expertos en la técnica, por ejemplo, mediante la formación de sales diastereoméricas que pueden separarse, por ejemplo, por cristalización; formación de derivados diastereoméricos o complejos que pueden separarse, por ejemplo, por cristalización, cromatografía gaseosa-líquida o líquida; reacción selectiva de un enantiómero con un reactivo específico del enantiómero, por ejemplo esterificación enzimática; o cromatografía gaseosa-líquida o líquida en un ambiente quiral; por ejemplo sobre un soporte quiral por ejemplo sílice con un ligando quiral unido o en

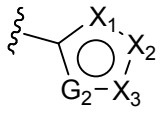
presencia de un solvente quiral. Cuando el enantiómero deseado se convierte en otra entidad química mediante uno de los procedimientos de separación que se describió anteriormente, se requiere otro paso para liberar la forma enantiomérica deseada. En forma alternative, los enantiómeros específicos pueden ser sintetizados por síntesis asimétrica utilizando reactivos ópticamente activos, sustratos, catalizadores o solventes, o convirtiendo un enantiómero en el otro por transformación asimétrica.

[0061] Cuando un compuesto divulgado tiene al menos dos centros quirales, la presente invencióin abarca un diastereómero libre de otros diastereómeros, un par de diastereómeros libres de otros pares diastereoméricos, mezclas de diastereómeros, mezclas de pares diastereoméricos, mezclas de diastereómeros en las cuales un diastereómero está enriquecido con relación a los otros diastereómeros y mezclas de pares diastereoméricos en los cuales un par diastereomérico está enriquecido con relación a los otros pares diastereoméricos. Cuando una mezcla está enriquecida en un diastereómero o par diastereomérico con relación a los otros diastereómeros o pares diastereoméricos, la mezcla está enriquecida con el diastereómero o par diastereoméricos descripto o referenciado con relación a otros diastereómeros o pares diastereoméricos para el compuesto, por ejemplo, por un exceso molar de al menos 50%, 75%, 90%, 95%, 99% o 99.5%.

[0062] Los pares diastereoméricos pueden separarse mediante métodos conocidos por los expertos en al técnica, por ejemplo cromatografía o cristalización y los enantiómeros individuales dentro de cada para pueden separarse como se describió anteriormente. Los procedimientos específicos para separar por cromatografía los pares diastereoméricos de los precursores que se utilizan en la preparación de los compuestos que se divulgan en la presente se proporcionan en los ejemplos en la presente.

[0063] *3. Descripción de ejemplos de compuestos:*

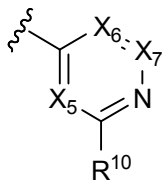
[0064] En ciertas realizaciones, parar los compuestos de la fórmula general **IA**, **IA-a**, **IB** o **IB-a**, CY es:



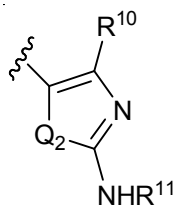
.

[0065] En ciertas realizaciones, para los compuestos de fórmula general **IA**, **IA-a**, **IB** o **IB-a**,, X_1 es N, G_2 es $-N(R^{3'})-$, y X_2 y X_3 son CH. En ciertas realizaciones, X_1 y X_2 son N, G_2 es $-N(R^{3'})-$, y X_3 es CH. En ciertas realizaciones, X_3 es N, G_2 es $-N(R^{3'})-$, y X_1 y X_2 son CH. En ciertas realizaciones, X_1 es N, X_2 es CH, X_3 es $-N(R^{3'})-$ y G_2 es =N-.

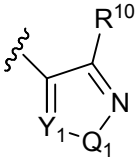
[0066] En ciertas realizaciones, parar los compuestos de la fórmula general **IA**, **IA-a**, **IB** o **IB-a**, HY se selecciona de:



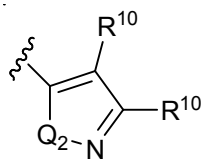
H,



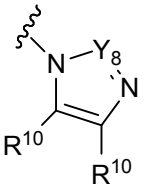
J,



K,



L, o



M;

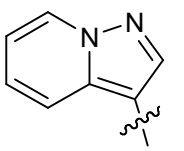
donde cada aparición de X_4, X_5, X_6, y X_7 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o $-NR^5$;

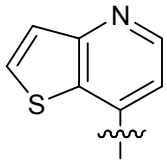
cada aparición de Y_1 e Y_7 es independientemente $-CR^{10}$ o N;

o donde dos apariciones adyacentes de X_6 y X_7, o Y_1 y Q_1, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre.

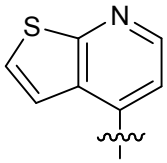
[0067] En ciertas realizaciones, parar los compuestos de la fórmula general **IA**, **IA-a**, **IB** o **IB-a**, HY se selecciona de:



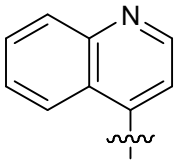
i



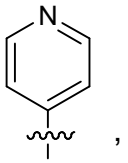
ii



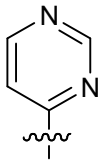
iii



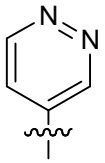
iv



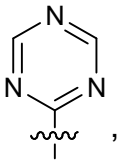
v



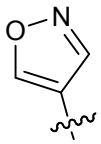
vi



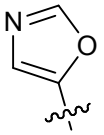
vii



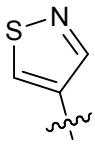
viii



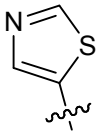
ix



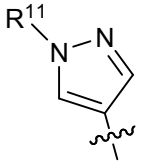
x



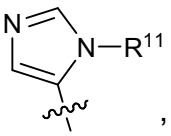
xi



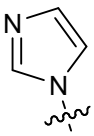
xii



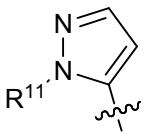
xiii



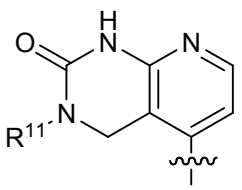
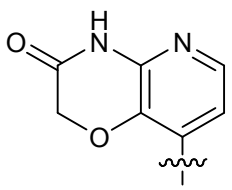
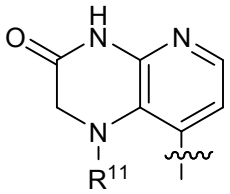
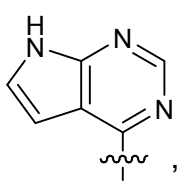
xiv



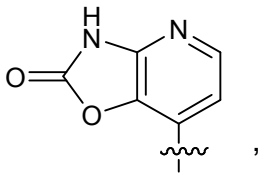
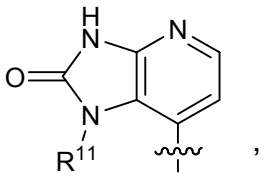
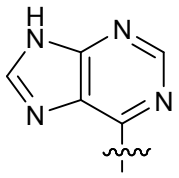
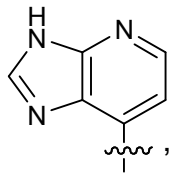
xv



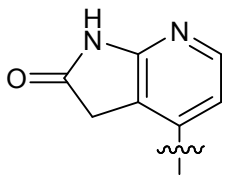
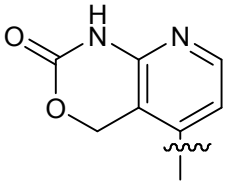
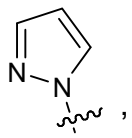
xvi


,

,

,

,

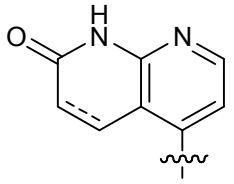
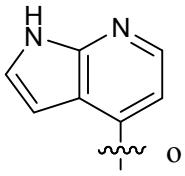
xvii **xviii** **xix** **xx**


,

,

,

,

xxi **xxii** **xxiii** **xxiv**


,

,

,

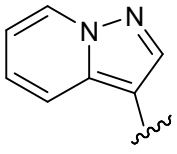
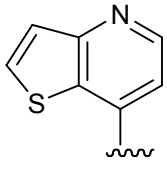
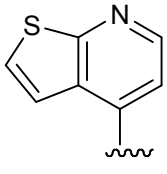
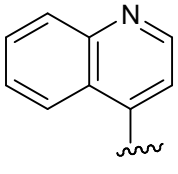
xxv **xxvi** **xxvii**


, or

o

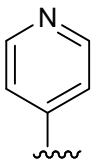
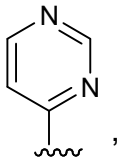
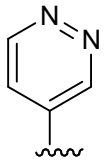
xxviii **xxix**

donde cada grupo HY está además opcionalmente sustituido con una o más apariciones de R^{10}, y ------ en **xviii** representa un enlace simple o un enlace doble.

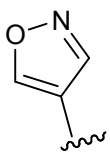
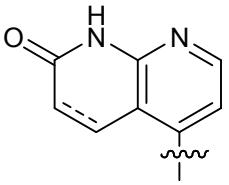
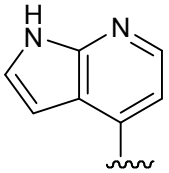
[0068] En ciertas realizaciones, parar los compuestos de la fórmula general **IA**, **IA-a**, **IB** o **IB-a**, HY se selecciona de:


,

,

,

,

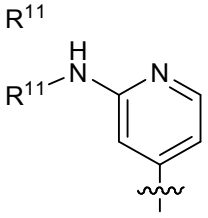
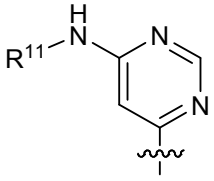
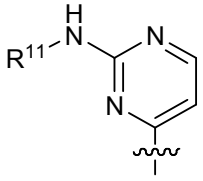
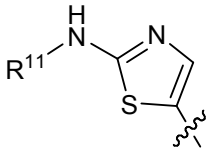
i **ii** **iii** **iv**


,

,

,

v **vi** **vii**


,

,

,

ix **xxviii** **xxix;**


,

,

,

;

xxx **xxxi** **xxxii** **xxxiii**

donde cada grupo HY está además opcionalmente sustituido con una o más apariciones de R^{10}, y ------ en **xviii** representa un enlace simple o un enlace doble.

[0069] Incluso en ciertas realizaciones, parar los compuestos de la fórmula general **IA, IA-a, o IB** o **IB-a,** G_1 es $C(R^8)$. En otras realizaciones, G_1 es CH.

[0070] Incluso en otras realizaciones, G_1 es N.

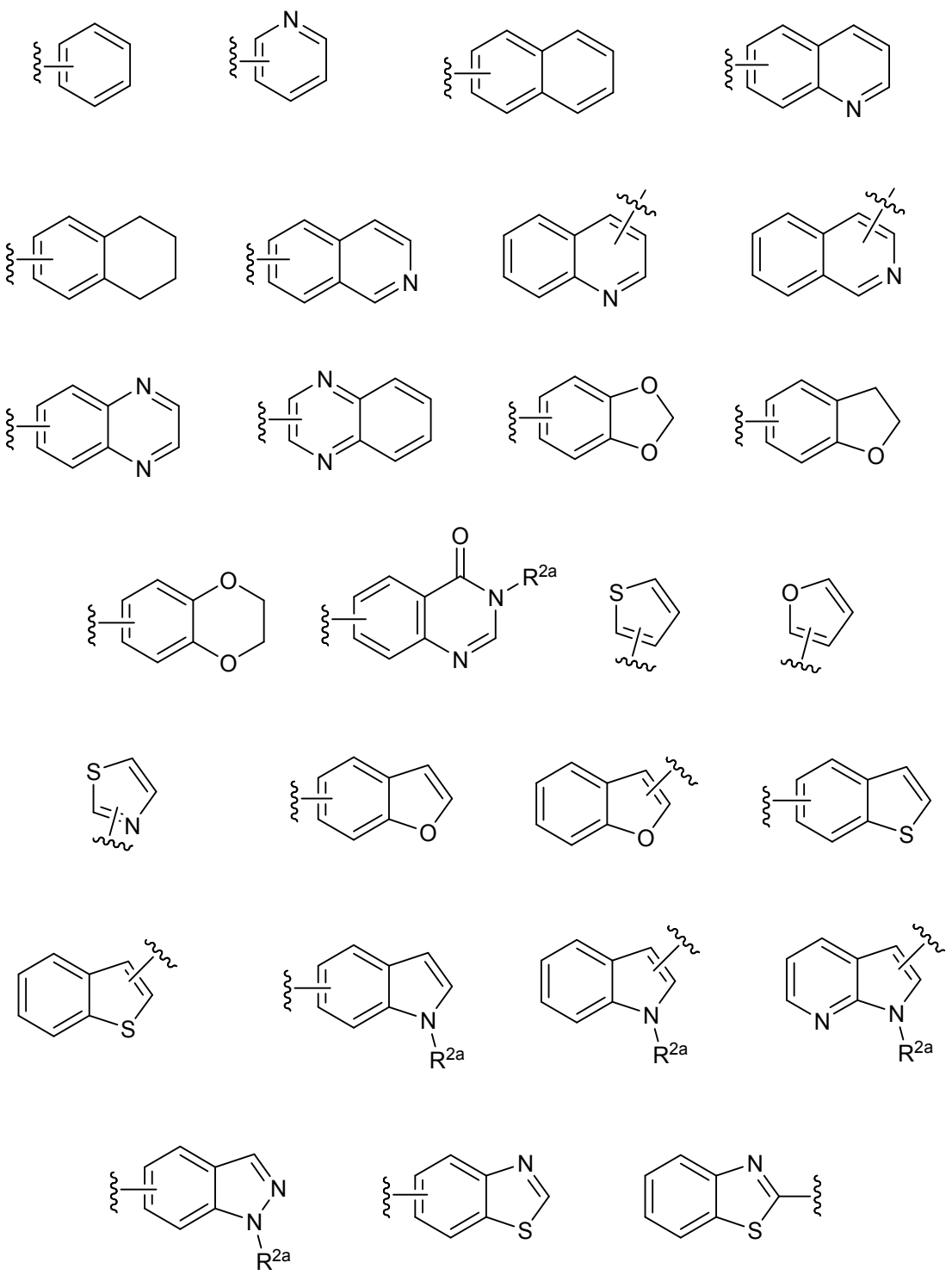
[0071] En ciertas realizaciones, para los compuestos de fórmula general **IA, IA-a, IB** o **IB-a,,** W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, alifático

C_{1-6} opcionalmente sustituido, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN; y donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 3 a 6 miembros opcionalmente sustituido.

[0072] En ciertas realizaciones, para los compuestos de fórmula general **IA**, **IA-a**, **IB** o **IB-a**,, W es $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, o $-N(R^{7a})C(O)-$, donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido; y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

[0073] En ciertas realizaciones, para los compuestos de fórmula general **IA**, **IA-a**, **IB** o **IB-a**,, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

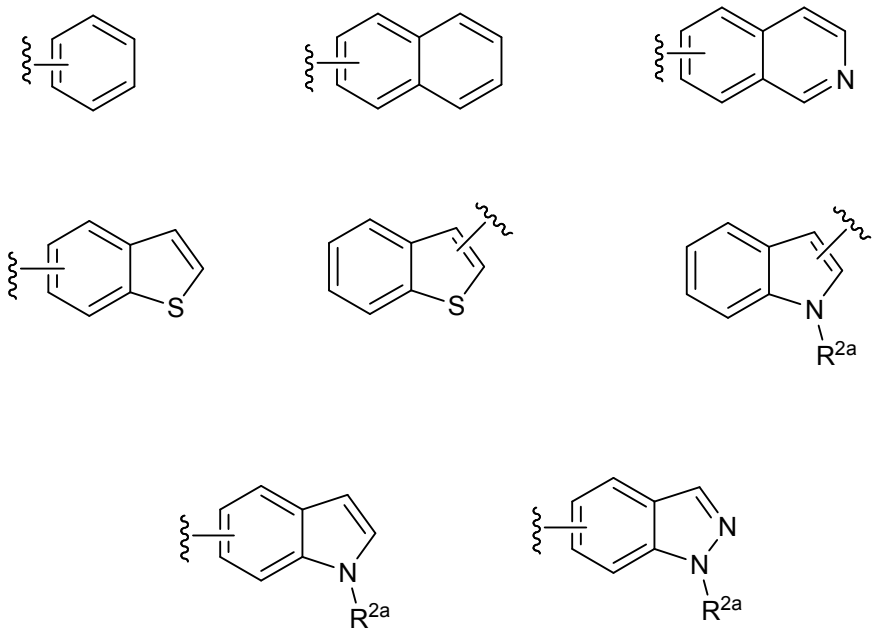
[0074] En otras realizaciones, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4 – 10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[0075] En determinadas otras realizaciones, para compuestos de la fórmula general **IA**, **IA-a**, **IB** o **IB-a**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

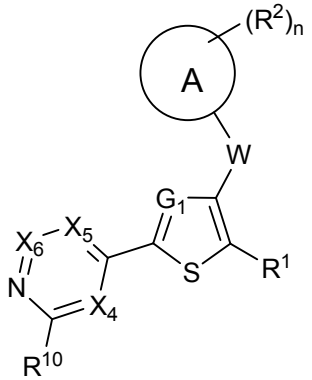
[0076] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O) alquilo C_{1-3}, -NHC(O) NH-alquilo C_{1-3}, $-NHS(O)_2$ alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[0077] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[0078] En ciertas realizaciones, para los compuestos de fórmula general **IA**, **IA-a**, **IB** o **IB-a**,, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3} , $-OC_{1-3}$ alquilo, $–OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H;

[0079] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[0080] Incluso en otras realizaciones, se provee un compuesto que tiene la estructura de fórmula II:



II

donde:

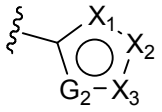
X_4, X_5 y X_6 son cada uno de ellos independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5 y X_6 sean N;

o dos grupos adyacentes seleccionados de R^{10}, X_4, X_5, y X_6, tomados juntos, forman un grupo opcionalmente sustituido seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,; arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

[0081] En algunas realizaciones, para los compuestos de fórmula **II**, uno de X^4, X^5, o X^6 es N.

[0082] Incluso en otras realizaciones, para los compuestos de fórmula **II**, todos de X^4, X^5, o X^6 son CR^{10}.

[0083] En otras realizaciones, para los compuestos de fórmula II, cada aparición de R^{10} se selecciona independientemente de –CN, $-OR^{10a}$, $-N(R^{11})_2$, alquilo C_{1-4}, $-N(R^{11})COR^{10a}$, o donde dos apariciones de R^{10} tomadas juntas con los átomos a los cuales están unidos forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 5 o 6 miembros fusionado, heterociclilo de 4 a 10 miembros, arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros, donde los anillos heterociclilo y heteroarilo tienen 1 a 3 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre.

[0084] En algunas otras realizaciones, para los compuestos de fórmula **II**, CY es 

.

[0085] En algunas otras realizaciones, para los compuestos de fórmula **II**, X_1 es N, G_2 es $-N(R^{3'})-$, y X_2 y X_3 son CH.

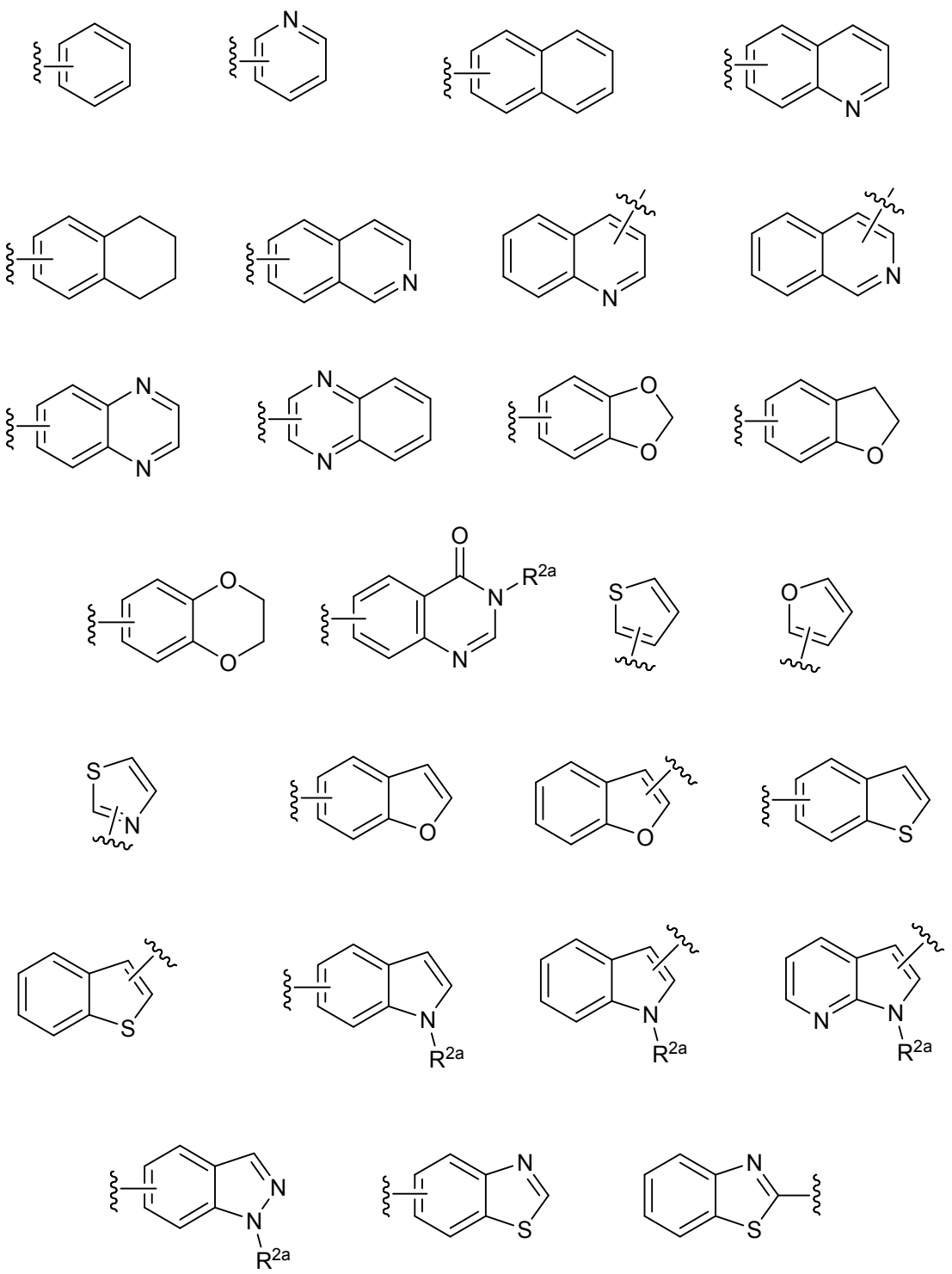
[0086] En algunas otras realizaciones, para los compuestos de fórmula **II**, X_1 y X_2 son N, G_2 es $-N(R^{3'})-$, y X_3 es CH.

[0087] En algunas otras realizaciones, para los compuestos de fórmula **II**, X_3 es N, G_2 es $-N(R^{3'})-$, y X_1 y X_2 son CH.

[0088] En algunas otras realizaciones, para los compuestos de fórmula **II**, X1 es N, X_2 es CH, X_3 es $-N(R^{3'})-$, y G_2 es =N-.

[0089] En algunas otras realizaciones, para los compuestos de fórmula **II**, el anillo A es arilo de 6 a 10 miembros opcionalmente sustituido o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

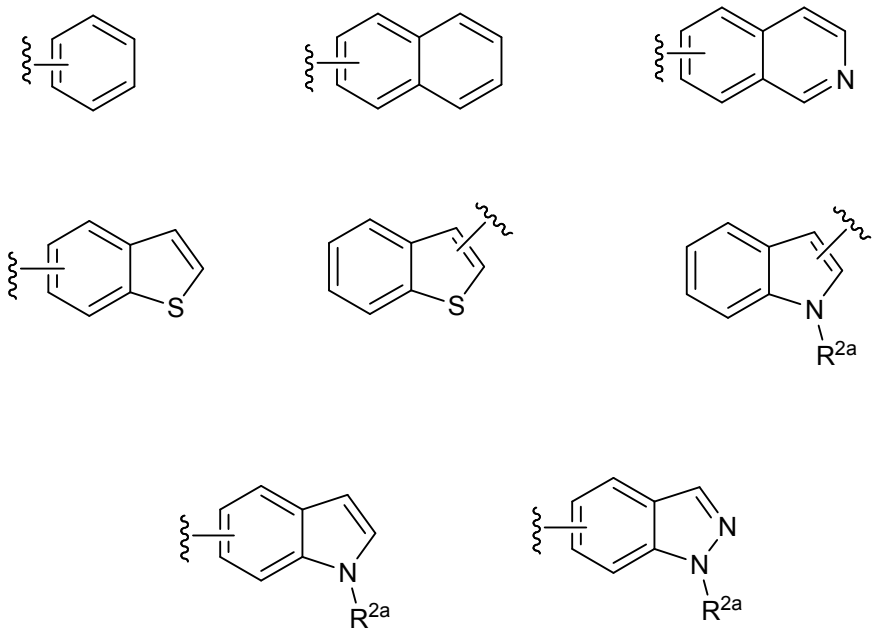
[0090] En otras realizaciones, para los compuestos de la fórmula **II**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[0091] En determinadas otras realizaciones, para compuestos de la fórmula general **II**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de un heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[0092] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$ alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[0093] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[0094] En algunas otras realizaciones, para los compuestos de fórmula general **II**, el anillo A es un grupo fenilo opcionalmente sustituido con 1 a 3 apariciones independientes de halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, -NHC(O)C_{1-3} alquilo, -$NHC(O)NHC_{1-3}$ alquilo, -$NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

[0095] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[0096] En algunas otras realizaciones, para los compuestos de fórmula II, W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 se selecciona de hidrógeno, alifático C_{1-4} opcionalmente sustituido, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN; y

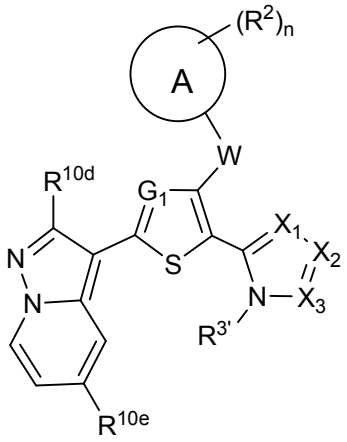
donde cada aparición de R^{7e} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de las apariciones de R^7, R^{7a}, o R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomados juntos con el átomo de nitrógeno al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

[0097] En algunas otras realizaciones, para los compuestos de fórmula II, W es $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, o $-N(R^{7a})C(O)-$, donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido; y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

[0098] Incluso en otras realizaciones, se provee un compuesto que tiene la estructura de fórmula III:



III

donde R^{10d} es hidrógeno, o alquilo C_{1-4} opcionalmente sustituido, y R^{10e} es R^{10}.

[0099] En algunas otras realizaciones, para los compuestos de fórmula III, R^{10e} es $-T_1-R^{10b}$, o hidrógeno.

[00100] Incluso en otras realizaciones, para los compuestos de formula III, R^{10e} es hidrógeno, $-CH_2N(R^{11})_2$, o $-CH_2N(R^{11})C(=NR^{11})N(R^{11})_2$, donde R^{11} es $--C(O)R^{11a}$, un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

[00101] En algunas otras realizaciones, para los compuestos de fórmula III, R^{11} es un grupo alifático C_{1-6} opcionalmente sustituido, el grupo alifático C_{1-6} además se define como $-(CH_2)_xR^{11b}$ o $-(CH_2)_xN(R^{11b})_2$, $-(CH_2)_xN(R^{11b})C(O)R^{11b}$, o $-(CH_2)_xN(R^{11b})C(O)OR^{11b}$, donde R^{11b} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10

miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, y x es 1 a 3.

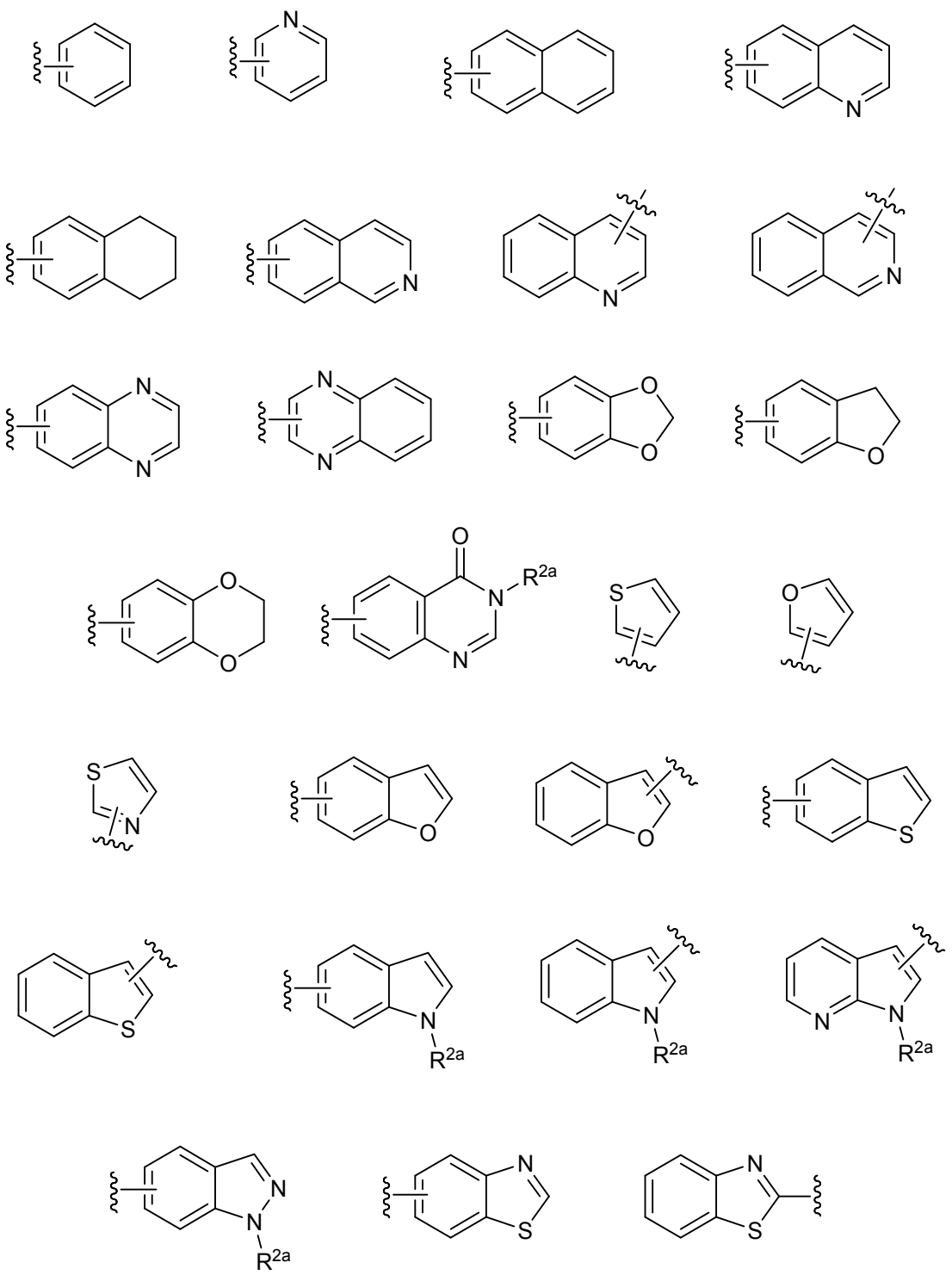
[00102] En algunas otras realizaciones, para los compuestos de fórmula III, X_1 es N, y X_2 y X_3 son CH.

[00103] En algunas otras realizaciones, para los compuestos de fórmula III, X_1 y X_2 son N, y X_3 es CH.

[00104] En algunas otras realizaciones, para los compuestos de fórmula III, X_3 es N, y X_1 y X_2 son CH.

[00105] En algunas otras realizaciones, para los compuestos de fórmula III, el anillo A es arilo de 6 a 10 miembros opcionalmente sustituido o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

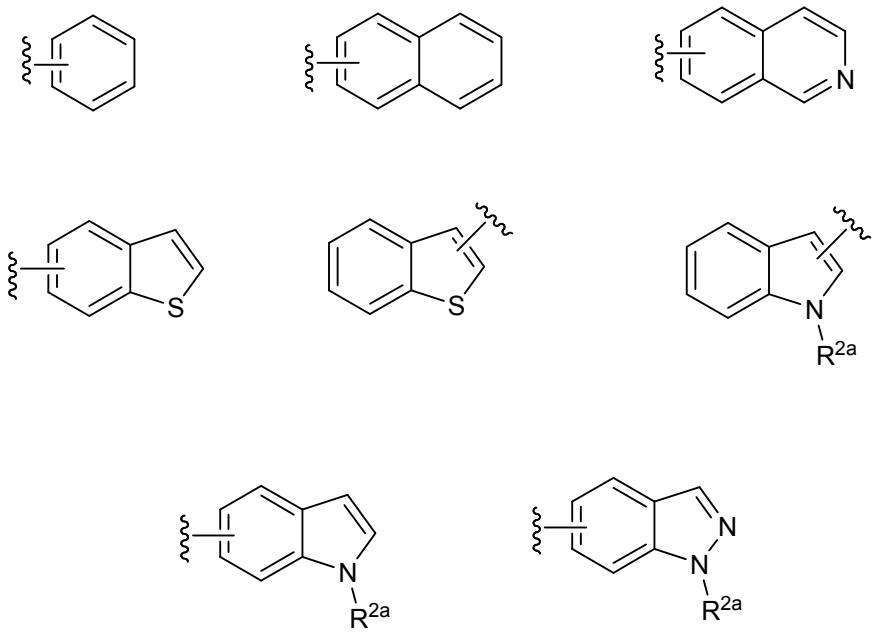
[00106] En otras realizaciones, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00107] En determinadas otras realizaciones, para compuestos de la fórmula general **III**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00108] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[00109] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00110] En algunas otras realizaciones, para los compuestos de fórmula general **III**, el anillo A es un grupo fenilo opcionalmente sustituido con 1 a 3 apariciones independientes de halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, -NHC(O)C_{1-3} alquilo, -$NHC(O)NHC_{1-3}$ alquilo, -$NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

[00111] En algunas otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00112] En algunas otras realizaciones, para los compuestos de fórmula III, W es -$C(R^7)_2$-, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 se selecciona de hidrógeno, alifático C_{1-4} opcionalmente sustituido, -$N(R^{7b})_2$, -OR^{7a}, -SR^{7a}, halo, o –CN; y

donde cada aparición de R^{7e} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido;

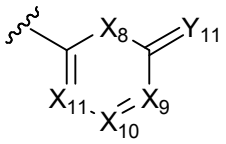
cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

[00113] En algunas otras realizaciones, para los compuestos de fórmula III, W es $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, o $-N(R^{7a})C(O)-$, donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido; y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

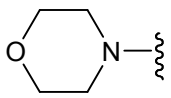
[00114] En ciertas realizaciones, parar los compuestos de la fórmula general **IA-a**, **IB-a**, **IA**, **IB**, **II o III**, CY es:



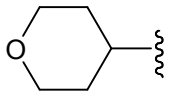
.

[00115] En ciertas realizaciones para los compuestos de fórmula general IA-a, IB-a,IA, IB, II o III, X_8 y X_{11} son N, X_9 y X_{10} son CR^4, y Y_{11} es O.

[00116] En ciertas realizaciones, parar los compuestos de la fórmula general **IA-a**, **IB-a**, **IA**, **IB**, **II o III**, HY se selecciona de:



; y



;

donde cada grupo HY está además opcionalmente sustituido con una o más apariciones de R^{14}.

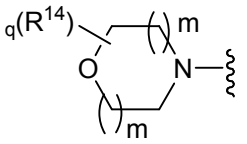
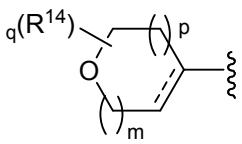
[00117] Incluso en otras realizaciones, para los compuestos de la fórmula general **IA-a**, **IB-a**, **IA**, **IB**, **II o III**, G_1 es N.

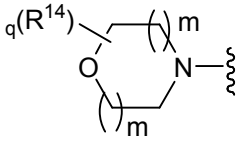
[00118] Incluso en otras realizaciones, para los compuestos de la fórmula general **IA-a**, **IB-a**, **IA**, **IB**, **II o III**, R^1 es -C(O)OH.

[00119] En ciertas otras realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, R^3 es H. En ciertas otras realizaciones, R^3 es alifático C_{1-6}. En ciertas realizaciones, R^3 es alquilo C_{1-4}. En ciertas realizaciones, R^3 es metilo o etilo.

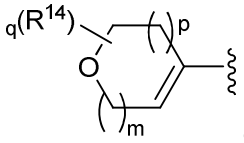
[00120] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**,**IB-i-a**, **IA-i** o **IB-i**, G_1 es N. En ciertas otras realizaciones, G1 es $C(R^8)$. En ciertas realizaciones, G_1 es $C(R^8)$ y R^8 es –CN, halógeno, o alifático C_{1-6}. En ciertas realizaciones, R^8 es alquilo C_{1-4}, alquenilo C_{2-4}, o alquinilo C_{2-4}. En ciertas realizaciones, R^8 es –CN o alquinilo C_{2-4}.

[00121] En ciertas realizaciones, parar los compuestos de la fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, HY se selecciona de:


o

.



[00122] En ciertas realizaciones, HY es donde cada aparición de m es 1 y q es 0 o 1. En ciertas realizaciones, q es 0.



[00123] En ciertas realizaciones, HY es donde m y p son 1 y q es 0 o 1. En ciertas realizaciones, q es 0.

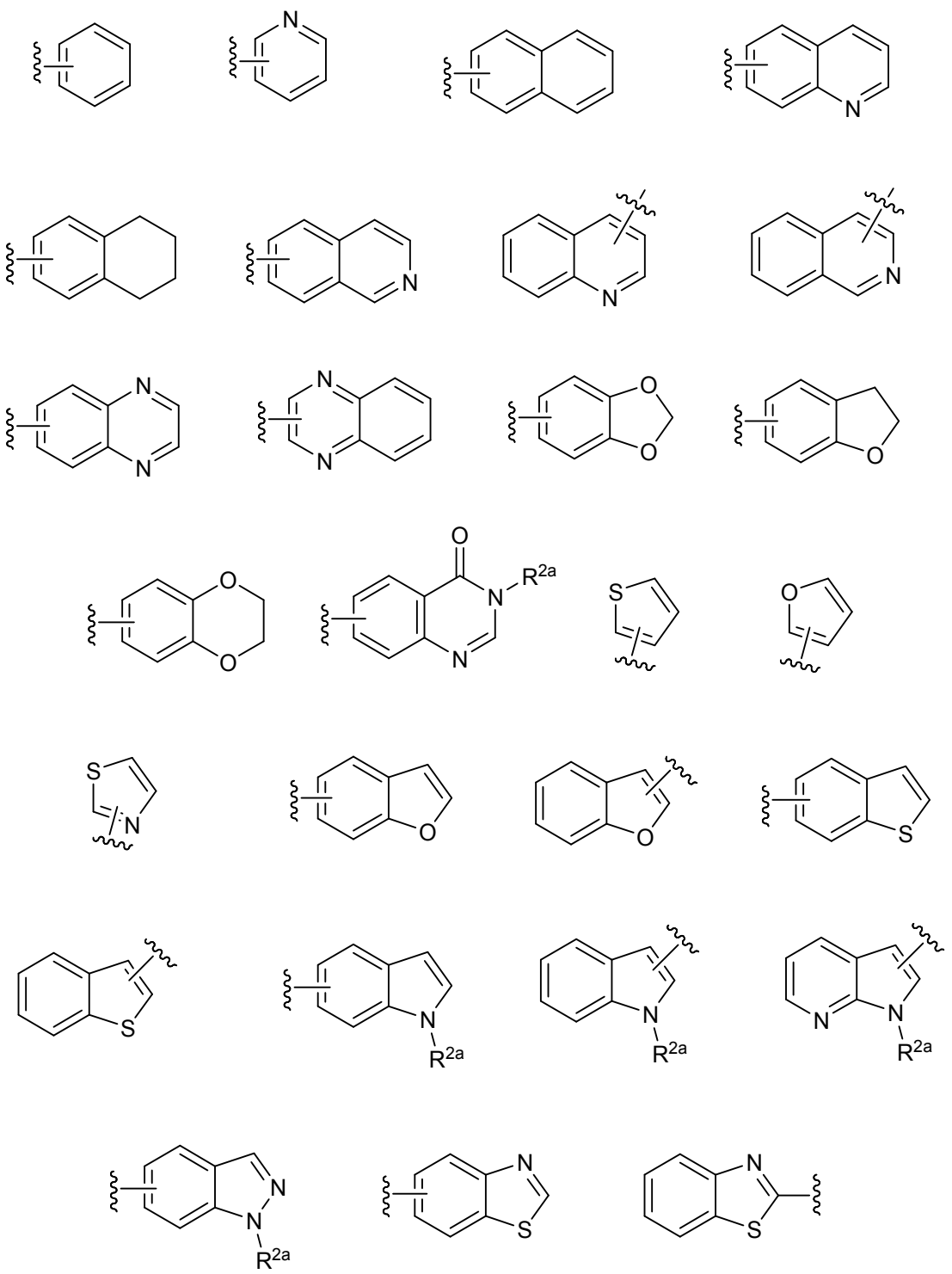
[00124] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i** o **IB-i**, W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-N(R^{7b})_2$, o F; y cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 3 a 6 miembros opcionalmente sustituido; y donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

[00125] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i** o **IB-i**, W es $-C(H)(N(R^{7b})_2)-$ o $-CH_2-$, donde cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

[00126] En ciertas realizaciones, para los compuestos de la fórmula general **IA-i-a**, **IB-i-a**, **IA-i** o **IB-i**, W es un enlace covalente.

[00127] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i** o **IB-i**, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

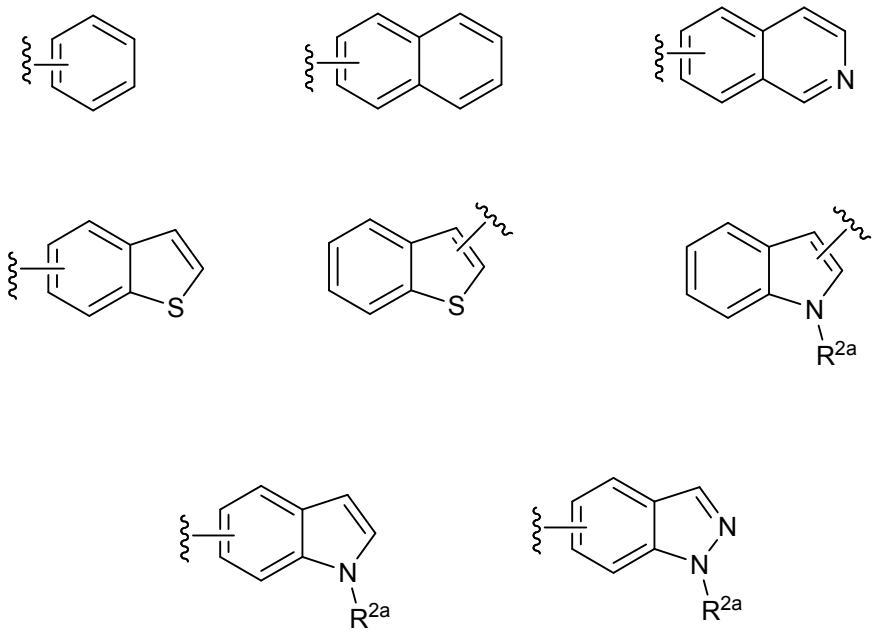
[00128] En otras realizaciones, para compuestos de la fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00129] En determinadas otras realizaciones, para compuestos de la fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, , , el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00130] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[00131] En aún otras realizaciones, el anillo A es un grupo fenilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[00132] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00133] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $–C(H)(N(R^{7b})_2)-$ o $-CH_2-$, donde cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido. En ciertas realizaciones, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $–CH_2-$.

[00134] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3} , $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

[00135] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, o $-T_2-R^{12d}$, T_2 es una cadena alquileno C_{1-6} opcionalmente sustituido, , R^{12d} es $-N(R^{7b})_2$, y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

[00136] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, o $-OC_{1-3}$ haloalquilo; y n es 0 a 3. En ciertas realizaciones, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN, $-OCH_3$, o $-OCF_3$; y n e 0 a 3.

[00137] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

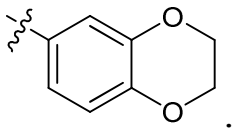
[00138] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno o $-(CH_2)N(R^{7b})_2$ y cada aparición de R^{7b} es

independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 2.

[00139] En ciertas realizaciones, el anillo A es un grupo fenilo, n es 1, y R^2 está en la posición para. En ciertas realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones para y meta. En ciertas otras realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones orto y meta, y para con respecto uno con otro.

[00140] En ciertas realizaciones, el anillo A es 2-cloro-5(dimetilaminometil)fenilo. En ciertas otras realizaciones, el anillo A es 2-cloro-5(pirrolidin-1-ilmetil)fenilo.

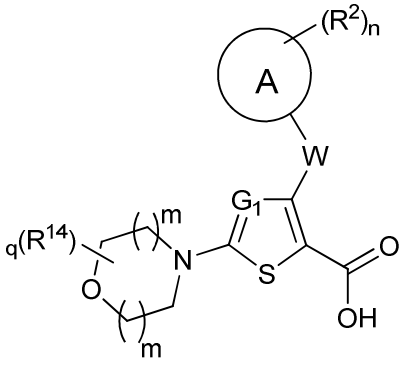
[00141] En ciertas realizaciones, para los compuestos de la fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es un grupo 2-naftilo. En ciertas otras realizaciones, el anillo A es



.

[00142] En ciertas realizaciones, para los compuestos de fórmula general **IA-i-a**, **IB-i-a**, **IA-i o IB-i**, el anillo A es un cicloalifático de 3 a 10 miembros o heterociclilo de 4 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre. En ciertas realizaciones, el anillo A es un anillo heterociclilo de 3, 4, 5, 6, o 7 miembros N-enlazados. En algunas realizaciones, el anillo A está sustituido con uno o más grupos alquilo C_{1-3}.

[00143] Incluso en otras realizaciones, se provee un compuesto que tiene la estructura de fórmula II-i:



II-i

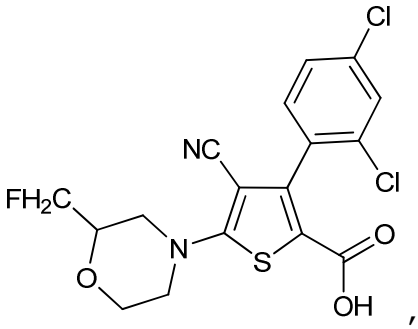
donde el anillo A, G_1, W, R^2, n, m, q, y R^{14} son como se definen para los compuestos que se describen en forma general más arriba en subconjuntos en la presente.

[00144] En ciertas realizaciones, para los compuestos de fórmula general II-i:

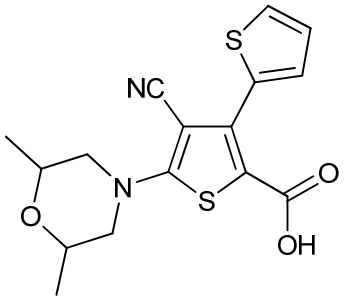
a) cuando G_1 es C-CN, HY es morfolina no sustituida, R^1 es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido, 2-clorofenilo, 4-clorofenilo, 2-fluorofenilo, 4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 4-metilfenilo, 3-metoxifenilo, 4-metoxifenilo, 3,4-dimetoxifenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, o 3-(acetilamino)fenilo;

b) cuando G_1 es N, HY es morfolina no sustituida, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido o 2-clorofenilo; y

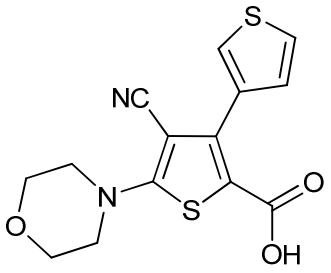
c) el compuesto es diferente de:



,



, o



.

[00145] En ciertas realizaciones, para los compuestos de fórmula general **II-i**,, W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-N(R^{7b})_2$, o F; y cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 3 a 6 miembros opcionalmente sustituido; y donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

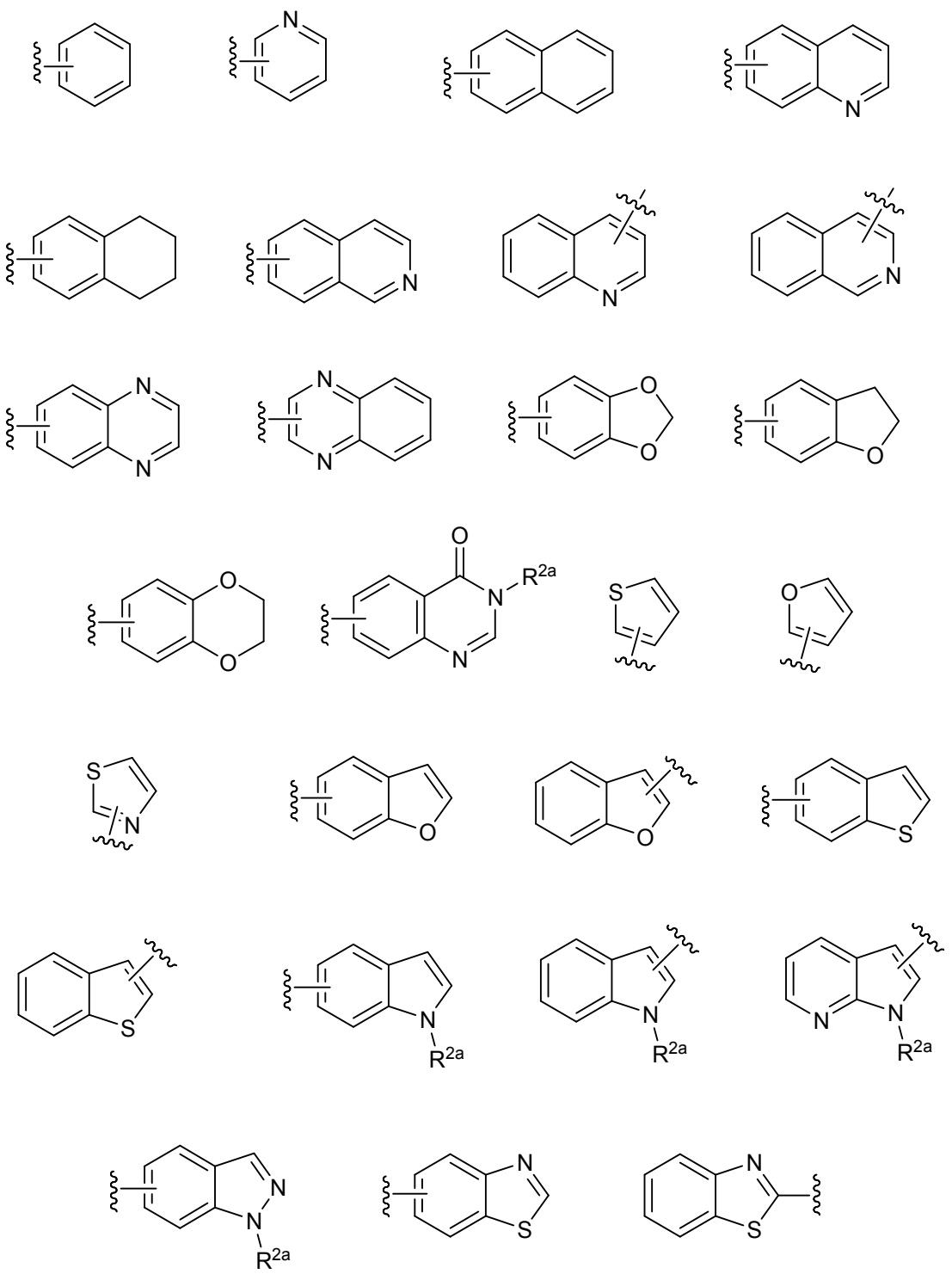
[00146] En ciertas realizaciones, para los compuestos de fórmula general **II-i**, W es $-C(H)(N(R^{7b})_2)-$ o $-CH_2-$, donde cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

[00147] En ciertas realizaciones, para los compuestos de la fórmula general **II-i**, W es un enlace covalente.

[00148] En ciertas realizaciones, para los compuestos de fórmula general **II-i**, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos

independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

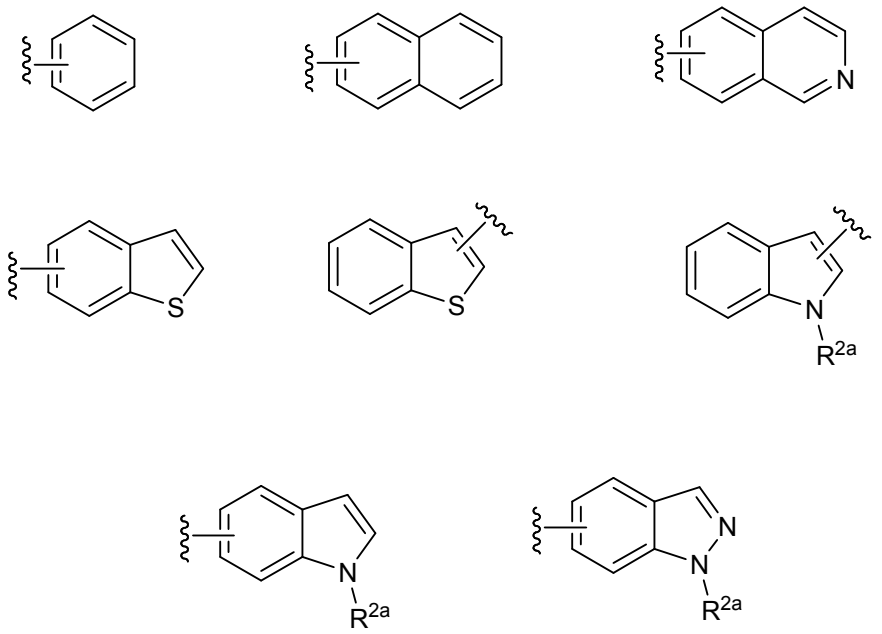
[00149] En otras realizaciones, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00150] En determinadas otras realizaciones, para compuestos de la fórmula general **II-i**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00151] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$ alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[00152] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00153] En ciertas realizaciones, para los compuestos de fórmula general **II-i**, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $–C(H)(N(R^{7b})_2)-$ o $-CH_2-$, donde cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido. En ciertas realizaciones, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $–CH_2-$.

[00154] En ciertas realizaciones, para los compuestos de fórmula general II-i, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $–OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H;

[00155] En ciertas realizaciones, para los compuestos de fórmula general II-i, el anillo A es un grupo fenilo; cada aparición de R^2

es independientemente halógeno, alquilo C_{1-3}, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, o $-T_2-R^{12d}$, T_2 es una cadena alquileno C_{1-6} opcionalmente sustituido, , R^{12d} es $-N(R^{7b})_2$, y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

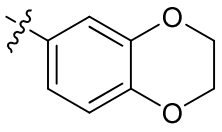
[00156] En ciertas realizaciones, para los compuestos de fórmula general **II-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, o $-OC_{1-3}$ haloalquilo; y n es 0 a 3. En ciertas realizaciones, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN, $-OCH_3$, o $-OCF_3$; y n e 0 a 3.

[00157] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00158] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno o $-(CH_2)N(R^{7b})_2$ y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 2.

[00159] En ciertas realizaciones, el anillo A es un grupo fenilo, n es 1, y R^2 está en la posición para. En ciertas realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones para y meta. En ciertas otras realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones orto y meta, y para con respecto uno con otro.

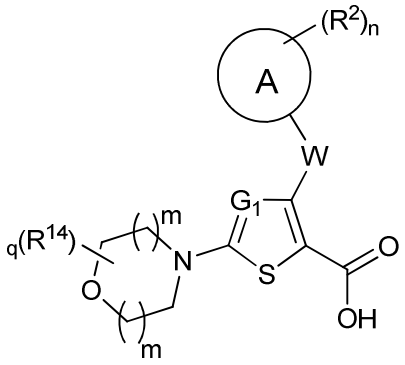
[00160] En ciertas realizaciones, el anillo A es 2-cloro-5(dimetilaminometil)fenilo. En ciertas otras realizaciones, el anillo A es 2-cloro-5(pirrolidin-1-ilmetil)fenilo.

[00161] En ciertas realizaciones, para los compuestos de la fórmula general **II-i**, el anillo A es un grupo 2-naftilo. En ciertas otras realizaciones, el anillo A es  .

[00162] En ciertas realizaciones, para los compuestos de fórmula general **II-i**, el anillo A es un cicloalifático de 3 a 10 miembros o heterociclilo de 4 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre. En ciertas realizaciones, el anillo A es un anillo heterociclilo de 3, 4, 5, 6, o 7 miembros N-enlazados. En algunas realizaciones, el anillo A está sustituido con uno o más grupos alquilo C_{1-3}.

[00163] En ciertas realizaciones, para los compuestos de fórmula general **II-i**, cada aparición de m es 1 y q es 0.

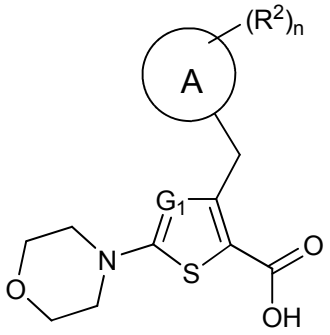
[00164] En otras realizaciones más, se provee un compuesto que presenta la estructura de la fórmula **II-i**:



II-i

[00165] donde G_1 es N o $-CR^8$, y R^8 es $-CN$; el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, $-O$-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, $-NHS(O)_2$alquilo C_{1-3} o $-C(O)H$; y n es 0 a 3; y W es $-C(R^7)_2-$ o >=O, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, C_{1-6} alifático opcionalmente sustituido, $-OR^{7a}$, $-N(R^{7b})_2$ o F; y donde cada aparición de R^{7b} es independientemente hidrógeno, C_{1-6} alifático opcionalmente sustituido, $-C(O)R^{7a}$ o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, consideradas junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3-6 miembros opcionalmente sustituido; y cada aparición de R^{7a} es independientemente hidrógeno o C_{1-6} alifático opcionalmente sustituido.

[00166] Incluso en otras realizaciones, se provee un compuesto que tiene la estructura de fórmula III-i:

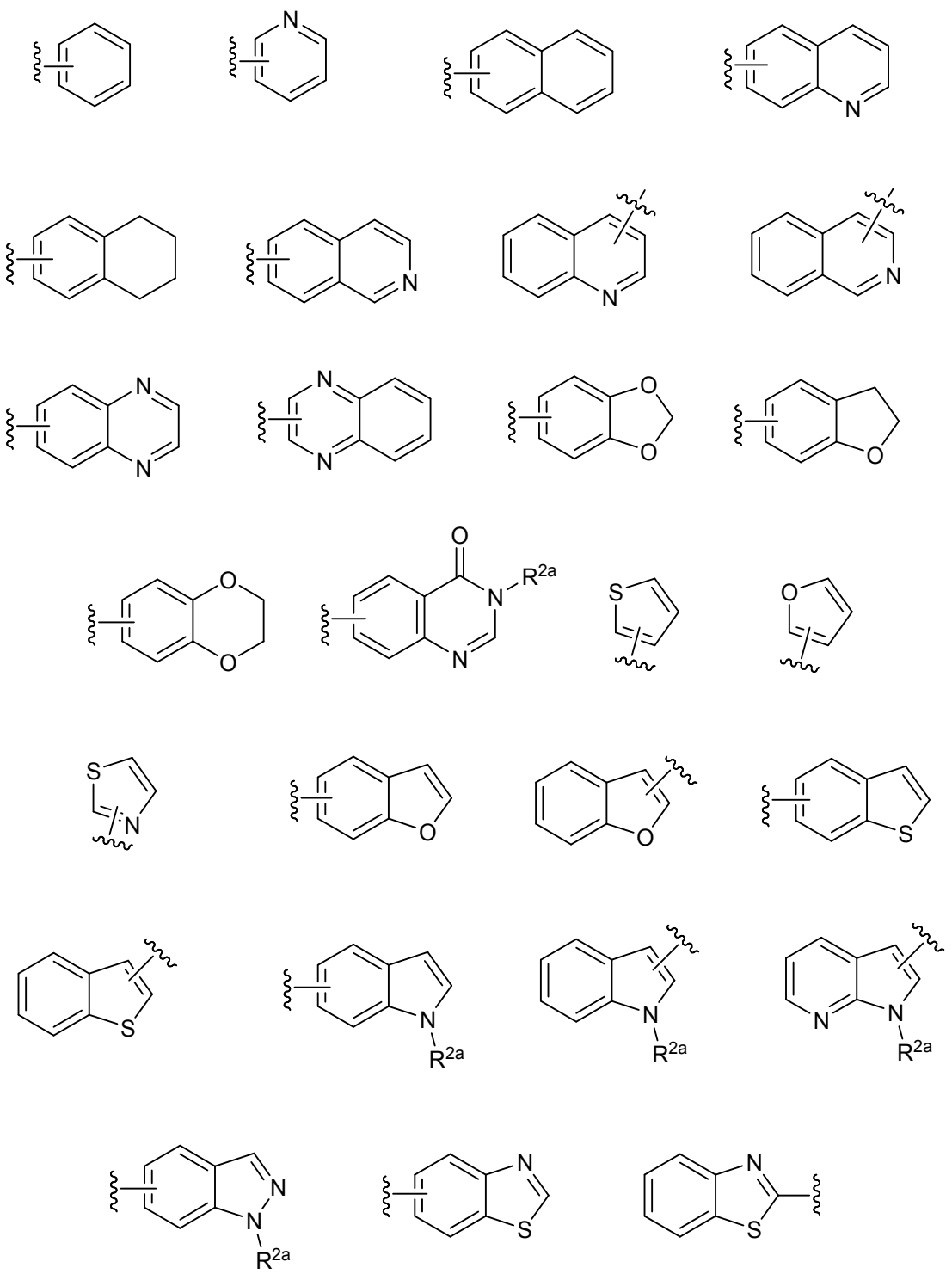


III

donde G_1 es N o $-CR^8$, y R^8 es $-CN$; y donde el anillo A, n y R^2 son como se definen para los compuestos que se describen en forma general en los subconjuntos en la presente.

[00167] En ciertas realizaciones, para los compuestos de fórmula general **III-i**, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

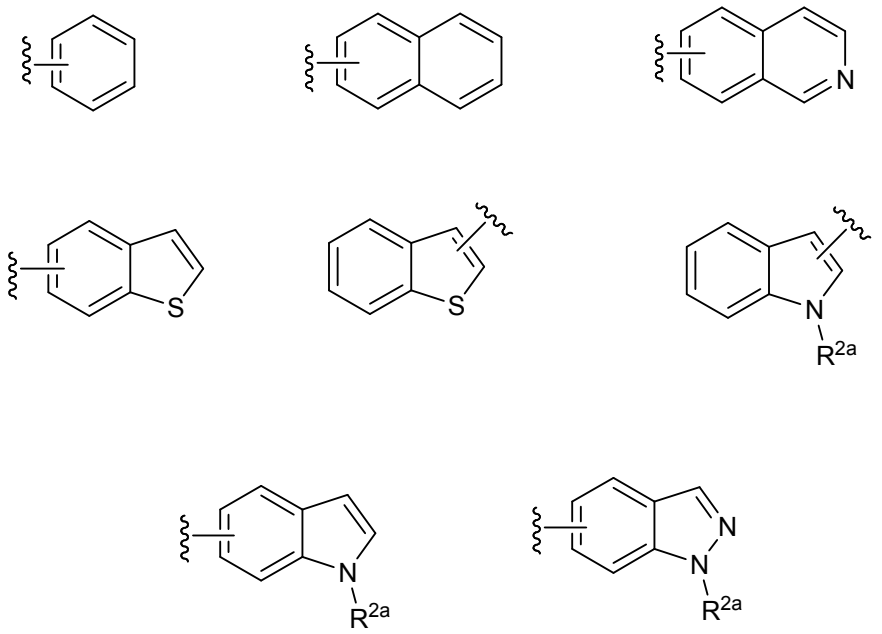
[00168] En otras realizaciones, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00169] En determinadas otras realizaciones, para compuestos de la fórmula general **III-i**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00170] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[00171] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00172] En ciertas realizaciones, para los compuestos de fórmula general **III-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo $C_{1-3,}$ -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $–OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H;

[00173] En ciertas realizaciones, para los compuestos de fórmula general III-i, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $–OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, o $-T_2-R^{12d}$, T_2 es una cadena alquileno C_{1-6} opcionalmente sustituido, , R^{12d} es $-N(R^{7b})_2$, y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno,

oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

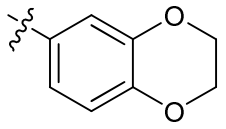
[00174] En ciertas realizaciones, para los compuestos de fórmula general **III-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, o $-OC_{1-3}$ haloalquilo; y n es 0 a 3. En ciertas realizaciones, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN, $-OCH_3$, o $-OCF_3$; y n e 0 a 3.

[00175] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00176] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno o $-(CH_2)N(R^{7b})_2$ y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 2.

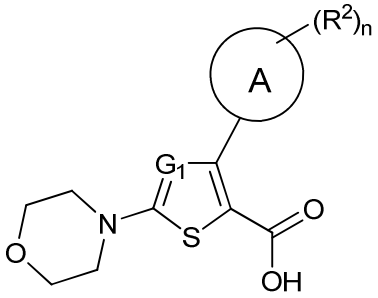
[00177] En ciertas realizaciones, el anillo A es un grupo fenilo, n es 1, y R^2 está en la posición para. En ciertas realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones para y meta. En ciertas otras realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones orto y meta, y para con respecto uno con otro.

[00178] En ciertas realizaciones, el anillo A es 2-cloro-5(dimetilaminometil)fenilo. En ciertas otras realizaciones, el anillo A es 2-cloro-5(pirrolidin-1-ilmetil)fenilo.

[00179] En ciertas realizaciones, para los compuestos de la fórmula general **III-i**, el anillo A es un grupo 2-naftilo. En ciertas otras realizaciones, el anillo A es  .

[00180] En ciertas realizaciones, para los compuestos de fórmula general **III-i**, el anillo A es un cicloalifático de 3 a 10 miembros o heterociclilo de 4 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre. En ciertas realizaciones, el anillo A es un anillo heterociclilo de 3, 4, 5, 6, o 7 miembros N-enlazados. En algunas realizaciones, el anillo A está sustituido con uno o más grupos alquilo C_{1-3}.

[00181] Incluso en otras realizaciones, se provee un compuesto que tiene la estructura de fórmula IV-i:



IV-i

donde el anillo A, G_1, n y R^2, son como se definen para los compuestos que se describen en forma general más arriba en subconjuntos en la presente.

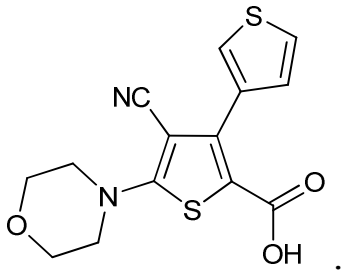
[00182] En ciertas realizaciones, para los compuestos de fórmula general IV-i:

a) cuando G_1 es C-CN, entonces el anillo A es diferente de fenilo no sustituido, 2-clorofenilo, 4-clorofenilo, 2-fluorofenilo, 4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 4-metilfenilo, 3-metoxifenilo, 4-metoxifenilo, 3,4-

dimetoxifenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, o 3-(acetilamino)fenilo;

b) cuando G_1 es N, entonces el anillo A es diferente de fenilo no sustituido o 2-clorofenilo; y

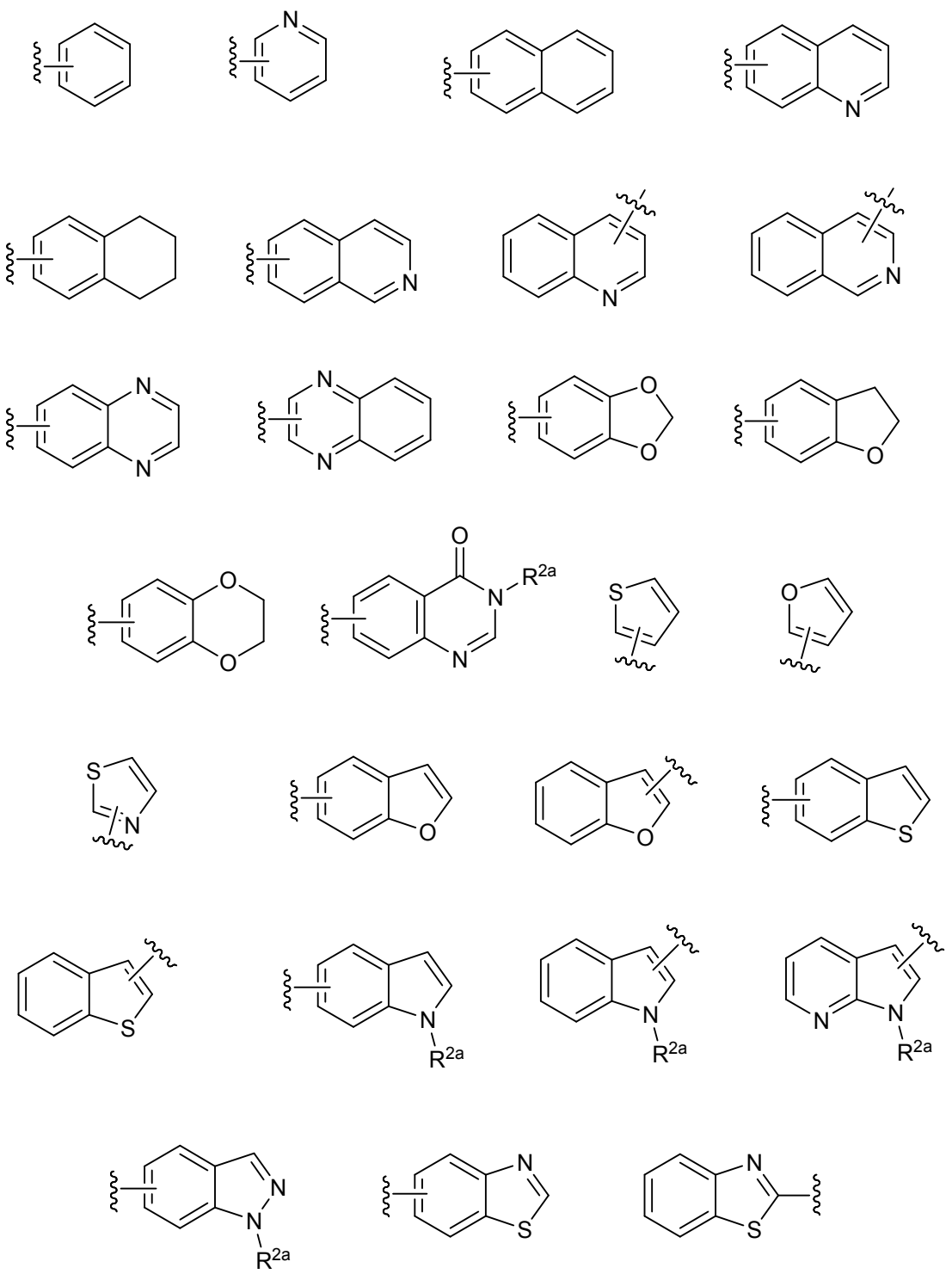
c) el compuesto es diferente de:



.

[00183] En ciertas realizaciones, para los compuestos de fórmula general **IV-i**, el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

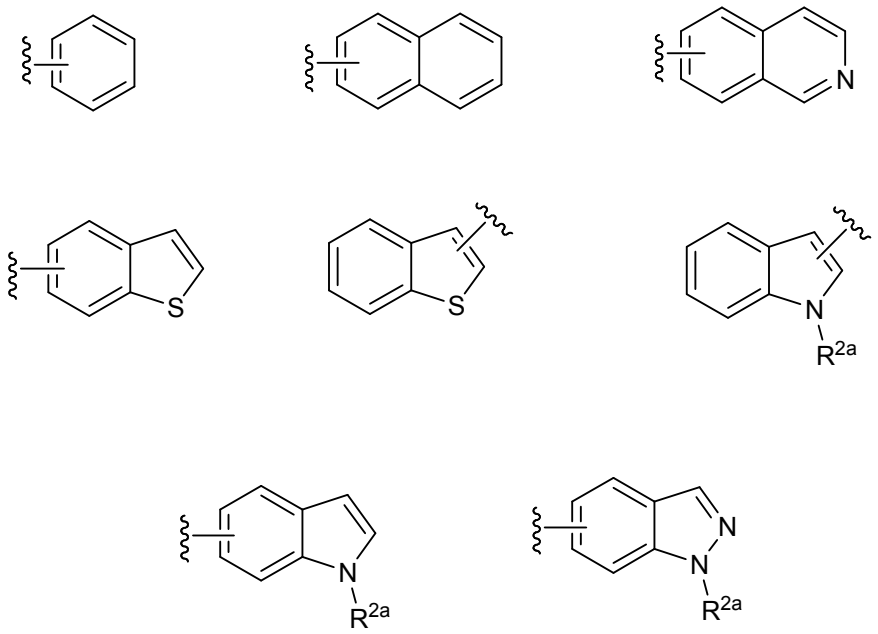
[00184] En otras realizaciones, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo

opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00185] En determinadas otras realizaciones, para compuestos de la fórmula general **VI-i**, el anillo A es un grupo seleccionado de:



donde el anillo A está opcionalmente sustituido además con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de heterociclilo C_{1-6} alifático de 4-10 miembros, cicloalifático de 3-10 miembros, que presenta 1-5 heteroátomos seleccionados

independientemente de nitrógeno, oxígeno o azufre, arilo de 6-10 miembros o heteroarilo de 5-10 miembros que presenta 1-5 heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre.

[00186] En otras realizaciones más, el anillo A es un grupo naftilo; cada aparición de R^2 independientemente es halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, -O-alquilo C_{1-3}, –O-haloalquilo C_{1-3}, -NHC(O)alquilo C_{1-3}, -NHC(O)NH-alquilo C_{1-3}, -$NHS(O)_2$alquilo C_{1-3} o –C(O)H; y n es 0 a 3.

[00187] En otras realizaciones más, el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2. En aún otras realizaciones, el anillo A es un grupo naftilo y n es 0. En aún otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00188] En ciertas realizaciones, para los compuestos de fórmula general **IV-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $–OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H;

[00189] En ciertas realizaciones, para los compuestos de fórmula general IV-i, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $–OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, o $-T_2-R^{12d}$, T_2 es una cadena alquileno C_{1-6} opcionalmente sustituido, , R^{12d} es $–N(R^{7b})_2$, y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos

independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

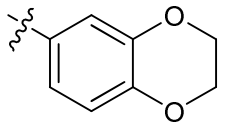
[00190] En ciertas realizaciones, para los compuestos de fórmula general **IV-i**, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, o $-OC_{1-3}$ haloalquilo; y n es 0 a 3. En ciertas realizaciones, el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN, $-OCH_3$, o $-OCF_3$; y n e 0 a 3.

[00191] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

[00192] Incluso en otras realizaciones, el anillo A es un grupo fenilo, R^2 es halógeno o $-(CH_2)N(R^{7b})_2$ y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, o cualquiera de dos apariciones de R^{7b} tomados juntos con el átomo al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 2.

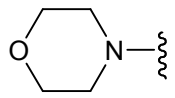
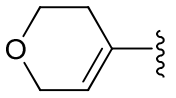
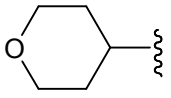
[00193] En ciertas realizaciones, el anillo A es un grupo fenilo, n es 1, y R^2 está en la posición para. En ciertas realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones para y meta. En ciertas otras realizaciones, el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones orto y meta, y para con respecto uno con otro.

[00194] En ciertas realizaciones, el anillo A es 2-cloro-5(dimetilaminometil)fenilo. En ciertas otras realizaciones, el anillo A es 2-cloro-5(pirrolidin-1-ilmetil)fenilo.

[00195] En ciertas realizaciones, para los compuestos de la fórmula general **IV-i**, el anillo A es un grupo 2-naftilo. En ciertas otras realizaciones, el anillo A es  .

[00196] En ciertas realizaciones, para los compuestos de fórmula general **IV-i**, el anillo A es un cicloalifático de 3 a 10 miembros o heterociclilo de 4 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre. En ciertas realizaciones, el anillo A es un anillo heterociclilo de 3, 4, 5, 6, o 7 miembros N-enlazados. En algunas realizaciones, el anillo A está sustituido con uno o más grupos alquilo C_{1-3}.

[00197] En ciertas realizaciones, parar los compuestos de la fórmula general **IA-i o IB-i**, HY se selecciona de:

 ,  y  ;

donde cada grupo HY está además opcionalmente sustituido con una o más apariciones de R^{14}.

[00198] Incluso en otras realizaciones, para los compuestos de la fórmula general **IA-i o IB-i**, G_1 es N.

[00199] *4. Usos, Formulación y Administración*

[00200] Como se describió antes, la presente invención proporciona compuestos que son útiles como inhibidores de las enzimas PI3K, y en consecuencia los presentes compuestos son útiles para tratar trastornos proliferativos inflamatorios, o cardiovasculares tales como tumor y/o crecimiento de células cancerosas mediado por P3K. En particular, los compuestos son

útiles para el tratamiento de los cánceres en un sujeto, que incluye, pero sin limitación, pulmón y bronquios, próstata, mamas, páncreas, colon y recto, tiroides e hígado y conductos biliares intrahepáticos, hepatocelular, gástrico, glioma/glioblastoma, endometrial, melanoma, riñón y pelvis renal, vejiga urinaria, cuerpo uterino, cuello uterino, ovario, mieloma múltiple, esófago, leucemia mielógena aguda, leucemia mielógena crónica, leucemia linfocítica, leucemia mieloide, cerebro, cavidad oral y faringe, intestino delgado, linfoma no Hodgkin y adenoma velloso de colon.

[00201] En algunas formas de realización, los compuestos de la invención son adecuados para el tratamiento de cáncer de mamas, cáncer de vejiga, cáncer de colon, glioma, glioblastoma, cáncer de pulmón, cáncer hepatocelular, cáncer gástrico, melanoma, cáncer de tiroides, cáncer de endometrio, cáncer renal, cáncer cervical, cáncer pancreático, cáncer esofágico, cáncer de próstata, cáncer cerebral o cáncer ovárico.

[00202] En otras formas de realización, los compuestos de la invención son adecuados para el tratamiento de trastornos inflamatorios y cardiovasculares que incluyen, pero sin limitación, alergias/anafilaxis, inflamación aguda y crónica, artritis reumatoide; trastornos de autoinmunidad, trombosis, hipertensión, hipertrofia cardiaca, e insuficiencia cardiaca.

[00203] Por consiguiente, en otro aspecto de la presente invención, se proporcionan composiciones, donde estas composiciones comprende cualquiera de los compuestos descriptos en la presente, y opcionalmente comprende n un portador, adyuvante o vehículo farmacéuticamente aceptable.

En ciertas formas de realización, estas composiciones opcionalmente también comprenden uno o más agentes terapéuticos adicionales.

[00204] También se apreciará que ciertos compuestos de la presente invención pueden existir en forma libre para el tratamiento, o cuando sea apropiado, como un derivado farmacéuticamente aceptable de este. De acuerdo con la presente invención, un derivado farmacéuticamente aceptable incluye, pero sin limitación, profármacos, sales, ésteres, sales de tales ésteres, o cualquier otro aducto o derivado que después de la administración a un paciente que lo necesita es capaz de proporcionar, en forma directa o indirecta, un compuesto descripto de otro modo en la presente, o un metabolito o residuo de este.

[00205] Como se usa en la presente, el término "sal farmacéuticamente aceptable" se refiere a las sales que son, dentro del alcance del buen criterio médico, adecuadas para el uso en contacto con los tejidos de seres humanos y animales inferiores sin toxicidad excesiva, irritación, respuesta alérgica, y similares, y acorde con una relación de riesgo/beneficio razonable. Una “sal farmacéuticamente aceptable” significa cualquier sal no tóxica o sal de un éster de un compuesto de esta invención que, después de la administración a un receptor, es capaz de proporcionar, en forma directa o indirecta, un compuesto de esta invención o un metabolito activo o residuo de este activo como inhibidor. Como se usa en la presente, el término "metabolito activo o residuo de este activo como inhibidor" significa que el metabolito o residuo de este también es un inhibidor de PI3K.

[00206] Las sales farmacéuticamente aceptables son bien conocidas en la técnica. Por ejemplo, S. M. Berge et al., describe sales farmacéuticamente aceptables en detalle en J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporadas en la presente por referencia. Las sales farmacéuticamente aceptables de los compuestos de esta invención incluyen las derivadas de ácidos y bases inorgánicas y orgánicas adecuadas. Los ejemplos de sales de adición de ácidos farmacéuticamente aceptables no tóxicas son sales de un grupo amino formado con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico y ácido perclórico o con ácidos orgánicos tales como ácido acético, ácido oxálico, ácido maleico, ácido tartárico, ácido cítrico, ácido succínico o ácido malónico o por el uso de otros métodos usados en el arte tales como intercambio iónico. Otras sales farmacéuticamente aceptable incluyen sales adipato, alginato, ascorbato, aspartato, bencensulfonato, benzoato, bisulfato, borato, butirato, canforato, canforsulfonato, citrato, ciclopentanopropionato, digluconato, dodecilsulfato, etansulfonato, formato, fumarato, glucoheptonato, glicerofosfato, gluconato, hemisulfato, heptanoato, hexanoato, yohidrato, 2-hidroxi-etansulfonato, lactobionato, lactato, laurato, laurilsulfato, malato, maleato, malonato, metansulfonato, 2-naftalensulfonato, nicotinato, nitrato, oleato, oxalato, palmitato, pamoato, pectinato, persulfato, 3-fenilpropionato, fosfato, picrato, pivalato, propionato, estearato, succinato, sulfato, tartrato, tiocianato, p-toluensulfonato,

undecanoato, valerato y similares. Las sales derivadas de bases apropiadas incluyen sales de metal alcalino, metal alcalinotérreo, amonio y N^+(alquilo C_{1-4})$_4$. Esta invención también prevé la cuaternización de cualquier grupo que contiene nitrógeno básico descripto en la presente. Se pueden obtener productos hidrosolubles o liposolubles o dispersables por dicha cuaternización. Las sales de metales alcalinos o alcalinotérreos representativas incluyen sodio, litio, potasio, calcio, magnesio y similares. . Otras sales farmacéuticamente aceptables incluyen, cuando es apropiado, amonio no tóxico, amonio cuaternario y cationes amina formados mediante contraiones tales como haluro, hidróxido, carboxilato, sulfato, fosfato, nitrato, sulfonato C_{1-8} y arilsulfonato.

[00207] Como se describió anteriormente, las composiciones farmacéuticamente aceptables de la presente invención comprenden adicionalmente un portador, adyuvante o vehículo farmacéuticamente aceptable, que, como se usa en la presente, incluya alguno y todos los solventes, diluyentes u otro vehículo líquido, auxiliares de dispersión o suspensión, agentes tensioactivos, agentes isotónicos, agentes espesantes o emulsionantes, conservantes, aglutinantes sólidos, lubricantes y similares, adecuados para la forma de dosis particular deseada. Remington's Pharmaceutical Sciences, 16° Edición, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) describe varios portadores usados en la formulación de composiciones farmacéuticamente aceptables técnicas conocidas para su preparación. Excepto en el grado en que cualquier medio portador convencional sea incompatible

con los compuestos de la invención, tal como por la producción de cualquier efecto biológico no deseado o interacción de otro modo en forma perjudicial con cualquier otro componente(s) de la composición farmacéuticamente aceptable, su uso están contemplado en el alcance de esta invención. Algunos de los ejemplos de materiales que pueden servir como portadores farmacéuticamente aceptable incluyen, pero sin limitación, intercambiadores de iones, alúmina, estearato de aluminio, lecitina, proteínas séricas, tales como albúmina sérica humana, sustancias tampón tales como fosfatos, glicina, ácido sórbico o sorbato de potasio, mezclas de glicéridos parciales de los ácidos grasos vegetales saturados, agua, sales o electrolitos, tales como sulfato de protamina, fosfato hidrógeno disódico, fosfato hidrógeno potásico, cloruro de sodio, sales de zinc, sílice coloidal, trisilicato de magnesio, polivinilpirrolidona, poliacrilatos, ceras, polímeros en bloque polietilen-polioxipropileno, grasa de lana, azúcares tales como lactosa, glucosa y sacarosa; almidones tales como almidón de maíz y almidón de papa; celulosa y sus derivados tales como carboximetilcelulosa sódica, etilcelulosa y acetato de celulosa, tragacanto en polvo; malta; gelatina; talco; excipientes tales como manteca de cacao y ceras de supositorio; aceites tales como aceite de maní, aceite de semillas de algodón, aceite de cártamo; aceite de sésamo; aceite de oliva; aceite de maíz y aceite de soja; glicoles tales como propilenglicol o polietilenglicol; ésteres tales como oleato de etilo y laurato de etilo; agar; agentes tampón

tales como hidróxido de magnesio e hidróxido de aluminio; ácido algínico; agua libre de pirógenos; solución salina isotónica; solución de Ringer; alcohol etílico y soluciones tampón de fosfato además de otros lubricantes no tóxicos compatibles tales como laurilsulfato de sodio y estearato de magnesio, además de agentes colorantes, agentes de liberación, agentes de recubrimiento, agentes edulcorantes, saborizantes y perfumantes, conservantes y antioxidantes también pueden estar presentes en la composición, de acuerdo con el criterio del formulador.

[00208] En aún otro aspecto, se proporciona un método para tratar un trastorno proliferativo, inflamatorio o cardiovascular que comprende administrar una cantidad efectiva de un compuesto, o una composición farmacéutica a un sujeto que lo necesita. En ciertas formas de realización de la presente invención una "cantidad efectiva" del compuesto o composición farmacéutica es que la cantidad efectiva para tratar un trastorno proliferativo, inflamatorio o cardiovascular, o es esta cantidad efectiva para tratar el cáncer. En otras formas de realización, una “cantidad efectiva” de un compuesto es una cantidad que inhibe la unión de PI3K y de este modo bloquea las cascadas de señalización resultantes que llevan a la actividad anormal de los factores de crecimiento, receptor de tirosina quinasas, proteína serina/treonina quinasas, receptores acoplados a la proteína G y fosfolípido quinasas y fosfatasas.

[00209] Los compuestos y composiciones, de acuerdo con el método de la presente invención, se

pueden administrar mediante cualquier cantidad y cualquier vía de administración efectiva para trata la enfermedad. La cantidad exacta necesaria para variará de sujeto a sujeto, de acuerdo con la especie, edad y condición general del sujeto, la gravedad de la infección, el agente particular, su modo de administración y similares. Los compuestos de la invención con preferencia se formulan en una forma unitaria de dosis para facilitar la administración y la uniformidad de la dosis. La expresión "forma de dosis unitaria" como se usa en la presente se refiere a una unidad físicamente diferenciada de agente apropiado para el paciente tratado. Se considerará, sin embargo, que el uso diario total de los compuestos y las composiciones de la presente invención será decidido por el médico asistente dentro del sólido criterio médico. El nivel de dosis efectivo específico para un paciente u organismo particular dependerá de una variedad de factores que incluye el trastorno tratado y la gravedad del trastorno; la actividad del compuesto específico empleado; la composición específica empleada; la edad, peso corporal, salud general, sexo y dieta del paciente; el tiempo de administración, vía de administración y tasa de excreción del compuesto específico empleado; la duración del tratamiento; fármacos usados en combinación o coincidentes con el compuesto específico empleado y factores similares bien conocidos en la técnica. El término “paciente”, como se usa en la presente, significa un animal, con preferencia un mamífero, y con máxima preferencia un ser humano.

[00210] Las composiciones farmacéuticamente aceptables de esta invención se pueden administrar a seres humanos y otros animales por vía oral, rectal, parenteral, intracisternal, intravaginal, intraperitoneal, tópica (como polvos, ungüentos o gotas), bucal, como un spray oral o nasal, o similares, de acuerdo con la gravedad de la infección tratada. En ciertas formas de realización, los compuestos de la invención se pueden administrar por vía oral o parenteral a niveles de dosis de aproximadamente 0,01 mg/kg a aproximadamente 50 mg/kg y con preferencia de aproximadamente 1 mg/kg a aproximadamente 25 mg/kg, del peso corporal del sujeto por día, una o más veces por día, para obtener el efecto terapéutico deseado.

[00211] Las formas de dosis líquidas para administración oral incluyen, peor sin limitación, emulsiones, microemulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Además de los compuestos activos, las formas de dosis líquidas pueden contener diluyentes inertes comúnmente usados en la técnica, tales como, por ejemplo, agua u otros solventes, agentes solubilizantes y emulsionantes tal como, alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida; aceites (en particular, aceites de semilla de algodón, maní, germen, oliva, ricino y sésamo), glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácido graso de sorbitanos, ciclodextrina y sus mezclas. Además de

diluyentes inertes, las composiciones orales también pueden incluir adyuvantes tales como agentes humectantes, agentes emulsionantes y de suspensión, agentes edulcorantes, saborizantes y perfumantes.

[00212] Las preparaciones inyectables, por ejemplo, suspensiones acuosas u oleaginosas inyectables estériles se pueden formular de acuerdo con la técnica conocida usando agentes de dispersión o humectantes y agentes de suspensión. La preparación inyectable estéril también puede ser una solución, suspensión o emulsión inyectable estéril en un diluyente o solvente aceptable para uso parenteral no tóxico, por ejemplo, como una solución de 1,3-butanodiol. Entre los vehículos y solventes adecuados que se pueden emplear están agua, solución de Ringer, U.S.P. y solución de cloruro de sodio isotónico. Además, se emplean en forma convencional aceites fijos estériles como un solvente o medio de suspensión, Para este propósito, se pueden emplear cualquier aceite fijo blando que incluye mono o diglicéridos sintéticos. Además, los ácidos grasos, tales como ácido oleico se usan en la preparación de inyectables.

[00213] Las formulaciones inyectables se pueden esterilizar, por ejemplo, por filtración a través de un filtro de retención bacteriana o por la incorporación de agentes esterilizantes en la forma de composiciones sólidas estériles que se pueden disolver o dispersar en agua estéril u otro medio inyectable estéril antes de usar.

[00214] Con el fin de prolongar el efecto de un compuesto de la presente invención, con frecuencia se desea lentificar la absorción del compuesto de la inyección subcutánea o intramuscular. Esto se puede lograr por el uso de una suspensión líquida de material cristalino o amorfo con escasa solubilidad en agua. La tasa de absorción del compuesto entonces depende de su tasa de disolución que, a su vez, puede depender del tamaño del cristal y forma cristalina. En forma alternativa, la disolución o suspensión del compuesto en un vehículo oleoso logra una absorción retardada de una forma de compuesto administrada por vía parenteral. Las formas en depósito inyectables se obtienen por la formación de matrices microencapsuladas del compuesto en polímeros biodegradables tales como poliláctido-poliglicólido. De acuerdo con la proporción del compuesto al polímero y la naturaleza del polímero particular empleado, se puede controlar la tasa de liberación del compuesto. Los ejemplos de otros polímeros biodegradables incluyen poli(ortoésteres) y poli(anhídridos). Las formulaciones inyectables en depósito también se preparan por la captura del compuesto en liposomas o microemulsiones que son compatibles con tejidos corporales.

[00215] Las composiciones para la administración rectal o vaginal con preferencia son supositorios que se pueden preparar por la mezcla de los compuestos de esta invención con excipientes o vehículos no irritantes adecuados tales como manteca de cacao, polietilenglicol o una cera de supositorio que son

sólidos a temperatura ambiente pero líquidos a la temperatura corporal y en consecuencia se funden en el recto o cavidad vaginal para liberar el compuesto activo.

[00216] Las formas de dosis sólidas para la administración oral incluyen cápsulas, comprimidos, pastillas, polvos y gránulos. En dichas formas de dosis sólidas, el compuesto activo se mezcla con al menos un excipiente o vehículo inerte farmacéuticamente aceptable tal como citrato de sodio o fosfato dicálcico y/o a) rellenos o expansores tales como almidones, lactosa, sacarosa, glucosa, manitol y ácido silícico, b) aglutinantes tales como, por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidinona, sacarosa y acacia, c) humectantes tales como glicerol, d) agentes desintegrantes tales como agar-agar, carbonato de calcio, almidón de papa o tapioca, ácido algínico, ciertos silicatos y carbonato de sodio e) agentes retardadores de la solución tales como parafina, f) aceleradores de la absorción tales como compuestos de amonio cuaternario, g) agentes humectantes tales como, por ejemplo, alcohol cetílico y monoestearato de glicerol, h) absorbentes tales como caolín y arcilla bentonita, y i) lubricantes tales como talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, laurilsulfato de sodio y sus mezclas. En el caso de las cápsulas, comprimidos y pastillas, la forma de dosis también puede comprender agentes tampón.

[00217] Las composiciones sólidas de tipo similar también se pueden emplear como rellenos de cápsulas de gelatina blandas y duras mediante excipientes

tales como lactosa o leche azucarada además de polietilenglicoles de alto peso molecular, y similares. Las formas de dosis orales sólidas de comprimidos, grageas, cápsulas, pastillas y gránulos se pueden preparar con cubiertas y cáscaras tales como cubiertas entéricas y otras cubiertas bien conocidas en el arte de la formulación farmacéutica. Opcionalmente estas pueden contener agentes opacificantes y también pueden ser de una composición de la que se libere el componente activo(s) solo, o con preferencia, en un determinada parte del tracto intestinal, opcionalmente, de una manera retardada. Los ejemplos de las composiciones incrustadas que se pueden usar incluyen sustancias poliméricas y ceras. También se pueden usar composiciones sólidas de tipo similar como rellenos de cápsulas de gelatina blandas y duras as de usando excipientes tales como lactosa o leche azucarada además de polietilenglicoles de alto peso molecular y similares.

[00218] Los compuestos activos también pueden estar en forma microencapsulada con uno o más excipientes indicados anteriormente. Las formas de dosis orales sólidas de comprimidos, grageas, cápsulas, pastillas y gránulos se pueden preparar con cubiertas y cáscaras tales como cubiertas entéricas, de liberación controlada y otras cubiertas bien conocidas en el arte de la formulación farmacéutica. En dichas formas de dosis orales sólidas, el compuesto activo se puede mezclar con al menos un diluyente inerte tal como sacarosa, lactosa o almidón. Dichas formas de dosis orales también pueden comprender, como práctica normal, sustancias adicionales

diferentes de los diluyentes inertes, por ejemplo, lubricantes para la preparación de comprimidos y otros auxiliares de la preparación de comprimidos tales como estearato de magnesio y celulosa microcristalina. En el caso de cápsulas, comprimidos y pastillas, las formas de dosis también pueden comprender agentes tampón. Opcionalmente estos pueden contener agentes opacificantes y también pueden ser de una composición de la que se libere el componente activo(s) solo, o con preferencia, en un determinada parte del tracto intestinal, opcionalmente, de una manera retardada. Los ejemplos de las composiciones incrustadas que se pueden usar incluyen sustancias poliméricas y ceras.

[00219] Las formas de dosis para administración tópica o transdérmica de un compuesto de esta invención incluye ungüentos, pastas, cremas, lociones, geles, polvos, soluciones, spray, inhalantes o parches. El componente activo se mezcla en condiciones estériles con un portador farmacéuticamente aceptable y cualquiera de los conservantes o tampones necesarios. La formulación oftálmica, gotas óticas y gotas oculares también están contempladas dentro del alcance de esta invención. Adicionalmente, la presente invención contempla el uso de parches transdérmicos, que tienen la ventaja adicional de proporcionar la liberación controlada de un compuesto al cuerpo. Dichas formas de dosis se pueden preparar por la disolución o dispersión del compuesto en el medio apropiado. Los potenciadores de la absorción también se pueden usar para aumentar el flujo del compuesto a través de la piel. La tasa se puede

controlar tanto por la provisión de una membrana de control de la tasa o por dispersión del compuesto en una matriz polimérica o gel.

[00220] Si bien uno o más de los compuestos de la invención se pueden usar en una aplicación de monoterapia para tratar un síntoma, también se pueden usar en la terapia de combinación, en la que el uso de un compuesto o composición de la invención (agente terapéutico) se combina con el uso de uno o más agentes terapéuticos diferentes para tratar los mismo y/u otros tipos de trastornos, síntomas y enfermedades. La terapia de combinación incluye la administración de los agentes terapéuticos en forma concurrente o secuencial. En forma alternativa, los agentes terapéuticos se pueden combinar en una composición que se administra al paciente.

[00221] En una forma de realización, los compuestos de esta invención se usan en combinación con otros agentes terapéuticos, tales como otros inhibidores de PI3K. En algunas formas de realización, un compuesto de la invención se administra en conjunto con un agente terapéutico seleccionado del grupo que consiste en agentes citotóxicos, radioterapia, e inmunoterapia. Se considera que se pueden llevar a cabo otras combinaciones mientras que permanezcan dentro del alcance de la invención.

[00222] Otro aspecto de la invención se refiere a la inhibición de la actividad de PI3K, en una muestra biológica o un paciente, tal método comprende administrar al paciente, o poner en contacto dicha

muestra biológica con un compuesto de fórmula I o una composición que comprenda dicho compuesto. El término "muestra biológica" como se usa en la presente, generalmente incluye, materiales in vivo, in vitro, y ex vivo y también incluye, sin limitación, cultivos celulares o sus extractos; material de biopsia obtenida de un mamífero o sus extractos; y sangre, saliva, orina, heces, semen, lágrimas u otros fluidos corporales o sus extractos.

[00223] Aún otro aspecto de esta invención es proporcionar un kit que comprende recipientes separados en un envase individual, donde los compuestos, composiciones y/o sus sales farmacéuticos de la invención se usan en combinación con portadores farmacéuticamente aceptables para tratar trastornos, síntomas y enfermedades con la PI3K cumple una función.

PROCEDIMIENTOS EXPERIMENTALES

[00224] **I–A. PREPARACIÓN DE CIERTOS EJEMPLOS DE COMPUESTOS DE FÓRMULA GENERAL I–A y I–B:** Los compuestos 1 a 92 (Mostrados en la siguiente Tabla 1) se prepararon usando los métodos generales y ejemplos específicos que se describen directamente más adelante.

[00225] 1. Métodos de síntesis general e intermediarios:

[00226] Los compuestos de la presente invención se pueden preparar por métodos conocidos por los expertos en la técnica y/o por referencia a los

esquemas mostrados a continuación y los ejemplos de síntesis siguientes. Los ejemplos de vías de síntesis se exponen en los siguientes Esquemas 1–52, y en los Ejemplos.

[00227] En los métodos definidos más adelante X representa halógeno (Br, I o Cl), P es HY mismo o un sustituyente convertible a HY por la aplicación de un método conocido general, R^A representa el Anillo A, W^R es W–R^A mismo o un sustituyente convertible a W–R^A por la aplicación de un método conocido general, W^L es R^A mismo o una parte del ligador W conectado a R^A y Q es R^1 mismo o un sustituyente convertible a R^1 por la aplicación de un método conocido general.

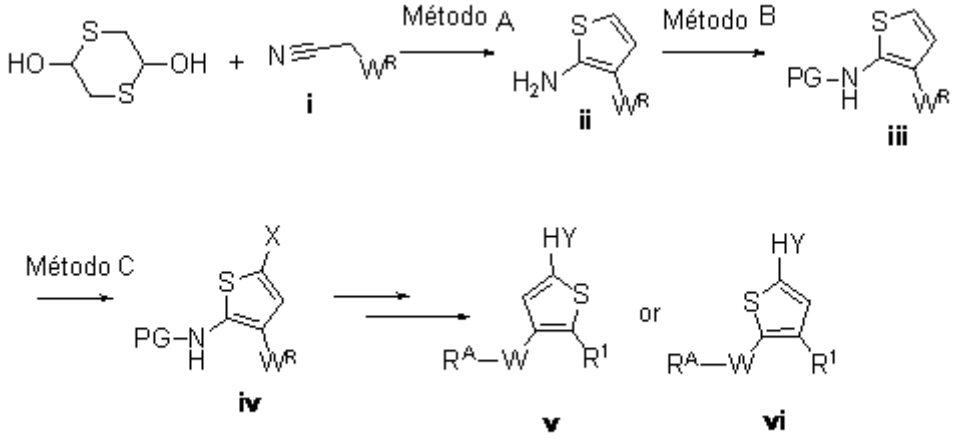
[00228] Los ejemplos del solvente para las reacciones mencionadas más adelante incluyen, pero sin limitación hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares, Laclos tales como metanol, etanol, isopropanol, ter–butanol, fenol y similares, éteres tales como éter dietílico, tetrahidrofurano, dioxano, DME y similares, acetona, acetonitrilo, acetato de etilo, N,N–dimetilformamida, N,N–dimetilacetamida, 1–metil–2–pirrolidona, dimetil sulfóxido, hexametilfosforamida, agua o un solvente mixto de esto y similares.

[00229] Los expertos en la técnica reconocerán que numerosas variaciones en las condiciones

de reacción que incluyen variaciones de solvente, reactivos, catalizadores, temperaturas y tiempos de reacción son posibles para cada una de las reacciones descriptas. La variación del orden de las etapas de síntesis y vías de síntesis alternativas son también posibles.

[00230] En muchos casos, la síntesis se puede comenzar a partir tiofeno/ análogos de tiazol disponible en el comercio para preparar compuestos blanco. En algunos casos, los análogos de tiofeno / tiazol especialmente funcionalizados se pueden preparar con los procedimientos descriptos en los Esquemas 1-4.

[00231] **Esquema 1: Método general para la síntesis de 2-aminotiofenos**

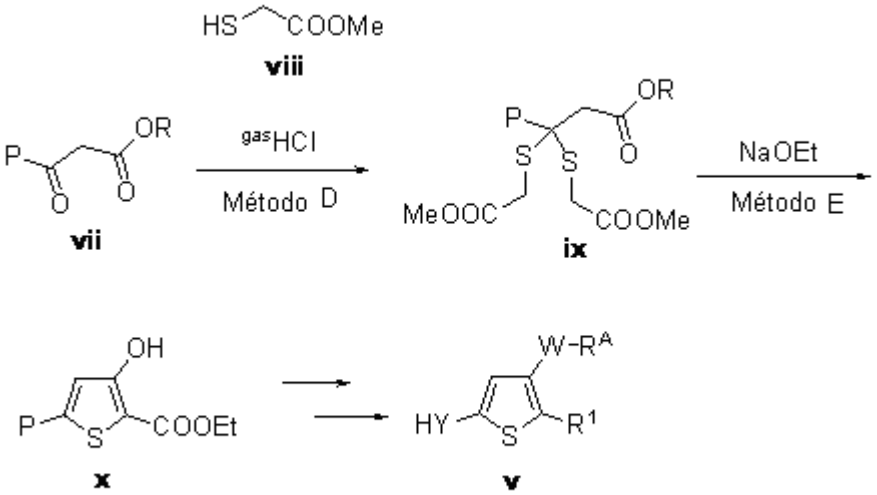


[00232] El Esquema 1 muestra un procedimiento para preparar compuestos de fórmula **v**. La condensación de nitrilos **i** con 2,5-dihidroxi-1,4-ditiano se puede obtener usando el procedimiento

informado (C. E. Stefens et al. Bioorg. Med. Chem., 2001, 9, 1123–1132, método A). Los aminotiofenos **ii** luego se pueden proteger con un grupo protector apropiado, por ejemplo, Boc usando condiciones estándares, tales como anhídrido Boc, DMAP, dioxano (método B). La halogenación de los tiofenos protegidos **iii** se pueden obtener usando un reactivo adecuado, por ejemplo NBS en DCM para proporcionar haluros de fórmula **iv** (método C), que se puede convertir en los compuestos de fórmula **v** por una combinación de reacciones de conversión del grupo funcional generalmente conocidas descriptas a continuación.

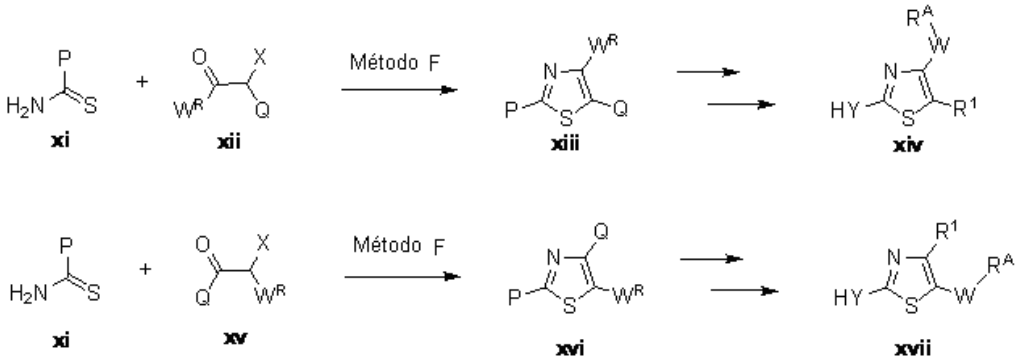
[00233] En forma alternativa, el tipo inverso de análogos de tiofeno **vi** también se pueden preparar usando las transformaciones del grupo funcional que se describe a continuación.

[00234] **Esquema 2: Método general para la síntesis de 4–hidroxil tiofenos**



[00235] Los 4-hidroxil tiofenos adecuadamente funcionalizadas se puede preparar de acuerdo con el procedimiento publicado tal como M. D. Mullican, et al., J. Med. Chem., 1991, 34, 2186—2194. Por ejemplo, el esquema 2 describe un procedimiento general para preparar 4-hidroxitiofenos de fórmula **x**. Los beta-cetoésteres **vii** se pueden tratar con tioles, tales como tioglicolato de metilo **viii** en presencia del ácido adecuado, tales como HCl en etanol (método D), para proporcionar ditio-cetal **ix**, que luego se pueden tratar con una base apropiada, como etóxido de sodio en un solvente adecuado, por ejemplo, etanol, para dar 4-hidroxitiofenos de fórmula **x** (método E). Estos 4-hidroxitiofenos se pueden convertir para dirigirse a compuestos **v** de acuerdo con los procedimientos que se describen a continuación.

[00236] **Esquema 3: Método general para la síntesis de tiazoles sustituidos**



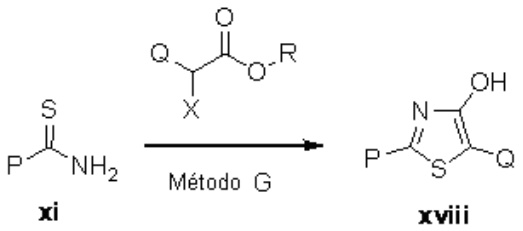
[00237] El Esquema 3 muestra una vía general para la síntesis de los compuestos de fórmula **xiii** y **xvi**. Las tioamidas **xi** o tioureas (Cuando P = NHR) se pueden

tratar con compuestos carbonilo alfa halogenados compuestos **xii** en un solvente adecuado, tales como isopropanol a temperatura elevada para dar tiazoles **xiii**. (método F).

Cuando P = NH_2, 2-aminotiazoles **xiii** que se obtienen se pueden someter a reacción de Sandmeyer para proporcionar 2-halotiazoles **xxxi** (P = X), que se pueden usar para transformaciones funcionales adicionales que se describen más adelante. Una reacción de conversión de **xiii** a los compuestos **xiv** se puede realizar, por ejemplo, por una combinación de reacciones de conversión del grupo funcional generalmente conocido que se muestra a continuación

Si un compuesto carbonilo alfa halogenado se selecciona de modo adecuado, es decir, **xv**, análogos de tiazol tipo inverso **xvi** y **xvii** también se pueden preparar usando reacciones de transformación del grupo funcional orgánico bien conocidos que se describen a continuación.

[00238] Esquema 4: Método general para la preparación de 4-hidroxitiazoles



xi **xviii**

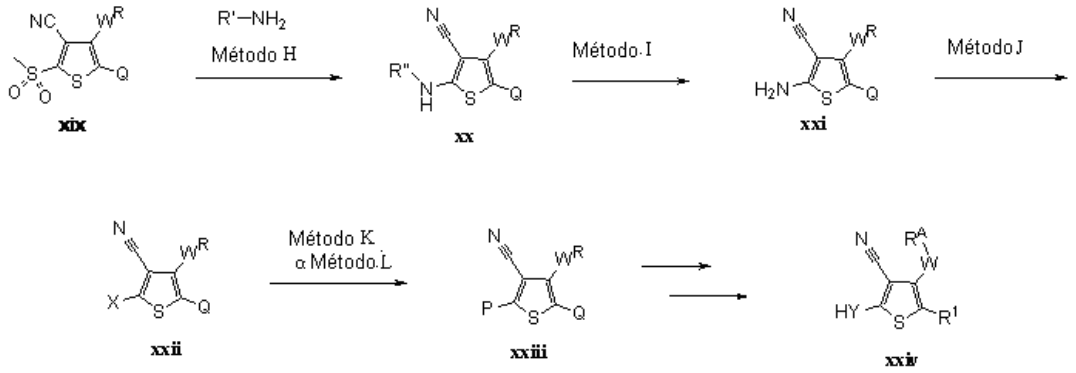
Como se muestra en el esquema 4, las tioamidas **xi** se pueden condensar con ésteres alfa halogenados de una manera similar a la informada por Rzasa, R.M. et al, Bioorg. Med. Chem.

2007, *15*, 6574 para obtener derivados de 4-hidroxitiazol **xviii**. La reacción se puede llevar a cabo en un solvente adecuado, tales como etanol, en presencia de una base apropiada, *es decir*, piridina, a temperatura elevada (método G).

[00239] Los Esquemas 5-19 describen procedimientos para las transformaciones del grupo funcional básico en las estructuras del núcleo central tiofeno / tiazol.

[00240] En los esquemas 5-8, se describen los procedimientos para las transformaciones del grupo funcional general para la introducción del grupo HY.

[00241] **Esquema 5: Introducción de HY al 3-cianotiofenos**



[00242] El Esquema 5 describe el procedimiento para la introducción de HY a análogos de 3-cianotiofeno por una reacción de transformación del grupo funcional.

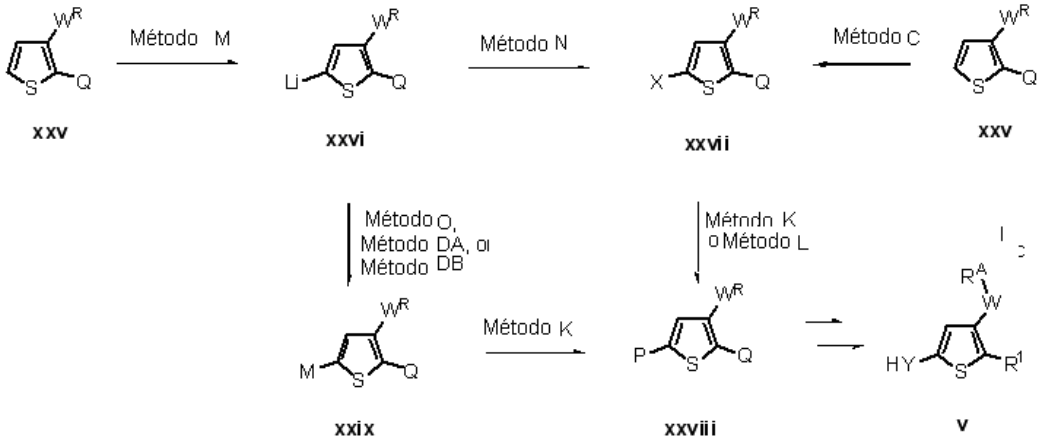
Como se muestra en el esquema 5, las sulfonas de fórmula **xix** (los ejemplos de síntesis se dan en Mansanet et al, WO 2005070916) se puede tratar con aminas R'–NH_2, tales como 2,4–dimetoxibencilamina, en un solvente adecuado, *por ejemplo*, THF, a temperatura elevada (método H) para dar **xx**.

La desprotección del grupo R'' se puede llevar a cabo usando un procedimiento estándar, en el caso de grupo dimetoxibencilo con un ácido, tales como TFA en DCM, para proporcionar aminas **xxi** (método I).

Las aminas **xxi** luego se pueden someter a la reacción de Sandmeyer usando reactivos apropiados, tales como yoduro de metileno y nitrito de amilo en ACN (método J). Los tiofenos halogenados **xxii** resultantes se pueden acoplar con aril estannanos en condiciones adecuadas, por ejemplo $Pd(PF_3)_4$, CuI, LiCl en un solvente adecuado, tales como dioxano, a temperatura elevada para dar compuestos de fórmula **xxiii** (método K). En forma alternativa, se pueden usar ácidos o ésteres borónicos para tales reacciones de acoplamiento, por ejemplo $Pd(PF_3)_4$, Na_2CO_3, DME/agua, temperatura elevada o irradiación de microondas (método L).

Se puede realizar una reacción de conversión de **xxiii** a los compuestos **xxiv**, por ejemplo, por una combinación de reacciones de conversión del grupo funcional generalmente conocido que se muestra a continuación.

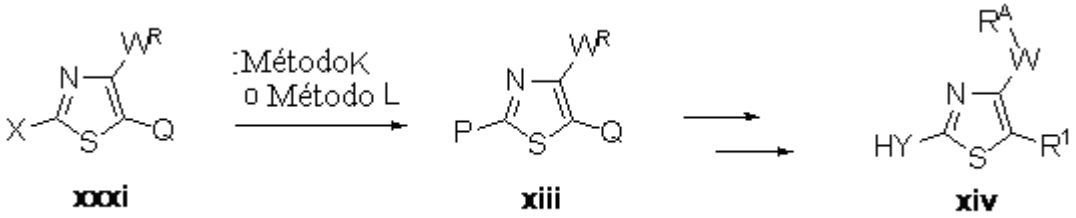
[00243] Esquema 6: Método general para la introducción de HY a tiofenos 2 no sustituidos.



[00244] El Esquema 6 muestra una vía general para introducir HY en la posición 2 no sustituida del núcleo de tiofeno. Los tiofenos 2 no sustituidos **xxv** se pueden tratar con base adecuada, tales como n-BuLi en THF a temperatura baja, para producir intermediarios de tiofeno litiados **xxvi** (método M). La especie de organolitio intermedia se pueden inactivar con molécula de halógeno, por ejemplo yodo en un solvente adecuado, tales como THF, para proporcionar compuestos de fórmula halogenados **xxvii** (método N). En forma alternativa, los tiofenos **xxv** se pueden halogenar directamente usando condiciones adecuadas, por ejemplo NBS en DCM para proporcionar compuestos de fórmula halogenados **xxvii** (método C). Los haluros **xxvii** se puede acoplar con aril stannanos en condiciones adecuadas, por ejemplo $Pd(PF_3)_4$, CuI, LiCl en un solvente adecuado, tales como dioxano a temperatura elevada para dar compuestos de fórmula **xxviii** (método K), o ácidos o ésteres borónicos. con un catalizador

apropiado, por ejemplo $Pd(PF_3)_4$, en presencia de una base adecuada, tales como, carbonato de sodio, en una mezcla de DME–agua a temperatura elevada (método L) para proporcionar compuestos de fórmula **xxviii**.
En forma alternativa, los intermediarios de litio **xxvi** se pueden transformar en reactivos organometálicos, tales como estannanos por inactivación con haluro de estaño adecuado, tales como cloruro de tributilestaño (método O), o ésteres borónicos, tales como alcoxi–tetrametil–1,3,2–dioxaborolano (método DA), o trifluoroboratos por el tratamiento posterior de los ésteres borónicos con una fuente de flúor adecuada, tales como KHF_2 (método DB). Los estannanos **xxix** luego se pueden acoplar con los haluros, triflatos o mesilatos de arilo usando condiciones apropiadas, tales como $Pd(PF_3)_4$, CuI, LiCl en un solvente adecuado, tales como dioxano, a temperatura elevada para dar compuestos de fórmula **xxviii** (método K). Los ácidos, ésteres o trifluoroboratos borónicos luego se pueden acoplar con haluros, triflatos o mesilatos de arilo con un catalizador apropiado, por ejemplo $Pd(PF_3)_4$, en presencia de una base adecuada, tales como carbonato de sodio en mezcla de DME–agua a temperatura elevada (método L) para proporcionar compuestos de fórmula **xxviii**.
Se puede realizar una reacción de conversión del **xxviii** a los compuestos **v**, por ejemplo, por una combinación de reacciones de conversión del grupo funcional generalmente conocido que se muestra más adelante.

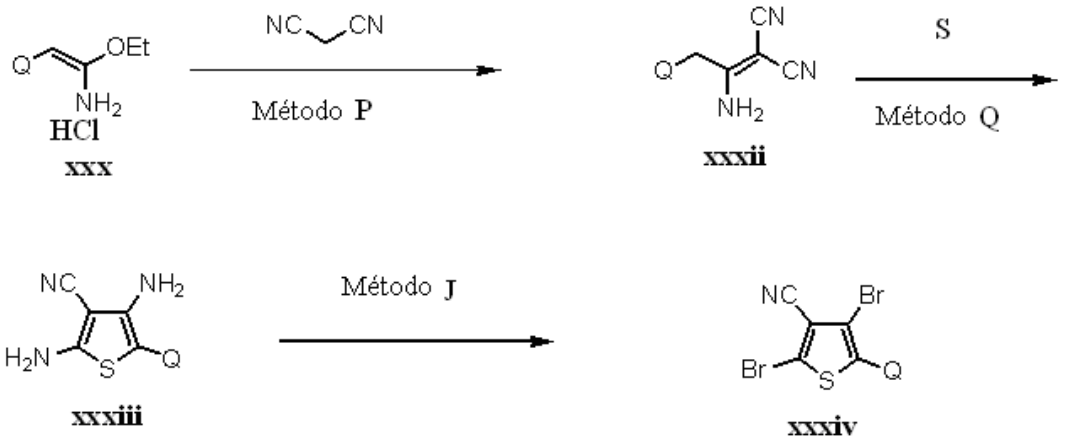
[00245] Esquema 7: Método general para introducción del HY a la posición 2 del núcleo tiazol.



xxxi **xiii** **xiv**

[00246] El Esquema 7 muestra una vía general para introducir HY a la posición 2 de la estructura del núcleo tiazol. Los tiazoles halogenados **xxxi**, que pueden estar disponibles como se describe en el esquema 3, se pueden acoplar con los compañeros adecuados, tales como ácidos borónicos, estannanos, etc en condiciones de Suzuki estándar, tales como $Pd(PF_3)_4$, Na_2CO_3, DME/agua, temperatura elevada o irradiación de microondas (método L), o en condiciones de Stille estándar, tales como $Pd(PF_3)_4$, CuI, LiCl, dioxano a temperatura elevada (método K) para proporcionar compuestos de fórmula **xiii**.
Se puede realizar una reacción de conversión de **xiii** a compuestos **xiv**, por ejemplo, por una combinación de reacciones de conversión del grupo funcional generalmente conocido que se muestra más adelante.

[00247] **Esquema 8: Método general para la síntesis de 3-cianotiofenos**



xxx **xxxii** **xxxiii** **xxxiv**

[00248] El Esquema 8 describe el procedimiento para la síntesis de 3-cianotiofenos **xxxiv**. La alcoxietenamina sustituida **xxx** se puede tratar con malononitrilo en presencia de una base adecuada, tales como TEA, en un solvente adecuado, como cloroformo, a temperatura elevada para proporcionar aminoetilen malononitrilos sustituidos **xxxii** (método P), que se tratan con azufre en condiciones adecuadas, tales como DMF y temperatura elevada, para dar diaminocianotiofenos **xxxiii** (método Q). Las diaminas **xxxiii** luego se pueden someter a una reacción de Sandmeyer usando reactivos apropiados, tales como bromuro de cobre (II), nitrito de amilo en ACN a temperatura elevada (método J) para proporcionar los compuestos de fórmula **xxxiv**.

[00249] Los esquemas 9—21 describe métodos para la introducción de los grupos R^1 y $W-R^A$.

[00250] **Esquema 9: Método general para la síntesis de preparación de los derivados de 4-alcoxi**

tiofeno / tiazol.



xviii **xxxv**

Los 4-alcoxi tiofenos/tiazoles se pueden obtener por el método de alquilación por el método de alquilación convencional de derivados de 4-hidroxitiazol obtenidos en el esquema 4.

Como se muestra en el esquema 9, 4-hidroxi tiofenos / tiazoles **xviii** se pueden tratar con haluros de alquilo usando una base adecuada, tales como carbonato de potasio, en un solvente adecuado, por ejemplo DMF, a temperatura elevada para proporcionar compuestos de fórmula **xxxv** (método R).

[00251] Esquema 10: Método general para halogenación de tiofenos / tiazoles



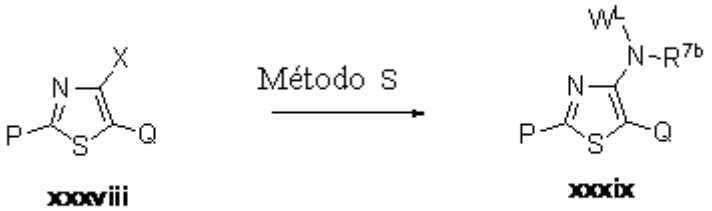
xxxvi **xxxvii**

[00252] El Esquema 10 muestra una vía general para introducir funcionalidad de halógeno en la posición 4 no sustituida posición del núcleo tiofeno/tiazol.

La halogenación de tiofeno / tiazoles se puede obtener de una manera similar a la informada en la bibliografía

(Takami et al, Tetrahedron **2004**, *60*, 6155). Por ejemplo, **xxxvi** se trata con un reactivo de halogenación generalmente conocido tales como bromo o N-bromosuccinimida, en un solvente adecuado, tales como DCM, a temperatura elevada para proporcionar los compuestos de fórmula **xxxvii** (método C). El tiazol halogenado **xxxvii** se puede usar para la transformación del grupo funcional adicional que se muestra más adelante.

[00253] Esquema 11: Método general para la preparación de 4-aminotiazoles

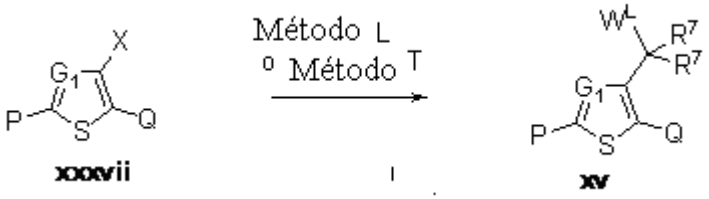


xxxviii **xxxix**

[00254] El Esquema 11 muestra métodos generales para la síntesis de derivados de 4-aminotiazol **xxxix** de los 4-tiazoles halogenados **xxxviii**, que se puede preparar por el procedimiento descripto en el esquema 10.

El desplazamiento de un grupo halógeno con una amina se puede obtener de manera similar a la informada en la bibliografía (J. Med. Chem **2006**, *49*, 5769). El tratamiento de **xxxviii** con una amina a temperatura elevada en un solvente adecuado, tal como DMF, puede producir las aminas **xxxix** (método S). Si es necesario se puede añadir una base, tal como carbonato de sodio.

[00255] **Esquema 12: Método general para introducir la funcionalidad carbono a tiofenos / tiazoles 4-halogenados.**

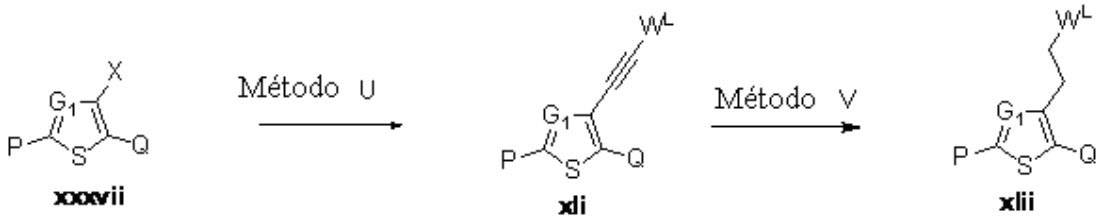


xxxvii **xv**

[00256] Como se muestra en el esquema 12, la funcionalidad carbono se puede introducir por la técnica de acoplamiento cruzado bien conocido a partir de los tiofenos / tiazoles 4-halogenados **xxxvii** que se pueden preparar por el procedimiento descripto en el esquema 10.

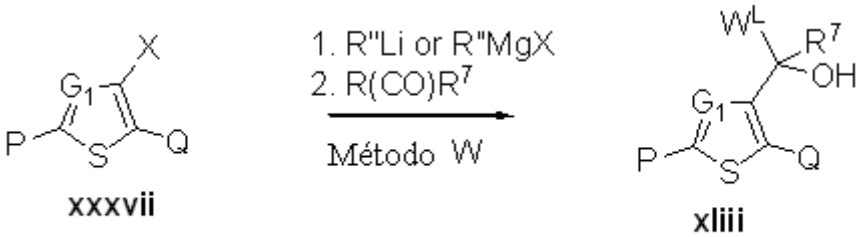
Por ejemplo, **xv** se pueden obtener de tiofenos / tiazoles 4-halogenados **xxxvii** por la reacción con un reactivo ácido borónico orgánico, o un reactivo de cinc orgánico en presencia de un catalizador de paladio. Los acoplamientos de Suzuki con ácidos o ésteres alquil, alquenil borónicos se pueden realizar usando $Pd(PF_3)_4$, o a similar catalizador de paladio, a base adecuada, tales como carbonato de sodio en un solvente apropiado, tales como DME/agua, K_D a temperatura elevada (método L), mientras que se puede usar $Pd(t\text{Bu}_3P)_2$ para las reacciones de acoplamiento Negishi, junto con en un solvente adecuado, tales como THF, a temperatura elevada (método T).

[00257] **Esquema 13: Método general para introducir la funcionalidad carbono a tiofenos / tiazoles 4-halogenados.**



[00258] El Esquema 13 muestra un método general para la síntesis de tiofenos / tiazoles sustituidos en carbono. Los tiofenos / tiazoles 4-halogenados **xxxvii** se pueden tratar con un alquino en presencia de un catalizador adecuado, por ejemplo $Pd(PF_3)_4$, CuI, base, tales como TEA en un solvente adecuado, como DCM, para proporcionar alquinos **xli** (método U). Los compuestos **xli** luego se pueden reducir a tiofenos / tiazoles sustituidos con alquilo **xlii**, por ejemplo usando la hidrogenación con Pd/C en un solvente adecuado, tales como etanol (método V)

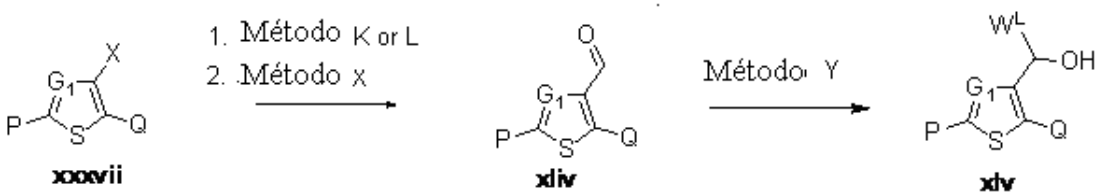
[00259] **Esquema 14: Método general para introducir la funcionalidad carbono en los tiofenos halogenados.**



[00260] El Esquema 14 muestra un método general para la síntesis de tiofenos sustituidos con carbono. Los tiofenos halogenados **xxxvii** se pueden tratar con reactivos de alquillitio, arrillitio o

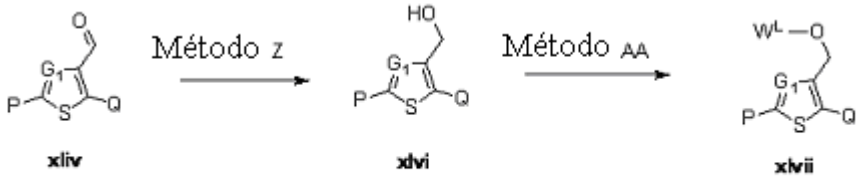
alquilmagnesio, tales como de *n*–BuLi a temperatura baja para generar tiofenos metalados intermediarios que se tratan posteriormente con aldehídos o cetonas para proporcionar carbinoles **xliii** (método W).

[00261] **Esquema 15: Método general para introducir la funcionalidad carbono a tiofenos / tiazoles 4–halogenados.**



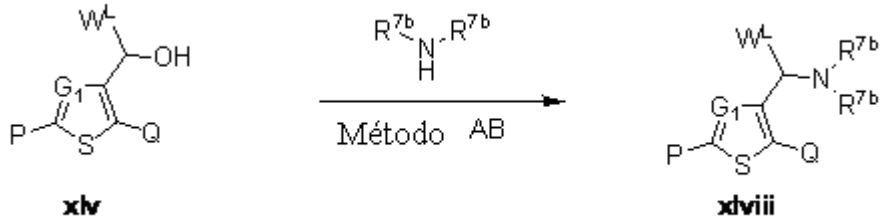
[00262] Esquema 15 muestra a método general para la síntesis de tiofenos / tiazoles sustituidos en carbono. Los Tiofenos/tiazoles halogenados **xxxvii** se pueden tratar con reactivos vinilorganometálicos, por ejemplo viniltributilestannano en condiciones de Stille (método K), o viniltrifluoroborato en condiciones de Suzuki (método L) para proporcionar vinil tiofenos/tiazoles, que se pueden oxidar a aldehídos **xliv** usando un método adecuado, por ejemplo OsO_4, peryodato de sodio en mezcla de agua–dioxano (método X). Los aldehídos **xliv** luego se pueden tratar con reactivos organometálicos, tales como compuestos de Grignard o alquil/arillitio en un solvente adecuado, tales como THF, a temperatura baja para proporcionar carbinoles de fórmula **xlv** (método Y).

[00263] **Esquema 16: Método general para la síntesis de éteres**



[00264] El Esquema 16 muestra un método general para la síntesis de alcoholes **xlvi** y éteres **xlvii**. Los aldehídos preparados como se describe en el Esquema 15 anterior se pueden tratar con un agente reductor adecuado, tales como $NaBH_4$ en un solvente apropiado, por ejemplo THF, para proporcionar alcoholes de fórmula **xlvi** (método Z). Los alcoholes **xlvi** luego se puede alquilar usando condiciones estándares, por ejemplo con haluros de alquilo en presencia de base, tales como K_2CO_3, en THF para proporcionar éteres **xlvii** (método AA).

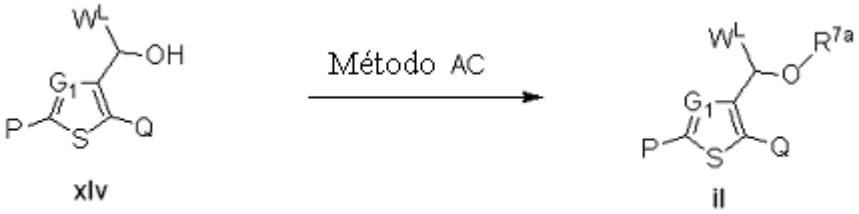
[00265] **Esquema 17: Método general para la síntesis de aminas**



[00266] El Esquema 17 muestra un método general para la síntesis de aminas **xlviii**. Como se muestra en el Esquema 17, los alcoholes se pueden activar por medio de ésteres de sulfonilo, por ejemplo por la reacción con cloruro de metansulfónico y a base, tales como piridina en un solvente adecuado, por ejemplo DCM.

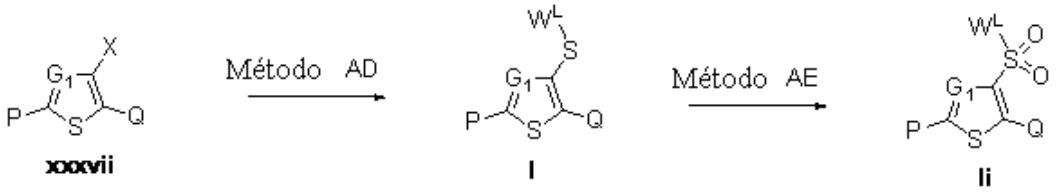
Los ésteres de sulfonilo luego se tratan con aminas a temperatura elevada para proporcionar aminas blanco **xlviii** (método AB).

[00267] **Esquema 18: Método general para la síntesis de éteres**



[00268] El Esquema 18 muestra un método general para la síntesis de éteres **il** cuando W^L es un grupo aromático o heteroaromático. Como se muestra en el Esquema 18, los alcoholes **xlv** se tratan con exceso de alcohol, tal como metanol, en presencia de un ácido, como HCl acuoso con un cosolvente opcional, por ejemplo dioxano a temperatura ambiente para proporcionar éteres de fórmula **il**.

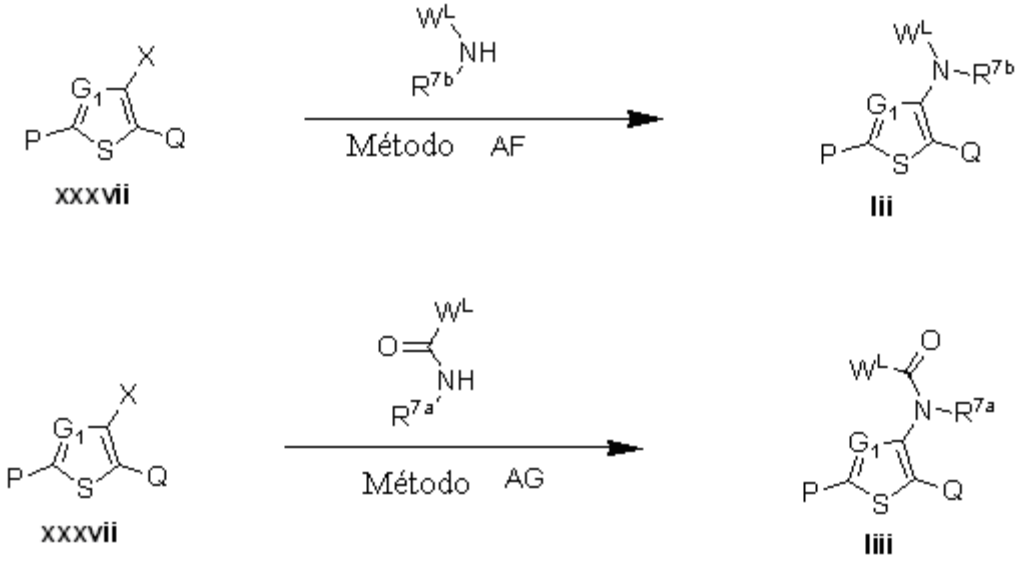
[00269] **Esquema 19: Método general para introducir funcionalidad azufre**



[00270] Como se muestra en el esquema 19, la funcionalidad azufre se puede introducir en los tiazoles/tiofenos 4-halogenados **xxxvii** por una manera similar a la descripta por Rossignol et al, US2009036467.

El tratamiento de **xxxvii** con tioles en presencia de un catalizador de cobre, como CuI en un solvente adecuado, tales como DMF, con una base apropiada, por ejemplo, hidróxido de sodio, a temperatura elevada da tioéteres de fórmula **l** (método AD). Los tioéteres **l** se pueden oxidar posteriormente a sulfonas **li** usando un agente oxidante adecuado, por ejemplo mCPBA en DCM (método AE).

[00271] **Esquema 20: Método general para aminación /amidación catalizada con Pd de tiofenos / tiazoles 4-halogenados**

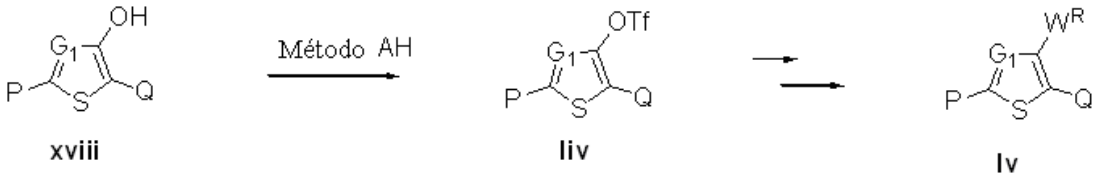


[00272] Como se muestra en el esquema 20, la funcionalidad amina o amida se puede introducir por la reacción bien conocida de aminación / amidación catalizada con Pd, llamada acoplamiento de Buchwald, de los tiofenos / tiazoles 4-halogenados **xxxvii**.

Por ejemplo, los haluros **xxxvii** se pueden tratar con aminas usando un catalizador de Pd apropiado, tales como Pd_2dba_3/BINAP, con una combinación adecuada de

solvente/base, por ejemplo NaOtBu en tolueno a temperatura elevada o usando irradiación de microondas para proporcionar aminas de fórmula **lii** (método AF). El acoplamiento con las amidas también se puede realizar usando un catalizador de Pd adecuado, por ejemplo Pd_2dba_3/XantFos, con una combinación adecuada de solvente/base, como Cs_2CO_3 en dioxano a temperatura elevada o usando irradiación de microondas para dar amidas de fórmula **liii** (método AG).

[00273] **Esquema 21: Método general para la funcionalización del grupo 4-hidroxilo de derivados de tiofeno / tiazol**



xviii liv lv

[00274] Como se muestra en el esquema 21, los 4-hidroxitiazoles o tiofenos **xviii** se pueden transformar en varios derivados de tiazol / tiofeno funcionalizados por medio de triflato **liv**.

Por ejemplo, los compuestos **xviii** se pueden transformar en triflatos **liv**, usando, *por ejemplo*, anhídrido tríflico, con piridina como base en DCM (método U). Los triflatos **liv** luego se pueden someter a reacciones de acoplamiento con aminas, ésteres borónicos, estannanos, o tioles en condiciones similares a las descriptas para los haluros análogos de los Esquemas 11 – 14 (ejemplos de la bibliografía análogos incluyen Rzasa, R. et al, Bioorg. Med. Chem. **2007**, *15*, 6574; Langille, N.F., Org. Lett.

2002, *4*, 2485.) para proporcionar compuestos de fórmula **lv**.

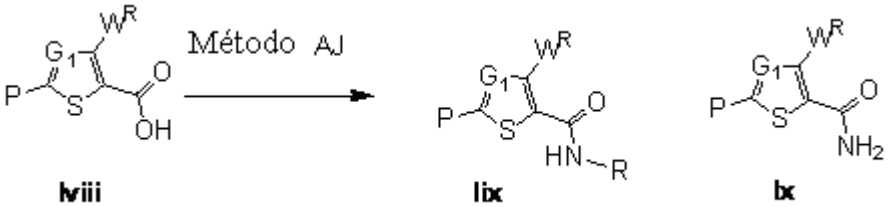
[00275] Esquema 22: Método general para halogenación de la posición 3 de tiofeno / tiazoles.



lvi **lvii**

[00276] El Esquema 22 muestra una vía general para introducir la funcionalidad de halógeno en la posición 5 no sustituida de la estructura del núcleo de tiofeno /tiazol.
La halogenación de tiazoles/ tiofenos 5-no sustituidos se puede obtener de manera similar a la informada en la bibliografía (Haelmmerle et al, Synlett **2007,** 2975). Por ejemplo, **lvi** se trata con un reactivo de halogenación generalmente conocido tal como bromo o N–bromosuccinimida en un solvente adecuado, tal como DCM para proporcionar compuestos de fórmula **lvii** (método AI).
Los tiofenos / tiazoles halogenados **lvii** se pueden usar para la reacción de transformación adicional del grupo funcional tal como se describe en el esquema 11—15.

[00277] Esquema 23: Vía general para la síntesis de carboxamidas

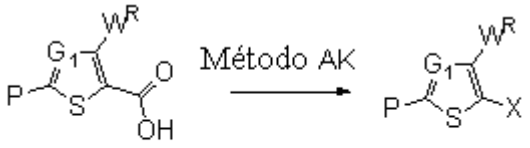


lviii **lix** **lx**

[00278] El esquema 23 muestra una vía general para preparar compuestos amida de fórmula **lix**. Como se muestra en el esquema 23, los ácidos **lviii** se pueden tratar con aminas usando condiciones de acoplamiento estándares, tales como EDCI y HOBt en DCM para proporcionar amidas **lix** (método AJ).

Cuando se usa amoníaco como fuente de amina, se pueden obtener derivados de amida primaria **lx**, que se pueden usar como intermediarios para la construcción de azoles como se describe en los Esquemas 25, 26, 28 y 37.

[00279] **Esquema 24: Vía general para la síntesis de 5-tiofenos / tiazoles halogenados por la reacción de Hunsdiecker**

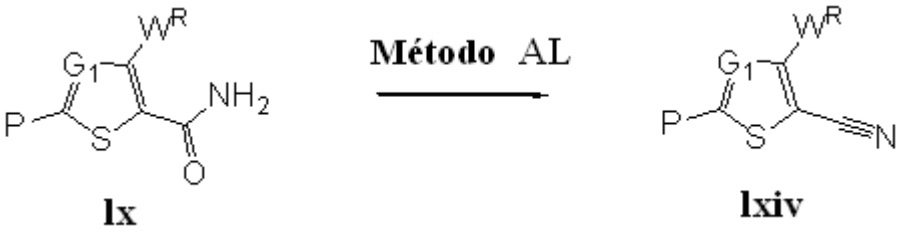


lviii **lvii**

[00280] Como se muestra en el Esquema 24, 5-tiofenos / tiazoles halogenados **lvii** se puede preparar por la reacción de Hunsdiecker de los análogos de ácido carboxílico de tiofeno /tiazol **lviii**.

Como se muestra en el esquema 24, los ácidos **xlviii** se pueden tratar con hidróxido de plata para formar una sal de plata, que se trata posteriormente con halógeno, por ejemplo bromo, en un solvente adecuado, tales como CCl_4 a temperatura elevada para formar **lvii** (método AK).

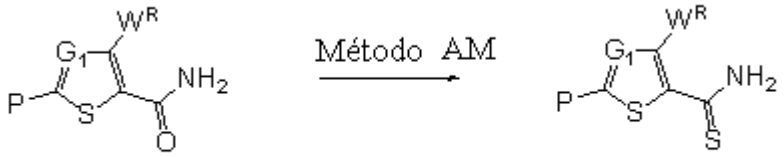
[00281] **Esquema 25: Vía general para la síntesis de 5-ciano tiofenos / tiazoles**



lx **lxiv**

[00282] Como se muestra en el esquema 25, las amidas **lx**, que se pueden preparar por el procedimiento descripto en el esquema 23, se tratan con cloruro de fosforilo, o reactivos similares para formar 5-ciano tiofenos / tiazoles de fórmula **lxiv** (método AL).

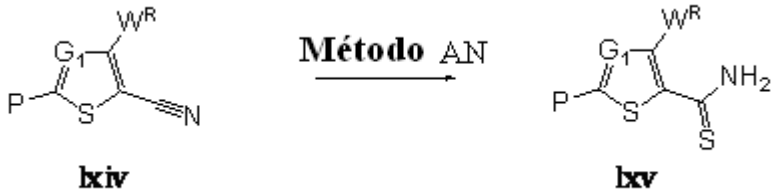
[00283] **Esquema 26: Vía general para la síntesis de tioamidas**



lx **lxv**

[00284] Como se muestra en el esquema 26, las amidas **lx**, que se pueden preparar por el procedimiento descripto en el esquema 23, se tratan con un reactivo adecuado, por ejemplo reactivo de Lawesson, o P_2S_5 en un solvente adecuado, tales como tolueno a temperatura elevada para proporcionar tioamidas de fórmula **lxv** (método AM).

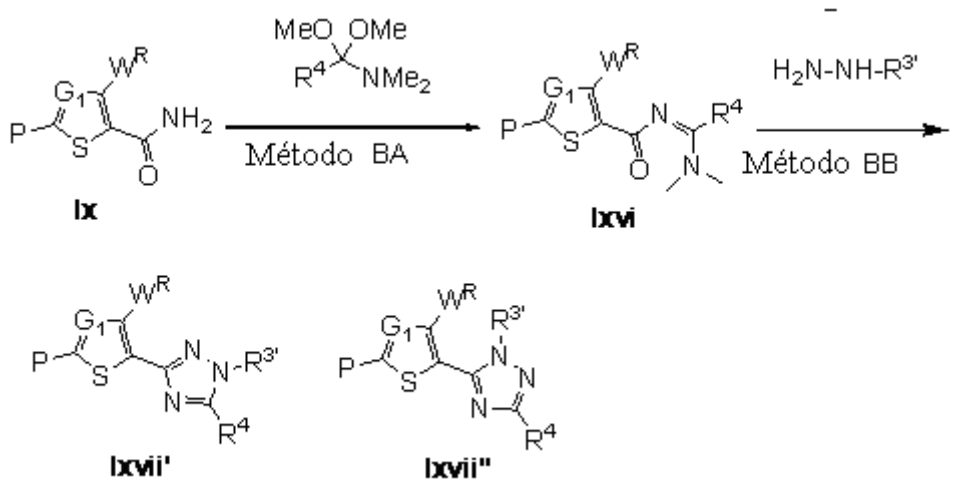
[00285] **Esquema 27: Vía alternativa para la síntesis de tioamidas**



[00286] Como se muestra en el esquema 27, los 5-ciano tiazoles / tiofenos **lxiv**, que se pueden preparar por el procedimiento descripto en el esquema 25, se tratan con un reactivo adecuado, por ejemplo, sulfuro de amonio en un solvente adecuado, tales como metanol para proporcionar tioamidas de fórmula **lxv** (método AN).

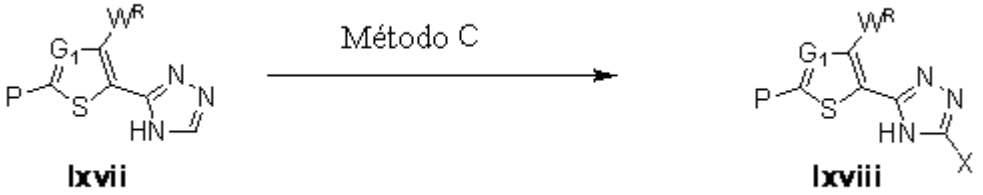
[00287] En los esquemas 28—46, se describen los procedimientos generales para la construcción de los representativos azoles como R^1.
Los Esquemas 28 -30 describen la formación del grupo 1,2,4-triazolilo como R^1.

[00288] **Esquema 28: Vía general para la construcción de 1,2,4- triazolilo**



[00289] Como se muestra en el esquema 28, las amidas **lx**, que se pueden preparar por el procedimiento descripto en el esquema 23, se pueden tratar con DMF-DMA a temperatura elevada o bajo irradiación de microondas (método BA) para dar amidinas intermediarias **lxvi** que se transforman en 1,2,4-triazoles **lxvii'** y **lxvii"** usando hidrazina o hidrazinas sustituidas en ácido acético a temperatura elevada o under irradiación de microondas (método BB).

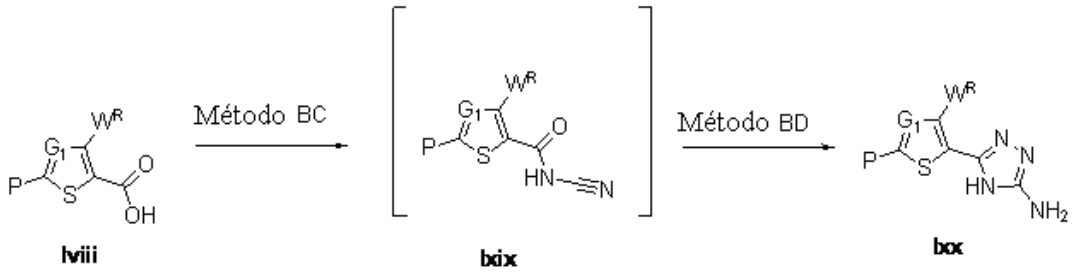
[00290] **Esquema 29: Vía general para la construcción de 1,2,4-triazolil 5-halogenado**



lxvii **lxviii**

[00291] Como se muestra en el esquema 29, los 1,2,4-triazoles **lxvii**, que se pueden preparar por el procedimiento descripto en el esquema 28, se tratan con un agente halogenante adecuado, como NBS, en un solvente adecuado, por ejemplo tetraclorometano, para proporcionar los compuestos de fórmula **lxviii** (método C).

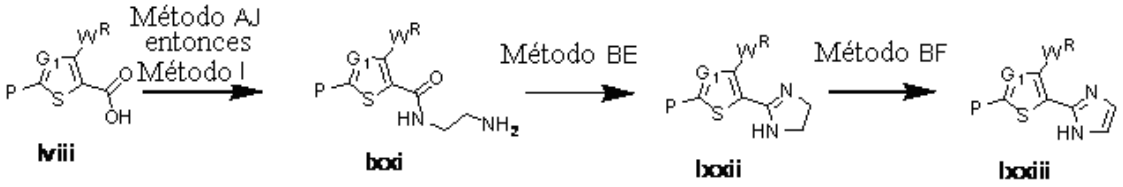
[00292] **Esquema 30: Vía general para la construcción de 5-amino-1,2,4-triazolilo**



[00293] Como se muestra en el esquema 30, los ácidos **lviii** se pueden acoplar con cianamida, por ejemplo por medio de un haluro ácido intermediario en un solvente adecuado, tal como DCM para acilcianamidas **lxix** (método BC), que a su vez se tratan con hidrazina usando condiciones apropiadas, por ejemplo ácido acético a temperatura elevada para dar compuestos de fórmula **lxx** (método BD).

[00294] El Esquema 31—39 describe la formación de grupos 2-imidazolilo como R^1.

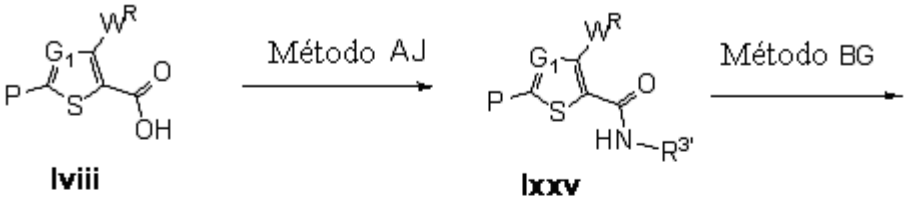
[00295] **Esquema 31: Vía general para la construcción de 2-imidazolilo**



[00296] Como se muestra en el esquema 31, los ácidos **lviii** se tratan con etilendiamina protegido Boc usando condiciones de acoplamiento estándares, tales como EDCI y HOBt en DCM (método AJ). El grupo protector se elimina usando un ácido apropiado, por ejemplo TFA en

DCM para dar amida **lxxi** (método I). La ciclización de **lxxi** se obtiene usando condiciones adecuadas, por ejemplo $POCl_3$ (método BE) para formar dihidroimidazoles **lxxii**. Los dihidroimidazoles **lxxii** se pueden oxidar a imidazoles **lxxiii** usando un método oxidante adecuado, por ejemplo, calentamiento con Magtrieve (método BF).

[00297] **Esquema 32: Vía alternativa para la construcción de 2-imidazolilo**



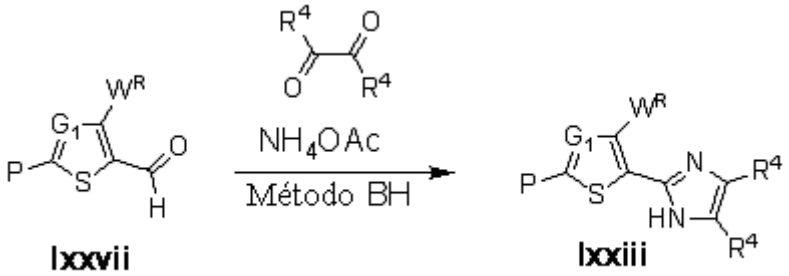


[00298] El Esquema 32 anterior muestra una vía alternativa para preparar imidazoles de fórmula **lxxiii**.

Como se muestra en el esquema 32, los ácidos **lviii** se tratan con aminas usando condiciones de acoplamiento estándares, tales como EDCI y HOBt en DCM para proporcionar amidas **lxxv** (método AJ). La ciclización de los imidazoles se puede obtener a través de un proceso en recipiente único de 3 etapas que involucra el tratamiento con pentacloruro de fósforo y HCl en dioxano para proporcionar los intermediarios cloruro de carbimidoílo

lxxvi, que luego se pueden tratar con aminoacetaldehído dimetilacetal seguido por HCl en dioxano a temperatura elevada para dar **lxxiii** (método BG). Cuando $R^{3'}$ = alilo, bencilo o bencilo sustituido, también puede servir como un grupo protector.

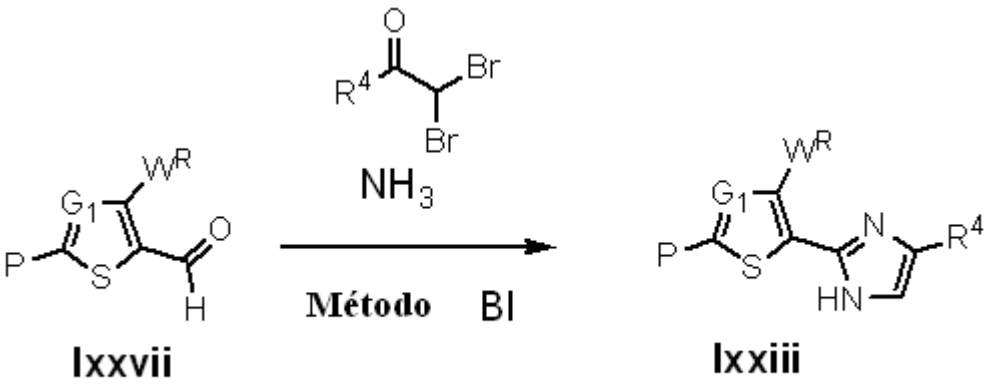
[00299] **Esquema 33: Vía alternativa para la síntesis de 2-imidazolilo**



lxxvii **lxxiii**

[00300] Como se muestra en el esquema 33, los aldehídos **lxxvii** se pueden condensar con compuestos de dicarbonilo, tales como dicetonas, cetoaldehídos, o glioxal con una fuente de amoníaco apropiado, tales como acetato de amonio, con ácido adecuado, tales como ácido acético en solvente tales como metanol para formar imidazoles **lxxiii** (método BH).

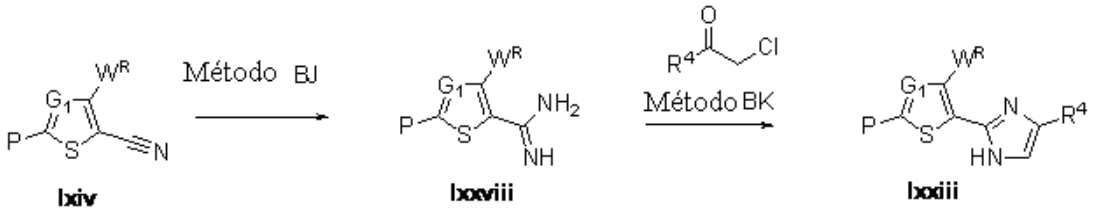
[00301] **Esquema 34: Método alternativo para la construcción de 2-imidazolilo sustituidos.**



lxxvii lxxiii

[00302] Como se muestra en el esquema 34, los aldehídos de fórmula **lxxvii** se pueden tratar con alfa, alfa-dihalo-cetonas en condiciones adecuadas, tales como hidróxido de amonio, acetato de sodio en un solvente apropiado, por ejemplo metanol y agua para proporcionar imidazoles de fórmula **lxxiii** (método BI).

[00303] **Esquema 35: Método alternativo para la construcción de 2-imidazolilo sustituido.**

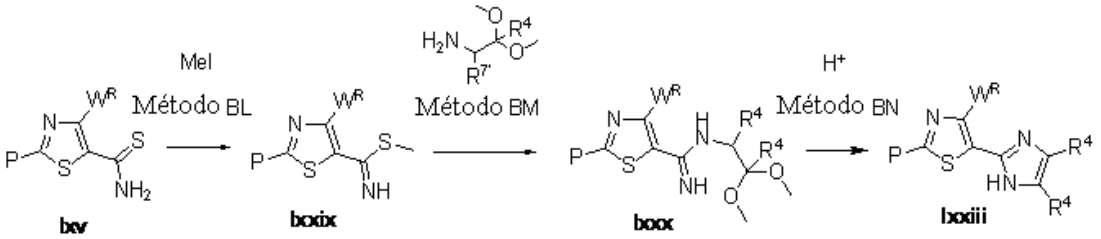


lxiv lxxviii lxxiii

[00304] Como se muestra en el esquema 35, el tratamiento de nitrilo **lxiv**, que se puede preparar por el procedimiento descripto en el esquema 25, con LiHMDS en una mezcla de solvente adecuada, tal como THF/éter/hexano da amidinas de fórmula **lxxviii** (método BJ) que se puede tratar con halocetonas en presencia de una base adecuada, tales como carbonato de potasio en un

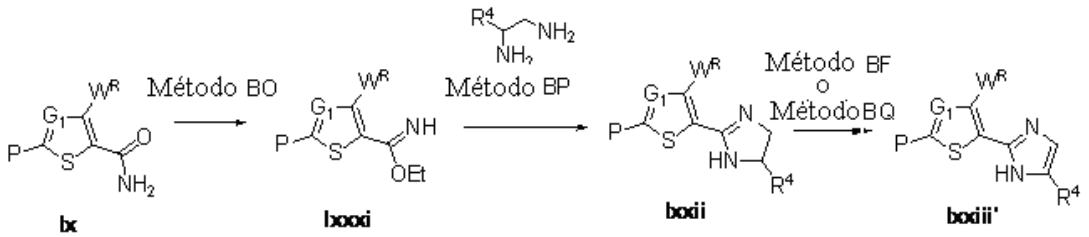
solvente apropiado, tales como DCM a temperatura elevada para dar imidazoles de fórmula general **lxxiii** (método BK).

[00305] Esquema 36: Método alternativo para la construcción de 2-imidazolilo sustituido.



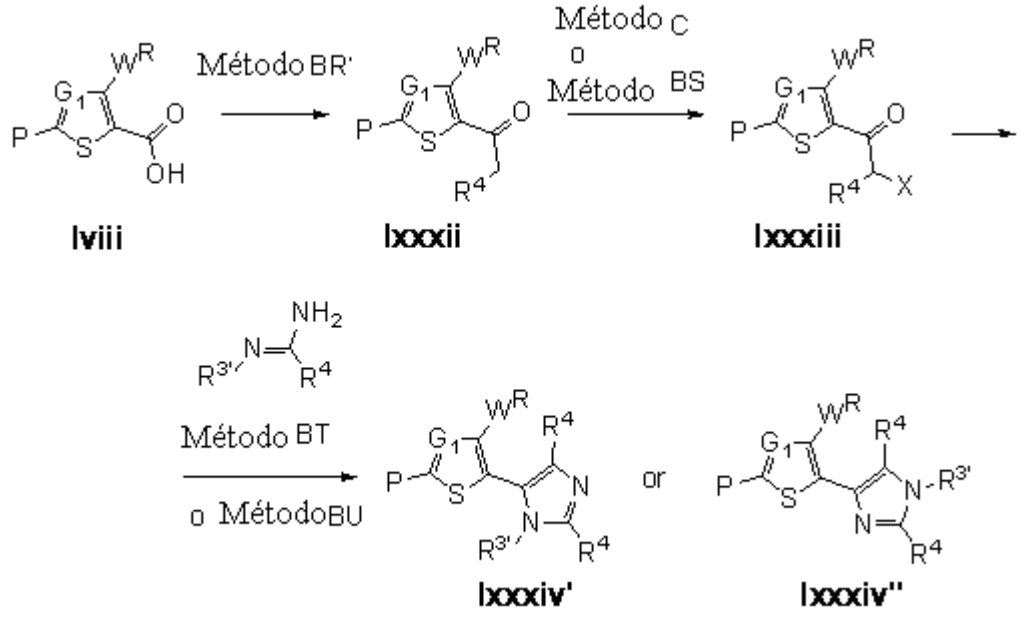
[00306] Como se muestra en el esquema 36, el tratamiento de las tioamidas **lxv**, que se pueden preparar por el procedimiento descripto en el esquema 26 o 27, con yoduro de metilo proporciona intermediarios imidotioato **lxxix** (método BL), que luego se pueden tratar con aminoacetaldehído dimetil acetal opcionalmente sustituido en un solvente adecuado, como ácido acético, a temperatura elevada para proporcionar las amidinas intermediarias **lxxx** (método BM). Las amidinas **lxxx** luego se pueden tratar con un ácido, tal como HCl acuoso y un cosolvente adecuado, como etanol, a temperatura elevada para dar imidazoles de fórmula **lxxiii** (método BN).

[00307] Esquema 37: Método alternativo para la construcción de 2-imidazolilo sustituido.



[00308] Como se muestra en el esquema 37, el tratamiento de amidas **lx**, que se puede preparar por el procedimiento descripto en el esquema 23, con un agente alquilante, tal como reactivo de Meerwein, en DCM (método BO) proporciona iminoésteres **lxxxi**, que luego se pueden tratar con diaminas usando las condiciones apropiadas, por ejemplo etanol a temperatura elevada (método BP) para formar dihidroimidazoles **lxxii**, que luego se pueden oxidar de una misma manera que en el método BF descripto en el Esquema 31, o cuando R^4 es un grupo saliente apropiado, la eliminación se puede llevar a cabo usando una base, tal como DBU en DCM (método BQ).

[00309] **Esquema 38: Vía general para la construcción de 4 (5)–imidazolilo sustituido.**



lviii **lxxxii** **lxxxiii**

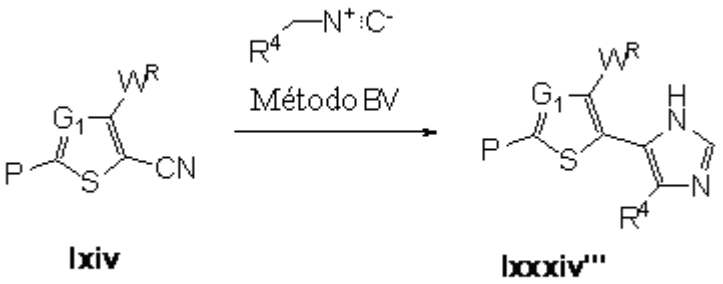
lxxxiv' **lxxxiv''**

[00310] Como se muestra en el esquema 38, los ácidos **lviii** se puede transformar a cetonas **lxxxii** usando una secuencia de síntesis adecuada, por ejemplo a través de un acoplamiento con *N*,*O*-dimetilhidroxilamina y posterior tratamiento de las amidas Weinreb resultantes con reactivos de alquillitio o Grignard en un solvente adecuado, como THF (método BR).

Las cetonas **lxxxii** luego se halogenan con un reactivo adecuado, tales como bromo o NBS en un solvente apropiado, como DCM (método C) para formar cetonas alfa halogenados **lxxxiii** (X = halógeno). En forma alternativa, el tratamiento de cetonas **lxxxii** con un reactivo sulfonilante oxidativo adecuado, como hidroxi(tosiloxi)yodobenceno usando condiciones adecuadas, por ejemplo calentamiento en acetonitrilo (método AS) proporcionan ésteres de sulfonilo de fórmula **lxxxiii** (X = OSO_2R).

El tratamiento de **lxxxiii** con reactivos de amidina en presencia de a base adecuada, como carbonato de potasio en un solvente adecuado, tales como mezcla de THF–agua a temperatura elevada o irradiación de microondas suministra los imidazoles finales **lxxxiv'** y **lxxxiv"** (método BT). En forma alternativa, los compuestos **lxxxiii** se pueden tratar con gran exceso de amidas, tales como formamida usando irradiación de microondas para proporcionar imidazoles **lxxxiv'** y **lxxxiv"** (método BU).

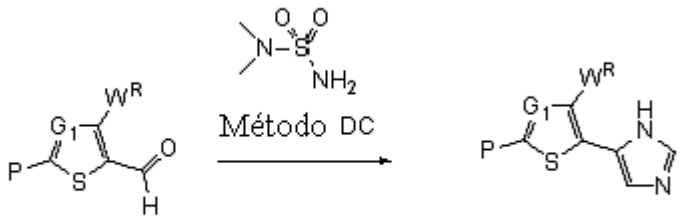
[00311] **Esquema 39: Método alternativo para la construcción de 4 (5)–imidazolilo sustituidos.**



lxiv **lxxxiv'"**

[00312] Como se muestra en el esquema 39, el tratamiento de nitrilos **lxiv**, que se puede preparar por el procedimiento descripto en el esquema 25, con isocianatos en presencia de a base adecuada, tal como tOBuK, en un solvente adecuado, por ejemplo THF da imidazoles de fórmula **lxxxiv'"**. método BV).

[00313] **Esquema 40: Método alternativo para la construcción de 4–imidazolil.**

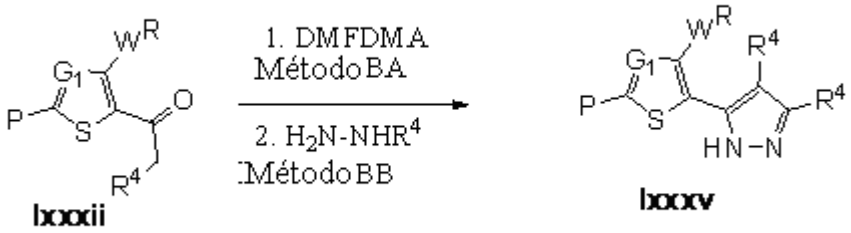


lxxvii lxxxiv

[00314] Como se muestra en el esquema 40, el tratamiento de aldehídos **lxxvii** con N,N-dimetilsulfonamida a temperatura elevada en un solvente adecuado, por ejemplo tolueno, para permitir la extracción azeotrópica de agua puede proporcionar las iminas intermediarias, que se tratan con TOSMIC, una base adecuada, como carbonato de potasio en un solvente adecuado, tales como DME a temperatura elevada para proporcionar imidazolsulfonamidas intermediarias, que se pueden hidrolizar a imidazoles **lxxxiv** con un ácido, por ejemplo HBr acuoso a temperatura elevada (método DC).

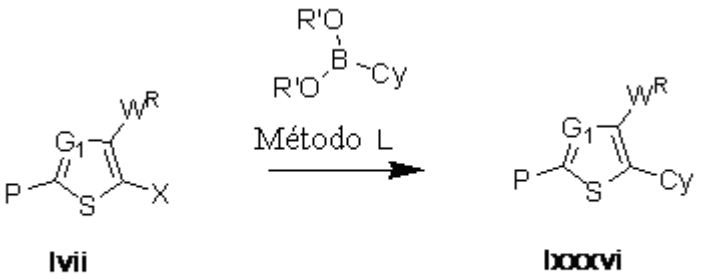
[00315] Los Esquemas 41 y 42 describen los procedimientos para introducir un grupo pirazolilo.

[00316] **Esquema 41: Vía general para la construcción de 3 (5)-pirazolilo.**



[00317] Como se muestra en el esquema 41, cetonas **lxxxii**, que se puede preparar por el procedimiento descripto en el esquema 38, se tratan con DMF-DMA para proporcionar enaminas intermediarias (método BA) seguido por la reacción con hidrazina sustituida, o hidrato de hidracina en un solvente adecuado, por ejemplo ácido acético, para dar pirazoles **lxxxv** (método BB).

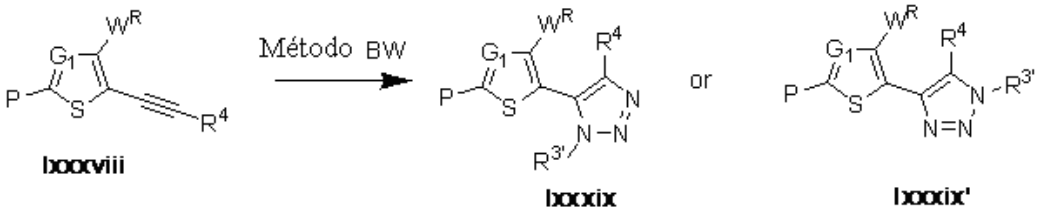
[00318] **Esquena 42: Vía general para la introducción del grupo heteroaromático.**



[00319] Como se muestra en el esquema 42, haluros **lvii**, que se puede preparar por el procedimiento descripto en el esquema 24, se tratan con ácidos o ésteres heteroaril borónicos, en presencia de un catalizador adecuado, por ejemplo $Pd(PF_3)_4$, usando a base, tales como carbonato de cesio en un solvente adecuado,

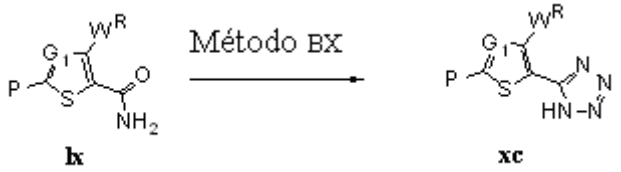
como mezcla de dioxano-agua a temperatura elevada para proporcionar compuestos de fórmula **lxxxvi** (método L).

[00320] **Esquema 43: Vía general para la construcción de 1,2,3-triazolilo.**



[00321] Como se muestra en el esquema 43, alquinos **lxxxviii**, que se puede preparar por la reacción de acoplamiento de Stille o Sonogashira conocida en que un haluro **lvii**, que se puede preparar por el procedimiento descripto en el esquema 24, y un derivado apropiado del derivado de alquino se puede tratar con azidas, un solvente inorgánico u orgánico adecuado, tales como dioxano, a temperatura elevada para proporcionar triazoles de fórmula **lxxxix** y **lxxxix'** (método BW).

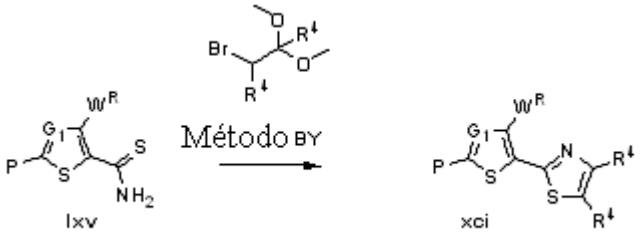
[00322] **Esquema 44: Vía general para la construcción de tetrazolilo.**



[00323] Como se muestra en el esquema 44, amidas **lx**, que se puede preparar por el procedimiento descripto en el esquema 23, se puede tratar con una fuente de azida, por ejemplo azida sódica usando un ácido de Lewis adecuado, por ejemplo tetracloruro de silicio en

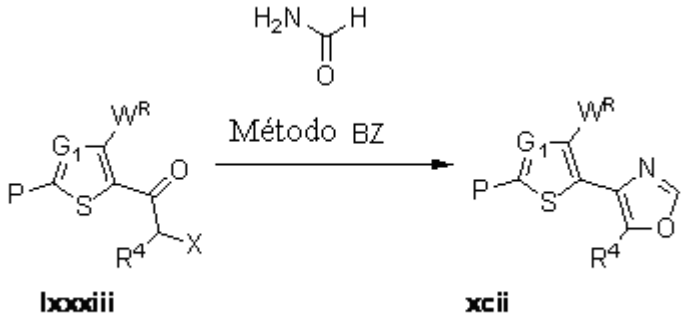
un solvente apropiado, tales como acetonitrilo para dar tetrazoles **xc** (método BX).

[00324] **Esquema 45: Vía general para la construcción de 2-tiazolilo.**



[00325] Como se muestra en el esquema 45, las tioamidas **lxv**, que se puede preparar por el procedimiento descripto en el esquema 26 o 27, se tratan con bromoacetaldehído dimetil acetales sustituidos para proporcionar tiazoles de fórmula **xci** (método BY).

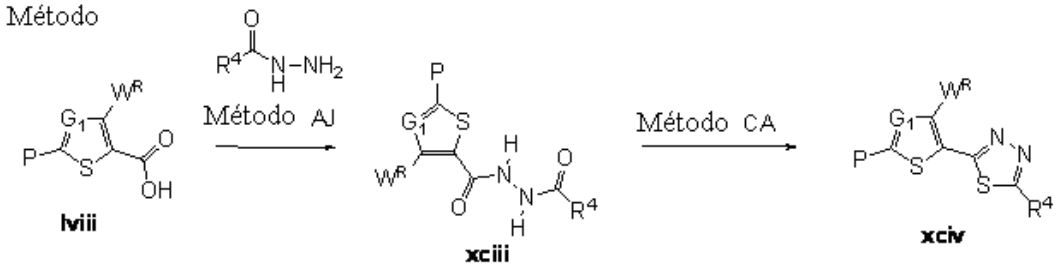
[00326] **Esquema 46: Vía general para la construcción de 4-oxazolilo**



[00327] Como se muestra en el esquema 46, alfa halogenados cetonas **lxxxiii**, que se puede preparar por el procedimiento descripto en el esquema 38, se puede tratar con formamida a temperatura elevada o irradiación

de microondas para proporcionar los 4-oxazoles finales **xcii** (método BZ).

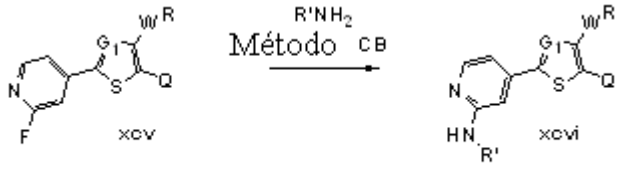
[00328] Esquema 47: Vía general para la construcción de 1,3,4-tiadiazolilo



[00329] Como se muestra en el esquema 47, ácidos **lviii** se acoplan con acilhidrazinas usando condiciones de acoplamiento estándares, tales como EDCI, HOBt, DMF a temperatura elevada para proporcionar intermediarios **xciii** (método AJ), que se tratan con reactivo de Lawesson usando condiciones adecuadas, por ejemplo en tolueno bajo reflujo para proporcionar tiadiazoles **xciv** (método CA).

[00330] El Esquema 48—51 describe el procedimiento general para la transformación del grupo funcional en HY.

[00331] Esquema 48: Método general para la introducción del grupo amino a 2-fluoropiridilo



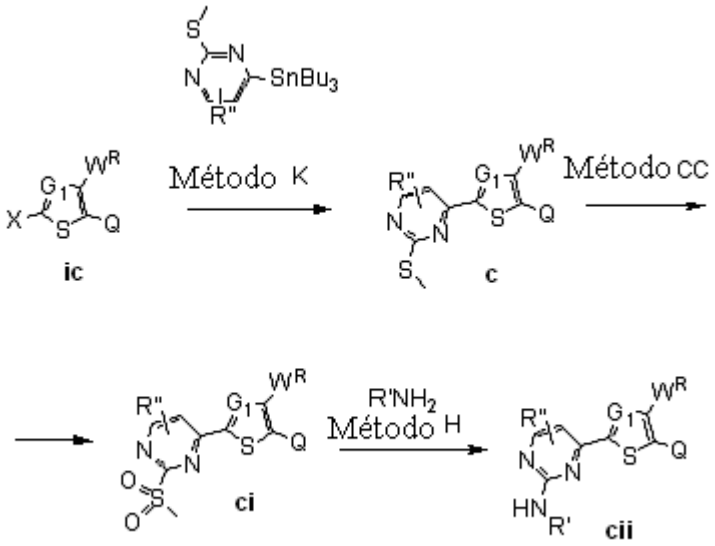
[00332] El Esquema 48 muestra una vía general para la transformación de 2-fluoropiridilo a aminopiridilo sustituido en 2 para dar los compuestos de fórmula **xcvi**.
Como se muestra en el esquema 48, compuestos **xcv** se pueden tratar con aminas a temperatura elevada o bajo irradiación de microondas para dar 2-aminopiridinas **xcvi** (método CB).

[00333] **Esquema 49: Método general para la introducción de 2-acilaminopiridinas por la reacción de Buchwald**



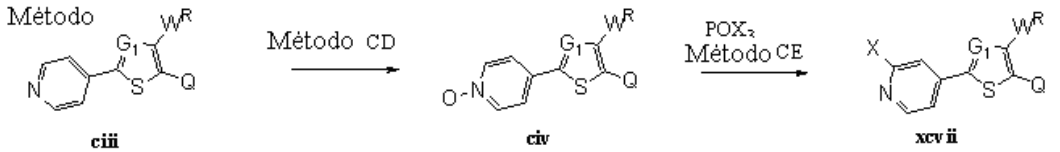
[00334] EL Esquema 49 muestra una vía general para la transformación de 2-halopiridilo a 2-acilaminopiridilo por la reacción de Buchwald para dar los compuestos fórmula **xcviii**.
Como se muestra en el esquema 49, los compuestos **xcvii** se pueden tratar con amidas o carboxamidas en presencia de un catalizador adecuado, tales como Pd_2dba_3, XantFos, base como carbonato de cesio en un solvente apropiado, por ejemplo dioxano a temperatura elevada o bajo irradiación de microondas para dar acilaminopiridinas **xcviii** (método AG).

[00335] **Esquema 50: Método general para la síntesis de 2-aminopirimidil tiofeno / tiazol**



[00336] Como se muestra en el esquema 50, los compuestos **ic** se puede acoplar con estannanos en condiciones adecuadas, por ejemplo $Pd(PF_3)_4$, CuI, LiCl en dioxano a temperatura elevada para dar los compuestos **c** (método K).
Oxidación de tioéteres **c** a sulfonas **ci** se puede obtener usando un oxidante adecuado, por ejemplo mCPBA en DCM (método CC).
El grupo metansulfonilo de las sulfonas **ci** se puede desplazar por el tratamiento con aminas en un solvente adecuado, por ejemplo THF para proporcionar 2-aminopirimidinas **cii** (método H).

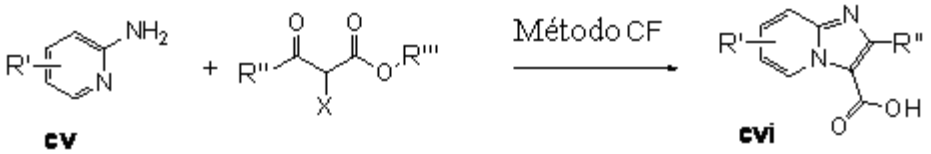
[00337] **Esquema 51: Método general para la introducción del sustituyente 2-halo en el grupo 4-piridilo**



[00338] El Esquema 51 muestra una vía general para la transformación de los compuestos 4-piridilo a 2-halo-4-piridilo de la fórmula **xcvii**.
Como se muestra en el esquema 51, compuestos **ciii** se pueden tratar con un oxidante, por ejemplo mCPBA en un solvente adecuado, tales como DCM para proporcionar intermediario N-óxidos **civ** (método CD), que se puede halogenar en la posición 2 usando haluros de fosforilo, por ejemplo cloruro de fosforilo, a temperatura elevada para proporcionar compuestos de fórmula **xcvii** (método CE).

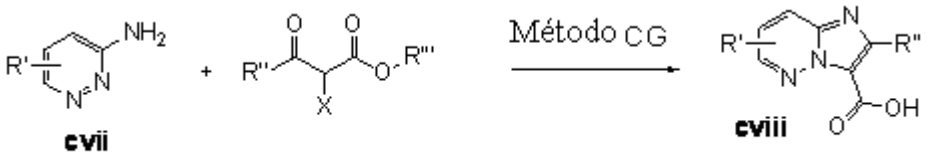
[00339] Los Esquemas 52—58 describen los procedimientos para la síntesis de los bloques de construcción para HY.

[00340] **Esquema 52: Método general para la síntesis de los bloques de construcción de imidazo[1,2-a]piridina.**



[00341] El Esquema 52 muestra un método general para la síntesis de imidazo[1,2-a]piridinas **cvi**. Como se muestra en el esquema 52, las 2-aminopiridinas **cv** se pueden condensar con beta-cetoésteres alfa halogenados en un solvente adecuado, por ejemplo etanol, a temperatura elevada para proporcionar intermediario ésteres, que se hidrolizan usando condiciones estándares, tales como hidróxido de sodio acuoso en THF seguido por desarrollo ácido para dar ácidos **cvi** (método CF).

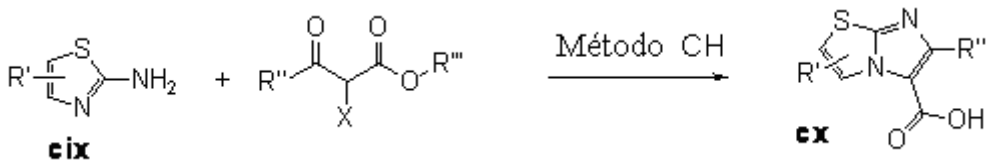
[00342] **Esquema 53: Método general para la síntesis de bloques de construcción de imidazo[1,2-b]piridazina**



[00343] Esquema 53 muestra un método general para la síntesis de imidazo[1,2-b]piridazinas **cviii**.

Como se muestra en el esquema 53, 2-aminopiridazinas **cvii** se pueden condensar beta-cetoésteres con α-halogenados en un solvente adecuado, por ejemplo etanol a temperatura elevada para proporcionar intermediario ésteres, que se hidrolizan usando condiciones estándares, tales como hidróxido de sodio acuoso en THF seguido por desarrollo ácido para dar ácidos **cviii** (método CG).

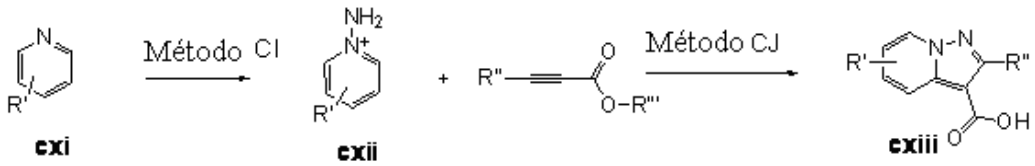
[00344] **Esquema 54: Método general para la síntesis de de bloques de construcción de imidazo[2,1-b][1,3]tiazol**



[00345] El Esquema 54 muestra un método general para la síntesis de imidazo[2,1-b][1,3]tiazoles **cx.**

Como se muestra en el esquema 54, los 2-aminotiazoles **cix** se pueden condensar con β-cetoésteres α-halogenados en un solvente adecuado, por ejemplo etanol, una temperatura elevada para proporcionar intermediario ésteres, que se puede hidrolizar usando condiciones estándares, tales como hidróxido de sodio acuoso en THF seguido por desarrollo ácido para dar ácidos **cx** (método CH).

[00346] **Esquema 55: Método general para la síntesis de bloques de construcción de pirazolo[1,5-a]piridina**



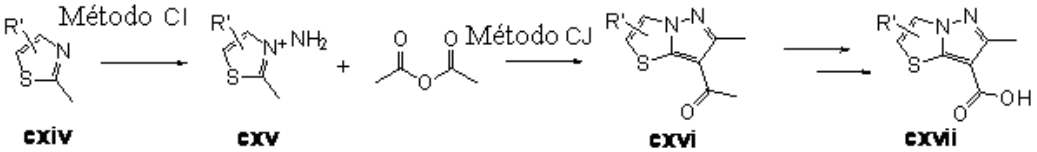
[00347] El Esquema 55 muestra un método general para la síntesis de pirazolo[1,5-a]piridinas **cxiii.**

Como se muestra en el esquema 55, las piridinas **cxi** se pueden *N*-aminar con un agente adecuado, tales como *O*-(mesitilsulfonil)hidroxilamina usando condiciones apropiadas, por ejemplo tolueno o acetato de etilo como solvente (método CI).

Las sales de *N*-aminopiridinio resultantes **cxii** luego se

pueden condensar con ésteres de ácido alquinilcarboxílico con una base adecuada, tales como carbonato de potasio en un solvente adecuado, por ejemplo DMF para proporcionar intermediario ésteres, que se pueden hidrolizar usando condiciones estándares, tales como hidróxido de sodio acuoso en THF seguido por desarrollo ácido para dar ácidos **cxiii** (método CJ).

[00348] Esquema 56: Método general para la síntesis de bloques de construcción de pirazolo[5,1-b][1,3]tiazol



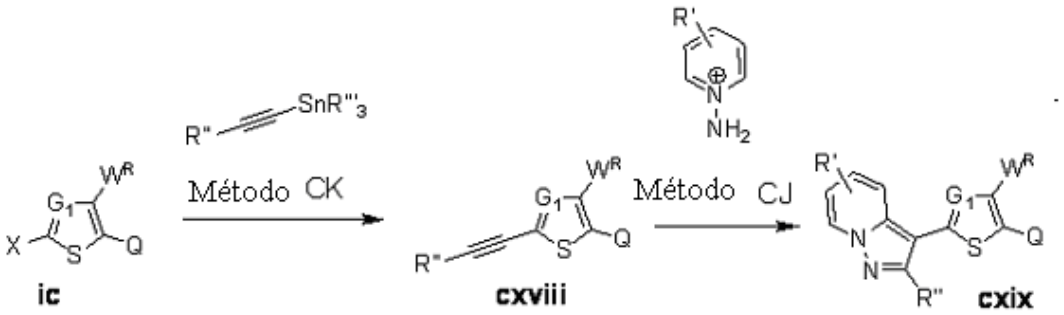
[00349] El Esquema 56 muestra un método general para la síntesis de pirazolo[5,1-b][1,3]tiazoles **cxvii**.

Como se muestra en el esquema 56, 2-metiltiazoles **cxiv** se pueden *N*-aminar con un agente adecuado, tales como *O*-(mesitilsulfonil)hidroxilamina usando condiciones apropiadas, por ejemplo tolueno o acetato de etilo como solvente (método CI).

Las sales *N*-aminotiazolio **cxv** luego se pueden condensar con anhídrido acético y acetato de potasio a temperatura elevada para proporcionar intermediario metilcetona **cxvi** (método CJ), que se pueden convertir al residuo de ácido carboxílico **cxvii** por transformación de metil cetona funcional bien conocida a ácido carboxílico.

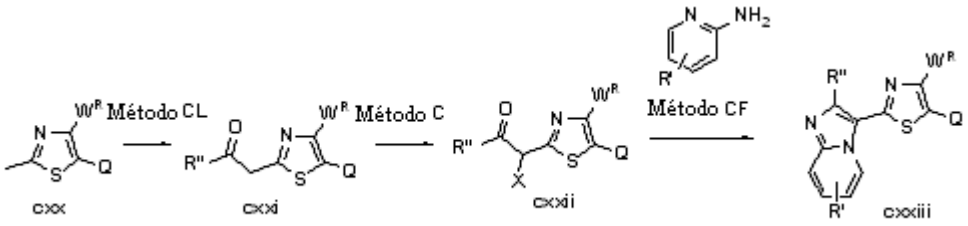
[00350] Esquema 57: Método alternativo para la síntesis de derivados de pirazolo[5,1-

b][1,3]tiazol



[00351] El Esquema 57 muestra an método alternativo para la síntesis de pirazolopiridinas **cxix**. Como se muestra en el esquema 57, haluros **ic** se tratan con alquinl estannanos en presencia de catalizadores adecuados, tales como $Pd(PF_3)_4$, CuI, con LiCl en un solvente apropiado, como dioxano a temperatura elevada para dar alquinos de fórmula **cxviii** (método CK). Alquinos **cxviii** luego se acoplan con sales *N*–aminopiridinio con una base, como carbonato de potasio en un solvente adecuado, por ejemplo DMF para proporcionar compuestos de fórmula **cxix** (método CJ).

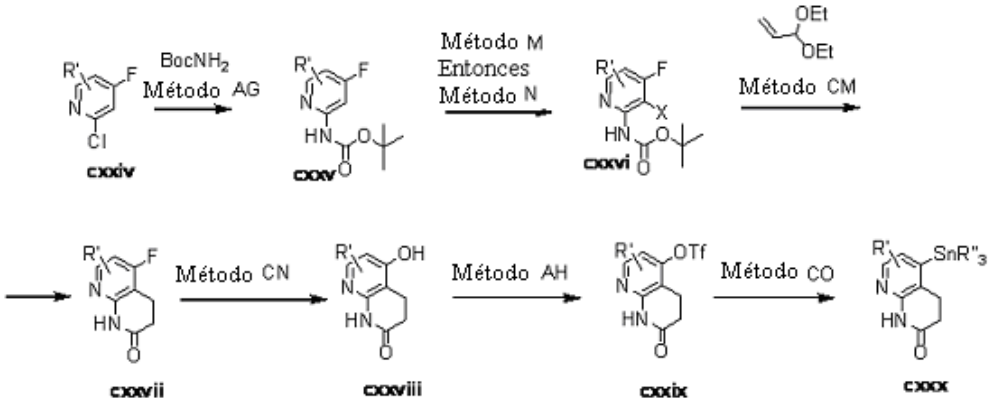
[00352] **Esquema 58: Método alternativo para la síntesis de bloques de construcción de imidazo[1,2–a]piridina.**



[00353] El Esquema 58 muestra un método alternativo para la síntesis de imidazolopiridinas **cxxiii**.

Como se muestra en el esquema 58, 2-metiltiazoles **cxx** se pueden desprotonar con un reactivo adecuado, tales como *n*-BuLi y posteriormente tratar con amidas de Weinreb en un solvente adecuado, tales como THF para dar cetonas **cxxi** (método CL). La halogenación de cetonas se puede obtener usando condiciones estándares, por ejemplo NBS en DCM (método C) y las halocetonas **cxxii** resultantes luego se tratan con aminopiridinas en un solvente adecuado, por ejemplo etanol a temperatura elevada para dar compuestos de fórmula **cxxiii** (método CF).

[00354] **Esquema 59: Método general para la síntesis de bloques de construcción de lactama bicíclica**

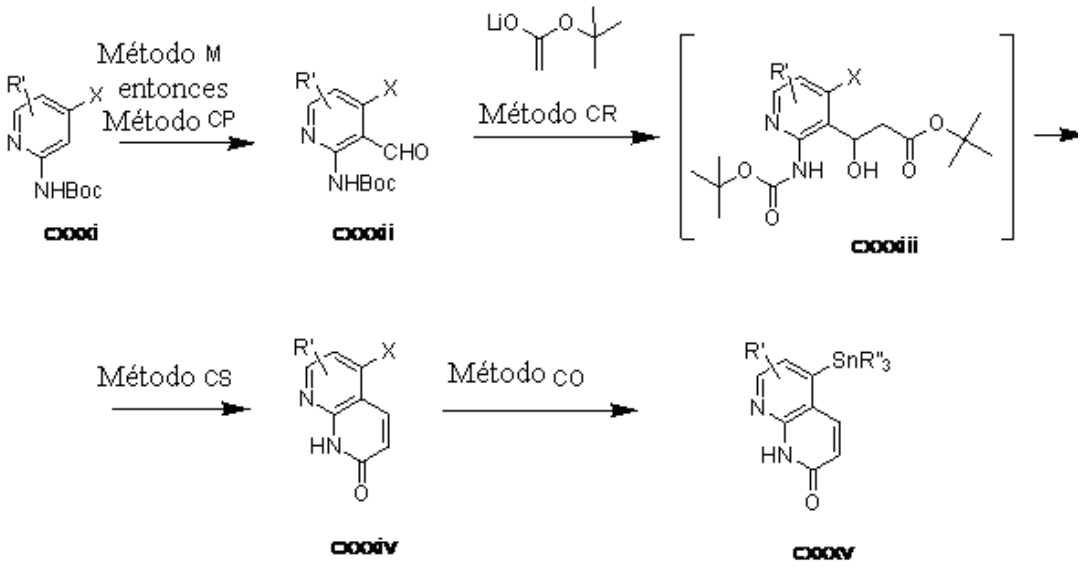


[00355] El Esquema 59 muestra un método general para la síntesis de bloques de construcción de lactama bicíclica **cxxix** y **cxxx**. Como se muestra en el esquema 59, las 2-cloro-4-fluoropiridinas sustituidas se pueden amidar, por ejemplo con $BocNH_2$, Pd_2dba_3 y un

ligando adecuado, tales como X-Fos en presencia de una base, por ejemplo carbonato de cesio en un solvente apropiado, como dioxano para proporcionar 2-aminopiridinas protegidas con Boc **cxxv** (método AG). Los compuestos **cxxv** se pueden desprotonar, por ejemplo usando *n*-BuLi/TMEDA en THF a temperatura baja (método M) y luego se inactivan con una molécula de halógeno, tales como yodo en THF (método N) para dar compuestos halogenados **cxxvi**. Los compuestos **cxxvi** se pueden acoplar con dietoxipropeno usando un catalizador de Pd adecuado, tales como Di-mu-clorobis[5-hidroxi-2-[1-(hidroxiimino-kappaN)etil]fenil-kappaC]paladio(II) dímero con una base apropiada, como *N,N*-diisopropiletilamina en un solvente adecuado, por ejemplo mezcla de DMF-agua (método CM) para proporcionar lactamas de fórmula **cxxvii**. La transformación de fluoro **cxxvii** en análogos de hidroxilo **cxxviii** se pueden llevar a cabo usando a procedimiento estándar, por ejemplo tratamiento con alcohol bencílico en presencia de una base, tal como hidruro de sodio a temperatura elevada y posterior desbencilación, tal como usando hidrogenación con catalizador de Pd/C en un solvente adecuado, tal como etanol (método CN). Los triflatos **cxxix** se pueden formar por el tratamiento de **cxxviii** en un reactivo adecuado, por ejemplo anhídrido tríflico usando condiciones apropiadas, tales como piridina como una base en DCM (método AH). Los triflatos **cxxix** se pueden acoplar con estannanos **xxix**, obtenidos en el Esquema 6 usando en condiciones de Stille estándares (método K). En forma alternativa, los triflatos **cxxix** se pueden transformar en estannanos **cxxx** usando un método

adecuado, tal como calentamiento con hexametildistannano, $Pd(PF_3)_4$ en un solvente adecuado, como THF (método CO). Los estannanos **cxxx** luego se pueden acoplar con haluros de tiofeno/tiazol **ic**, que se puede preparar por los procedimientos descriptos en los esquemas 3, 5, 6 usando en condiciones de Stille estándar (método K).

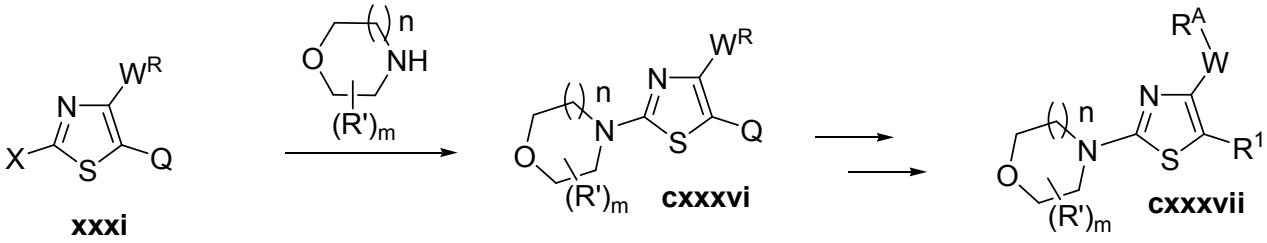
[00356] Esquema 60: Método alternativo para la síntesis de bloques de construcción de lactama bicíclica



[00357] El Esquema 60 muestra un método alternativo para la síntesis de bloques de construcción de lactama bicíclica **cxxxv**. Como se muestra en el esquema 60, los compuestos **cxxxi** se pueden desprotonar con un reactivo adecuado, tales como *n*–BuLi en THF a temperatura baja (método M) y luego tratar con DMF para producir carbaldehídos **cxxxii** (método CP). El grupo aldehído en **cxxxii** luego se puede tratar con enolato generado a

partir de *t*-Butilacetato y LDA en un solvente adecuado, tal como THF a temperatura baja (método CR) para el intermediario β-hidroxiésteres **cxxxiii** que se puede ciclar a lactamas **cxxxiv** usando un ácido, tal como HCl, en agua a temperatura elevada (método CS). Los haluros **cxxxiv** se pueden acoplar con estannanos **xxix**, obtenidos en el Esquema 6 usando condiciones de Stille estándares (método K). En forma alternativa, la transformación de haluros de arilo **cxxxiv** a estannanos **cxxxv** se puede realizar usando hexametildistannano, $Pd(PF_3)_4$ en un solvente adecuado, como THF (método CO). Los estannanos **cxxxv** luego se pueden acoplar con haluros de tiofeno/tiazol **ic**, que se pueden preparar por los procedimientos descriptos en los esquemas 3, 5, 6 usando en condiciones de Stille estándares (método K).

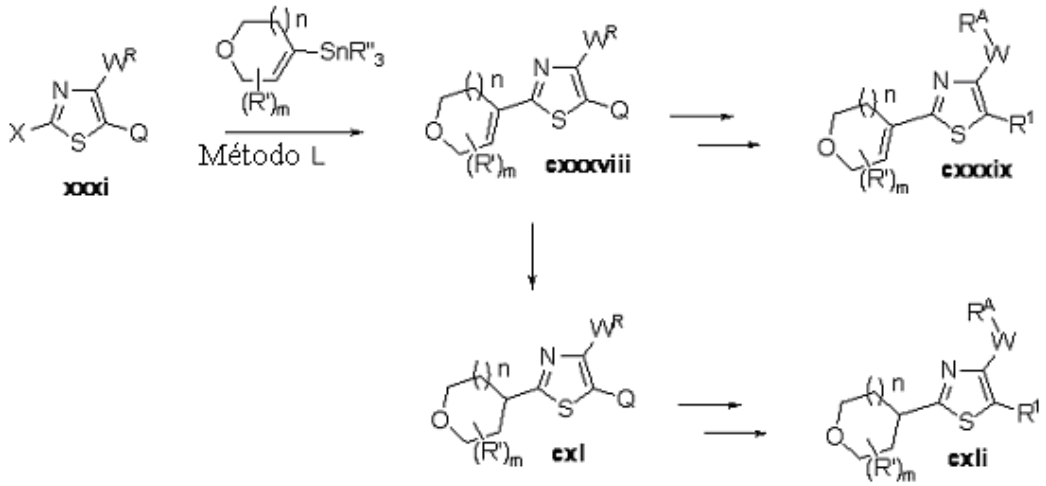
[00358] **Esquema 61: Método general para la preparación de 2-aminotiazoles**



[00359] El Esquema 61 muestra un método general para la preparación de compuestos de fórmula **cxxxvii**. Como se muestra en el esquema 61, los 2-halotiazoles se tratan con aminas a temperatura elevada, tanto puro como en un solvente adecuado, tales como NMP con una base apropiada, por ejemplo K_2CO_3 (método H) para proporcionar 2-aminotiazoles **cxxxvi**, que se pueden

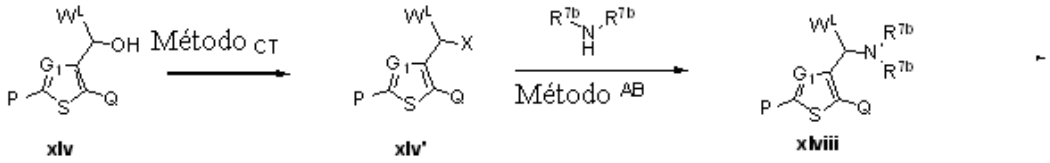
transformar adicionalmente a los compuestos **cxxxvii** usando métodos conocidos generalmente.

[00360] **Esquema 62: Método general para acoplamiento de halotiazoles con vinilestannanos**



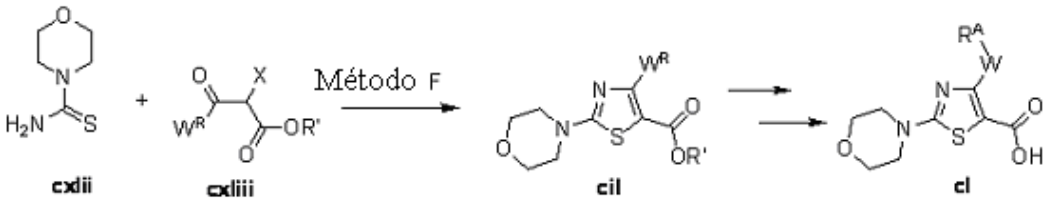
[00361] El Esquema 62 muestra un método general para la preparación de compuestos de fórmula **cxxxix** y **cxli**. Como se muestra en el esquema 62, los compuestos **xxxi** se pueden acoplar con vinilestananos en condiciones adecuadas, por ejemplo $Pd(PF_3)_4$, CuI, LiCl en dioxano a temperatura elevada para dar alquenos **cxxxviii** (método K), que se pueden transformar adicionalmente a compuestos **cxxxix** por métodos conocidos generalmente. En forma alternativa, la hidrogenación de **cxxxviii**, por ejemplo usando Pd/C como catalizador en un solvente adecuado, tal como etanol (método V) puede proporcionar compuestos **cxl**, que se pueden transformar adicionalmente a **cxli** by métodos conocidos generalmente.

[00362] **Esquema 71: Método general para la síntesis de aminas**



[00363] El Esquema 71 muestra un método general para la síntesis de aminas **xlviii.** Como se muestra en el Esquema 71, alcoholes **xlv** se pueden transformar a haluros **xlv'** usando el tratamiento con un reactivo adecuado, tal como PCl_5 en un solvente adecuado, tal como DCM. Los haluros **xlv'** luego se tratan con las aminas a temperatura elevada para proporcionar aminas blanco **xlviii** (método AB).

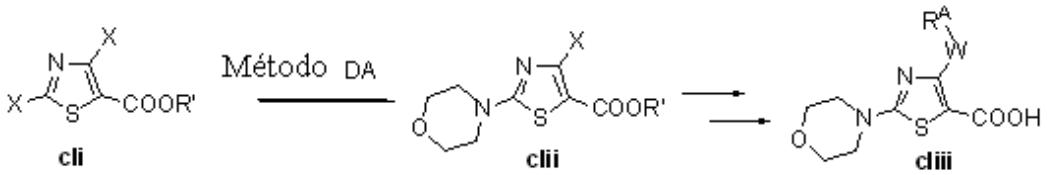
[00364] **Esquema 63: Método general para la síntesis de tiazoles sustituidos**



[00365] El Esquema 63 muestra una vía general para la síntesis de compuestos de fórmula **cl.** La tioamida **cxlii** se puede tratar con alfa halogenados carbonil compuestos **cxliii** en un solvente adecuado, tales como isopropanol a temperatura elevada para dar tiazoles **cil.** (método F). Una reacción de conversión de **cil** a los compuestos **cl** se pueden realizar por una combinación de

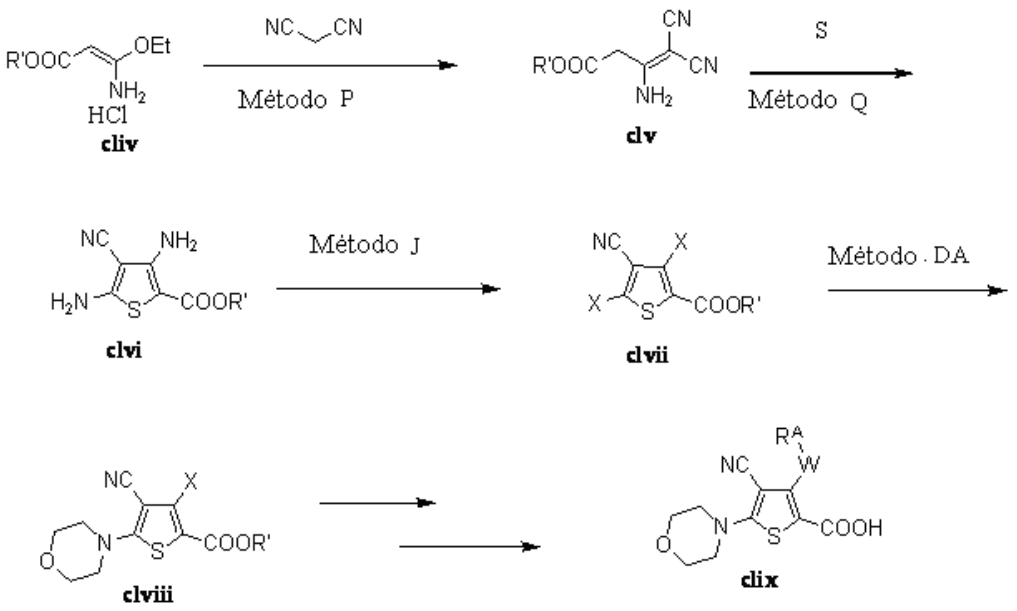
reacciones de conversión del grupo funcional generalmente conocido.

[00366] **Esquema 64: Método general para la introducción de morfolina en la posición 2 del núcleo tiazol.**



[00367] El Esquema 64 muestra una vía general para introducir morfolina en la posición 2 de la estructura del núcleo tiazol. Los ésteres de dihalotiazol, tales como 2,4-dibromo-5-tiazolcarboxilato de metilo se pueden tratar con morfolina a temperatura elevada, con una base adecuada, tales como carbonato de cesio en THF u otro solvente apropiado (método DA) para proporcionar compuestos de fórmula **clii**. Los compuestos **clii** luego se pueden transformar en compuestos **cliii** usando reacciones de conversión del grupo funcional generalmente conocido.

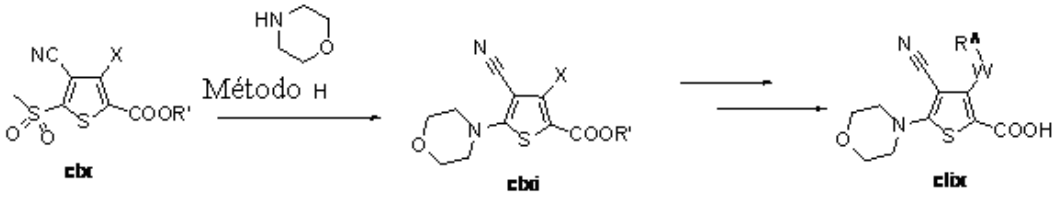
[00368] **Esquema 65: Método general para la síntesis de 3-cianotiofenos**



[00369] El Esquema 65 describe el procedimiento para la síntesis de 3-cianotiofenos **clix**. La alcoxietenamina sustituida **cliv** se puede tratar con malononitrilo en presencia de una base adecuada, tal como TEA, en un solvente adecuado, como cloroformo, a temperatura elevada para proporcionar aminoetilen malononitrilos sustituidos **clv** (método P), que se tratan con azufre en condiciones adecuadas, tales como DMF y temperatura elevada, para dar diaminocianotiofenos **xclvi** (método Q). Las diaminas **clvi** luego se pueden someter a la reacción de Sandmeyer usando reactivos apropiados, tales como bromuro de cobre (II), nitrito de amilo en ACN a temperatura elevada (método J) para proporcionar compuestos de fórmula **clvii**. Los dihalocianotiofenos luego se pueden tratar con morfolina a temperatura elevada, con una base adecuada, tales como carbonato de cesio en THF u otro solvente apropiado (método DA) para proporcionar compuestos de fórmula **clviii**. Los compuestos

clviii luego se pueden transformar en compuestos **clvix** usando reacciones de conversión del grupo funcional generalmente conocido.

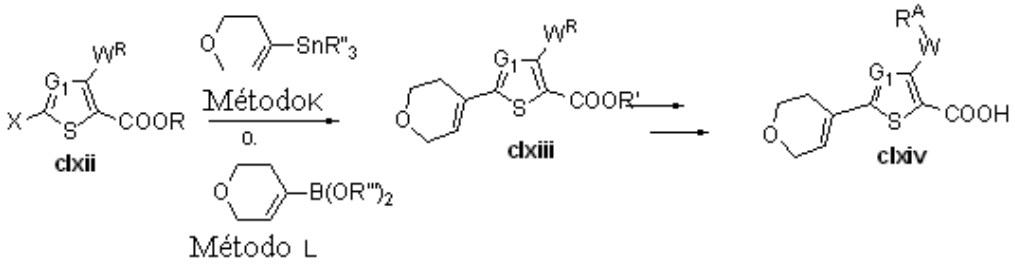
[00370] Esquema 66: Método alternativo para la síntesis de cianotiofenos



[00371] El Esquema 66 describe un procedimiento para la introducción de morfolina a análogos de 3-cianotiofeno. Como se muestra en el esquema 66, las sulfonas de fórmula **clx** (los ejemplos de síntesis se dan en Mansanet et al, WO 2005070916) se pueden tratar con morfolina en un solvente adecuado, *por ejemplo*, THF, a temperatura elevada (método H) para dar **clxi**. Las reacciones de conversión de **clxi** a los compuestos **clix** se pueden realizar, por ejemplo, por una combinación de reacciones de conversión del grupo funcional generalmente conocido.

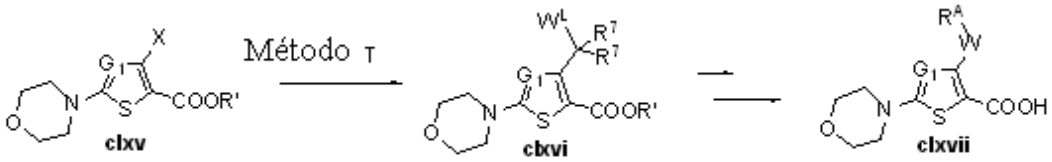
[00372] Esquema 67: Método general para acoplamiento de halotiofenos/ tiazoles con

vinilestannanos / ésteres borónicos



[00373] El Esquema 67 muestra un método general para la preparación de compuestos de fórmula **clxiv**. Como se muestra en el esquema 67, los compuestos **clxii** se pueden acoplar con vinilestananos en condiciones adecuadas, por ejemplo $Pd(PF_3)_4$, CuI, LiCl en dioxano a temperatura elevada para dar alquenos **clxiii** (método K). En forma alternativa, se pueden usar las condiciones de Suzuki, tales como $Pd(PF_3)_4$, $CsCO_3$, dioxano a temperatura elevada (método L). Los compuestos **clxiii** luego se pueden transformar adicionalmente en los compuestos **clxiv** por métodos conocidos generalmente.

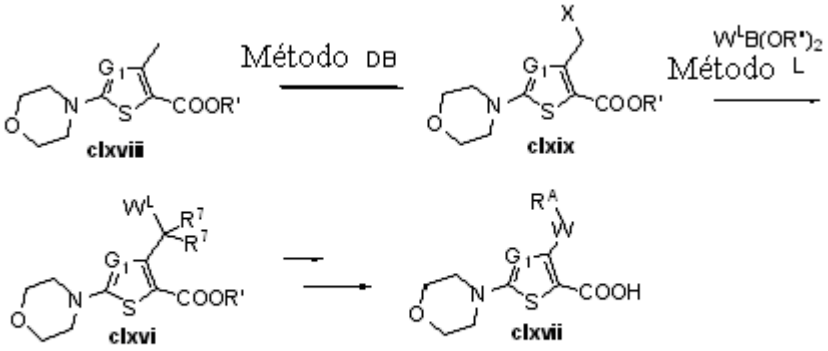
[00374] **Esquema 68: Método general para introducir la funcionalidad carbono en tiofenos / tiazoles halogenados.**



[00375] Como se muestra en el esquema 68 la funcionalidad carbono se puede introducir por la técnica de acoplamiento cruzado de Negishi bien conocida.

Los tiofenos / tiazoles halogenados **clxv** se pueden tratar con haluros de alquil zinc usando catalizador de Pd, tales como Pd(tBu$_3$P)$_2$ en condiciones de acoplamiento cruzado de Negishi estándares, tales como THF a temperatura elevada (método T) para proporcionar compuestos **clxvi**, que se pueden transformar adicionalmente a los compuestos **clxvii** usando métodos generalmente conocidos.

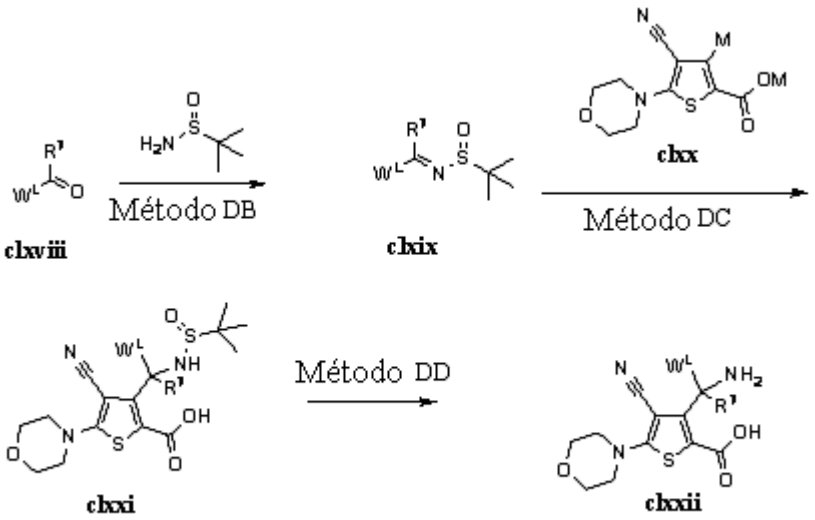
[00376] Esquema 69: Método alternativo para introducir funcionalidad carbono en tiofenos / tiazoles.



[00377] Como se muestra en el esquema 69, el sustituyente metilo de los tiofenos/tiazoles **clxviii** se puede halogenar usando un reactivo adecuado, por ejemplo NBS con una fuente de radical, tales como AIBN en un solvente apropiado, como DCM (método DB) para proporcionar haluros **clxix**. Los haluros **clxix** luego se pueden acoplar con ácidos o ésteres borónicos usando la bien conocida técnica de acoplamiento cruzado de Suzuki, por ejemplo Pd(PF$_3$)$_4$, Cs$_2$CO$_3$, dioxano-agua a temperatura elevada (método L) para proporcionar compuestos **clxvi**,

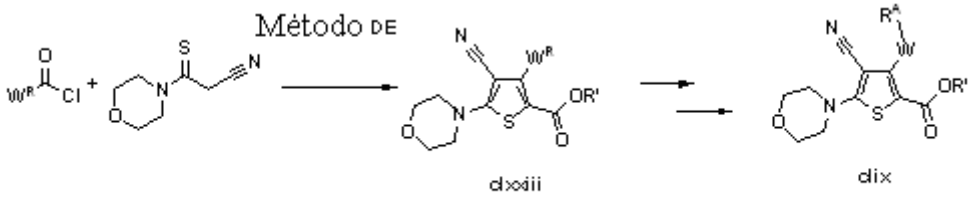
que se pueden transformar adicionalmente a los compuestos **clxvii** usando métodos generalmente conocidos.

[00378] **Esquema 70: Método general para la síntesis de amino ácidos**



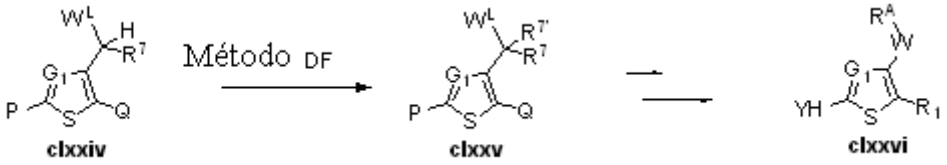
[00379] Como se muestra en el esquema 70, los aldehídos o cetonas **clxx** se pueden tratar con 2-Metil-2-propanesulfinamida en presencia de un ácido de Lewis adecuado, tal como $Ti(OiPr)_4$ en THF anhidro, u otro solvente adecuado para proporcionar sulfinamidas **clxixi** (método DC), que se pueden tratar posteriormente con compuestos metálicos de tiofeno **clxxii** (método DD), obtenidos de los correspondientes haluros de tiofeno a través del intercambio halógeno-metal, por ejemplo a partir del bromuro de tiofeno usando un exceso de fenillitio a temperatura baja. Las sulfinil aminas formadas **clxxiii** luego se pueden tratar con un ácido, tales como HCl en dioxano con un cosolvente opcional por ejemplo DCM (método DE) para proporcionar aminoácidos **clxxiv**.

[00380] **Esquema 72: Método alternativo para la síntesis de cianotiofenos**



[00381] Como se muestra en el esquema 72, los haluros de acilo se pueden acoplar con tiomorfolina y haloacetato de alquilo en presencia de una base adecuada, tales como diisopropilamina en un solvente apropiado, por ejemplo MeCN a temperatura elevada para proporcionar cianotiofenos **clxxiii** (método DE). Una reacción de conversión de **clxxiii** a los compuestos **clix** se pueden realizar por una combinación de manipulaciones del grupo funcional generalmente conocidas.

[00382] **Esquema 73: Método general para alquilación bencílica**

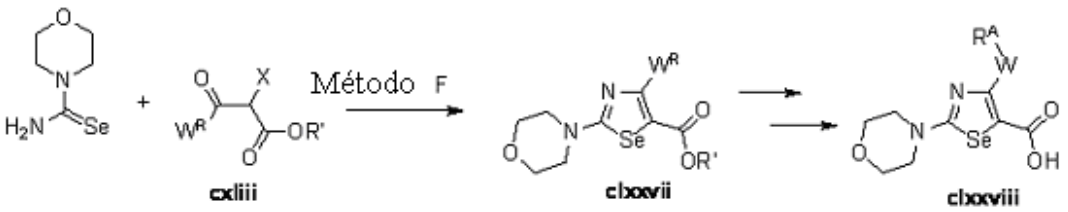


[00383] Como se muestra en el esquema 73, los compuestos **clxxiv** (donde W^L es un grupo aromático o heteroaromático) se puede desprotonar usando una base adecuada, tal como KO*t*Bu en un solvente apropiado, por ejemplo THF y posteriormente se alquila usando un haluro de alquilo $R^{7\prime}$–X (método DF) para proporcionar los productos de alquilaciones bencílicas **clxxv**. Los compuestos **clxxv** se pueden transformar adicionalmente a

los compuestos **clxxvi** usando métodos generalmente conocidos.

[00384]

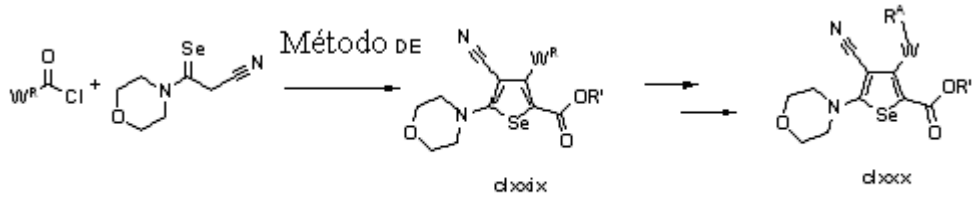
[00385] **Esquema 74: Método general para la síntesis de selenazoles sustituidos**



[00386] El Esquema 74 muestra una vía general para la síntesis de compuestos de fórmula **clxxvii.**

La selenoamida se puede tratar con compuestos carbonilo alfa halogenados **cxliii** en un solvente adecuado, tales como isopropanol a temperatura elevada para dar selenazoles **clxxvii.** (método F). Una reacción de conversión de **clxxvii** a los compuestos **clxxviii** se puede realizar por una combinación de manipulaciones del grupo funcional generalmente conocidas.

[00387] **Esquema 75: Método general para la síntesis de selenofenos**



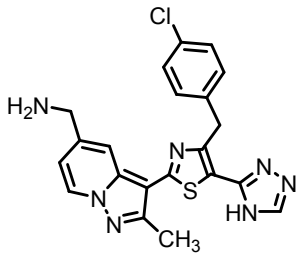
[00388] Como se muestra en el esquema 75, los haluros de acilo se pueden acoplar con bloques de

construcción de selenomorfolina y alquilhaloacetato en presencia de una base adecuada, tales como diisopropilamina en un solvente apropiado, por ejemplo MeCN a temperatura elevada para proporcionar selenofenes **clxxix** (método DE). Una reacción de conversión de **clxxix** a los compuestos **clxxx** se puede realizar por una combinación de manipulaciones del grupo funcional generalmente conocidas.

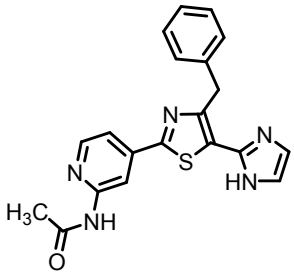
[00389] **EJEMPLOS**

[00390] La siguiente Tabla 1 representa ciertos compuestos representado por los compuestos de fórmula general **IA** e **IB**.

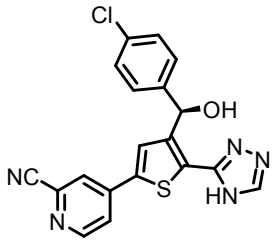
[00391] **Tabla 1**



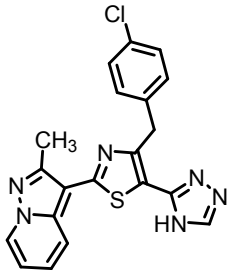
1



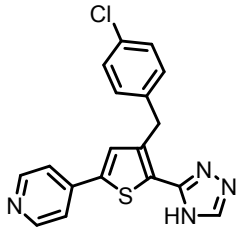
2



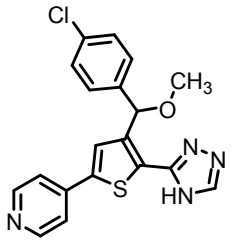
3



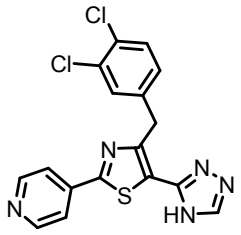
4



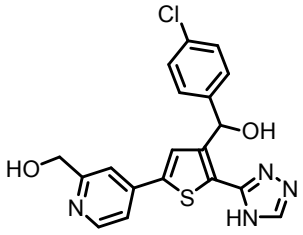
5



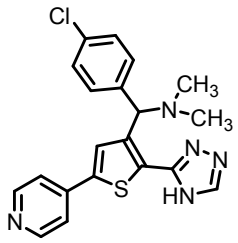
6



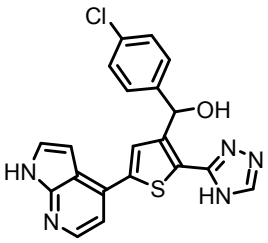
7



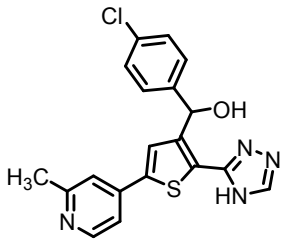
8



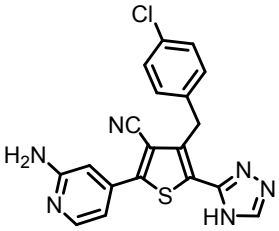
9



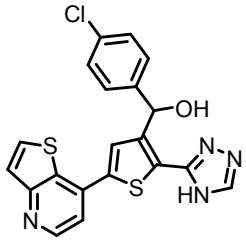
10



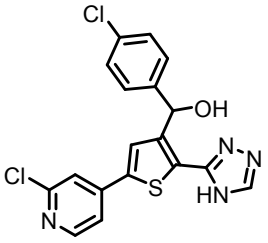
11



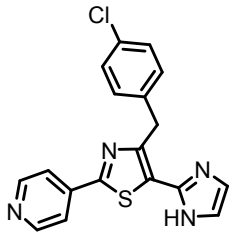
12



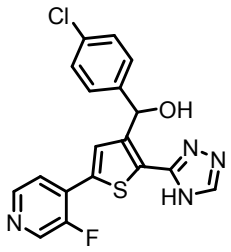
13



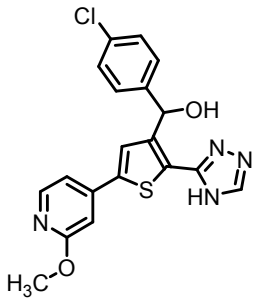
14



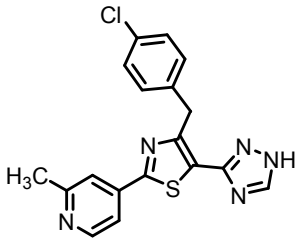
15



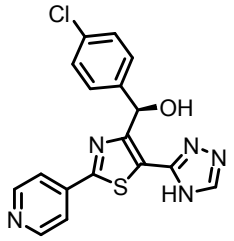
16



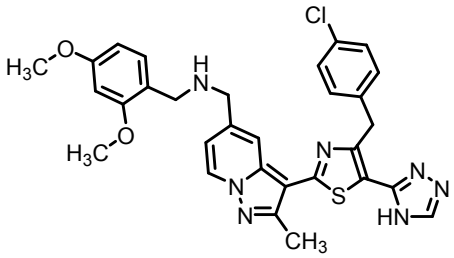
17



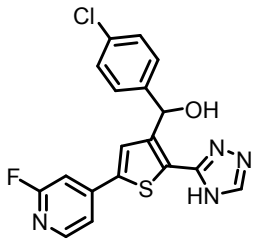
18



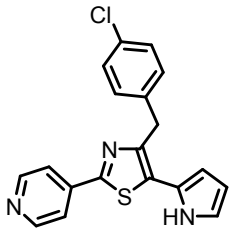
19



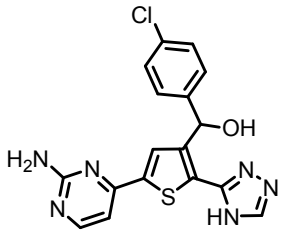
20



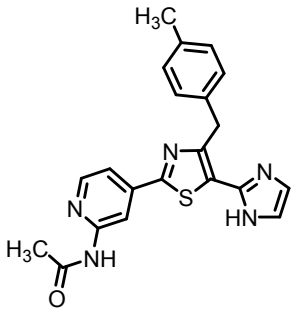
21



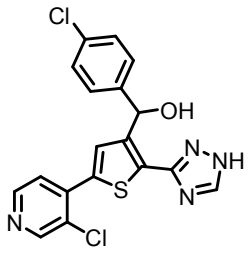
22



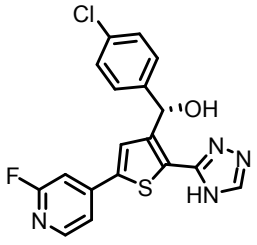
23



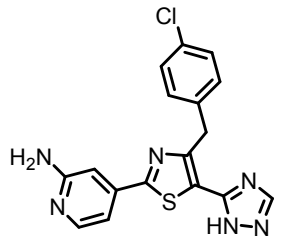
24



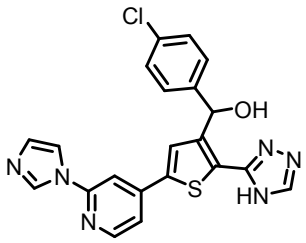
25



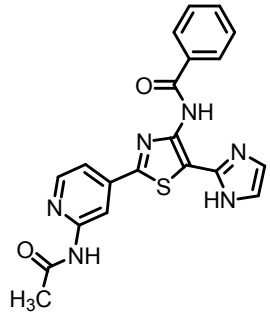
26



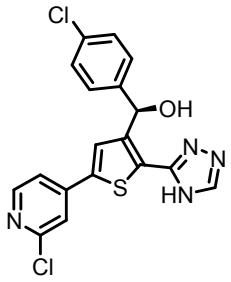
27



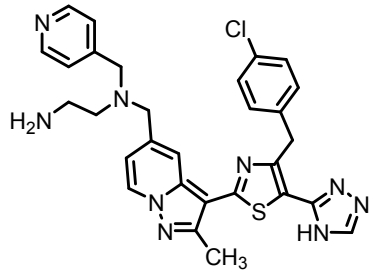
28



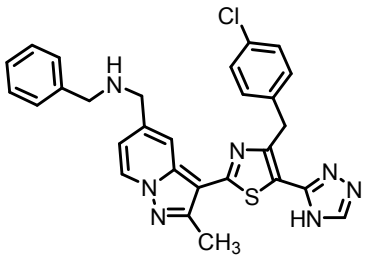
29



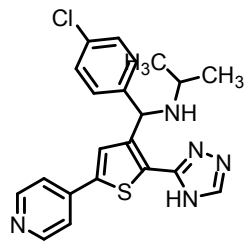
30



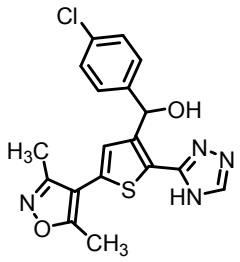
31



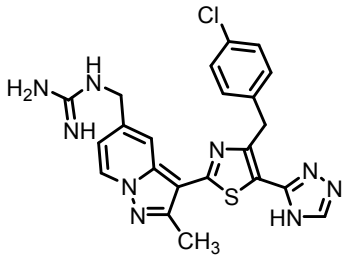
32



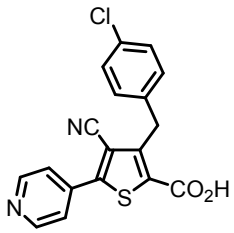
33



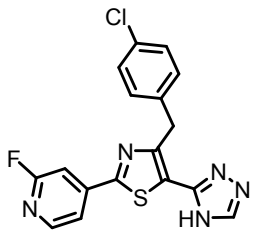
34



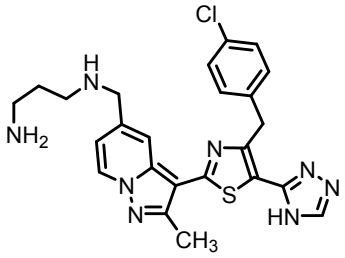
35



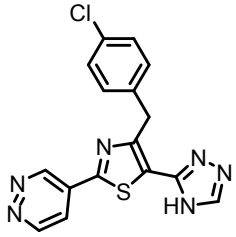
36



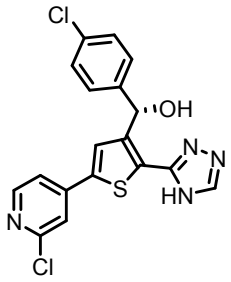
37



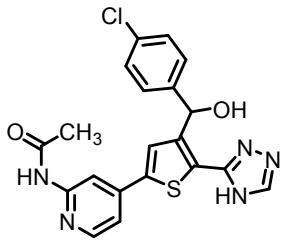
38



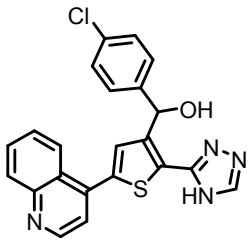
39



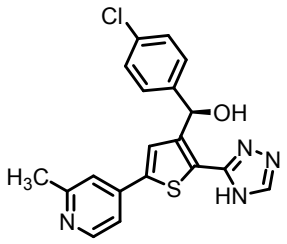
40



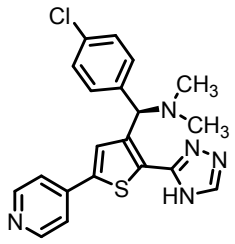
41



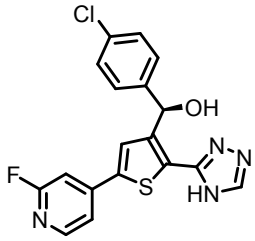
42



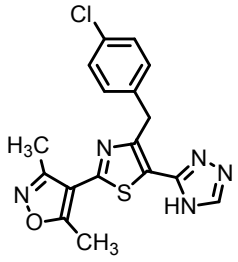
43



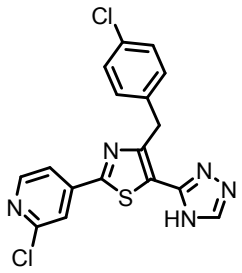
44



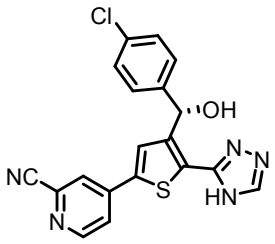
45



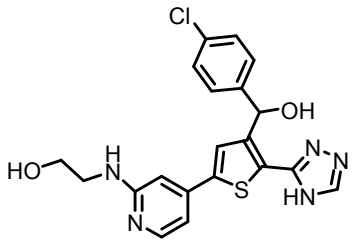
46



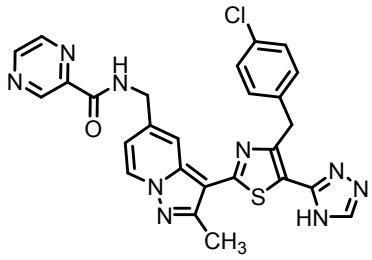
47



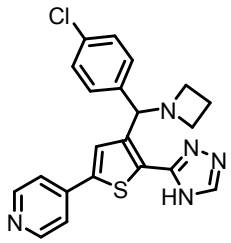
48



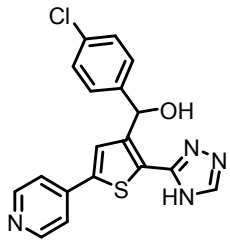
49



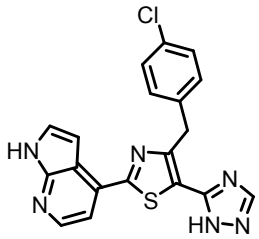
50



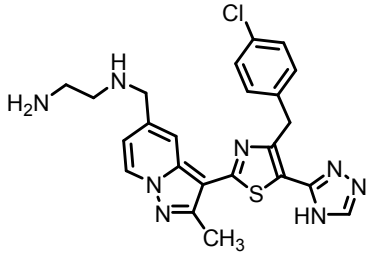
51



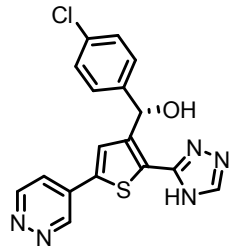
52



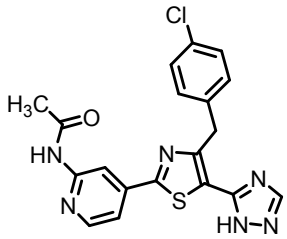
53



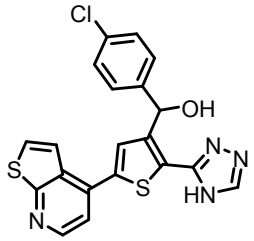
54



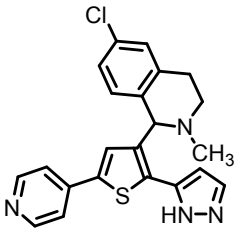
55



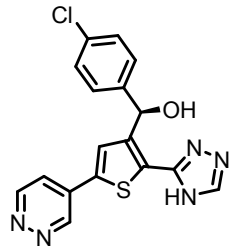
56



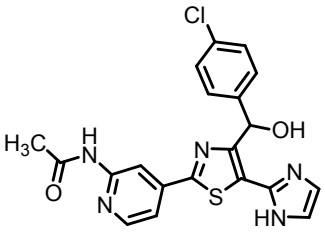
57



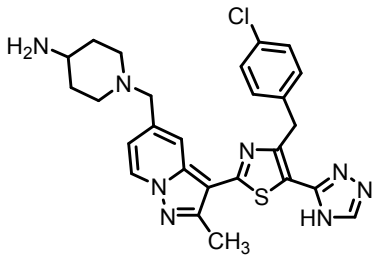
58



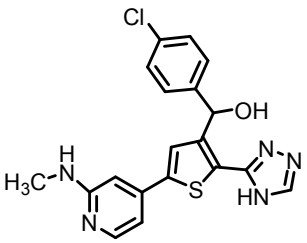
59



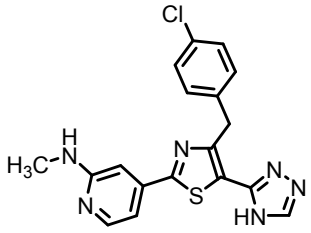
60



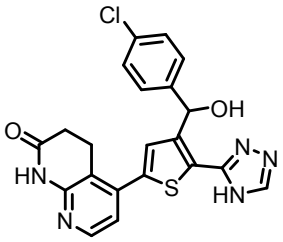
61



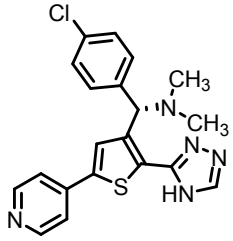
62



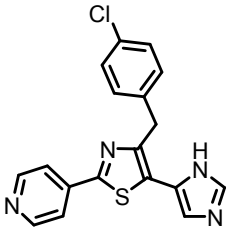
63



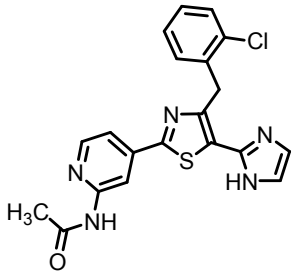
64



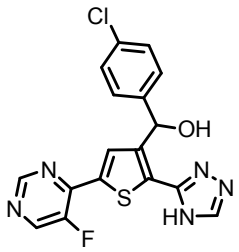
65



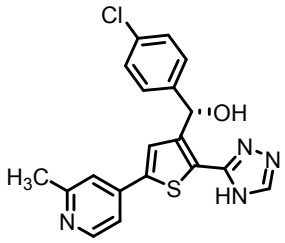
66



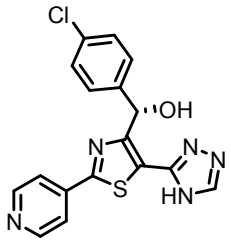
67



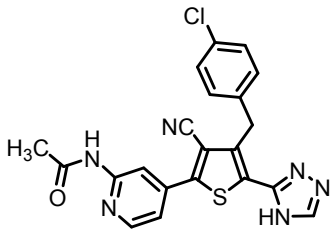
68



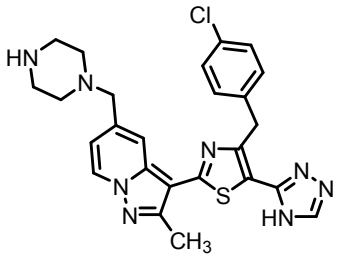
69



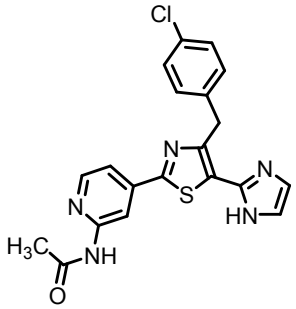
70



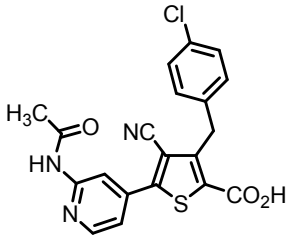
71



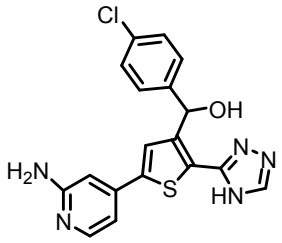
72



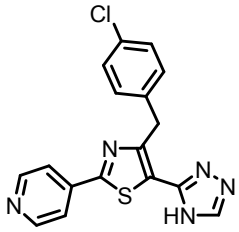
73



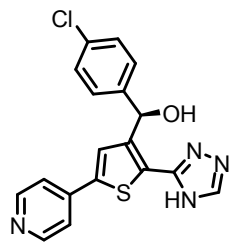
74



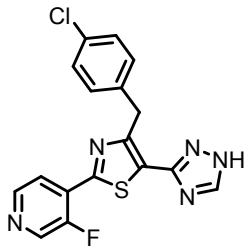
75



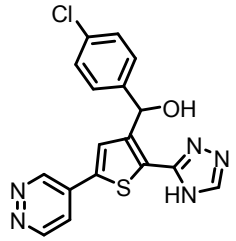
76



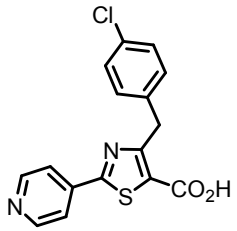
77



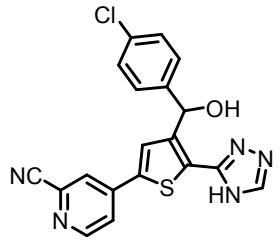
78



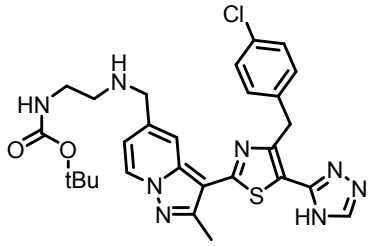
79



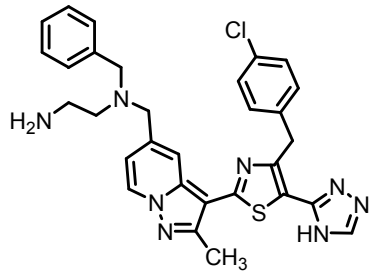
80



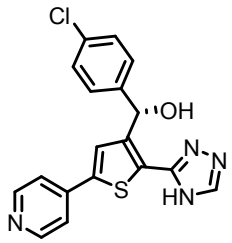
81



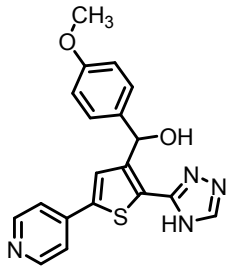
82



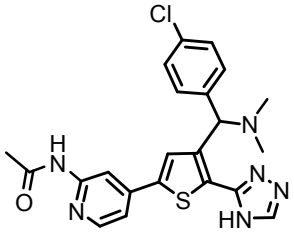
83



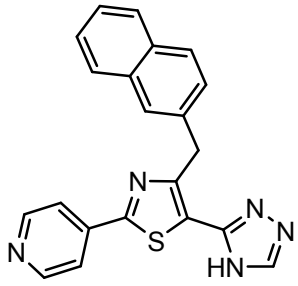
84



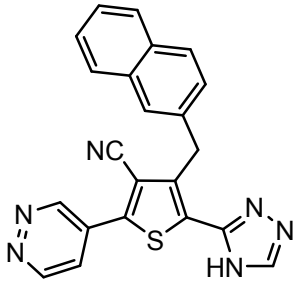
85



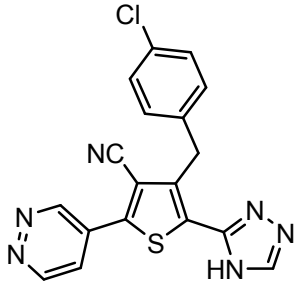
86



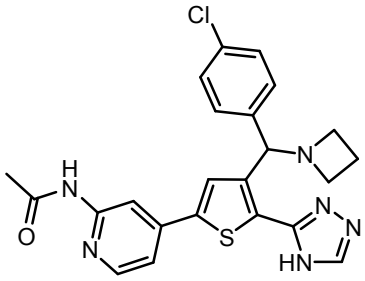
87



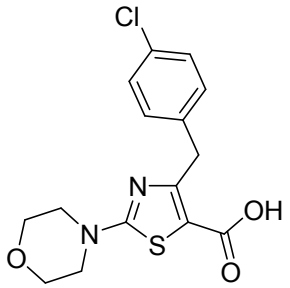
88



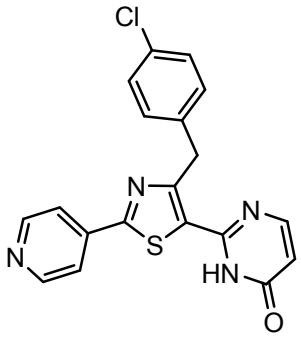
89



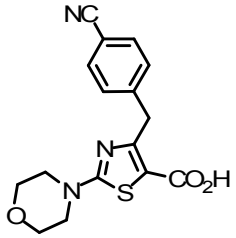
90



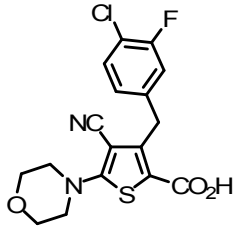
91



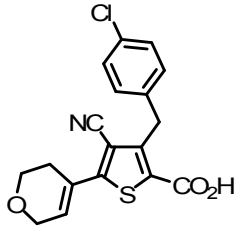
92



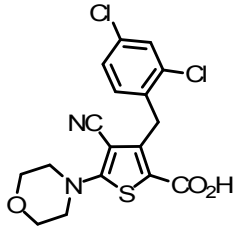
93



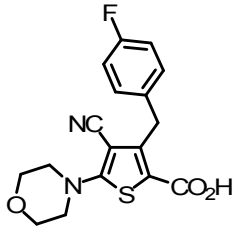
94



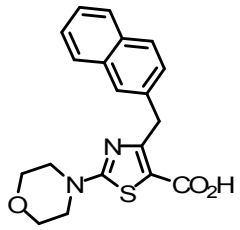
95



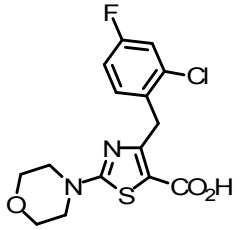
96



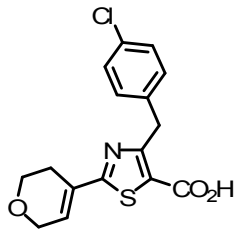
97



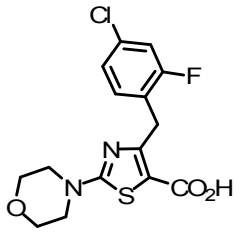
98



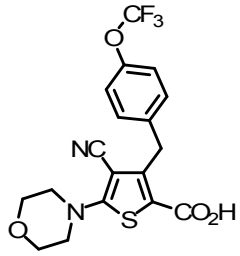
99



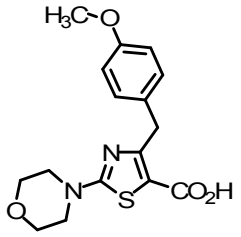
100



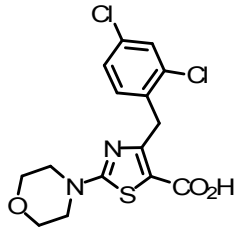
101



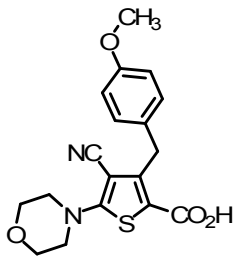
102



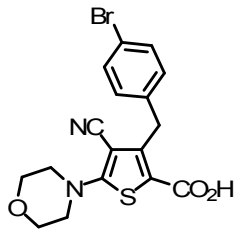
103



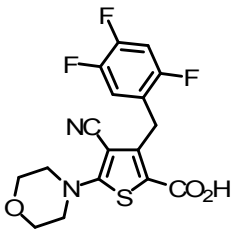
104



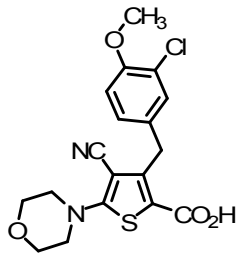
105



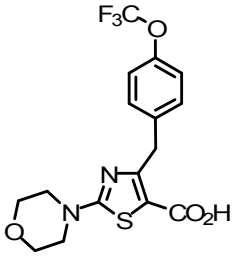
106



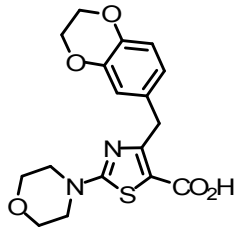
107



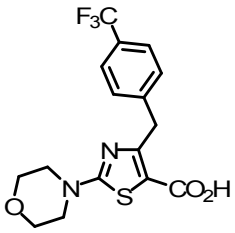
108



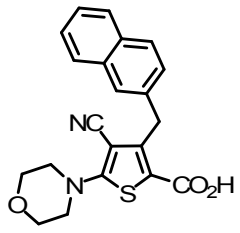
109

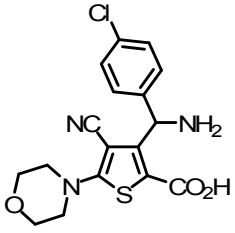


110

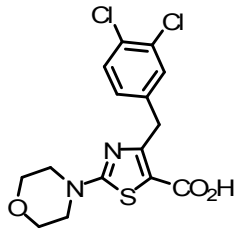


111

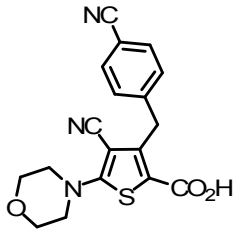




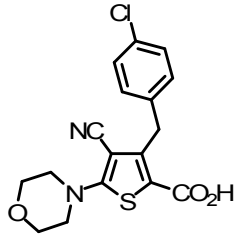
112



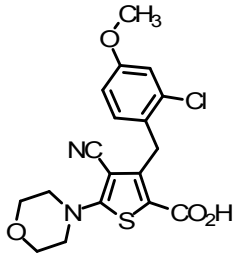
113



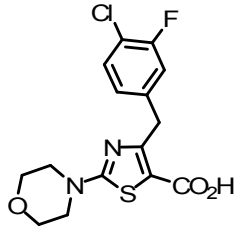
114



115



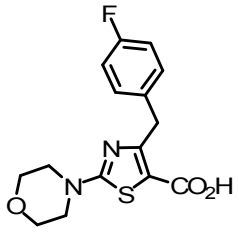
116

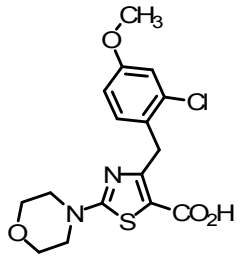


117

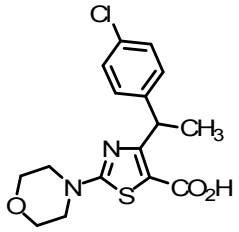
118

119

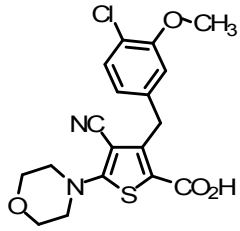




120



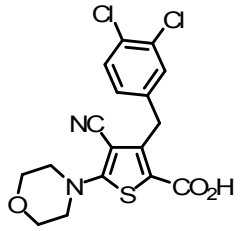
121



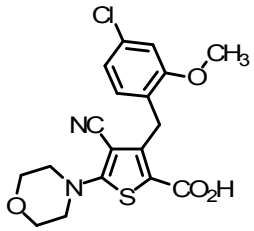
122



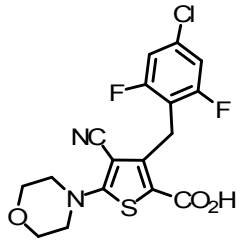
123



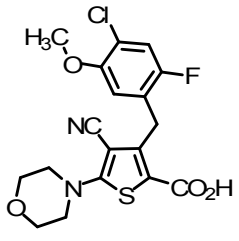
124



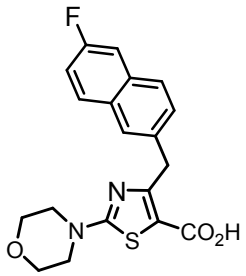
125



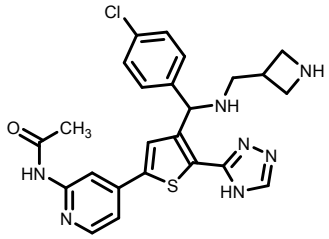
126



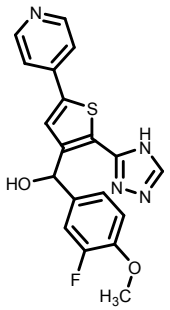
127



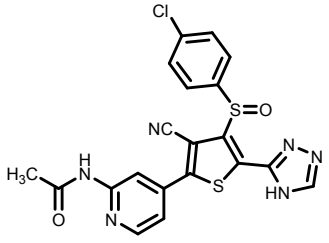
128



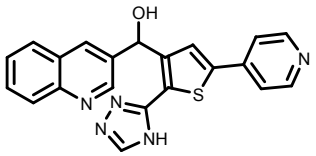
129



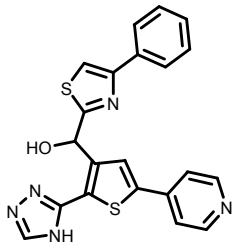
130



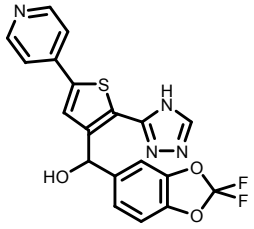
131



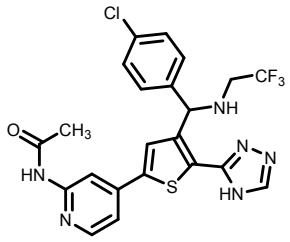
132



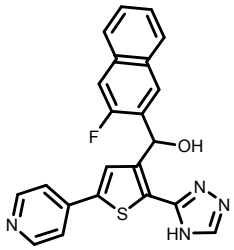
133



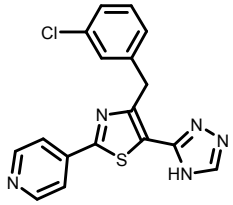
134



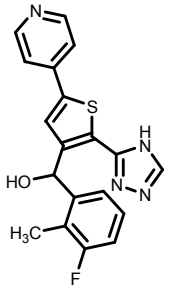
135



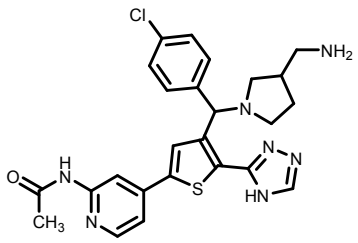
136



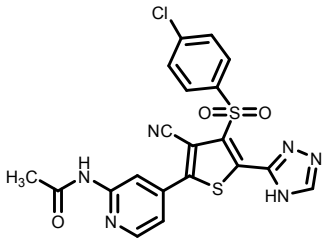
137



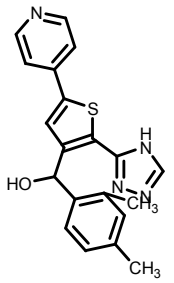
138



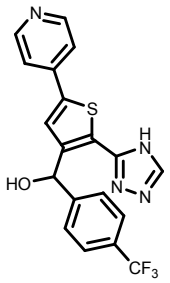
139



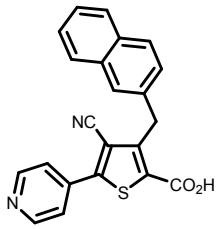
140



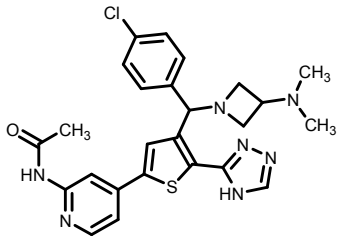
141



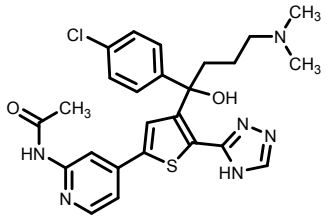
142



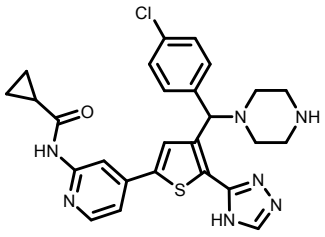
143



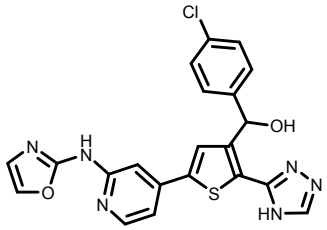
144



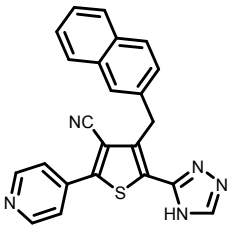
145



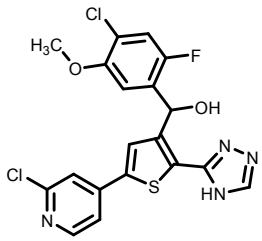
146



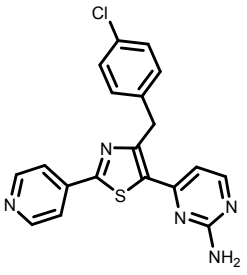
147



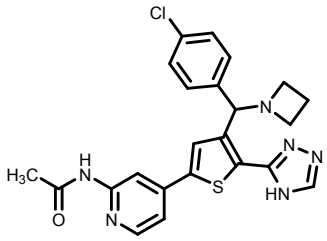
148

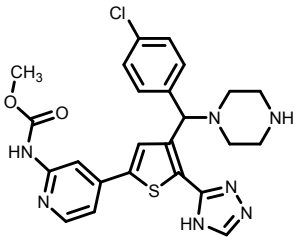


149

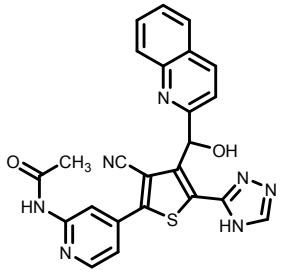


150

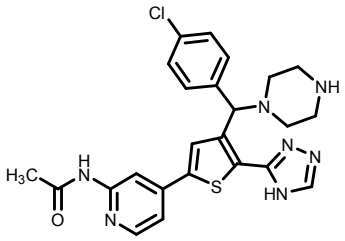




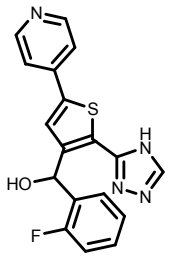
151



152

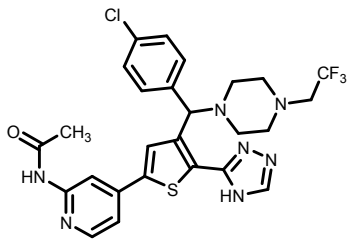


153

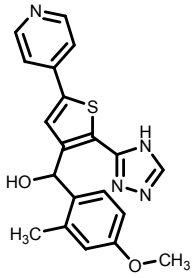


154

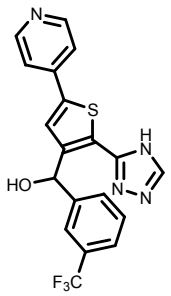
155



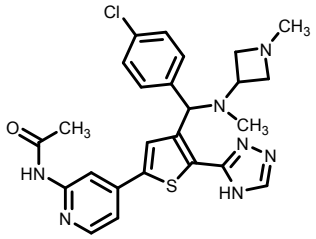
157



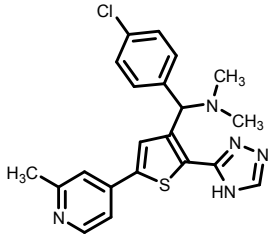
158



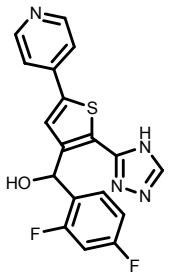
159



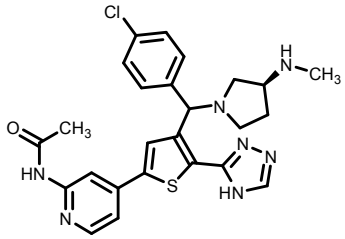
160



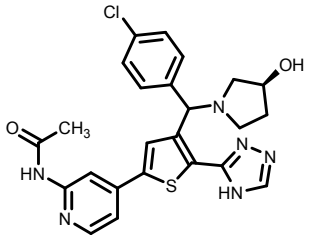
161



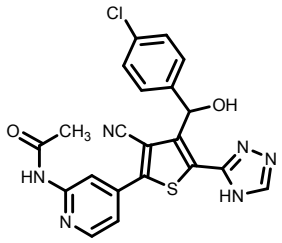
162



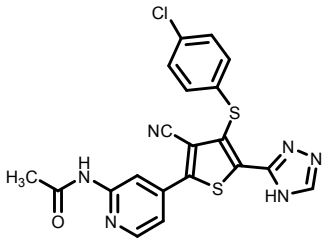
163



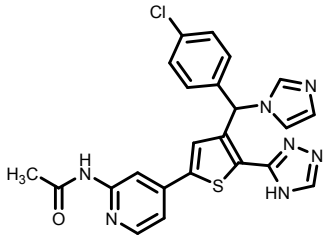
164



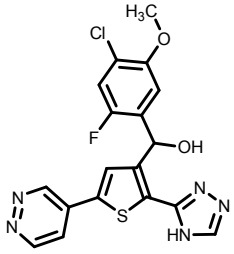
165



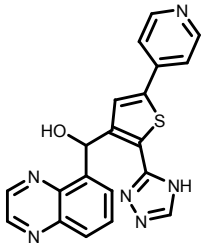
166



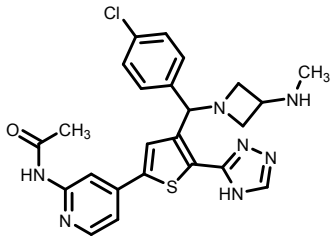
167



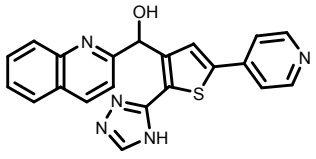
168



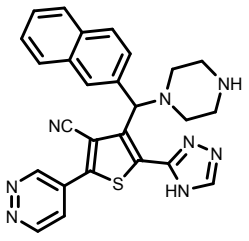
169



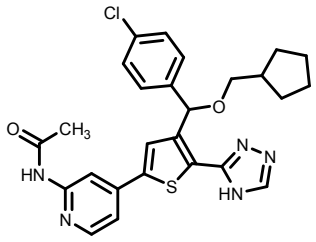
170



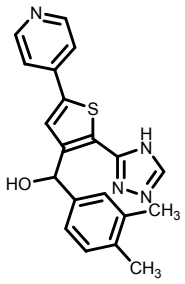
171



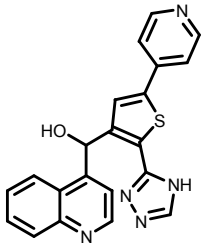
172



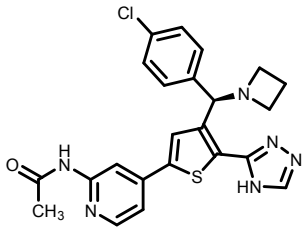
173



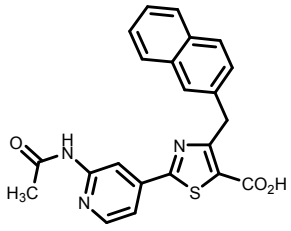
174



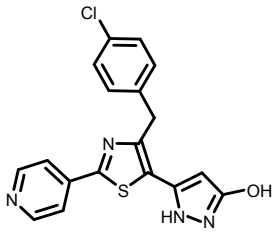
175



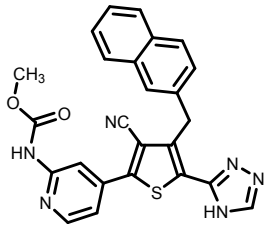
176



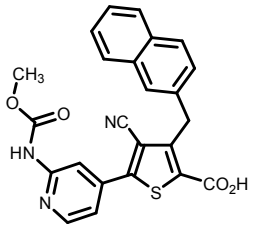
177



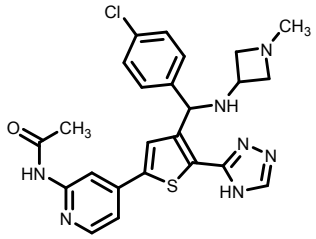
178



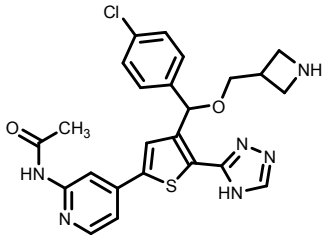
179



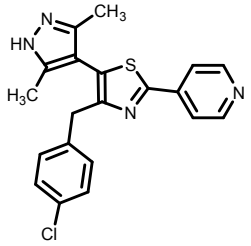
180



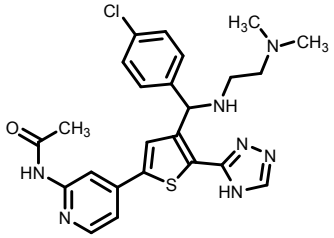
181



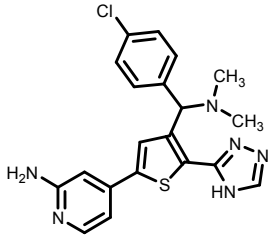
182



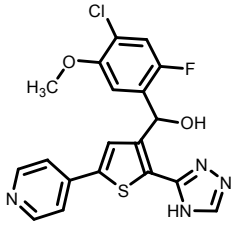
183



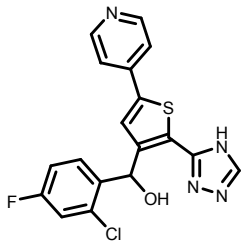
184



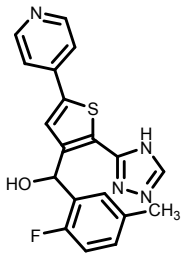
186



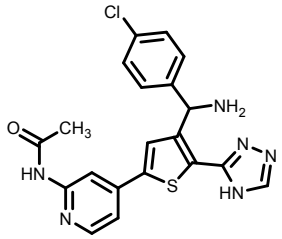
185



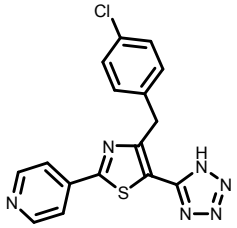
187



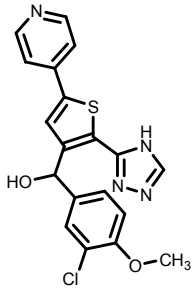
188



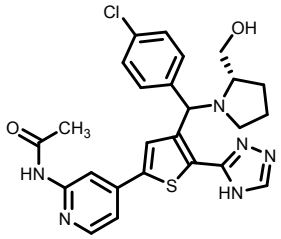
189



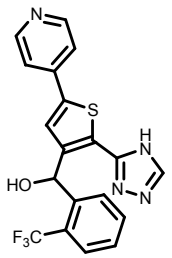
190



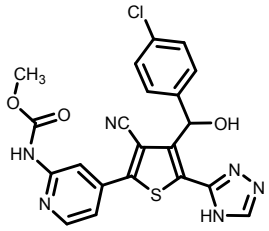
191



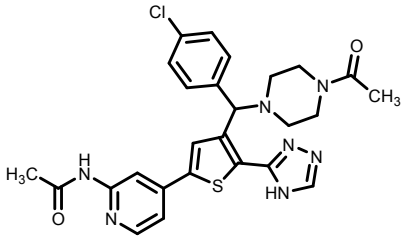
192



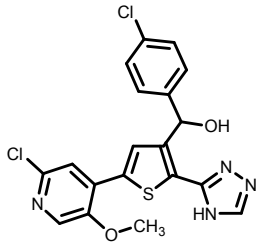
193



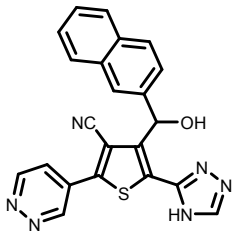
195



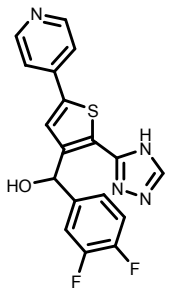
196



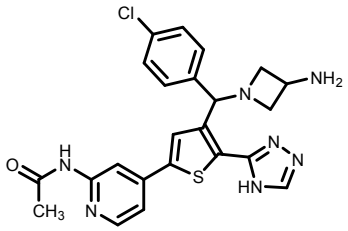
197



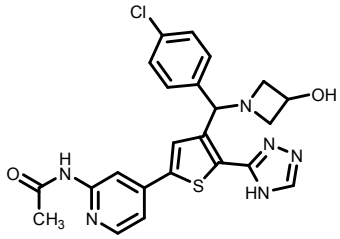
198



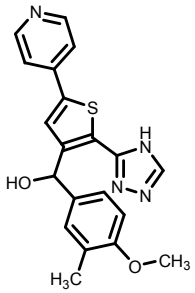
199



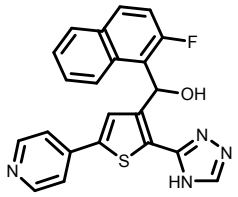
200



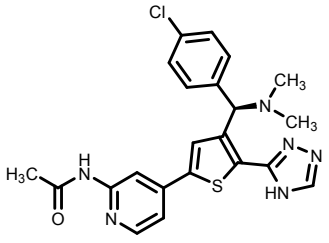
201



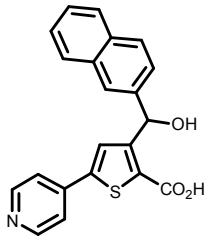
202



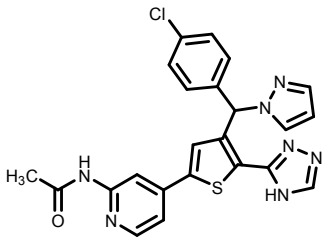
203



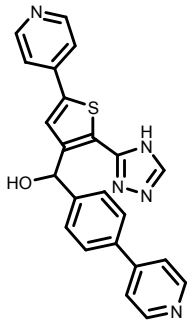
204



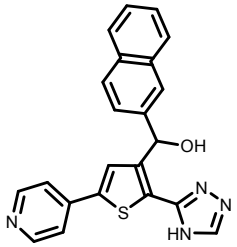
205



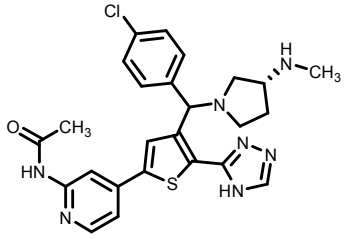
206



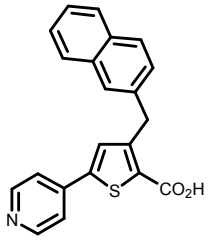
207



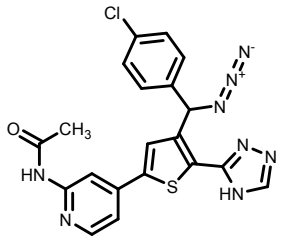
208



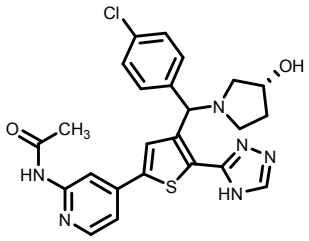
209



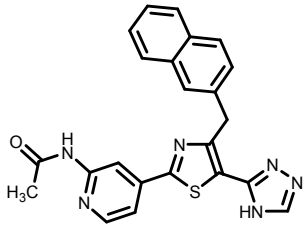
210



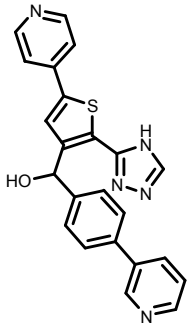
211



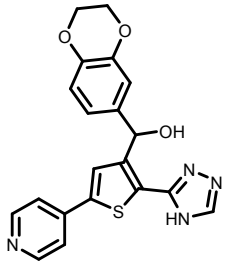
212



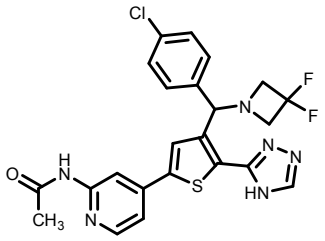
213



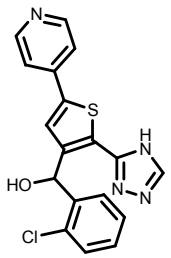
214



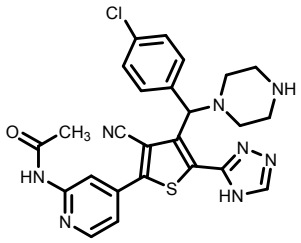
215



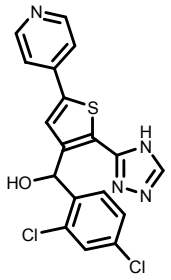
216



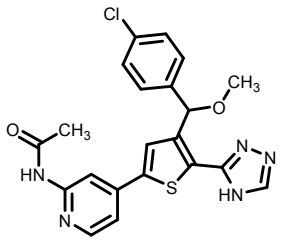
217



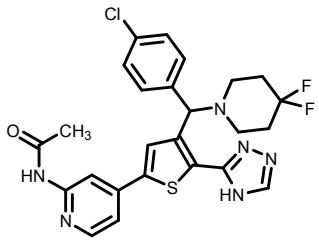
218



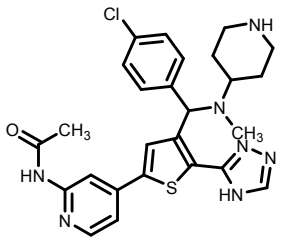
219



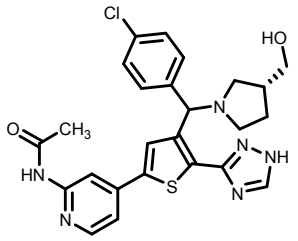
220



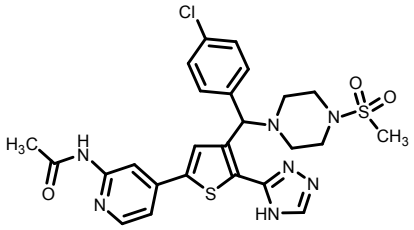
221



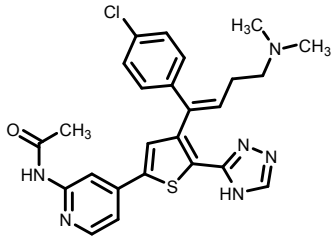
222



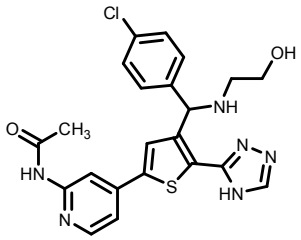
223



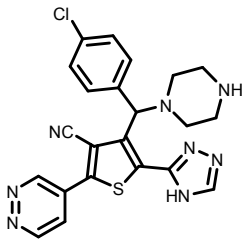
224



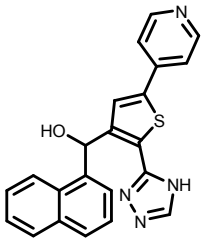
225



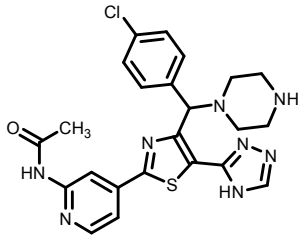
226

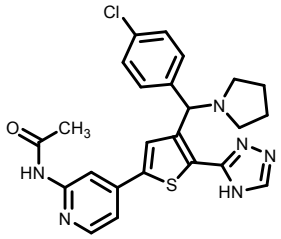


227

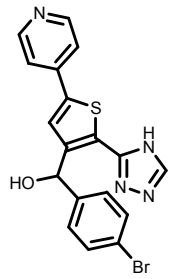


228

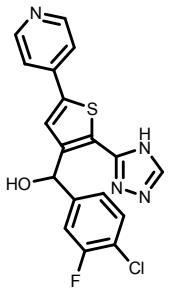




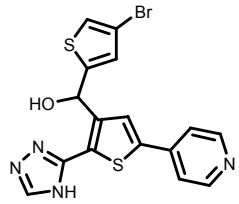
229



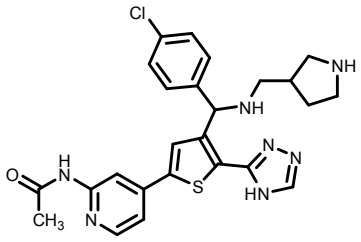
230



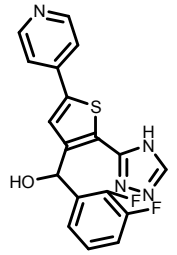
231



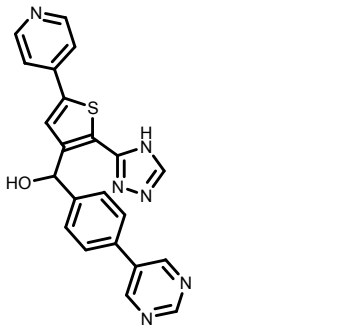
232



233

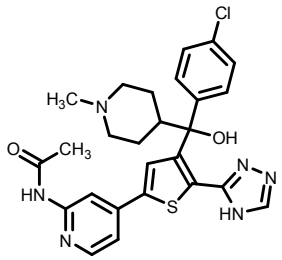


234

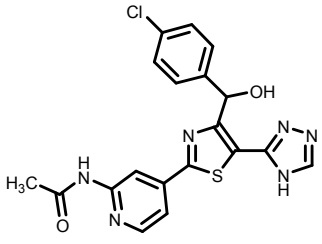


235

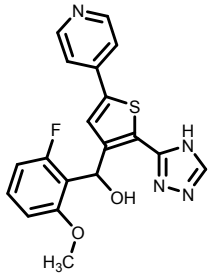
236



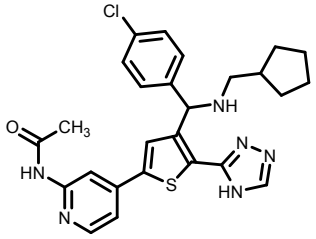
237



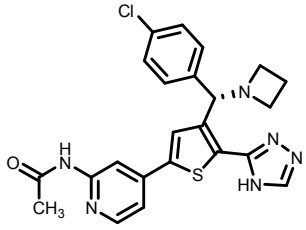
238



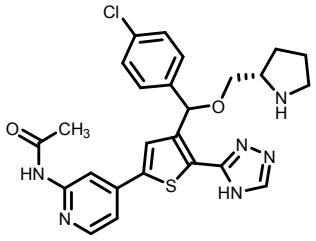
239



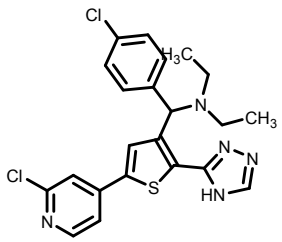
240



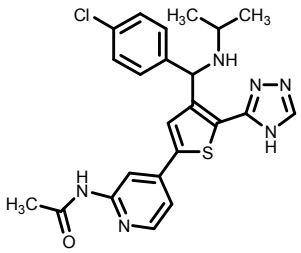
241



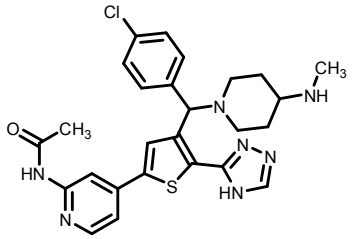
242



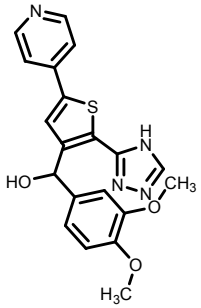
243



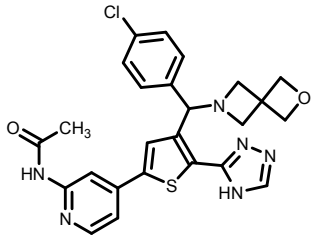
244



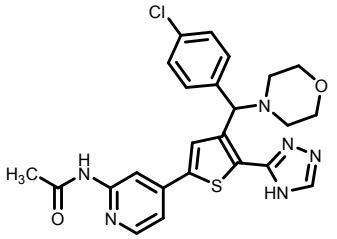
245



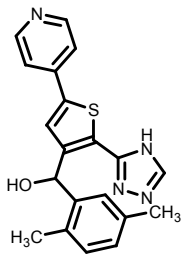
246



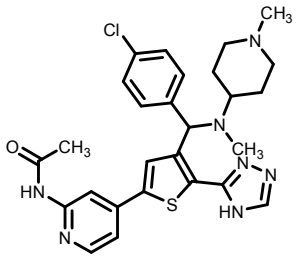
247



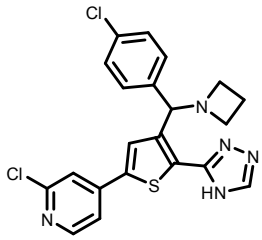
248



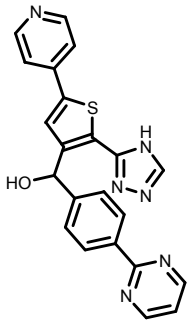
249



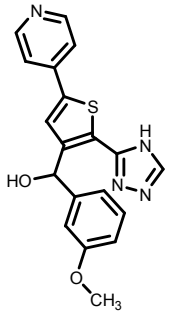
250



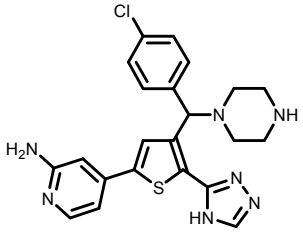
251



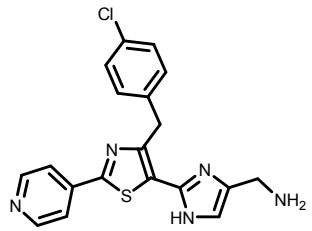
252



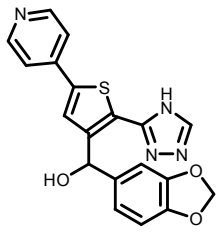
253



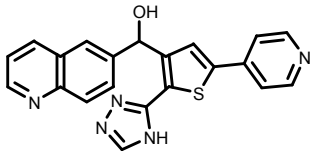
254



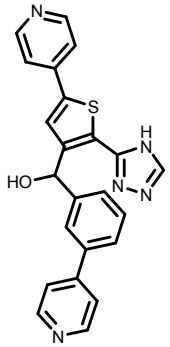
255



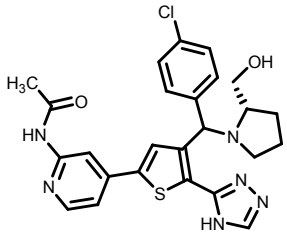
256



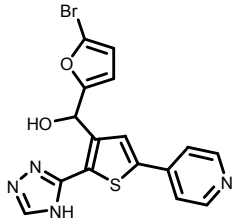
257



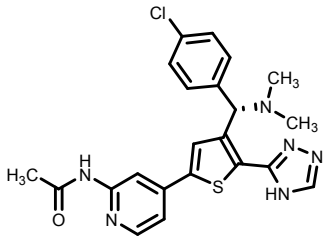
258



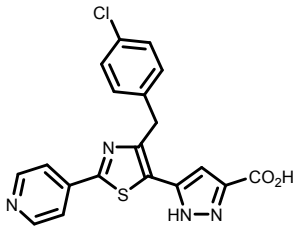
259



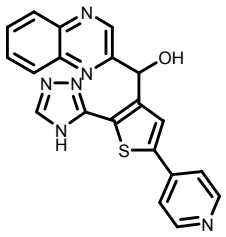
260



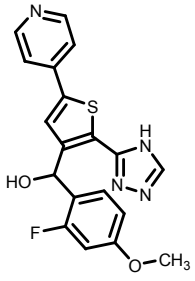
261



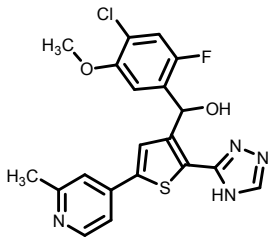
262



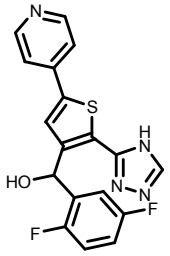
263



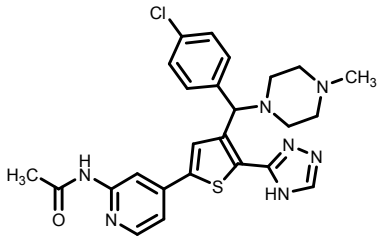
264



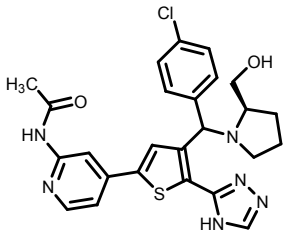
265



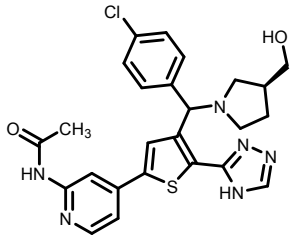
266



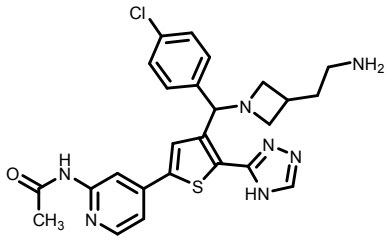
267



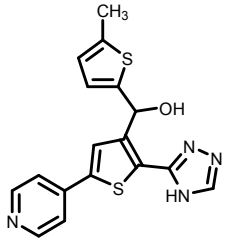
268



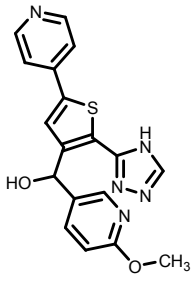
269



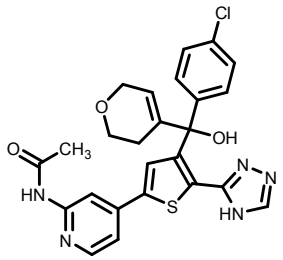
270



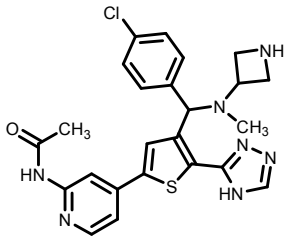
271



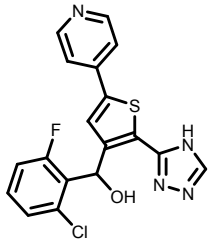
272



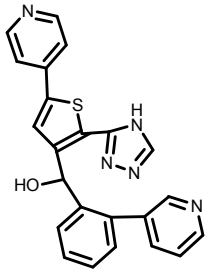
273



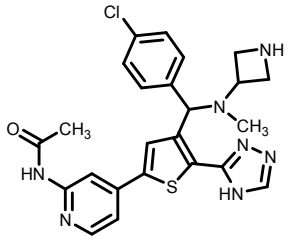
274



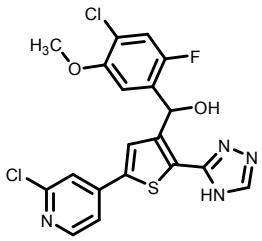
275



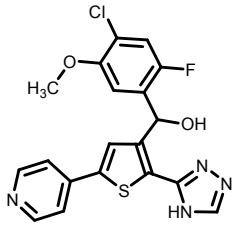
276



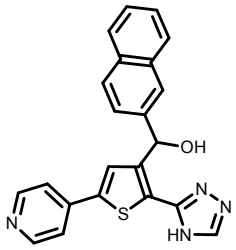
277



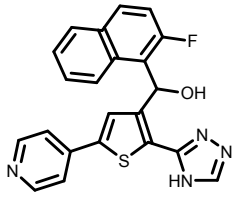
278



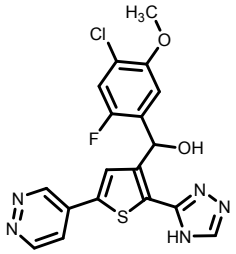
279



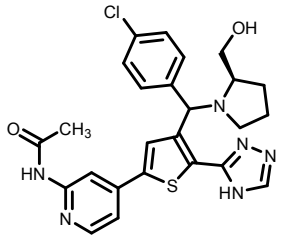
280



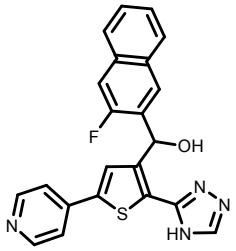
281



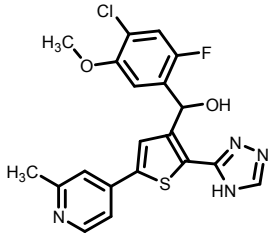
282



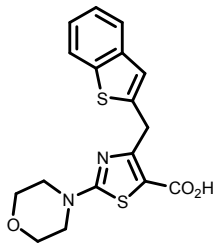
283



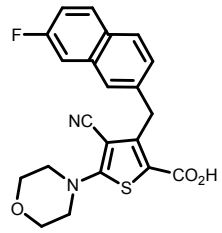
284



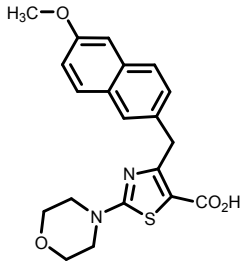
285



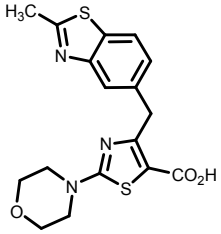
286



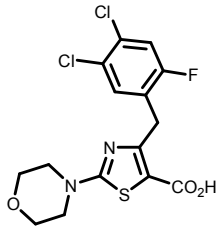
287



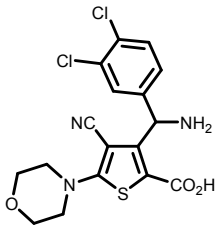
288



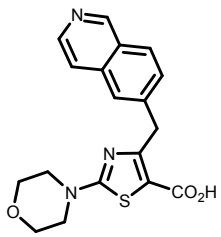
289



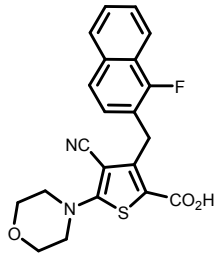
290



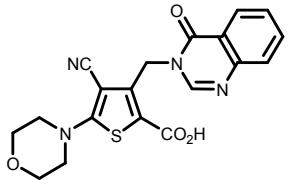
291



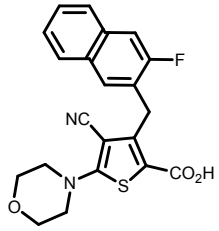
292



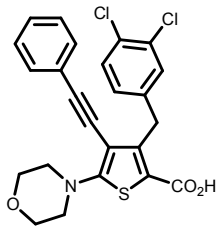
293



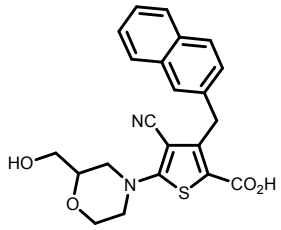
294



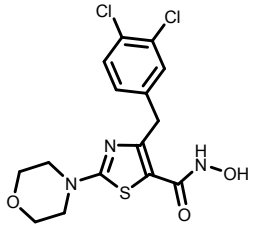
295



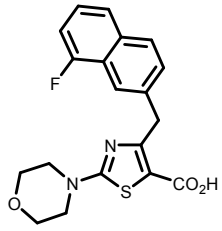
296



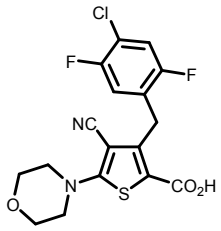
297



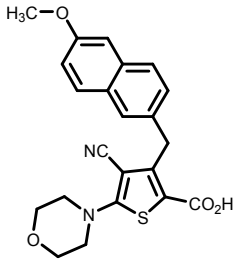
298



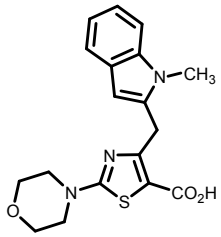
299



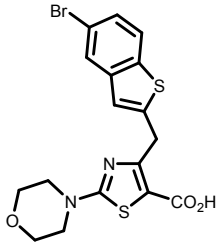
300



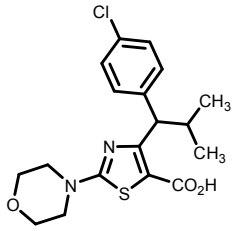
301



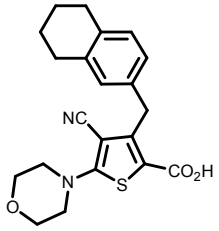
302



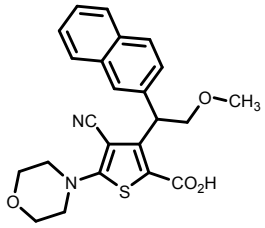
303



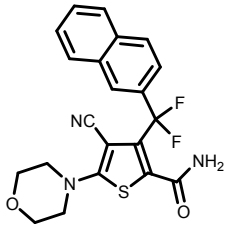
304



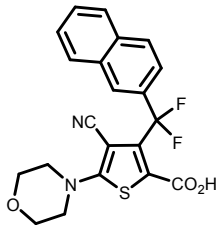
305



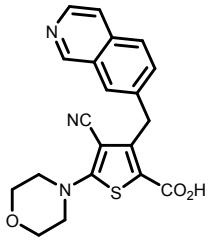
306



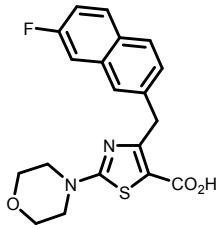
307



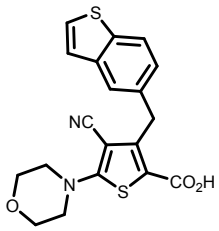
308



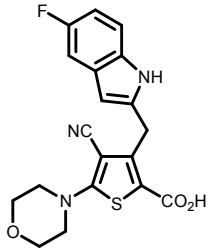
309



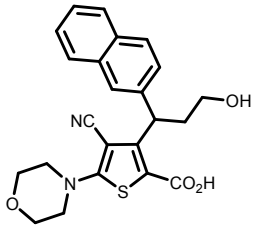
310



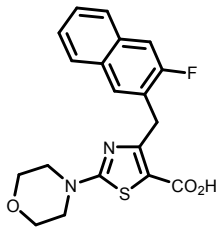
311



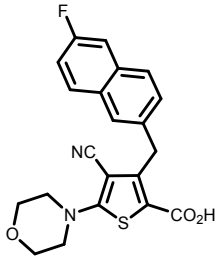
312



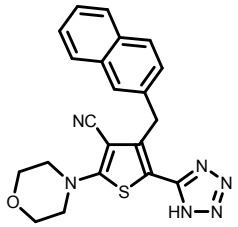
313



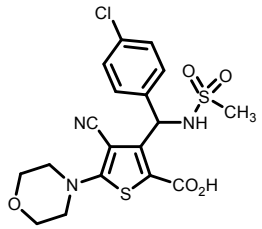
314



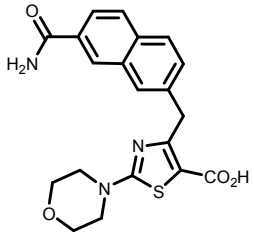
315



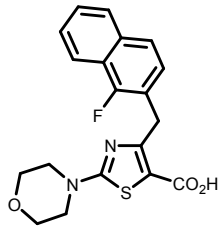
316



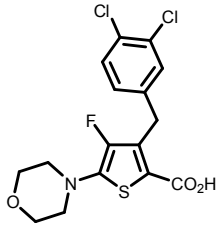
317



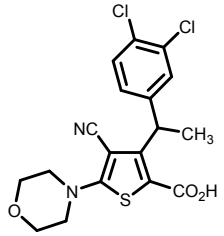
318



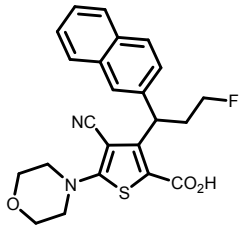
319



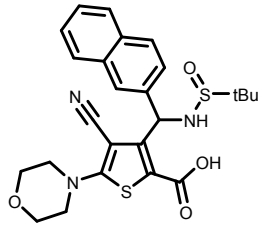
320



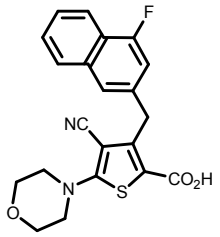
321



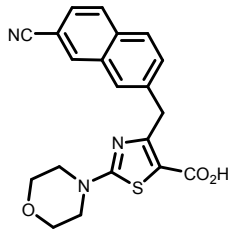
322



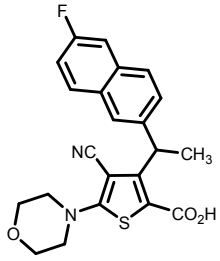
323



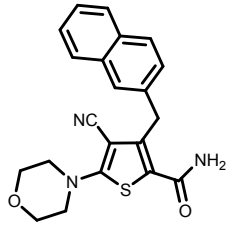
324



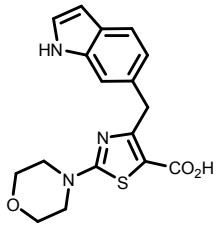
325



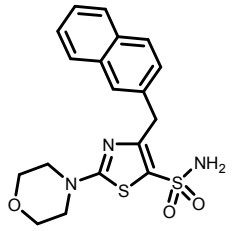
326



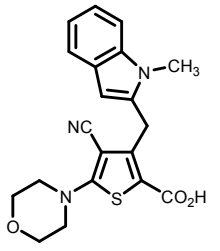
327



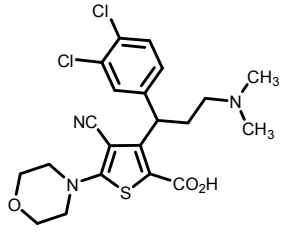
328



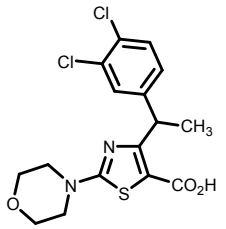
329



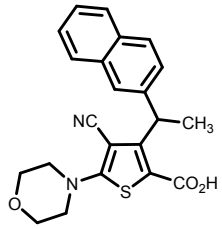
330



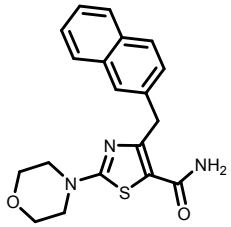
331



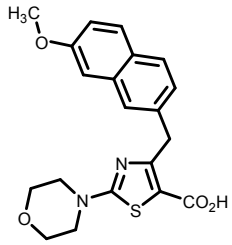
332



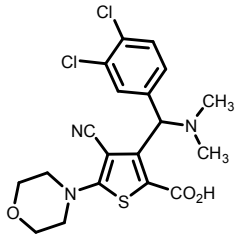
333



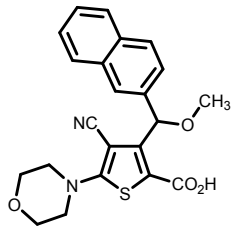
334



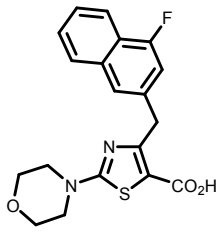
335



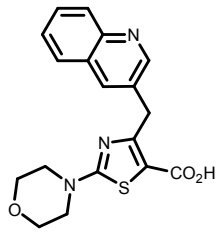
336



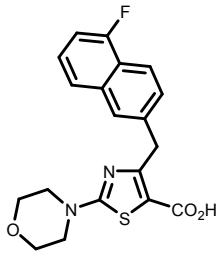
337



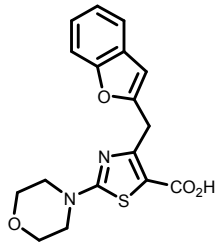
338



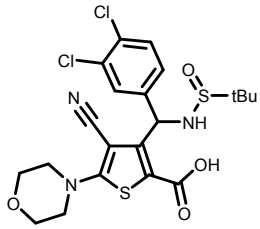
339



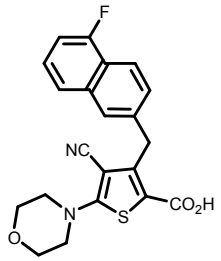
340



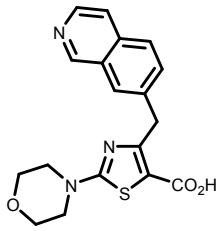
341



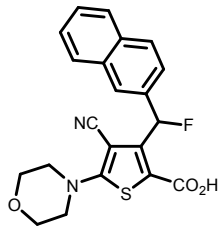
342



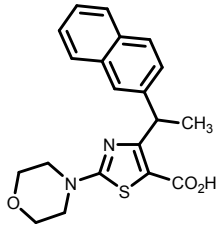
343



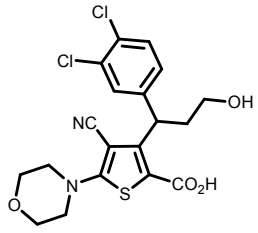
344



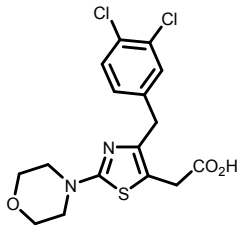
345



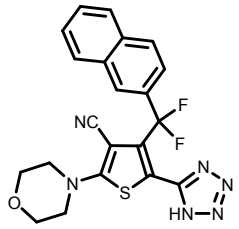
346



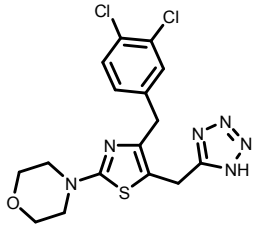
347



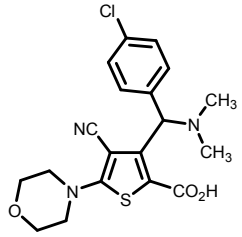
348



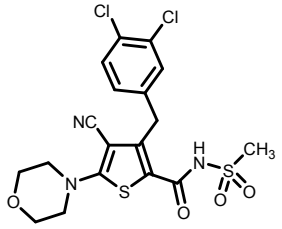
349



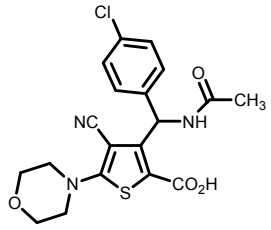
350



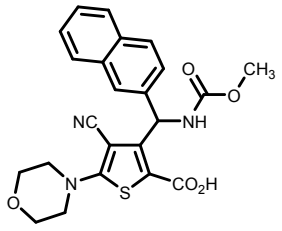
351



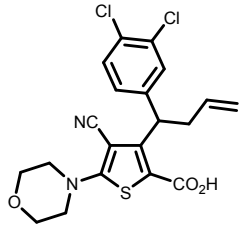
352



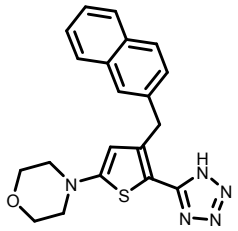
353



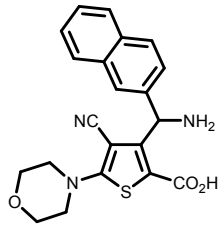
354



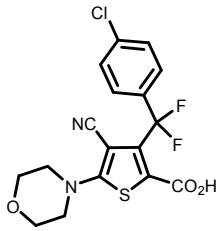
355



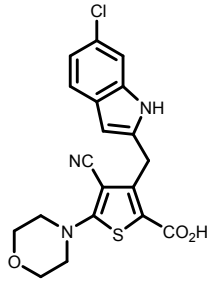
356



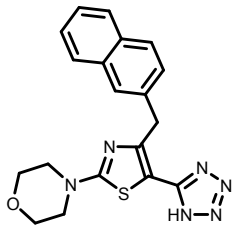
357



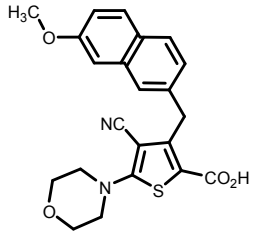
358



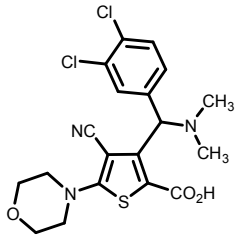
359



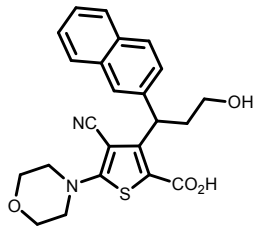
360



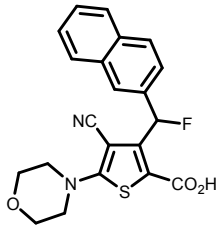
361



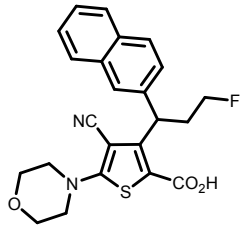
362



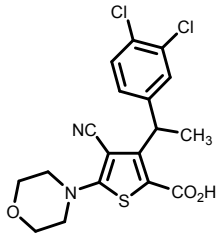
363



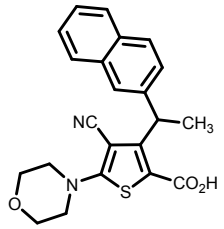
364



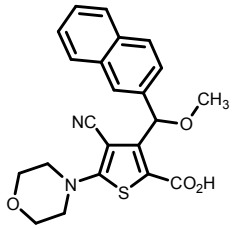
365



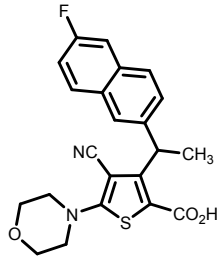
366



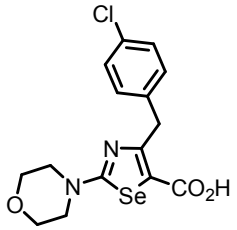
367



368



369



370

[00392] Definiciones

AcOH	ácido acético
ACN	acetonitrilo
ATP	adenosina trifosfato
br	ancho
BCA	ácido bicinchonínico
BSA	albúmina sérica bovina
BOC	ter-butoxicarbonilo
BuLi	butillitio
m-CPBA	ácido m-cloroperbenzoico
d	doblete
dd	doblete de doblete
DCE	dicloroetano
DCM	diclorometano
DDQ	2,3-dicloro-5,6-diciano-1,4-benzoquinona
DIPEA	diisopropiletil amina
DMAP	*N*,*N*-dimetilaminopiridina
DME	1,2-Dimetoxietano
DMEM	medio Eagle modificado de Dulbecco
DMF	N, N-dimetilformamida
DMF-DMA	N, N-dimetilformamida dimetil acetal
DMSO	dimetilsulfóxido
DPPA	difenilfosforil azida
DTT	ditiotreitol
dppf	difenilfosfinoferroceno
EDCI	Clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida
EDTA	ácido etilenediamintetraacético
EtOAc	acetato de etilo
EtOH	etanol
FA	ácido fórmico

FBS	suero bovino fetal
J	constante de acoplamiento
h	horas
Hz:	hertz
HATU	hexafluorofosfato de N,N,N',N'-tetrametil-o-(7-azabenzotriazol-1-il)uronio
HBTU	hexafluorofosfato de o-benzotriazol-1-il-N, N, N', N'-tetrametiluronio
HEPES	ácido N-(2-Hidroxietil)piperazin-N'-(2-etansulfónico)
HOBT	hidrato de 1-hidroxibenztriazol
HRMS	espectro de masa de alta resolución
LAH	hidruro de aluminio y litio
LCMS	espectro de masa de coromatografía líquida
LDA	diisopropilamida de litio
LiHMDS	bis(trimetilsilil)amida de litio
m	multiplete
m/z	masa a carga
Me	metilo
MeOH	metanol
min	minutos
MS	espectro de masa
MTT	metiltiazoltetrazolio
MWI	irradiación de microondas
NBS	N-bromosuccinimida
PBS	solución salina regulada con fosfato
PKA	proteína quinasa dependiente de AMPc
rt	temperatura ambiente

s	singlete
t	triplete
TEA	trietilamina
TFA:	ácido trifluoroacético
TFFA	anhídrido trifluoroacético
THF	tetrahidrofurano
TMB	3,3′,5,5′–Tetrametilbencidina
TMEDA	Tetrametiletilendiamina
q	cuarteto
WST	sal sódica de (4–[3–(4–yodofenil)–2–(4–nitrofenil)–2H–5–tetrazolio]–1,3–bencendisulfonato)

[00393] Se usaron los siguientes métodos analíticos:

[00394] Los espectros LCMS se corrieron en una columna Fenominex Luna 5 µm C18 50 × 4,6 mm en un Hewlett–Packard HP1100 usando los siguientes gradientes:

– Método del ácido fórmico (FA): Acetonitrilo que contiene 0 a 100 por ciento de 0,1% de ácido fórmico en agua (2,5 ml/min para una corrida de 3 minutos).

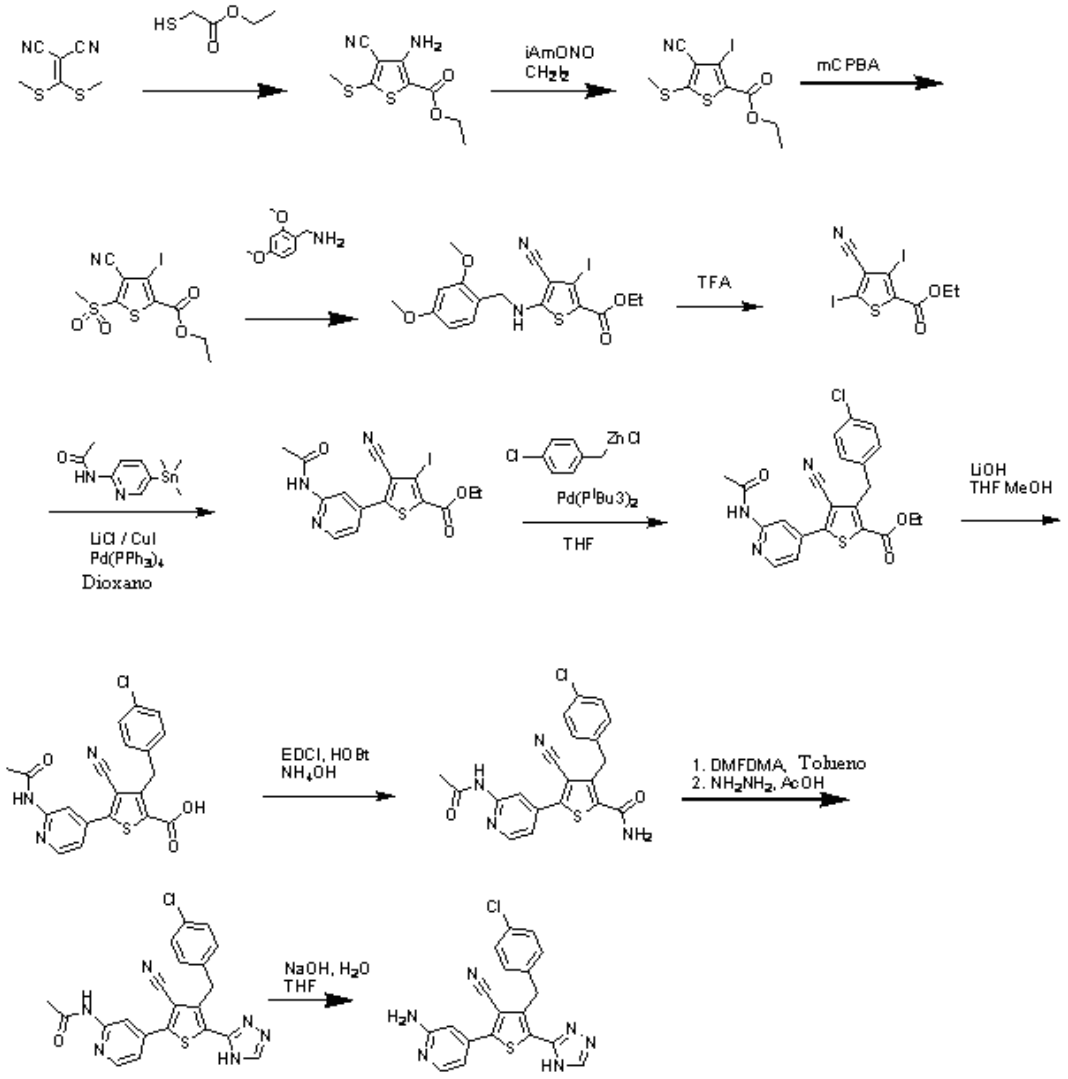
– Método Acetato de amonio (AA): Acetonitrilo que contiene 0 a 100 por ciento de acetato de amonio 10 mM en agua (2,5 ml/min para una corrida de 3 minutos).

[00395] Los isómeros quirales se separaron usando HPLC quiral en una columna Chiralpak IC 250x25 mm de 5 micrones usando hexano/etanol/dietilamina o hexano/isopropilalcohol/etanol/dietilamina como fase móvil. Las configuraciones absolutas de los isómeros

separados fueron desconocidos, las estructuras se asignaron arbitrariamente.

[00396] Los espectros de RMN se muestran por RMN de protones, con tetrametilsilano como estándar interno y usando el espectrofotómetro 300MHz Bruker Avance equipado con una sonda QNP 5 mm y el espectrómetro 400MHz Bruker Avance II equipado con una sonda QNP 5 mm para la medición; los valores de δ se expresan en ppm.

[00397] **Ejemplo 1: Síntesis de *N*-{4-[4-(4-clorobencil)-3-ciano-5-(4*H*-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamide (Compuesto 71) y 2-(2-aminopiridin-4-il)-4-(4-clorobencil)-5-(4*H*-1,2,4-triazol-3-il)tiofeno-3-carbonitrilo (Compuesto 12)**



[00398] **Etapa 1:** 3-amino-4-ciano-5-(metilsulfanil)tiofeno-2-carboxilato de etilo

[00399] Una mezcla de [bis(metilsulfanil)metilen]malononitrilo (40 g, 230 mmol), etiltioglicolato (29 g , 230 mmol) y TEA (24 mL, 173 mmol) en MeOH (600 mL) se dejó agitar a reflujo durante 2 h. La mezcla de reacción se dejó enfriar durante la noche y el precipitado se filtró luego se lavó

con metanol frío (3x50 mL) para dar 3-amino-4-ciano-5-(metilsulfanil)tiofeno-2-carboxilato de etilo (52,4 g, 99 %). LCMS: (FA) ES+ 275.

[00400] **Etapa 2:** 4-ciano-3-yodo-5-(metilsulfanil)tiofeno-2-carboxilato de etilo

[00401] Se disolvió 3-amino-4-ciano-5-(metilsulfanil)tiofeno-2-carboxilato de etilo (10 g, 41,3 mmol) en acetonitrilo (50 mL) bajo una atmósfera de argón. Se añadió diyodometano (11,6 mL, 0,144 mol) y la mezcla se calentó a 40°C. Se añadió nitrito de isoamilo (12,1g, 0,103 mol) y la reacción se dejó enfriar a temperatura ambiente y se agitó durante 2 horas. La mezcla se enfrió a 0°C, se diluyó con hexano (50 mL) y el precipitado se filtró, se lavó con 10:1 mezcla de hexano-acetonitrilo (10 mL), 3:1 hexano-éter (10 mL) y hexano (10 mL). El precipitado se secó para proporcionar 4-ciano-3-yodo-5-(metilsulfanil)tiofeno-2-carboxilato de etilo (6,90 g, 45%). LCMS: (FA) ES+ 354. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,38 (q, 2H), 2,70 (s, 3H), 1,40 (t, 3H).

[00402] **Etapa 3:** 4-ciano-3-yodo-5-(metilsulfonil)tiofeno-2-carboxilato de etilo

[00403] Se disolvió 4-ciano-3-yodo-5-(metilsulfanil)tiofeno-2-carboxilato de etilo (7,2 g, 20,4 mmol) en DCM (200 mL) y THF (100 mL) y se añadió m-CPBA (9,14 g, 40,8 mmol). La mezcla de reacción se agitó a rt durante la noche. Sulfito de sodio (5,14 g, 40,8 mmol) se añadió y la mezcla se agitó durante 10 minutos seguido por la adición de carbonato de potasio (8,45, 61,2 mmol). La suspensión se agitó a rt durante 1 hora y

se filtró a través de celite, se lavó con DCM y el solvente se evaporó para proporcionar 3-yodo-4-ciano-5-(metilsulfonil)tiofeno-2-carboxilato de etilo (6,80 g, 78%). LCMS: (FA) ES+ 386. ^{1}H RMN (400 MHz, $CDCl_3$) δ:4,45 (q, 2H), 3,38 (s, 3H), 1,43 (t, 3H).

[00404] **Etapa 4:** 4-ciano-5-[(2,4-dimetoxibencil)amino]-3-yodotiofeno-2-carboxilato de etilo

[00405] 4-ciano-3-yodo-5-(metilsulfonil)tiofeno-2-carboxilato de etilo (5,60 g, 0,0145 mol) y 2,4-dimetoxibencilamina (3,51 mL, 0,0234 mol) se combinaron en tetrahidrofurano (100 mL) y se agitaron a 60 °C durante 3 días. La reacción se concentró in vacuo, se diluyó con diclorometano y hexanos y el precipitado resultante se filtró para producir el compuesto del título (5,56, 81%) como un sólido amarillo. LCMS: (FA) ES^+, 473. ^{1}H RMN (400MHz, d_6-DMSO) δ: 9,05 (s, 1H) 7,10 (d, 1H, J = 8,57Hz), 6,60-6,50 (m, 2H), 4,30 (s, 2H), 4,22-4,14 (m, 2H), 3,80 (s, 3H), 3,75 (s, 3H), 1,26-1,21 (m, 3H).

[00406] **Etapa 5:** 4-ciano-3,5-diyodotiofeno-2-carboxilato de etilo

[00407] A una solución de 4-ciano-5-[(2,4-dimetoxibencil)amino]-3-yodotiofeno-2-carboxilato de etilo (4,50 g, 9,53 mmol) en diclorometano (100 mL) a temperatura ambiente se añadió ácido trifluoroacético (22,5 mL, 292 mmol). La mezcla luego se agitó a temperatura ambiente durante 10 minutos. El solvente se evaporó y el exceso de ácido trifluoroacético se extrajo

en forma ezeotrópica con tolueno. El material bruto se diluyó con acetato de etilo, luego se trató con solución de bicarbonato de sodio saturada. La mezcla se extrajo con acetato de etilo cinco veces y los extractos orgánicos combinados se secaron en sulfato de sodio anhidro, se filtraron y concentraron in vacuo. La cromatografía en columna se realizó para producir 5-amino-4-ciano-3-yodotiofeno-2-carboxilato de etilo (2,85 g, 88%). LCMS: (FA) ES^+, 323. ^1H RMN (400MHz, d_6-DMSO) δ: 8,18 (s, 2H), 4,20-4,16 (m, 2H), 2,50-2,48 (m, 3H). A una suspensión de 5-amino-4-ciano-3-yodotiofeno-2-carboxilato de etilo (2,85 g, 8,85 mmol) en acetonitrilo (46,2 mL) bajo argón se añadió diyodometano (2,49 mL, 31,0 mmol). La mezcla se calentó a 38°C durante 30 minutos, luego nitrito de amilo (2,59 g, 22,1 mmol) se añadió gota a gota durante 5 minutos. La reacción se dejó enfriar lentamente a temperatura ambiente luego la mezcla se concentró y se realizó la cromatografía en columna para producir el compuesto del título (3,20 g, 79%). LCMS: (FA) ES^+, 434. ^1H RMN (400MHz, d_6-DMSO) δ: 4,33-4,27 (m, 2H), 2,51-2,47 (m, 3H).

[00408] **Etapa 6:** 5-[2-(acetilamino)piridin-4-il]-4-ciano-3-yodotiofeno-2-carboxilato de etilo

[00409] A una solución de 4-ciano-3,5-diyodotiofeno-2-carboxilato de etilo (0,473 g, 1,09 mmol) y N-[4-(trimetilstannil)piridin-2-il]acetamida (0,392 g, 1,31 mmol) en dioxano (10,2 mL) se añadió cloruro de litio (0,139 g, 3,28 mmol), yoduro de cobre (0,0624 g, 0,328 mmol), y tetrakis(trifenilfosfina)paladio(0)

(0,0947 g, 0,0819 mmol). El matraz de reacción se evacuó y se llenó de nuevo con argón, luego la solución se calentó a 110°C durante 2 horas. La mezcla se enfrió a temperatura ambiente y se añadió una mezcla de diclorometano y metanol hasta que casi todos los sólidos se han disuelto. La suspensión se filtró a través de celite y el filtrado se evaporó. Se realizó la cromatografía en columna para producir el compuesto del título (0,312 g, 65%). LCMS: (FA) ES+ 442. ^{1}H RMN (400MHz, d_6–DMSO) δ: 8,54–8,49 (m, 2H), 8,31 (s, 1H), 4,38–4,32 (m, 2H), 2,13 (s, 3H), 1,36–1,29 (m, 3H).

[00410] **Etapa 7:** 5-[2-(acetilamino)piridin-4-il]-3-(4-clorobencil)-4-cianotiofeno-2-carboxilato de etilo

[00411] A una solución de 5-[2-(acetilamino)piridin-4-il]-4-ciano-3-yodotiofeno-2-carboxilato de etilo (0,209 g, 0,474 mmol) en tetrahidrofurano (3,3 mL) se añadió cloruro de 4-clorobencilzinc (0,50 M de solución en tetrahidrofurano, 1,89 mL, 0,947 mmol) y bis(tri-t-butilfosfina)paladio(0) (0,0182 g, 0,0355 mmol) bajo argón. La solución se agitó a 60°C durante 3 horas. La reacción se dejó enfriar a temperatura ambiente y luego el solvente se evaporó in vacuo. Se realizó la cromatografía en columna para producir el compuesto del título (0,159 g, 76%). LCMS: (FA) ES^+, 440. ^{1}H RMN (400MHz, $CDCl_3$) δ: 8,66 (br s, 1 H), 8,60 (br s, 1H), 8,38 (d, J=5,27Hz ,1H), 7,51–7,47 (m, 1H), 7,33–7,23 (m, 4H), 4,51 (s, 2H), 4,39 (q, J=7,03Hz, 2H), 2,24 (s, 3H), 1,39 (t, J=7,03Hz, 3H).

[00412] **Etapa 8:** Ácido 5-[2-(Acetilamino)piridin-4-il]-3-(4-clorobencil)-4-cianotiofeno-2-carboxílico

[00413] A una solución de 5-[2-(acetilamino)piridin-4-il]-3-(4-clorobencil)-4-cianotiofeno-2-carboxilato de etilo (0,080 g, 0,18 mmol) en tetrahidrofurano (1,28 mL) y agua (0,85 mL) se añadió hidróxido de sodio (1,0M solución en agua, 0,236 mL, 0,236 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La mezcla se acidificó a pH 6 usando HCl 1 N acuoso (0,300 mL). La mezcla se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, y luego se secaron en sulfato de sodio anhidro, se filtraron y concentraron in vacuo. Se realizó la cromatografía en columna para producir el compuesto del título (0,058 g, 78%). LCMS: (FA) ES^+, 412. ^1H RMN (400MHz, d_6–DMSO) δ: 10,72 (s, 1H), 8,46–8,41 (m, 2H), 7,42–7,39 (m, 1H), 7,36–7,32 (m, 4H) 4,53 (s, 2H), 2,11 (s, 3H).

[00414] **Etapa 9:** 5-[2-(Acetilamino)piridin-4-il]-3-(4-clorobencil)-4-cianotiofeno-2-carboxamida

[00415] A una solución de ácido 5-[2-(acetilamino)piridin-4-il]-3-(4-clorobencil)-4-cianotiofeno-2-carboxílico (0,0710 g, 0,172 mmol) en diclorometano (5,0 mL) se añadió clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (0,0991 g, 0,517 mmol) y hidrato de 1-hidroxibenzotriazol (0,0528 g, 0,345 mmol). La solución se agitó a temperatura ambiente

durante 30 minutos, luego se añadió 33% de hidróxido de amonio (33:67 amoníaco:agua, 0,298 mL, 3,45 mmol). La solución luego se agitó a temperatura ambiente durante 16 horas, luego la mezcla se concentró y se realizó la cromatografía en columna para producir el compuesto del título (0,031 g, 42%). LCMS: (FA) ES^+, 411. ^1H RMN (400MHz, d_6–DMSO) δ: 10,79 (s, 1H), 8,50–8,46 (m, 2H), 8,14 (br s, 1H), 7,85 (br s, 1H), 7,47–7,43 (m, 1H), 7,39–7,34 (m, 2H), 7,29–7,24 (m, 2H), 4,41 (s, 2H), 2,12 (s, 3H).

[00416] **Etapa 10:** *N*–{4–[4–(4–clorobencil)–3–ciano–5–(4*H*–1,2,4–triazol–3–il)–2–tienil]piridin–2–il}acetamida (Compuesto **71**)

[00417] A una solución de 5–[2–(acetilamino)piridin–4–il]–3–(4–clorobencil)–4–cianotiofeno–2–carboxamida (0,030 g, 0,073 mmol) en tolueno (0,75 mL) se añadió 1,1–dimetoxi–N,N–dimetilmetanamina (0,0970 mL, 0,730 mmol), y la mezcla se agitó a 100°C durante 90 minutos. La mezcla se concentró y el residuo se disolvió en ácido acético (0,75 mL). Hidrazina (0,0114 mL, 0,365 mmol) se añadió y la mezcla se agitó a 100°C durante 1 hora. La mezcla se concentró y el residuo se trató con agua. El precipitado se recolectó, se lavó con agua y secó en un horno de vacío para producir el compuesto del título (0,016 g, 48%). LCMS: (FA) ES^+, 435. ^1H RMN (400MHz, d_6–DMSO) δ: 10,76 (s, 1H), 8,77 (s, 1H), 8,54–8,46 (m, 2H), 7,50–7,47 (m, 1H), 7,37–7,26 (m, 4H), 4,63 (s, 2H), 2,12 (s, 3H).

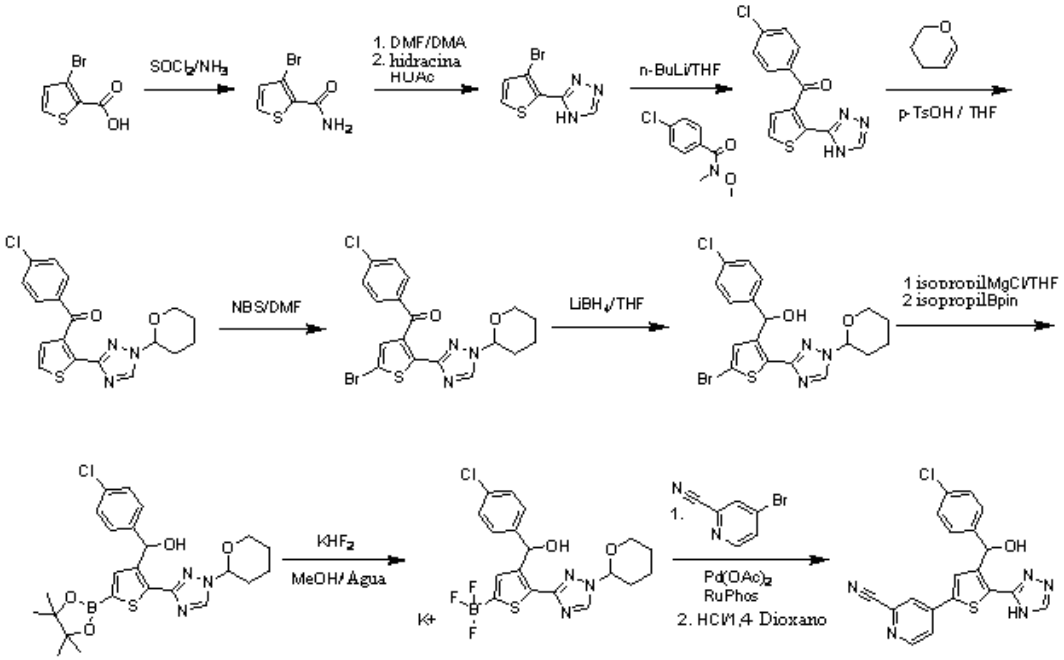
[00418] **Etapa 11:** 2-(2-Aminopiridin-4-il)-4-(4-clorobencil)-5-(4*H*-1,2,4-triazol-3-il)tiofeno-3-carbonitrilo (Compuesto **12**)

[00419] A una solución de *N*-{4-[4-(4-clorobencil)-3-ciano-5-(4*H*-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (0,020 g, 0,046 mmol) en tetrahidrofurano (5,0 mL) se añadió hidróxido de sodio (solución 1,0 M en agua, 2,0 mL, 2,0 mmol). La solución se agitó a temperatura ambiente durante 48 horas. La mezcla se extrajo con acetato de etilo tres veces, y los extractos orgánicos combinados luego se secaron con sulfato de sodio anhidro, se filtraron y concentraron al vacío. Se realizó la cromatografía en columna para producir el compuesto del título (0,007 g, 30%). LCMS: (FA) ES^+, 393. ^1H RMN (400MHz, d_6-DMSO) δ: 8,75 (s, 1H), 8,07-8,03 (m, 1H), 7,36-7,26 (m, 4H), 6,83-6,79 (m, 1H), 6,78-6,76 (m, 1H), 6,34-6,29 (m, 1H), 4,61 (s, 2H), 4,04 (s, 2H).

[00420] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 1:

36	LCMS: (FA) ES+ 355, 357
74	LCMS: (FA) ES+, 412, 414.
143	LC/MS: (FA) ES+ 371; ES- 369
148	LCMS: (FA) ES+ 394
179	LC/MS: (FA) ES+ 467
180	LC/MS: (FA) ES+ 444; ES- 442

[00421] Ejemplo 2 : Síntesis de 4-(4-((4-clorofenil)(hidroxi)metil)-5-(4H-1,2,4-triazol-3-il)tiofen-2-il)picolinonitrilo (Compuesto 81)



[00422] Etapa 1: 3-Bromotiofeno-2-carboxamida

[00423] Se pesó ácido 3-Bromotiofeno-2-carboxílico (63,61 g, 307,2 mmol) en un balón de 1 L equipado con condensador de reflujo y el balón se purgó con argón. A este balón se añadió tolueno (636,1 mL, 5972 mmol) y cloruro de tionilo (44,82 mL, 614,4 mmol) a temperatura ambiente, y la mezcla resultante se agitó durante 3 h a 100°C. La mezcla de reacción se evaporó y el residuo se destiló azeotrópicamente con tolueno (2 x 100 mL). El residuo resultante se disolvió en tetrahidrofurano (954,1 mL, 11760 mmol) luego se añadió lentamente amoníaco 10 M en agua (170 mL, 2500 mmol) en la solución. La mezcla se agitó durante 5h a temperatura

ambiente. La cromatografía en capa fina mostró la reacción completa. La mezcla de reacción se sometió a evaporación rotatoria para eliminar THF y el residuo sólido en agua se filtró a través de un embudo de vidrio sinterizado luego se lavó con agua y secó al vacío para dar 3-bromotiofeno-2-carboxamida como un sólido blanco (33,26 g, 52,5%). LCMS: (FA) ES+ 206,0, 208,0

[00424] **Etapa 2:** 3-(3-Bromotiofen-2-il)-4H-1,2,4-triazol

[00425] 3-Bromotiofeno-2-carboxamida (33,2 g, 161 mmol) en 1,1-dimetoxi-N,N-dimetilmetanamina (100 mL, 800 mmol) y tolueno (100 mL, 900 mmol) se calentó a 90 °C durante 2h. El solvente se evaporó y el residuo se disolvió en ácido acético (183 mL, 3220 mmol). Se añadió hidrazina (20 mL, 600 mmol) y la mezcla se calentó a 90°C nuevamente. Después de 40 min, LCMS mostró la reacción completa. La mezcla de reacción se evaporó para eliminar la mayor parte del ácido acético. Se añadió agua y el precipitado se recolectó y secó al aire durante la noche para proporcionar 3-(3-bromotiofen-2-il)-4H-1,2,4-triazol como un polvo blanco (31,7 g, 85,6%). LCMS: (FA) ES+ 230,0, 232,0

[00426] **Etapa 3:** (4-Clorofenil)[2-(4H-1,2,4-triazol-3-il)-3-tienil]metanona

[00427] A una solución de 3-(3-bromo-2-tienil)-4H-1,2,4-triazol (15,05 g, 65,41 mmol) en tetrahidrofurano (500 mL, 6000 mmol) se añadió gota a gota BuLi 2,5 M en hexanos (104 mL, 262 mmol) a -70°C (temperatura interna) y la solución se agitó durante 30

min a −78°C. Una solución de 4-cloro-N-metoxi-N-metilbenzamida (41,24 g, 206,6 mmol) en tetrahidrofurano (80 mL, 1000 mmol) luego se añadió gota a gota en la suspensión. La mezcla resultante se agitó durante 60 min a −78°C. Cloruro de amonio (17,49 g, 327,0 mmol) en agua (100 mL, 6000 mmol) se añadió a la mezcla a −78°C y la mezcla se agitó durante 15 min antes de calentar a rt. La fase orgánica se separó y la fase acuosa se extrajo con EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, secaron con sulfato de sodio, y luego se filtraron para eliminar el agente desecante. El solvente se evaporó y el residuo se purificó por cromatografía para proporcionar (4-clorofenil)[2-(4H-1,2,4-triazol-3-il)-3-tienil]metanona como sólido blanco (16,8g, 88,5%). LCMS: (FA) ES+ 289,9, 291,8

[00428] **Etapa 4:** (4-Clorofenil)(2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-3-il)metanona

[00429] En un balón de 500 ml, (4-clorofenil)[2-(4H-1,2,4-triazol-3-il)-3-tienil]metanona (16,89 g, 58,29 mmol) se disolvió en tetrahidrofurano (500,0 mL, 6164 mmol). A la solución se añadieron dihidropirana (31,9 mL, 3,50E2 mmol) y monohidrato de ácido p-toluensulfónico (16,6 g, 87,4 mmol). La mezcla se agitó durante 3h a rt. La reacción se inactivó por la adición de solución acuosa saturada de bicarbonato de sodio (200 mL). La fase acuosa se separó y luego se extrajo con EtOAc (300 mL). Las fases orgánicas combinadas se secaron en sulfato de sodio anhidro. El agente desecante se extrajo por filtración y el filtrado

se concentró a presión reducida. El residuo se purificó por cromatografía para proporcionar (4-clorofenil)(2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-3-il)metanona como un aceite que se secó al alto vacío durante la noche (19,4, 89,1%). LCMS: (FA) ES+ 374,2, 376,1.

[00430] **Etapa 5:** (5-Bromo-2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-3-il)(4-clorofenil)metanona

[00431] A una mezcla de (4-clorofenil){2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}metanona (20,2 g, 54,0 mmol) en N,N-dimetilformamida (350 mL, 4500 mmol) se añadió gota a gota una solución de N-bromosuccinimida (14,42 g, 81,05 mmol) en N,N-dimetilformamida (50 mL, 600 mmol) bajo argón. La mezcla se agitó a rt con cuidado para bloquear la reacción de la exposición a la luz ambiente. Después de 3 horas de reacción, LCMS mostró tanto material inicial como producto. Se añadió N-bromosuccinimida adicional (6,732 g, 37,82 mmol) y la mezcla se agitó a rt nuevamente. Después de agitar durante la noche, la mezcla se diluyó con agua y solución de bicarbonato de sodio y luego la mezcla se extrajo con EtOAc. La fase orgánica se lavó con agua y salmuera. La fase en EtOAc se secó y se evaporó al vacío a un residuo, que se purificó por cromatografía para proporcionar (5-bromo-2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-3-il)(4-clorofenil)metanona como un sólido blanco (18,0, 73,5%). LCMS: (FA) ES+ 451,9, 453,9

[00432] **Etapa 6:** (5-Bromo-2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-3-il)(4-clorofenil)metanol

[00433] A una solución de {5-bromo-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}(4-clorofenil)metanona (11,81 g, 26,08 mmol) en tetrahidrofurano (300 mL, 4000 mmol) se añadió tetrahidroborato de litio (52,17 mmol, 52,17 mmol) en tetrahidrofurano (26 mL, 320 mmol) bajo argón. La mezcla se agitó a rt durante 3h y luego enfrió en baño de hielo seco-acetona. Se añadió ácido acético (7,1 mL, 120 mmol). La mezcla se agitó durante 5 min y se añadió solución acuosa saturada de bicarbonato de sodio, seguido por EtOAc. La fase orgánica se separó y se lavó con salmuera, luego se secó con sulfato de sodio. El solvente se eliminó y el residuo se purificó por cromatografía en columna para proporcionar (5-bromo-2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-3-il)(4-clorofenil)metanol como un polvo blanco (11,2, 94,2%). LCMS: (FA) ES+ 454,0, 456,0

[00434] **Etapa 7:** (4-clorofenil)(2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)tiofen-3-il)metanol

[00435] A una mezcla de {5-bromo-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}(4-clorofenil)metanol (5,19 g, 11,4 mmol) en tetrahidrofurano (146,9 mL, 1811 mmol) se añadió cloruro de isopropilmagnesio (1 M en THF, 34,2 mL, 34,2 mmol) at

-40°C bajo argón. Después de la adición, la temperatura de reacción se elevó a rt durante 15 min. La mezcla luego se enfrió a -78°C y se añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolane (8,149 mL, 39,94 mmol). Después de la adición, la mezcla se llevó a rt. Después de 1h, la mezcla se calentó a 75°C durante la noche. La mezcla se enfrió a rt y se inactivó con solución saturada de cloruro de amonio. La mezcla se agitó durante 10 min luego se extrajo con EtOAc. La fase orgánica se secó y se evaporó al vacío. La mezcla se purificó por cromatografía para proporcionar (4-clorofenil)(2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)tiofen-3-il)metanol como un aceite espeso (5,32g, 65,0%). LCMS: (FA) ES+ 502,2, 504,1.

[00436] **Etapa 8:** (4-((4-clorofenil)(hidroxi)metil)-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-2-il)trifluoroborato de potasio

[00437] A una suspensión de (4-clorofenil)(2-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)tiofen-3-il)metanol en metanol (3,5 mL, 87 mmol) bajo argón se añadió fluoruro hidrógeno de potasio (3,13 g, 40,0 mmol) en una porción a 0 °C. Se añadió gota a gota agua (8,06 mL, 447 mmol). Después de la adición, se retiró el al baño de agua-hielo y la mezcla se agitó a rt durante el fin de semana. La mezcla se evaporó y el residuo se secó al alto vacío. La mezcla bruta se extrajo con acetona caliente 3 veces. Los extractos se combinaron

y evaporaron a sequedad para proporcionar (4-((4-clorofenil)(hidroxi)metil)-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-2-il)trifluoroborato de potasio como un polvo blanco (6,34g, 100%). LCMS: (AA) ES- 442,2, 444,2, ^{1}H RMN (400 MHz, d_6-DMSO) δ: 8,71 (d, J = 2,81 Hz, 1H), 7,35-7,24 (m, 2H), 7,45 (td, J = 4,77, 2,42, 2,42 Hz, 2H), 6,69-6,59 (m, 1H), 6,80 (d, J = 4,16 Hz, 1H), 5,81 (dd, J = 4,74, 1,41 Hz, 1H), 5,57 (td, J = 9,49, 2,15, 2,15 Hz, 1H), 4,02-3,89 (m, 1H), 3,74-3,59 (m, 1H), 2,21-1,88 (m, 3H), 1,76-1,47 (m, 3H).

[00438] **Etapa 9:** 4-(4-((4-Clorofenil)(hidroxi)metil)-5-(4H-1,2,4-triazol-3-il)tiofen-2-il)picolinonitrilo (Compuesto **81**)

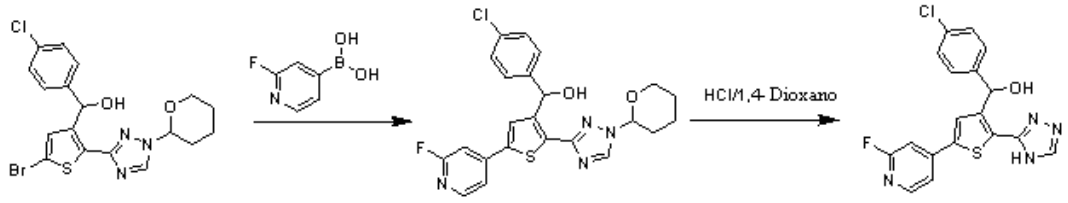
[00439] Una mezcla de (4-((4-clorofenil)(hidroxi)metil)-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-2-il)trifluoroborato de potasio (0,133 g, 0,276 mmol), 4-bromo-piridina-2-carbonitrilo (60,6 mg, 0,331 mmol) , 2-diciclohexilfosfino-2',6'-di-i-propoxi-1,1'-bifenilo (24,8 mg, 0,0533 mmol), acetato de paladio (4,6 mg, 0,020 mmol) y carbonato de sodio (77 mg, 0,73 mmol) en etanol (6,2 mL, 110 mmol) se desgasificó con argón y luego se calentó a 85°C durante 13 h. La mezcla se absorbió en gel de sílice y se purificó por cromatografía para proporcionar un intermediario. LCMS: (AA) ES+ 478,1, 480,0. Este intermediario en 1,4-dioxano (2,0 mL, 26 mmol), alcohol ter-butílico (2,0 mL, 21 mmol) y 4,00 M HCl en dioxano(3,0 mL, 14 mmol) se calentó a 60°C durante 1h. La mezcla se evaporó a sequedad y luego se purificó por HPLC para proporcionar 4-(4-((4-

clorofenil)(hidroxi)metil)-5-(4H-1,2,4-triazol-3-il)tiofen-2-il)picolinonitrilo (12,4mg, 11,4%). LCMS: (FA) ES+ 394,3, 396,1. 1H RMN (400 MHz, d_6-DMSO) δ: 14,69-13,48 (br, 1H), 8,69 (d, J = 6,79 Hz, 2H), 8,45 (s, 1H), 8,08-7,88 (m, 2H), 7,56 (d, J = 8,39 Hz, 2H), 7,35 (d, J = 8,40 Hz, 2H), 6,79 (s, 1H).

[00440] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 2:

3	LCMS: (AA) ES+ 394, 396.
8	LCMS: (FA) ES+ 399, 401.
10	LCMS: (AA) ES+ 408, 410.
13	LCMS: (AA) ES+ 425, 427.
16	LCMS: (AA) ES+ 387, 389.
17	LCMS: (AA) ES+ 399, 401.
23	LCMS: (FA) ES+ 385, 387.
25	LCMS: (AA) ES+ 403, 405, 407.
42	LCMS: (AA) ES+ 419, 421.
48	LCMS: (AA) ES+ 394, 396.
57	LCMS: (AA) ES+ 425, 427.
64	LCMS: (AA) ES+ 438, 440.
68	LCMS: (FA) ES+ 388, 390.
147	LCMS: (AA) ES+ 451, 453
197	LCMS: (AA) ES- 431, 433, 435

[00441] Ejemplo 3: Síntesis de (4-clorofenil)[5-(2-fluoropiridin-4-il)-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanol (Compuesto 21)



[00442] **Etapa 1:** (4-Clorofenil){5-(2-fluoropiridin-4-il)-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}metanol

Una mezcla de {5-bromo-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}(4-clorofenil)metanol (734 mg, 1,61 mmol), 2-fluoro-4-piridinilborónicoacid (455 mg, 3,23 mmol), tetrakis(trifenilfosfina)paladio(0) (93,3 mg, 0,0807 mmol) y carbonato de cesio (1,58 g, 4,84 mmol) en 1,4-dioxano (10,1 mL, 129 mmol) y agua (1,45 mL, 80,7 mmol) se irradió en un horno a microonda a 140 °C bajo argón durante 20 min. La mezcla de reacción se cargó seca en gel de sílice y se purificó por cromatografía en columna (SiO_2, elución con EtOAc en hexanos, 0-80% de gradiente) para proporcionar (4-clorofenil){5-(2-fluoropiridin-4-il)-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}metanol como un sólido blanco (0,71g, 92,8%). LCMS: (AA) ES+ 471,1, 473,1

[00443] **Etapa 2:** (4-clorofenil)[5-(2-fluoropiridin-4-il)-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanol (Compuesto **21**)

[00444] Una mezcla de (4-Clorofenil){5-(2-fluoropiridin-4-il)-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}metanol (0,261 g, 0,554 mmol), alcohol ter-butílico (3,9 mL, 41 mmol), 1,4-dioxano (2,6 mL, 33 mmol) y 4,00 M HCl en dioxano(3,66

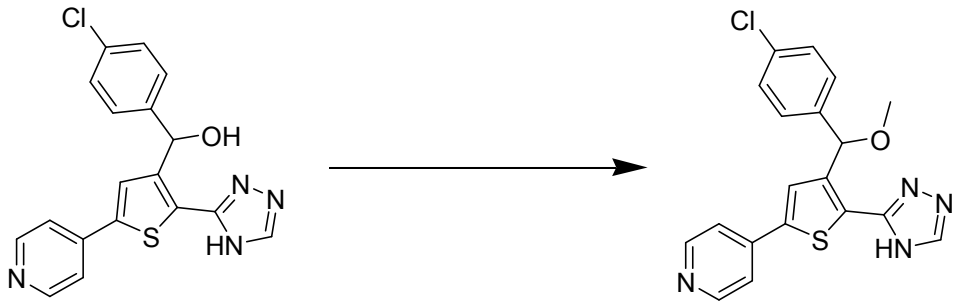
mL, 16,6 mmol) se calentó a 70 °C durante 2 h. La mezcla se enfrió. Se añadió una pequeña cantidad de agua, seguido por la adición de bicarbonato de sodio (0,745 g, 8,87 mmol). La mezcla se agitó durante 10 min y luego se evaporó al vacío. El residuo se purificó por (HPLC para proporcionar 4-clorofenil)[5-(2-fluoropiridin-4-il)-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanol como un sólido blanco. LCMS: (AA) ES+ 387,2, 389,1; 1H RMN (300 MHz, d_4-metanol) δ: 8,51 (s, 1H), 8,18 (d, J = 5,41 Hz, 1H), 7,73 (s, 1H), 7,60-7,44 (m, 3H), 7,37-7,23 (m, 3H), 6,76 (s, 1H).

[00445] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 3:

11	LCMS: (AA) ES+ 383, 385.
14	LCMS: (AA) ES+ 403, 405, 407.
26	LCMS: (AA) ES+ 387, 389.
30	LCMS: (AA) ES+ 403, 405, 407.
34	LCMS: (AA) ES+ 387, 389.
40	LCMS: (AA) ES+ 403, 405, 407.
41	LCMS: (AA) ES+ 426, 428.
43	LCMS: (AA) ES+ 383, 385.
45	LCMS: (AA) ES+ 387, 389.
52	LCMS: (AA) ES+ 369, 371.
55	LCMS: (AA) ES+ 370, 372.
59	LCMS: (AA) ES+ 370, 372.
69	LCMS: (AA) ES+ 383, 385.
75	LCMS: (AA) ES+ 384, 386.
77	LCMS: (AA) ES+ 369, 371.

79	LCMS: (AA) ES+ 370, 372.
84	LCMS: (AA) ES+ 369, 371.

[00446] **Ejemplo 4: Síntesis de 4-[4-[(4-clorofenil)(metoxi)metil]-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridina (Compuesto 6)**



[00447] A una solución de (4-clorofenil)[5-piridin-4-il-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanol (100 mg, 0,271 mmol) en metanol (10 mL) se añadió HCl concentrado (2,0 mL, 24 mmol) y la mezcla se agitó a rt durante la noche. La mezcla de reacción se concentró y alcalinizó con bicarbonato de sodio, se cargó en gel de sílice y se purificó por cromatografía en columna (SiO2, elución con 0-5% MeOH en DCM) para proporcionar el compuesto del título (80 mg, 78%). LCMS: (AA) ES+ 383,3, 385,2; 1H RMN (300 MHz, , d_6-DMSO) δ: 8,70 (s, 1H), 8,57 (d, J = 4,80 Hz, 2H), 7,79 (s, 1H), 7,68 (d, J = 4,79 Hz, 2H), 7,56 (d, J = 8,25 Hz, 2H), 7,38 (d, J = 8,30 Hz, 2H), 6,50 (s, 1H), 3,31 (d, J = 9,06 Hz, 3H).

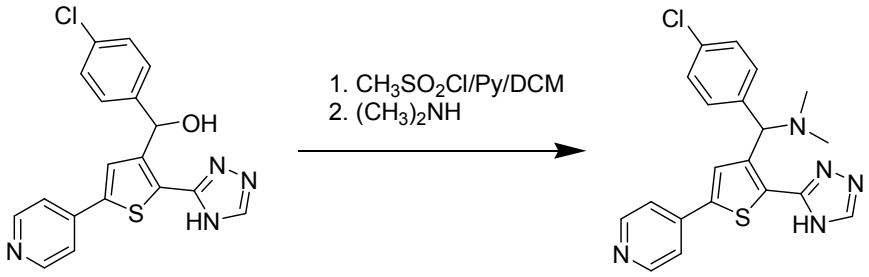
[00448] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 4:

220	LCMS: (AA) ES+ 440, 442.

[00449]

[00450] Ejemplo 5: Síntesis de 1-(4-clorofenil)-N,N-dimetil-1-[5-piridin-4-il-2-(4H-1,2,4-triazol-3- il)-3-tienil]metanamina (Compuesto 9)

[00451]



[00452] A una mezcla de (4-clorofenil)[5-piridin-4-il-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanol (141 mg, 0,382 mmol) (sintetizado de manera análoga a la que se describe en el Ejemplo 3) en cloruro de metileno (2,8 mL) se añadió piridina (6,0 mL, 74 mmol) y cloruro de metansulfonilo (0,148 mL, 1,91 mmol) a 0°C. Después de la adición, la mezcla se calentó a rt y se agitó durante 30 min y luego se calentó a 60°C durante 20 min. La mezcla se enfrió en un baño de hielo y dimetilamina (0,553 mL, 11,5 mmol) en THF se añadió a la mezcla. Después de la adición, el baño de hielo se retiró y la mezcla se agitó a rt durante 30 min y luego se calentó a 55°C durante 2 h. La mezcla se enfrió, concentró, y el residuo se purificó por HPLC para proporcionar 1-(4-clorofenil)-N,N-dimetil-1-[5-piridin-4-il-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanamina en forma de polvo blanco (115 mg, 76%). LCMS: (AA) ES+ 396,3, 398,1; ^{1}H RMN (400 MHz, d_6-DMSO) δ: 14,48-14,27 (m, 1H), 8,71 (s, 1H),

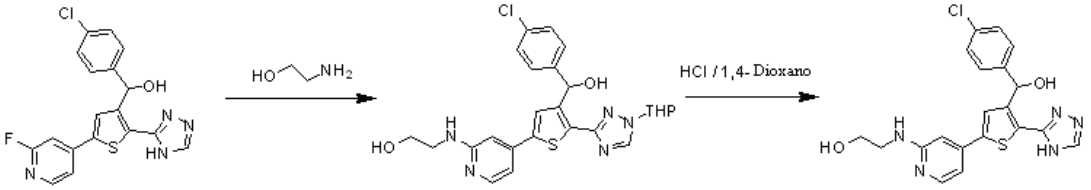
8,57 (dd, J = 4,55, 1,62 Hz, 2H), 7,95 (s, 1H), 7,73-7,63 (m, 4H), 7,39-7,30 (m, 2H), 5,53 (s, 1H), 2,13 (s, 6H).

[00453] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 5:

33	LCMS: (AA) ES+ 410, 412.
44	LCMS: (AA) ES+ 396, 398.
51	LCMS: (AA) ES+ 408, 410.
65	LCMS: (AA) ES+ 396, 398.
86	LCMS: (AA) ES+ 453, 455.
90	LCMS: (AA) ES+ 465, 467
135	LCMS: (AA) ES+ 507, 509.
139	LCMS: (AA) ES+ 508, 510
146	LCMS: (FA) ES+ 520, 522
151	LCMS: (AA) ES+ 465, 467
152	LCMS: (FA) ES+ 510, 512
154	LCMS: (FA) ES+ 494, 496
161	LCMS: (AA) ES+ 410, 412
163	LCMS: (AA) ES+ 508, 510
164	LCMS: (AA) ES+ 495, 497.
167	LCMS: (AA) ES+ 476, 478
173	LCMS: (AA) ES+ 508, 510
176	LCMS: (AA) ES+ 465, 467
182	LCMS: (AA) ES+ 495, 497
183	LCMS: (AA) ES+ 496, 498.
185	LCMS: (AA) ES+ 411, 413
192	LCMS: (AA) ES+ 509, 511.
196	LCMS: (AA) ES+ 536, 538
200	LCMS: (AA) ES+ 480, 482

201	LCMS: (AA) ES+ 481, 483
204	LCMS: (AA) ES+ 453, 455
206	LCMS: (AA) ES+ 476, 478
208	LCMS: (AA) ES+ 508, 510
209	LCMS: (AA) ES+ 508, 510
212	LCMS: (AA) ES+ 495, 497.
216	LCMS: (AA) ES+ 501, 503
221	LCMS: (AA) ES+ 529, 531
224	LC/MS: (FA) ES+ 572, 574; ES- 570, 572.
229	LCMS: (AA) ES+ 495, 497.
234	LCMS: (AA) ES+ 508, 510
240	LCMS: (AA) ES+ 507, 509
241	LCMS: (AA) ES+ 465, 467
242	LCMS: (AA) ES+ 507, 509
243	LCMS: (AA) ES+ 458, 460
247	LCMS: (AA) ES+ 507, 509
248	LCMS: (AA) ES+ 495, 497
251	LCMS: (AA) ES+ 442, 444
254	LCMS: (FA) ES+ 452, 454
259	LCMS: (AA) ES+ 509, 511.
261	LCMS: (AA) ES+ 453, 455
267	LCMS: (AA) ES+ 508, 510
268	LCMS: (AA) ES+ 509, 511.
270	LCMS: (AA) ES+ 508, 510
283	LCMS: (AA) ES+ 509, 511.

[00454] Ejemplo 6: Síntesis de 2-({4-[4-[(4-clorofenil)(hidroxi)metil]-5-(4H-1,2,4-triazol-3-il)-2- tienil]piridin-2-il}amino)etanol (Compuesto 49)

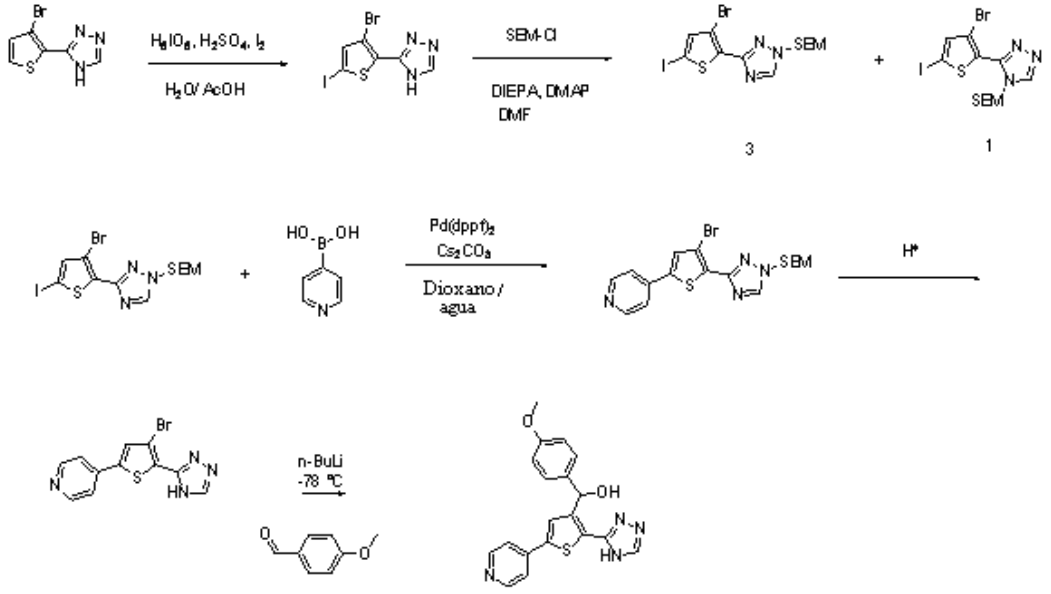


[00455] Una mezcla de (4-clorofenil){5-(2-fluoropiridin-4-il)-2-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-3-tienil}metanol (80,0 mg, 0,170 mmol), etanolamina (0,104 g, 1,70 mmol) y N,N-diisopropiletilamina (0,118 mL, 0,679 mmol) en dimetilsulfóxido (0,5 mL, 7 mmol) se calentó a 200°C durante 1 h bajo argón. La mezcla de reacción se enfrió, se diluyó con agua y se extrajo con butanol. La fase de butanol se recolectó y se evaporó a un residuo que se purificó por cromatografía (SiO_2, elución con 0-20% de MeOH en DCM) para proporcionar el intermediario. El intermediario en 1,4-dioxano (1,0 mL, 13 mmol) y HCl concentrado (1,0 mL, 12 mmol) se agitó a rt durante 1 h. El solvente se evaporó y el residuo se purificó por cromatografía (SiO_2, elución con 0-70% (MeOH/DCM/NH4OH, 13/85/2) en DCM) para proporcionar 2-({4-[4-[(4-clorofenil)(hidroxi)metil]-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}amino)etanol (17,6mg, 24,2%). LCMS: (AA) ES+ 428,2, 430,0; ^{1}H RMN (400 MHz, d_6-DMSO) δ: 14,66-14,13 (m, 1H), 8,68 (s, 1H), 7,94 (d, J = 5,30 Hz, 1H), 7,58-7,48 (m, 3H), 7,38-7,30 (m, 2H), 6,81-6,68 (m, 3H), 6,60 (s, 1H), 4,72 (s, 1H), 3,57-3,45 (m, 2H), 3,34 (d, J = 5,88 Hz, 3H).

[00456] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 6:

28	LCMS: (AA) ES+ 435, 437.
62	LCMS: (AA) ES+ 398, 400.

[00457] **Ejemplo 7: Síntesis de (4-metoxifenil)[5-piridin-4-il-2-(4H-1,2,4-triazol-3-il)-3-tienil]metanol (Compuesto 85)**



[00458] **Etapa 1:** 3-(3-Bromo-5-yodo-2-tienil)-4H-1,2,4-triazol.

A una mezcla de 3-(3-bromo-2-tienil)-4H-1,2,4-triazol (1,12 g, 4,87 mmol), yodo (1,12 g, 4,41 mmol) y ácido peryódico (4,80 g, 24,8 mmol) en ácido acético (11,0 mL, 200 mmol) se añadieron agua (8,0 mL, 400 mmol) y ácido sulfúrico (2,0 mL, 40 mmol) y la mezcla de reacción se agitó a rt durante dos

días. El precipitado blanco resultante se recolectó por filtración. La torta sólida se lavó con agua y secó bajo alto vacío a 40°C para dar el producto como un sólido blanco (1,74 g, 100% de rendimiento, como un sólido blanco). LCMS: (FA) ES^+, 357,7. ^1H RMN (400 MHz, d_6–DMSO) δ: 8,63(s, 1H), 7,43 (s, 1H)

[00459] **Etapa 2:** 3-(3-Bromo-5-yodo-2-tienil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol.

[00460] A una solución de 3-(3-bromo-5-yodo-2-tienil)-4H-1,2,4-triazol (500,0 mg, 1,40 mmol), N,N-dimetilaminopiridina (17,2 mg, 0,140 mmol) y N,N-diisopropiletilamina (0,32 mL, 1,83 mmol) en N,N-dimetilformamida (17,0 mL, 220 mmol) se añadió [β-cloruro de (Trimetilsilil)etoxi]metilo (0,270 mL, 1,55 mmol) y la solución se agitó durante 2 h a rt. Se añadieron agua (5,0 mL) y EtOAc (5mL), la fase orgánica se separó, se lavó con salmuera, se secó con $MgSO_4$, se filtró, concentró y el residuo obtenido se purificó por cromatografía en columna (SiO_2, elución con 0-30% de EtOAc en hexano) para dar el compuesto del título como un aceite amarillento (653 mg, (87% isómero mayor, 13% isómero menor) LCMS: (FA) ES^+, 486, 488. (isómero mayor) ^1H RMN (400 MHz, d_6–DMSO) δ: 8,81(s, ,1H), 7,45 (s, 1H), 5,540-5,545 (s, br, 2H), 3,62-3,66 (m, 2H), 0,840-0,880(m, 2H), -0,05 (s, 9H). LCMS: (FA) ES^+, 486, 488. (isómero menor) ^1H RMN (400 MHz, d_6–DMSO) δ: 8,215(s, ,1H), 7,615 (s, 1H), 5,48(s, br, 2H), 3,44-3,50 (m, 2H), 0,75-0,80(m, 2H), -0,08 (s, 9H).

[00461] **Etapa 3:** 4-[4-Bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridina.

[00462] Una mezcla de 3-(3-bromo-5-yodo-2-tienil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol (653,0 mg, 1,34 mmol), ácido piridin-4-borónico (248 mg, 2,02 mmol), dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II) (55,2 mg, 0,067 mmol) y carbonato de cesio (1,80 g, 5,37 mmol) en 1,4-dioxano (8,40 mL, 107 mmol) y agua (1,2 mL, 67,1 mmol) se calentó a 110°C bajo una atmósfera de argón durante la noche. Se añadieron agua (3 mL) y EtOAc (3 mL), la fase orgánica se separó, se lavó con salmuera, se secó con $MgSO_4$, se filtró, concentró y el residuo obtenido se purificó por cromatografía en columna (SiO_2, elución con 0-10% de MeOH en DCM) para dar el compuesto del título como un sólido blanco (438 mg, 74,6 %). LCMS: (FA) ES^+, 438, 440. ^1H RMN (400 MHz, d_6-DMSO) δ:8,87(s, 1H), 8,62-8,64 (dd, J = 1,5 Hz, 2H), 7,98 (s, 1H), 7,30-7,75 (dd, J = 1,5, 2H), 5,58-5,59 (s, br, 2H), 3,40-3,69 (m, 2H), 0,840-0,890(m, 2H), -0,04 (s, 9H).

[00463] **Etapa 4:** 4-[4-Bromo-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridina.

[00464] Se disolvió 4-[4-Bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridina (111,0 mg, 0,224 mmol) en cloruro de metileno (3,0 mL, 47 mmol). Se añadió ácido trifluoroacético (3,0 mL, 39 mmol) y la solución se agitó a rt durante la noche. Después de completar la reacción,

se añadió $NaHCO_3$ saturado (1 mL) y la reacción se agitó a rt durante 20 min. Se añadió EtOAc (5 mL), la fase orgánica se separó, se lavó con salmuera, se secó con $MgSO_4$, se filtró, concentró y el residuo obtenido se purificó por cromatografía en columna (SiO_2, elución con 2–20% de MeOH en DCM) para dar el compuesto del título como un sólido amarillo (222 mg, 54%). LCMS: (FA) ES^+, 307, 309. ^1H RMN (400 MHz, d_6–DMSO)) δ: 14,5(s,br,1H), 8,70–8,72 (dd, J = 1,5 Hz, 2H), 8,10 (s, 1H), 7,90–7,94 (dd, J = 1,5 Hz, 2H)

[00465] **Etapa 5**: (4–Metoxifenil)[5–piridin–4–il–2–(4H–1,2,4–triazol–3–il)–3–tienil]metanol (Compuesto **85**)

[00466] A una mezcla de 4–[4–bromo–5–(4H–1,2,4–triazol–3–il)–2–tienil]piridina (222,0 mg, 0,730 mmol) en tetrahidrofurano (5,9 mL, 72,3 mmol) enfriada a –78°C se añadió gota a gota n–BuLi en hexanos (2,50 M, 1,2 mL, 2,90 mmol) bajo una atmósfera de argón y la mezcla se agitó a –78°C durante 30 min. A la solución se añadió gota a gota una solución de 4–metoxibenzaldehído (0,53 mL, 4,34 mmol) en tetrahidrofurano (5,0 mL, 60 mmol) y la solución resultante se agitó durante 30 min a –78°C. La mezcla de reacción se inactivó por la adición de agua (2mL) y la mezcla resultante se calentó a temperatura ambiente y se agitó durante 30 min. La mezcla se extrajo con EtOAc (5mL) luego la fase orgánica se separó, se lavó con salmuera, se secó con $MgSO_4$, se filtró y concentró a presión reducida El residuo obtenido se purificó por HPLC preparativa para producir 62,0 mg como un sólido amarillo (23,5%). LCMS: (FA) ES^+, 365. ^1H

RMN (400 MHz, d_6–DMSO) δ: 8,68(s, 1H), 8,55–8,57 (dd, J = 1,5 Hz , 2H), 7,81(s, br, 1H), 7,63–7,65(dd, J = 1,5 Hz , 2H), 7,40–7,44(d, , J = 8,78 Hz, 2H), 6,82–6,84(d, J = 8,78 Hz, 2H), 6,72 (s, br, 1H), 3,68–3,69 (s, br, 3H).

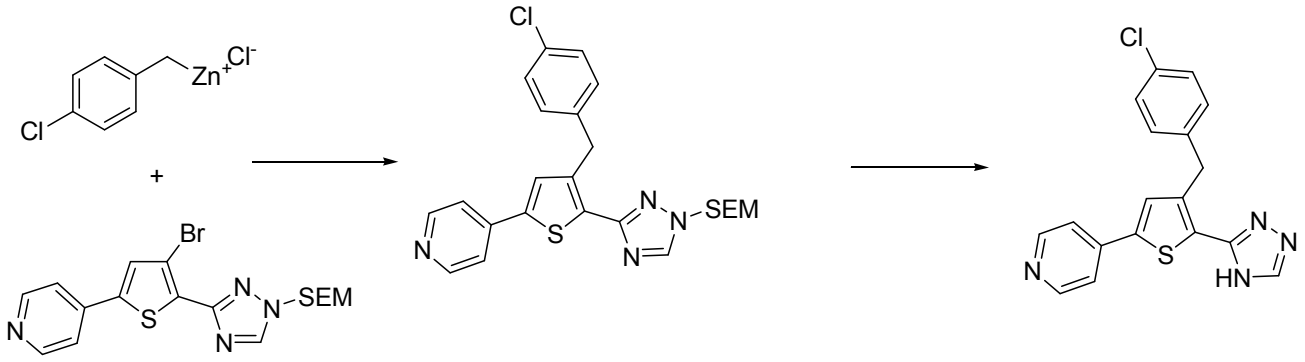
[00467] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 7:

130	LCMS: (FA) ES+ 383,4
132	LCMS: (FA) ES+ 386,3
133	LCMS: (FA) ES+ 418,3
134	LCMS: (FA) ES+ 415,3
136	LCMS: (FA) ES+ 403
138	LCMS: (FA) ES+ 367,4
141	LCMS: (FA) ES+ 363,3
142	LCMS: (FA) ES+ 403,3
155	LCMS: (FA) ES+ 353,4
158	LCMS: (FA) ES+ 379,4
159	LCMS: (FA) ES+ 403,3
162	LCMS: (FA) ES+ 371,3
169	LCMS: (FA) ES+ 387,3
171	LCMS: (FA) ES+ 386,4
174	LCMS: (FA) ES+ 363,5
175	LCMS: (FA) ES+ 386,4
183	LCMS: (FA) ES+ 381,4
186	LCMS: (FA) ES+ 417, 419.
187	LCMS: (FA) ES+ 387,3
188	LCMS: (FA) ES+ 367,4
191	LCMS: (FA) ES+ 399,4
193	LCMS: (FA) ES+ 403,4

198	LCMS: (FA) ES+ 411.
199	LCMS: (FA) ES+ 371,4
202	LCMS: (FA) ES+ 379,4
203	LCMS: (FA) ES+ 403.
207	LCMS: (FA) ES+ 412,3
208	LCMS: (FA) ES+ 385.
214	LCMS: (FA) ES+ 412,4
215	LCMS: (FA) ES+ 393.
217	LCMS: (FA) ES+ 369,4
219	LCMS: (FA) ES+ 403,4
228	LCMS: (FA) ES+ 385,4
231	LCMS: (FA) ES+ 413,3
232	LCMS: (FA) ES+ 387,3
233	LCMS: (FA) ES+ 419,2
235	LCMS: (FA) ES+ 371,3
236	LCMS: (FA) ES+ 413,4
239	LCMS: (FA) ES+ 383,4
246	LCMS: (FA) ES+ 395,4
249	LCMS: (FA) ES+ 365,3
252	LCMS: (FA) ES+ 413,4
253	LCMS: (FA) ES+ 363,3
256	LCMS: (FA) ES+ 379,4
257	LCMS: (FA) ES+ 386,4
258	LCMS: (FA) ES+ 412,3
260	LCMS: (FA) ES+ 403,2
263	LCMS: (FA) ES+ 387,3
264	LCMS: (FA) ES+ 383,4
266	LCMS: (FA) ES+ 371,3
271	LCMS: (FA) ES+ 355,4

272	LCMS: (FA) ES+ 366,3
275	LCMS: (FA) ES+ 387,4
276	LCMS: (FA) ES+ 412,3
279	LCMS: (FA) ES+ 417, 419.
280	LCMS: (FA) ES+ 385.
281	LCMS: (FA) ES+ 403.
284	LCMS: (FA) ES+ 403

[00468] **Ejemplo 8: Síntesis de 4-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridina (Compuesto 5)**



[00469] **Etapa 1:** 4-[4-(4-Clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4- triazol-3-il)-2-tienil]piridina

[00470] Bis(tri-*t*-butilfosfina)paladio(0) (4,38 mg, 0,00857 mmol) y 4-[4-bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridina (0,075 g, 0,17 mmol) se combinaron en un balón seco equipado con barra agitadora y sellado con un tabique. El balón se evacuó/cargó de nuevo con nitrógeno tres veces luego se añadió gota a gota una solución de

cloruro de 4-clorobencilzinc en tetrahidrofurano (0,50 M, 0,720 mL, 0,360 mmol) por medio de una jeringa. Se fijó una línea de nitrógeno y la reacción se agitó a rt durante 30 minutos, luego a 60°C durante ~2 horas. La reacción se enfrió a rt, se diluyó con EtOAc y solución saturada de cloruro de amonio, luego la mezcla se transfirió a un embudo de separación. La fase orgánica se separó y la fase acuosa se extrajo dos veces más con EtOAc. Las fases orgánicas se combinaron, se lavaron con solución de bicarbonato, luego salmuera, luego se secaron con sulfato de sodio. La mezcla se filtró luego se evaporó al vacío y el residuo se purificó por cromatografía en columna en sílice, elución 100% de hexano a 100% de EtOAc para proporcionar el compuesto del título como un aceite amarillo claro. Se produjeron 63 mg (76% de rendimiento). LCMS: (FA) ES+, 483, 485.

[00471] **Etapa 2:** 4-[4-(4-Clorobencil)-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridina (Compuesto **5**)

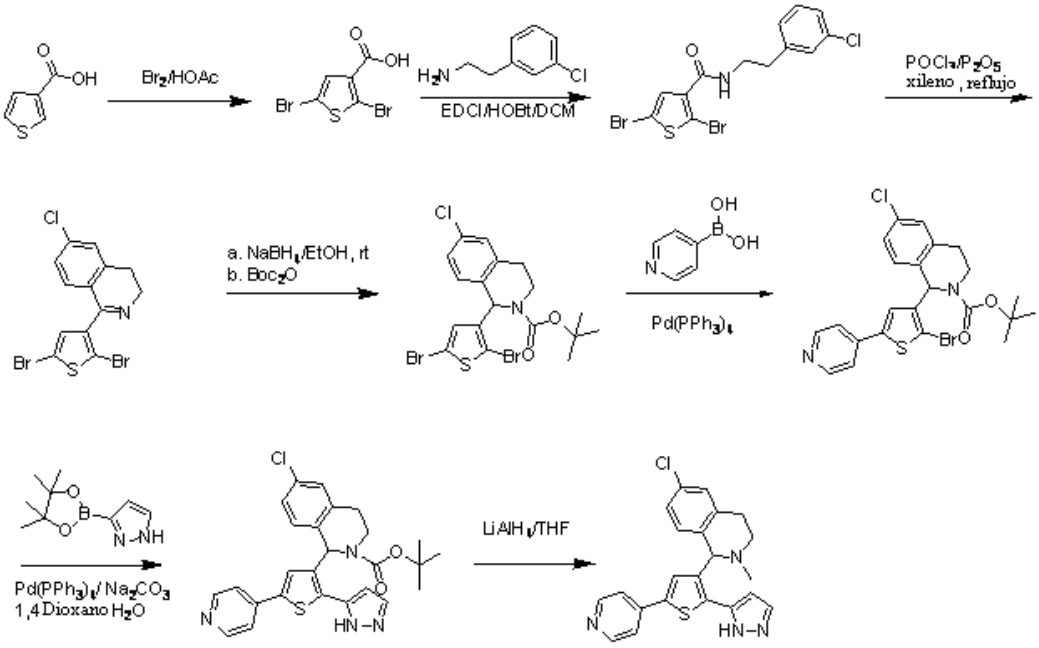
[00472] La 4-[4-(4-clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridina (58 mg, 0,12 mmol) y cloruro de metileno (4,0 mL, 62 mmol) se combinaron en un balón equipado con barra agitadora. La mezcla se agitó y ácido trifluoroacético (1,1 mL, 14 mmol) se añadió en una porción. La solución amarilla resultante se agitó durante la noche a rt bajo atmósfera de nitrógeno. El exceso de solvente se eliminó en el evaporador rotatorio y el residuo se digirió en una mezcla de EtOAc y solución acuosa de bicarbonato de sodio. La mezcla se agitó luego se transfirió a un embudo de separación. La fase orgánica

se separó y la fase acuosa se extrajo dos veces más con EtOAc. Las fases orgánicas se combinaron, se lavaron con solución de bicarbonato, luego salina, luego se secaron con sulfato de sodio. La mezcla se filtró luego se evaporó al vacío y el residuo se purificó por cromatografía en columna sobre sílice, elución 100% de DCM a 100% de EtOAc para proporcionar el compuesto del título como un polvo blancuzco. Produjo 41 mg (97% de rendimiento). LCMS: (FA) ES+, 353, 355. ^{1}H RMN (400MHz, d_6–DMSO) δ: 14,31 (1H, br s), 8,67 (1H, br s), 8,55 (2H, d, J = 6,3 Hz), 7,69 (1H, s), 7,63 (2H, d, J = 6,3 Hz), 7,36–7,30 (4H, m), 4,47 (2H, s).

[00473] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 8:

87	LCMS: (FA) ES+ 370.

[00474] Ejemplo 9: Síntesis de 6–cloro–2–metil–1–[2–(1H–pirazol–5–il)–5–piridin–4–il–3–tienil]–1,2, 3,4–tetrahidroisoquinolina (Compuesto 58)



[00475] **Etapa 1:** Ácido 2,5-Dibromo-3-tenoico

[00476] En un balón de 500 ml se colocó ácido 3-tenoico (16,04 g, 125,2 mmol) y ácido acético (200 mL, 4000 mmol). A la mezcla se añadió bromo (32,24 mL, 625,8 mmol) y la mezcla se agitó durante 18 h at 60 °C. La mezcla se dejó enfriar a rt luego se diluyó con hielo-agua. Se añadió bisulfito de sodio (52,10 g, 500,7 mmol). El precipitado resultante se recolectó por filtración y luego se lavó con agua para dar ácido 5-dibromo-3-tenoico como un polvo blancuzco (33,4, 93,3%). LCMS (FA) ES+ 284,9, 286,9.

[00477] **Etapa 2:** 2,5-dibromo-N-[2-(3-clorofenil)etil]tiofeno-3-carboxamida

[00478] A una mezcla de ácido 2,5-dibromo-3-tenoico (10,0 g, 35,0 mmol), 2-(3-

clorofenil)etanamina (7,08 g, 45,5 mmol) e hidrato de 1-hidroxibenzotriazol (5,89 g, 38,5 mmol) en cloruro de metileno (291 mL, 4550 mmol) se añadió clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (12,1 g, 62,9 mmol). La mezcla se agitó a rt durante la noche. La mezcla de reacción se lavó con 1NHCl, agua, bicarbonato de sodio saturado y salmuera. La fase de DCM se secó y evaporó para proporcionar 5-dibromo-N-[2-(3-clorofenil)etil]tiofeno-3-carboxamida (14,7, 99,2%). LCMS (FA) ES+ 423,9, 425,9.

[00479] **Etapa 3:** 6-cloro-1-(2,5-dibromo-3-tienil)-3,4-dihidroisoquinolina

[00480] A una mezcla de 2,5-dibromo-N-[2-(3-clorofenil)etil]tiofeno-3-carboxamida (5,15 g, 12,2 mmol) en xilenes (25,98 mL, 70,32 mmol) a 70°C se añadió pentóxido de fósforo (13,0 g, 45,8 mmol) y luego cloruro de fosforilo (12,0 mL, 129 mmol). La mezcla se calentó a 150°C durante 60 h, luego la mezcla se enfrió a rt. La solución se extrajo por decantación y se lavó con tolueno dos veces. Se añadieron agua (20 mL) y 20% de NaOH (20 mL) y la mezcla se sometió a sonicación. La mezcla se extrajo con EtOAc. La fase orgánica se lavó con agua, se secó con MgSO4, y se evaporó al vacío para dar un residuo que se purificó por cromatografía para proporcionar 6-cloro-1-(2,5-dibromo-3-tienil)-3,4-dihidroisoquinolina en forma de espuma sólida (2,8g, 57%).

[00481] **Etapa 4:** 6-cloro-1-(2,5-dibromo-3-tienil)-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo

[00482] A una mezcla de 6-cloro-1-(2,5-dibromo-3-tienil)-3,4-dihidroisoquinolina (2,60 g, 6,41 mmol) en etanol (37,43 mL, 641,1 mmol) se añadió di-ter-butildicarbonato (2,80 g, 12,8 mmol) y tetrahidroborato de sodio (0,485 g, 12,8 mmol) a 0°C. La mezcla se agitó durante 20 min a 0°C y luego durante la noche a rt. La mezcla de reacción se concentró y el residuo se extrajo con EtOAc. La fase orgánica se separó, se lavó con agua, se lavó con salmuera, y luego se secó con MgSO4. El solvente se evaporó y el residuo se purificó por cromatografía para proporcionar 6-cloro-1-(2,5-dibromo-3-tienil)-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo como un polvo blanco (2,45 g, 75,3%).

[00483] **Etapa 5:** 1-(2-bromo-5-piridin-4-il-3-tienil)-6-cloro-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo

[00484] Una mezcla de 6-cloro-1-(2,5-dibromo-3-tienil)-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo (177,0 mg, 0,3486 mmol), ácido piridin-4-borónico (51,43 mg, 0,4184 mmol) tetrakis(trifenilfosfina)paladio(0) (20,1 mg, 0,0174 mmol) y carbonato de cesio (0,341 g, 1,04 mmol) en 1,4-dioxano (6,0 mL, 77 mmol) y agua (2,0 mL, 110 mmol) se desgasificó y se calentó a 100 °C durante 1h. La mezcla se extrajo con EtOAc. La fase orgánica se separó y se lavó con agua. La fase orgánica se secó y se evaporó para dejar un residuo que se purificó por cromatografía para proporcionar 1-(2-bromo-5-piridin-4-il-3-tienil)-6-cloro-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo

como un sólido blanco (72 mg, 41%). LCMS AA ES+ 505,1, 507,1

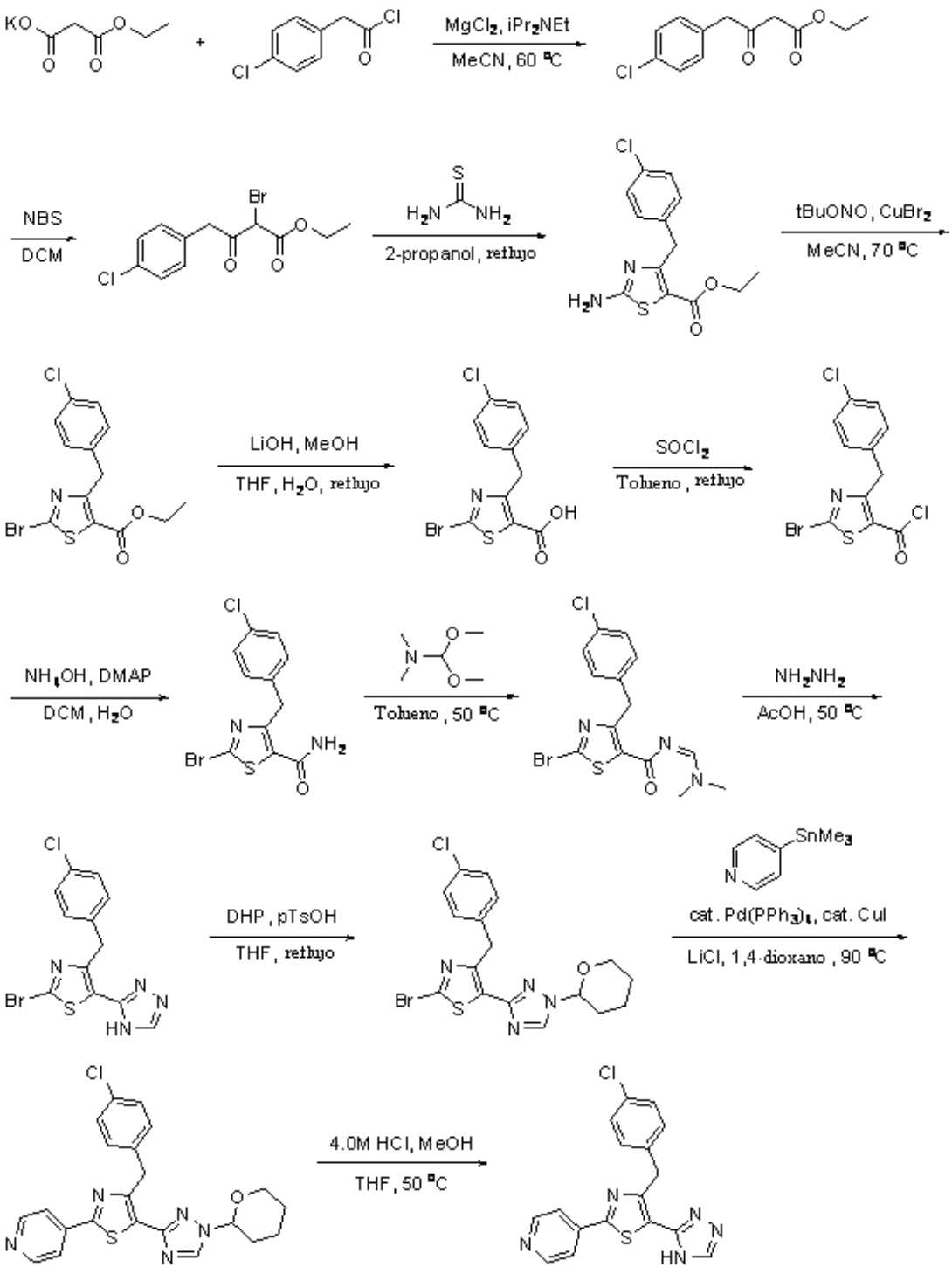
[00485] **Etapa 6:** 6-cloro-1-[2-(1H-pirazol-5-il)-5-piridin-4-il-3-tienil]-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo

[00486] Una mezcla de 1-(2-bromo-5-piridin-4-il-3-tienil)-6-cloro-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo (72,0 mg, 0,142 mmol), 3-(4,4,5,5-tetrametil-1,3,2-dioxabolone)-pirazol (27,6 mg, 0,142 mmol), dicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II) (11,7 mg, 0,0142 mmol) y carbonato de sodio (29 mg, 0,27 mmol) en 1,2-dimetoxietano (3,0 mL, 29 mmol) y agua (1,0 mL, 56 mmol) se calentó a 95°C durante 4,5 h. Un LCMS mostró el producto deseado junto con el material de partida sin reaccionar. Se añadieron dicloruro de (1,1'-bis(difenilfosfino)ferroceno]paladio(II) (11,7 mg, 0,0142 mmol) 3-(4,4,5,5-Tetrametil-1,3,2-dioxabolone)-pirrazol (56 mg, 0,29 mmol), tetrakis(trifenilfosfina)paladio(0) (15 mg, 0,013 mmol), carbonato de sodio (100 mg, 0,9 mmol) y 1,2-dimetoxietano (3,0 mL, 29 mmol). La mezcla se calentó a 100°C durante otras 4 h. La mezcla se cargó seca en gel de sílice y se purificó por cromatografía para proporcionar 6-cloro-1-[2-(1H-pirazol-5-il)-5-piridin-4-il-3-tienil]-3, 4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo (41 mg, 58%). LCMS AA ES+ 493,2, 495,1.

[00487] **Etapa 7:** 6-Cloro-2-metil-1-[2-(1H-pirazol-5-il)-5-piridin-4-il-3-tienil]-1,2,3,4-tetrahidroisoquinolina (Compuesto **58**)

[00488] A una solución de 6-cloro-1-[2-(1H-pirazol-5-il)-5-piridin-4-il-3-tienil]-3,4-dihidroisoquinolina-2(1H)-carboxilato de ter-butilo (41 mg, 0,083 mmol) en tetrahidrofurano (3,0 mL, 37 mmol) se añadió tetrahidroaluminato de litio (0,249 mmol, 0,249 mmol) en THF (2,0 mM) a -78°C. Después de la adición, la temperatura de la reacción se elevó a rt durante 30 min y luego se calentó a 85°C durante 5 h. La mezcla se inactivó con agua, se diluyó con metanol, y se extrajo con acetato de etilo. La fase orgánica se secó, filtró y evaporó. El residuo se cargó en gel de sílice y se purificó por cromatografía para proporcionar 6-cloro-2-metil-1-[2-(1H-pirazol-5-il)-5-piridin-4-il-3-tienil]-1,2,3,4-tetrahidroisoquinolina (5,1 mg, 15%). LCMS AA ES+ 407,2, 409,1; ^{1}H RMN (400 MHz, d_4-metanol) δ: 8,48 (d, J = 5,06 Hz, 2H), 7,89-7,66 (m, 1H), 7,61 (s, 2H), 7,50-7,31 (br, 1H), 7,17 (s, 1H), 7,00 (d, J = 7,98 Hz, 1H), 6,87-6,48 (m, 2H), 5,16-4,94 (m, 1H), 3,34 (s, 1H), 3,28-3,10 (m, 2H), 2,94-2,79 (m, 1H), 2,72-2,56 (m, 1H), 2,26 (s, 3H)

[00489] **Ejemplo 10: Síntesis de 4-(4-clorobencil)-2-(piridin-4-il)-5-(4H-1,2,4-triazol-3-il)tiazol (Compuesto 76)**


MgCl2, iPr2NEt
MeCN, 60 °C
NBS
DCM
2-propanol, reflujo
tBuONO, CuBr2
MeCN, 70 °C
LiOH, MeOH
THF, H2O, reflujo
SOCl2
Tolueno, reflujo
NH4OH, DMAP
DCM, H2O
Tolueno, 50 °C
NH2NH2
AcOH, 50 °C
DHP, pTsOH
THF, reflujo
SnMe3
cat. Pd(PPh3)4, cat. CuI
LiCl, 1,4-dioxano, 90 °C
4.0M HCl, MeOH
THF, 50 °C

[00490] **Etapa 1:** 4-(4-clorofenil)-3-oxobutanoato de etilo

[00491] A una suspensión de etil malonato de potasio (17,12 g, 100,6 mmol) en acetonitrilo (150 mL) se añadieron N,N-diisopropiletilamina (28 mL, 160 mmol) y cloruro de magnesio (12,11 g, 127,2 mmol). La mezcla resultante se agitó durante 1 hora. Una solución de cloruro de 4-clorofenilacetilo (10,12 g, 53,53 mmol) en acetonitrilo (100 mL) luego se añadió y la mezcla se calentó a 60° C y se agitó durante 20 horas. La mezcla se enfrió a temperatura ambiente y se concentró a presión reducida. El residuo se suspendió en HCl acuoso 1 N (250 mL) y se extrajo con EtOAc (100 mL x 2). Las fases orgánicas combinadas se secaron en MgSO4 anhidro y los materiales insolubles se extrajeron por filtración. El filtrado se concentró a presión reducida y el residuo se purificó por cromatografía en columna sobre sílice, elución con una mezcla de 0%-80% de EtOAc en hexano (gradiente lineal, 45 min) para obtener 4-(4-clorofenil)-3-oxobutanoato de etilo (5,0 g, 39%) como un aceite amarillo. LC/MS (FA) ES- 239. ^{1}H RMN (d_6-DMSO, 400 MHz): δ: 7,37 (2H, d, J = 13,8 Hz), 7,20 (2H, d, J = 13,8 Hz), 4,07 (2H, q, J = 7,2 Hz), 3,89 (2H, s), 3,66 (2H, s), 1,17 (3H, t, J = 7,2 Hz).

[00492] **Etapa 2:** 2-bromo-4-(4-clorofenil)-3-oxobutanoato de etilo

[00493] En un balón de 250 mL se colocaron 4-(4-clorofenil)-3-oxobutanoato de etilo (4,04 g, 16,8 mmol) y cloruro de metileno (100 mL). A la

solución se añadió N-bromosuccinimida (3,13 g, 17,6 mmol) y la mezcla se agitó durante 3 h a rt. A la mezcla se añadió una solución de NaHSO3 acuosa 10% recién preparada (5 g $NaHSO_3$ disuelto en 50 mL de agua) y la mezcla bifásica resultante se agitó vigorosamente durante 15 min a rt. La fase orgánica se separó y la fase acuosa se extrajo con DCM (30 mL). Las fases orgánicas se combinaron y se lavaron una solución de $NaCO_3$ acuosa saturada (50 mL) y se secó con $MgSO_4$ anhidro. Los materiales insolubles se extrajeron por filtración y el filtrado se concentró a presión reducida. El aceite amarillo residual era esencialmente puro y se usó en la próxima etapa sin purificación adicional. LC/MS (FA) ES-319.

[00494] **Etapa 3:** 2-amino-4-(4-clorobencil)tiazol-5-carboxilato de etilo

[00495] En un balón de 100 mL se colocaron 2-bromo-4-(4-clorofenil)-3-oxobutanoato de etilo (990 mg, 3,1 mmol) y alcohol isopropílico (20 mL). A la mezcla se añadió tiourea (590 mg, 7,8 mmol) y la reacción luego se sometió a reflujo durante 16 h con agitación. La mezcla se dejó enfriar a rt y luego se concentró a presión reducida. El residuo se suspendió en EtOAc (50 mL) y luego se lavó con una solución acuosa saturada de $NaHCO_3$ (50 mL), salmuera (50 mL), y se secó con MgSO4 anhidro. Los materiales insolubles se extrajeron por filtración y el filtrado se concentró a presión reducida. El sólido cristalino amarillento blanquecino residual era esencialmente puro por LCMS y se usó en la próxima etapa sin purificación adicional. LC/MS

(FA) ES+ 296. ^{1}H RMN (d_6–DMSO, 400 MHz): δ: 7,80 (2H, br s), 7,32 (2H, d, J = 8,8 Hz), 7,23 (2H, d, J = 8,8 Hz), 4,14—4,20 (4H, m), 1,22 (3H, t, J = 7,1 Hz).

[00496] **Etapa 4:** 2–bromo–4–(4–clorobencil)tiazol–5–carboxilato de etilo.

En a balón de 250 mL se colocaron 2–amino–4–(4–clorobencil)–1,3–tiazol–5–carboxilato de etilo (786 mg, 2,65 mmol) y acetonitrilo (75 mL). A la mezcla se añadió bromuro de cobre (II) (963 mg, 4,31 mmol). La suspensión se agitó durante 15 min a rt. A la mezcla se añadió nitrito de ter–butilo (0,630 mL, 5,30 mmol) y la agitación continuó durante 1,5 h adicionales a 70° C. La mezcla de reacción se dejó enfriar a rt y luego se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre sílice, elución con a 10%–50% mixture de EtOAc en hexano para obtener 2–bromo–4–(4–clorobencil)–1,3–tiazol–5–carboxilato de etilo (820 mg; 86%) como un jarabe amarillo, que se solidificó espontáneamente por decantación a rt para proporcionar un sólido cristalino blancuzco. LC/MS (FA) ES+ 362. ^{1}H RMN (CDCl3, 400 MHz): δ:7,29 (2H, d, J = 8,8 Hz), 7,24 (2H, d, J = 8,8 Hz), 4,44 (2H, s), 4,35 (2H, q, J = 7,3 Hz), 1,36 (3H, t, J = 7,3 Hz).

[00497] **Etapa 5:** Ácido 2–bromo–4–(4–clorobencil)tiazol–5–carboxílico.

[00498] En un balón de 100 mL se colocaron 2–bromo–4–(4–clorobencil)–1,3–tiazol–5–carboxilato de etilo (955 mg, 2,65 mmol) y tetrahidrofurano (50 mL, 600 mmol). A esta solución se añadió una solución acuosa de hidróxido de sodio recién

preparada [(hidróxido de sodio•H_2O (177 mg, 4,22 mmol) y agua (15 mL, 830 mmol)). La mezcla se agitó durante 4 h a rt luego se añadió MeOH (20 mL) y la mezcla se sometió a reflujo durante 3 h. La mezcla se dejó enfriar a rt y luego se acidificó por la adición de HCl aq 1,0 N (4,5 mL). La mezcla se agitó durante 1 h a rt. La mezcla luego se concentró a presión reducida hasta reducir a aprox 5 mL de volumen. Se añadió EtOAc (50 mL) y la mezcla se lavó con agua (50 mL), luego salmuera (50 mL), luego se secó con MgSO4 anhidro. Los materiales insolubles se extrajeron por filtración y el filtrado se concentró a presión reducida. El sólido cristalino amarillo residual se usó en la próxima etapa sin purificación adicional. LC/MS (FA) ES+ 332.

[00499] **Etapas 6 y 7:** 2-Bromo-4-(4-clorobencil)tiazol-5-carboxamida.

[00500] En a balón de 250 mL se colocaron 2-bromo-4-(4-clorobencil)-1,3-tiazol-5-carboxílico (800 mg, 2 mmol) y tolueno (30 mL, 300 mmol). A la suspensión se añadió cloruro de tionilo (700 uL, 10 mmol) y la mezcla se sometió a reflujo durante 2 h, durante el tiempo en que la suspensión se tornó una solución. La reacción se dejó enfriar a rt y luego se concentró a presión reducida. El residuo se coevaporó con tolueno (10 mL). El aceite anaranjado residual se disolvió en cloruro de metileno (30 mL, 500 mmol) luego se añadió N,N-dimetilaminopiridina (21,2 mg, 0,174). A la mezcla se añadió hidróxido de amonio en agua (8,5 M, 20 mL) y la mezcla se agitó durante 1,5 h a rt. La fase orgánica se separó y la fase acuosa se extrajo con DCM (30 mL). La

fase orgánica y el extracto se combinaron y se secaron con MgSO4 anhidro. Los materiales insolubles se extrajeron por filtración y el filtrado se concentró a presión reducida. El jarabe amarillo residual se usó en la próxima etapa sin purificación adicional. LC/MS (FA) ES+ 333.

[00501] **Etapa 8:** (Z)-2-bromo-4-(4-clorobencil)-N-((dimetilamino)metilen)tiazol-5-carboxamida.

[00502] En un balón de 250 mL se colocaron 2-bromo-4-(4-clorobencil)-1,3-tiazol-5-carboxamida (0,66 g, 2,0 mmol) y tolueno (30 mL, 300 mmol). La mezcla se tornó en una suspensión por ultrasonicación. A la suspensión se añadió 1,1-dimetoxi-N,N-dimetilmetanamina (80 uL, 6,0 mmol) y la mezcla se agitó durante 2 h at 50°C. La mezcla se dejó enfriar a rt luego se concentró a presión reducida. El residuo se usó en la próxima etapa sin purificación adicional. LC/MS (FA) ES+ 388.

[00503] **Etapa 9:** 2-Bromo-4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)tiazol.

[00504] En un balón de 250 mL se colocaron 2-bromo-4-(4-clorobencil)-N-[(1Z)-(dimetilamino)metilen]-1,3-tiazol-5-carboxamida y ácido acético (50 mL, 900 mmol). Se añadió hidrato de hidrazina (490 uL, 10 mmol) y la mezcla se agitó durante 1 h a 50°C. La mezcla se dejó enfriar a rt, luego se concentró a presión reducida para obtener 3-[2-bromo-4-(4-clorobencil)-1,3-tiazol-5-il]-4H-1,2,4-triazol como un

sólido cristalino blancuzco amarillento. El material bruto se usó en la próxima etapa sin purificación adicional. LC/MS (FA) ES+ 357.

[00505] **Etapa 10:** 2-Bromo-4-(4-clorobencil)-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiazol

[00506] En un balón de 250 mL se colocaron 3-[2-bromo-4-(4-clorobencil)-1,3-tiazol-5-il]-4H-1,2,4-triazol (0,7 g, 2 mmol) y tetrahidrofurano (50 mL, 600 mmol). A la mezcla se añadieron dihidropirano (2 mL, 20 mmol) y monohidrato del ácido p-toluensulfónico (911,3 mg, 4,791 mmol). La mezcla se sometió a reflujo durante 2 h luego se dejó enfriar a rt y luego se añadió una solución acuosa saturada de $NaHCO_3$ (50 mL). La mezcla bifásica resultante se agitó vigorosamente durante 30 min a rt. La fase acuosa se separó luego se extrajo con EtOAc (50 mL x 2). Las fases orgánicas combinadas se secaron en $MgSO_4$ anhidro. Los materiales insolubles se extrajeron por filtración y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre sílice, elución con una mezcla 10%-80% de EtOAc en hexano (gradiente lineal, 30 min) para proporcionar 3-[2-bromo-4-(4-clorobencil)-1,3-tiazol-5-il]-1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol (778 mg; 67% seis etapas) como un jarabe amarillo que solidificó espontáneamente por decantación a rt durante 2 días. LC/MS (FA) ES+ 441. ^{1}H RMN (d_6-DMSO, 400 MHz): δ: 8,89 (1H, s), 7,28—7,34 (4H, m), 5,62 (1H, dd, J = 2,8 y 9,6 Hz), 4,52 (2H, s), 3,92—3,96 (1H, m), 3,63—3,70 (1H, m), 1,91—2,14 (3H, m), 1,52—1,72 (3H, m)

[00507] **Etapa 11:** 4-(4-Clorobencil)-2-(piridin-4-il)-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiazol.

[00508] A un vial de 20 mL se añadió una solución de 3-[2-bromo-4-(4-clorobencil)-1,3-tiazol-5-il]-1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol (0,1500 g, 0,3411 mmol) y 4-(tributilstannil)piridina (0,2511 g, 0,6822 mmol) en 1,4-dioxanos anhidro (5,000 mL). La solución se desgasificó durante 10 minutos. Se añadieron cloruro de litio (0,108 g, 2,56 mmol) y yoduro de cobre (I) (0,0487 g, 0,256 mmol) seguido por tetrakis(trifenilfosfina)paladio(0) (0,0492 g, 0,0426 mmol). La mezcla de reacción se calentó a 90°C y se dejó agitar durante 18 h. La reacción se enfrió a temperatura ambiente y se inactivó por la adición de una solución acuosa saturada de bicarbonato de sodio (10 mL). La mezcla de inactivación se extrajo con EtOAc (10 mLx3). Las fases orgánicas combinadas se secaron en Na_2SO_4 anhidro, se filtraron y concentraron a presión reducida. El material bruto se purificó por cromatografía en columna sobre sílice (gradiente de DCM a 10% de MeOH durante 30 min) para proporcionar el producto (0,2245 g, 73%) como un sólido amarillo. LC/MS (AA) ES+ 438. ^{1}H RMN (400 MHz, d_6-DMSO) δ: 8,92 (s, 1H), 7,90 (d, J = 4,8 Hz, 2H), 7,65 (d, J = 1,2 Hz, 2H), 7,38-7,32 (m, 4H), 5,66 (dd, J = 9,6, 2,8 Hz, 1H), 4,65 (s, 2H), 3,97-3,94 (m, 1H), 3,72-3,66 (m, 1H), 1,59-1,48 (m, 2H), 1,32-1,23 (m, 2H), 1,10-1,06 (m, 2H).

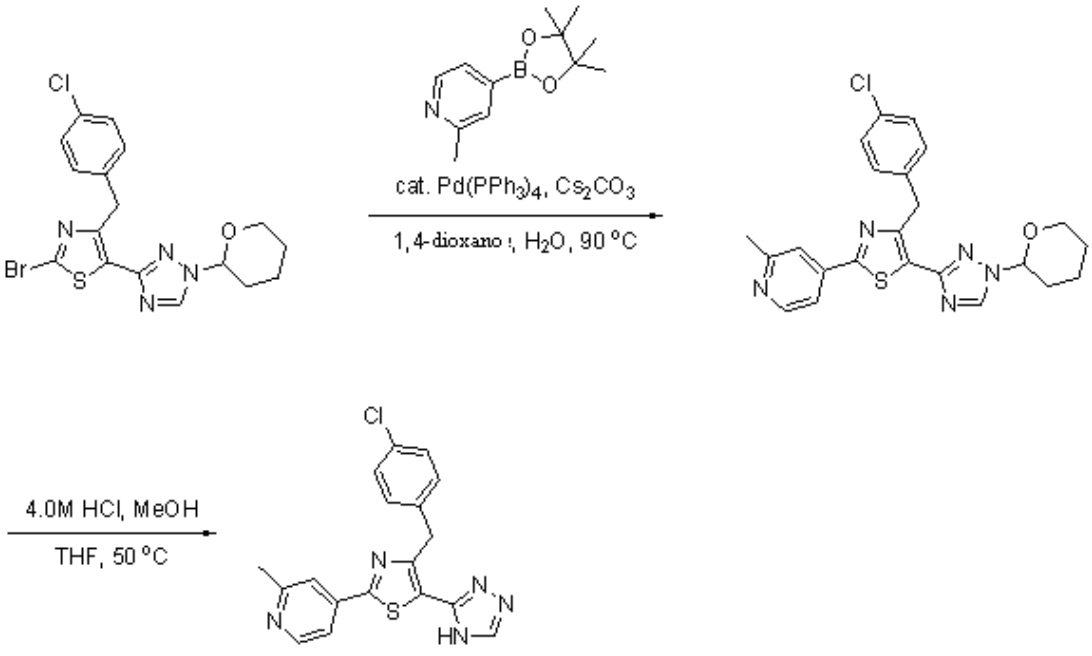
[00509] **Etapa 12:** 4-(4-Clorobencil)-2-(piridin-4-il)-5-(4H-1,2,4-triazol-3-il)tiazol (Compuesto **76**).

[00510] A un vial de 20 mL se añadió una solución de 4-{4-(4-clorobencil)-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-1,3-tiazol-2-il}piridina (0,2245 g, 0,635 mmol) en tetrahidrofurano anhidro (2,000 mL) y metanol (2,000 mL). Se añadió ácido clorhídrico 4,0 M en 1,4-dioxano (1,0 mL, 4,0 mmol) y la mezcla de reacción se dejó agitar a 50°C durante 18 horas. La reacción se enfrió a temperatura ambiente y se inactivó por la adición de una solución acuosa saturada de bicarbonato de sodio (10 mL) y se extrajo con EtOAc (10 mLx3). Las fases orgánicas combinadas se secaron en Na_2SO_4, se filtraron y concentraron a presión reducida. El material bruto se purificó por HPLC para proporcionar el producto (0,0423 g, 45%) como un sólido blancuzco. LC/MS (AA) ES+ 354. ^{1}H RMN (400 MHz, d_6-DMSO) δ: 14,48 (s, 1H), 8,71 (dd, J = 4,4, 1,2 Hz, 2H), 7,89-7,87 (m, 2H), 7,38-7,32 (m, 4H), 4,67 (s, 2H).

[00511] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 10:

37	LCMS: (FA) ES+ 372, 374.
39	LCMS: (AA) ES+ 355, 357.
46	LCMS: (AA) ES- 370, 372.
63	LCMS: (FA) ES+ 383, 385.
78	LCMS: (AA) ES+ 372, 374.

[00512] **Ejemplo 11: Síntesis de 4-(4-Clorobencil)-2-(2-metilpiridin-4-il)-5-(4H-1,2,4-triazol-3-il)tiazol (Compuesto 18)**



[00513] **Etapa 1:** 4-(4-clorobencil)-2-(2-metilpiridin-4-il)-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiazol.

[00514] A un vial de 20 mL se añadió una solución de 3-[2-bromo-4-(4-clorobencil)-1,3-tiazol-5-il]-1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol (0,1000 g, 0,2274 mmol) y 2-metil-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)piridina (0,0931 g, 0,425 mmol) en una solución de 1,4-dioxano (2,5000 mL, 32,036 mmol) y agua (0,2500 mL). se añadió carbonato de cesio (0,2223 g, 0,6822 mmol) seguido por

tetrakis(trifenilfosfina)paladio(0) (0,031533 g, 0,027288 mmol). La mezcla de reacción se calentó a 90°C y se dejó agitar durante 18 h. La reacción se enfrió a temperatura ambiente y se inactivó por la adición de una solución acuosa saturada de bicarbonato de sodio (10 mL) y se extrajo con EtOAc (10 mLx3). Las fases orgánicas combinadas se secaron en Na_2SO_4 anhidro, se filtraron y concentraron a presión reducida. El material bruto se cargó seco en gel de sílice luego se purificó por cromatografía en columna sobre sílice (gradiente DCM a 10% de MeOH durante 30 min) para proporcionar el producto con impurezas F_3PO (0,1654 g, 96,6%) como un aceite marrón. LC/MS (AA) ES+ 452. ^{1}H RMN (400 MHz, d_6–DMSO) δ: 8,91 (s, 1H), 7,64–7,53 (m, 3H), 7,37–7,31 (m, 4H), 5,66 (dd, J = 9,6, 2,8 Hz, 1H), 4,61 (s, 2H), 3,72–3,66 (m, 2H), 2,55 (s, 3H), 1,70–1,68 (m, 2H), 1,62–1,48 (m, 2H), 1,45–1,38 (m, 2H).

[00515] **Etapa 2:** 4–(4–Clorobencil)–2–(2–metilpiridin–4–il)–5–(4H–1,2,4–triazol–3–il)tiazol (Compuesto **18**).

[00516] A un vial de 20 mL se añadió una solución de 4–{4–(4–clorobencil)–5–[1–(tetrahidro–2H–piran–2–il)–1H–1,2,4–triazol–3–il]–1,3–tiazol–2–il}–2–metilpiridina (0,1654 g, 0,365 mmol) en tetrahidrofurano anhidro (2,000 mL) y metanol (2,000 mL). se añadió ácido clorhídrico 4,0 M en 1,4–dioxano (1,0 mL, 4,0 mmol) y la mezcla de reacción se dejó agitar a 50°C durante 18 horas. La reacción se enfrió a temperatura ambiente y se inactivó por la adición de a solución acuosa saturada de bicarbonato de sodio (10 mL) luego se extrajo con EtOAc

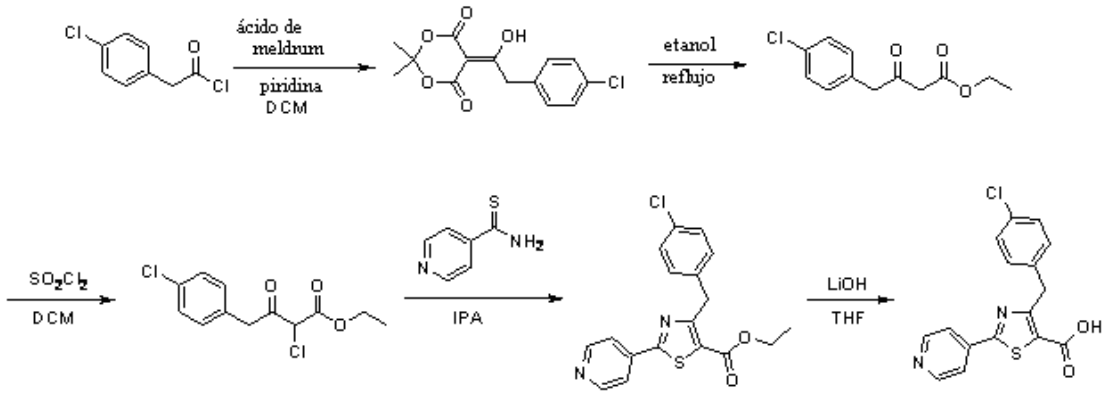
(10 mLx3). Las fases orgánicas combinadas se secaron en Na2SO4 anhidro, se filtraron y concentraron a presión reducida. El material bruto se purificó por HPLC para proporcionar el producto (0,0351 g, 39,9%) como un sólido blanco. LC/MS (AA) ES+ 368, 370. ^{1}H RMN (400 MHz, d_6–DMSO) δ: 8,73 (s, 1H), 8,56 (d, J = 5,2 Hz, 1H), 7,75 (s, 1H), 7,67 (dd, J = 5,2, 1,6 Hz, 1H), 7,37–7,32 (m, 4H), 4,65 (s, 2H) 2,55 (s, 3H).

[00517] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 11:

137	LCMS: (FA) ES+ 354, 356.
213	LCMS: (FA) ES+ 427.

[00518]

[00519] Ejemplo 12: Síntesis de ácido 4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–carboxílico (Compuesto 80)



[00520] Etapa 1: 5–(2–(4–Clorofenil)–1–hidroxietilidene)–2,2–dimetil–1,3–dioxano–4,6–diona.

[00521] A una mezcla de 2,2-dimetil-1,3-dioxano-4,6-diona (52,7 g, 366 mmol) en DCM (205 mL) a -10°C en un baño de hielo/metanol se añadió piridina (72,5 mL, 897 mmol) durante 10 minutos. A la solución resultante a -10°C se añadió una solución de cloruro de 2-(4-clorofenil)acetilo (69,1 g, 366 mmol) en DCM (144 mL) gota a gota durante 1 hora. La mezcla se agitó a -10°C durante 1 hora, luego a temperatura ambiente durante 1 hora. La mezcla se vertió en una mezcla de HCl 2 M (820 mL) y hielo (400 mL) y la fase acuosa se extrajo con DCM (2 x 200 mL). Las fases DCM combinadas se lavaron con HCl 1 N (100 mL) y salmuera (100 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío para dar 103 g del compuesto del título. (95% de rendimiento). LC/MS (FA) ES- 295. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 15,25 (br s, 1H), 7,34-7,26 (m, 4H), 4,37 (s, 2H), 1,72 (s, 6H).

[00522] **Etapa 2:** 4-(4-clorofenil)-3-oxobutanoato de etilo

[00523] Una solución de 5-(2-(4-clorofenil)-1-hidroxietiliden)-2,2-dimetil-1,3-dioxano-4,6-diona (103 g, 347 mmol) en etanol (718 mL) se sometió a reflujo durante 3 horas. La reacción se enfrió y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/hexano = 0/100→20/80) para dar 61 g del compuesto del título como un aceite anaranjado. (73% de rendimiento). LC/MS (FA) ES+ 241. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 7,32-7,28 (m, 2H),

7,15–7,11 (m, 2H), 4,17 (q, 2H, J = 7,2 Hz), 3,81 (s, 2H), 3,45 (s, 2H), 1,26 (t, 3H, J = 7,2 Hz).

[00524] **Etapa 3:** 2–cloro–4–(4–clorofenil)–3–oxobutanoato de etilo

[00525] A una solución de 4–(4–clorofenil)–3–oxobutanoato de etilo (61,0 g, 253 mmol) en DCM (811 mL) en un baño de hielo se añadió cloruro de sulfurilo (34,2 g, 253 mmol) y la solución resultante se dejó agitar a temperatura ambiente durante la noche. La reacción se inactivó con solución de bicarbonato de sodio saturada (200 mL) y las fases se separaron. La fase orgánica se lavó con salmuera (100 mL), se secó con $MgSO_4$, se filtró y concentró al vacío para dar 70,8 g de compuesto del título. (100 % de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ: 7,33–7,30 (m, 2H), 7,17–7,14 (m, 2H), 4,85 (s, 1H), 4,26 (dq, 1H, J = 7,2, 1,2 Hz), 4,02 (d, 1H, J = 16,8 Hz), 3,97 (d, J = 16,8 Hz, 1H), 1,29 (t, 3H, J = 7,2 Hz).

[00526] **Etapa 4:** 4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–carboxilato de etilo

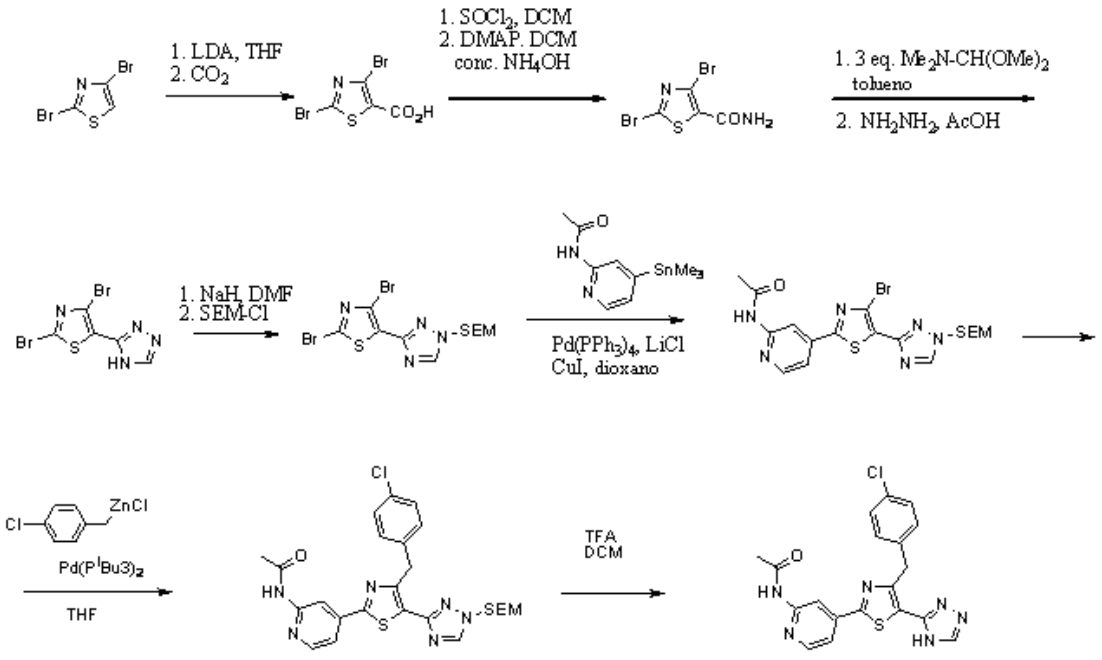
[00527] A una solución de 2–cloro–4–(4–clorofenil)–3–oxobutanoato de etilo (70,8 g, 257 mmol) en IPA (2,96 L) se añadió tioisonicotinamida (71,1 g, 515 mmol) y la mezcla resultante se sometió a reflujo durante 3 días. La reacción se enfrió y concentró al vacío y el residuo se dividió entre DCM (300 ml) y solución de bicarbonato de sodio saturada (200 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (100 mL). Las fases DCM combinadas se lavaron con salmuera (100

mL), se secó con $MgSO_4$, se filtró y concentró al vacío para dar el producto bruto que se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→40/60) seguido por recristalización de acetato de etilo/hexanos para dar 33 g del compuesto del título como cristales amarillo. (36% de rendimiento). LC/MS (FA) ES+ 359. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,74–8,72 (m, 2H), 7,81–7,80 (m, 2H), 7,36–7,32 (m, 2H), 7,27–7,23 (m, 2H), 4,54 (s, 2H), 4,38 (q, 2H, J = 7,2 Hz), 1,40 (t, 3H, J = 7,2 Hz).

[00528] **Etapa 5:** Ácido 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxílico (Compuesto **80**)

[00529] A una solución de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxilato de etilo (12,8 g, 35,7 mmol) en THF (200 mL) y agua (100 mL) se añadió 1,0 M de LiOH (46,4 mL, 46,4 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La mezcla se acidificó a pH 4 con HCl 1 N. Los sólidos precipitados se filtraron, se lavó con agua y secó para dar 11 g del compuesto del título como un sólido blanco. (93 % de rendimiento). LC/MS (FA) ES+ 331. ^{1}H RMN (400 MHz, d_6–DMSO) δ: 13,86 (br s, 1H), 8,72–8,71 (m, 2H), 7,89–7,87 (m, 2H), 7,36–7,29 (m, 4H), 4,50 (s, 2H).

[00530] **Ejemplo 13: Síntesis de *N*-{4-[4-(4-clorobencil)-5-(4*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (Compuesto 56)**



[00531] **Etapa 1:** Ácido 2,4-dibromo-1,3-tiazol-5-carboxílico:

[00532] A un balón de tres bocas de 500 ml equipado con embudo de decantación y control de temperatura interna se añadió THF (200 mL) y N,N-diisopropilamina (14,7 mL, 105 mmol) bajo atmósfera de argón. Después de enfriar a -75°C, 2,50 M de n-butillitio en hexano (41,1 mL, 103 mmol) se añadió gota a gota en la solución durante 30 min. La temperatura interna se mantuvo por debajo de -70°C y la solución resultante se agitó durante 15 min a -75 °C. A esta solución LDA se añadió una solución de 2,4-dibromotiazol (25,0 g, 99,8 mmol) en THF (60 mL) por medio del embudo de decantación over 40 min y la temperatura interna se mantuvo por debajo de -70°C, luego esta solución se agitó durante 20 min a -75°C. A esta solución se añadió hielo seco

triturado a −75°C y la mezcla se agitó durante 15 min. En este momento, 10 mL agua se añadió gota a gota. El baño refrigerante se retiró y la mezcla se llevó a rt durante 1 h con un baño de agua. El solvente se evaporó a presión reducida para dar un residuo sólido. El residuo se suspendió en 100 mL de agua, se alcalinizó con 1,00 M de hidróxido de sodio en agua (110 mL) y se extrajo con 100 mL de éter. La fase etérea se lavó con NaOH 0,5 N (2 x 30 mL). La solución acuosa combinada se acidificó con HCl concentrado a pH 2, se extrajo con éter (5 x 100 mL, ajustando el pH a ~2 cada vez después de separación). Las solucione etéreas combinadas se lavaron con salmuera, se secaron Na_2SO_4, se filtraron, evaporaron para dar un producto sólido (28,04 g, 98%). LCMS: (FA) ES+ 288, ES- 286.

[00533] **Etapa 2:** 2,4-Dibromo-1,3-tiazol-5-carboxamida:

[00534] Una suspensión de ácido 2,4-dibromo-1,3-tiazol-5-carboxílico (16,33 g, 56,91 mmol) en DCM seco (250 mL) y DMF (0,400 mL) se enfrió en un baño de hielo. Se añadió gota a gota el cloruro de tionilo (40,0 mL, 548 mmol). El baño refrigerante se eliminó y la suspensión se agitó a rt durante 2,5 horas. El tolueno (80 mL, 800 mmol) se añadió y la suspensión se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente, el solvente se eliminó y el residuo se destiló azeotrópicamente con tolueno (2 x 100 mL) para dar un intermediario bruto. Este material se suspendió en DCM (230 mL) y se enfrió en un baño de hielo. Se añadió N,N-Dimetilaminopiridina (0,70 g, 5,7 mmol), seguido por la

adición lenta de 8,5 M de hidróxido de amonio en agua (100,0 mL, 850,0 mmol). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se filtró y la fase acuosa se separó y se extrajo con DCM (3 x 100 mL). Las fases DCM combinadas se lavaron con agua, salmuera, se secaron con Na_2SO_4, filtraron y evaporaron para dar a producto sólido (11,2 g, 69%). LCMS: (FA) ES+ 287 y ES- 285.

[00535] **Etapa 3:** 3-(2,4-Dibromo-1,3-tiazol-5-il)-4H-1,2,4-triazol :

[00536] A una suspensión de 2,4-dibromo-1,3-tiazol-5-carboxamida (0,110 g, 0,385 mmol) en tolueno seco (8,0 mL, 75 mmol) se añadió DMF-DMA (0,204 mL, 1,54 mmol). La mezcla se agitó a 60°C bajo atmósfera de nitrógeno durante 3 horas. El solvente se eliminó y al intermediario se añadió ácido acético (2,0 mL, 35 mmol), seguido por hidrazina (0,0604 mL, 1,92 mmol). La mezcla se calentó a 120°C durante 30 min. La mezcla se enfrió a temperatura ambiente, el solvente se eliminó y el ácido acético residual se destiló azeotrópicamente con tolueno (2 x 5 mL) para dar un material oleoso, que se alcalinizó con NaHCO3 acuoso saturado a pH~8 y se extrajo con EtOAc (3 x 30 mL). La fase en EtOAc se lavó con agua, salmuera, se secó con Na_2SO_4, filtró y evaporó para dar el producto bruto. La cromatografía en la columna de silice usando EtOAc/hexano (0/100 a 50/50) dio un producto sólido (0,073 g, 61%). LCMS: (FA) ES+ 311 y ES- 309. ^{1}H RMN (400MHz, d_4-metanol) δ:8,53 (s, 1H).

[00537] **Etapa 4:** 3-(2,4-Dbromo-1,3-tiazol-5-il)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol

[00538] A la solución de 3-(2,4-dibromo-1,3-tiazol-5-il)-4H-1,2,4-triazol (1,16 g, 3,74 mmol) en DMF seco (5,0 mL) a 0°C se añadió en porciones hidruro de sodio (60%, 0,180 g, 4,49 mmol). El baño de hielo se retiró, la mezcla se agitó durante 5 min a temperatura ambiente luego se enfrió en un baño de hielo. Se añadió gota a gota [β-cloruro de (trimetilsilil)etoxi]metilo (0,795 mL, 4,49 mmol) en DMF seco (2,0 mL) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla se inactivó con hielo-agua, se extrajo con EtOAc, se lavó con salmuera, se secó con Na_2SO_4, filtró, evaporó para dar un aceite crudo. El producto se purificó por cromatografía en columna en gel de sílice, eluyendo con EtOAc/hexano (0/100 a 20/80) para proporcionar un producto sólido blanco (1,10 g, 67%). LCMS: (FA) ES+ 441. ^{1}H RMN (400MHz, $CDCl_3$) δ: 8,29 (s, 1H), 5,54 (s, 2H), 3,71 (t, J = 8,28 Hz, 2H), 0,95 (t, J = 8,28 Hz, 2H), 0,00 (s, 9H) .

[00539] **Etapa 5:** N-{4-[4-Bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]piridin-2-il}acetamida:

[00540] La mezcla de 3-(2,4-dibromo-1,3-tiazol-5-il)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol (1,10 g, 2,50 mmol), N-[4-(trimetilstannil)piridin-2-il]acetamida (0,896 g, 3,00 mmol), tetrakis(trifenilfosfina)paladio (0) (0,155 g,

0,125 mmol), yoduro de cobre (0,143 g, 0,750 mmol) y cloruro de litio (0,318 g, 7,50 mmol) en 1,4-dioxanos seco (100 mL) se sometió a sonicación durante 2 min, se desgasificó y se llenó de nuevo con nitrógeno 5 veces. La mezcla se calentó bajo atmósfera de nitrógeno a reflujo durante 90 min, luego se enfrió a temperatura ambiente, se filtró a través de celite y se lavó con dioxano/DCM. El filtrado se evaporó a presión reducida para dar un residuo bruto, que se purificó por cromatografía en columna en gel de sílice que eluye con MeOH/DCM (0/100 a 5/95) para dar un producto, que se purificó adicionalmente en una columna de gel de sílice usando MeOH/EtOAc/hexano (0/0/100 a 5/45/50) para dar el producto puro (0,150 g, 13%). LCMS: (FA) ES+ 495, 497. ^{1}H RMN (400MHz, $CDCl_3$) δ: 8,72 (s, 1H), 8,37 (m, 1H), 8,33 (s, 1H), 8,26 (s, 1H), 7,68 (m, 1H), 5,57 (s, 2H), 3,73 (t, J = 8,28 Hz, 2H), 2,25 (s, 3H), 0,97 (t, J = 8,28 Hz, 2H), 0,00 (s, 9H) .

[00541] **Etapa 6:** *N*-{4-[4-(4-Clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-1,2,4-triazol-5-il)-1,3-tiazol-2-il]piridin-2-il}acetamida

[00542] A una solución de *N*-{4-[4-bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-1,2,4-triazol-5-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (0,292 g, 0,589 mmol) en tetrahidrofurano (4,1 mL) se añadió cloruro de 4-clorobencilzinc (0,50 M solución en tetrahidrofurano, 2,36 mL, 1,18 mmol) y bis(tri-t-butilfosfina)paladio(0) (0,0226 g, 0,0442 mmol) bajo argón. La solución se agitó a 60°C durante 2 horas. La

reacción estuvo incompleta por LCMS, se añadió cloruro de 4-clorobencilzinc adicional (solución 0,50 M en tetrahidrofurano, 2 mL, 1 mmol), luego la reacción se agitó a 60°C durante 2 horas adicionales. La reacción se dejó enfriar a temperatura ambiente luego el solvente se evaporó al vacío. Se realizó la cromatografía en columna para producir el compuesto del título (0,112 g, 35%). LCMS: (FA) ES^+, 542. ^1H RMN (400MHz, d_4-metanol) δ: 8,73-8,69 (m, 1 H), 8,42-8,38 (m, 1H), 8,14 (s ,1H), 7,58-7,55 (m, 1H), 7,27-7,20 (m, 4H), 5,52 (s, 2H), 4,32 (s, 2H), 3,68-3,61 (m, 2H), 2,20 (s, 3H), 0,90-0,84 (m, 2H), 0,040 (s, 9H).

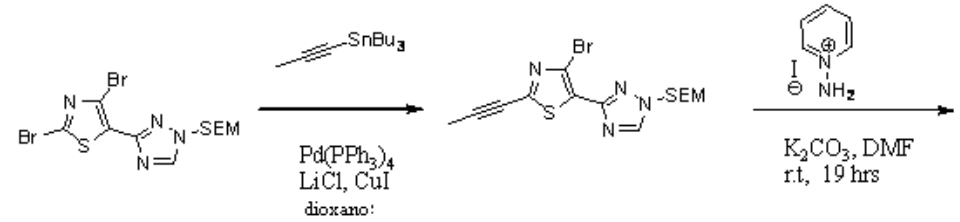
[00543] **Etapa 7:** *N*-{4-[4-(4-Clorobencil)-5-(4*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (Compuesto **56**)

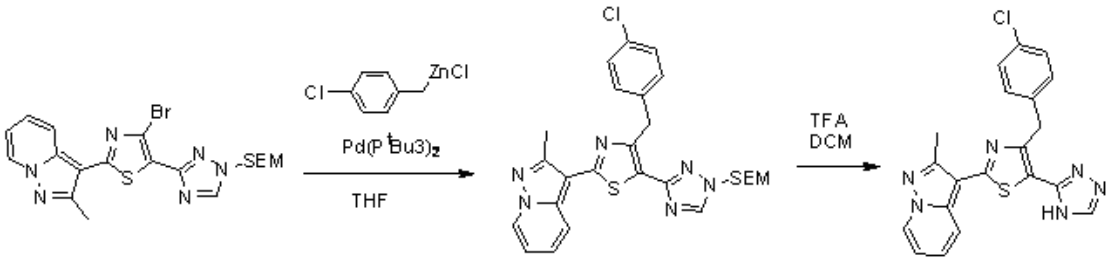
[00544] A una solución de *N*-{4-[4-(4-clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-1,2,4-triazol-5-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (0,112 g, 0,207 mmol) en diclorometano (2,0 mL) a temperatura ambiente se añadió ácido trifluoroacético (3,1 mL, 40 mmol). La mezcla luego se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó y el exceso de ácido trifluoroacético se extrajo por mezcla azeotrópica con tolueno. Se realizó la cromatografía en columna para producir el compuesto del título (0,0520 g, 61%). LCMS: (FA) ES^+, 411. ^1H RMN (400MHz, d_6-DMSO) δ: 14,46 (s, 1H), 10,69 (s, 1H), 8,80-8,73 (m, 1H), 8,64-8,60 (m, 1H), 8,43-8,37 (m, 1H), 7,59-7,54 (m, 1H), 7,37-7,28 (m, 4H), 4,66 (s, 2H), 2,12 (s, 3H).

[00545] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 13:

7	LCMS: (FA) ES+ 388, 390.
27	LCMS: (AA) ES+ 369, 371.
53	LCMS: (AA) ES+ 393, 395.

[00546] **Ejemplo 14: Síntesis de 3-[4-(4-clorobencil)-5-(4*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-*a*]piridina (Compuesto 4)**





[00547] **Etapa 1:** 3-(4-Bromo-2-prop-1-in-1-il-1,3-tiazol-5-il)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol

[00548] Una mezcla de 3-(2,4-dibromo-1,3-tiazol-5-il)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol (6,00 g, 13,6 mmol), cloruro de litio (1,73 g,

40,9 mmol), yoduro de cobre (0,779 g, 4,09 mmol) y tetrakis(trifenilfosfine)platino (0) (0,848 g, 0,681 mmol) en 1,4-dioxanos anhidro (120 mL, 1500 mmol) se sometió a sonicación bajo atmósfera de argón durante 2 minutos en a 250 mL RBF. Se añadió tributil(1-propinil)estaño (4,80 mL, 15,0 mmol). La mezcla se calentó a 100°C durante 1 hora bajo atmósfera de argón. La mezcla se enfrió a rt, se diluyó con DCM (~150 mL), se filtró a través de celite, y se lavó con DCM. El filtrado se sometió a evaporación con rotavapor para dar un residuo bruto que luego se purificó por cromatografía en columna (SiO2, elución con 0-100% EtOAc en hexano) para proporcionar un producto sólido puro (4,14 g, 76% de rendimiento). LCMS: (FA) ES^+ 399, 401. ^1H RMN (400MHz, $CDCl_3$) δ:8,29 (s, 1H), 5,54 (s, 2H),3,69-3,74 (m, 2H), 2,15 (s, 3H), 0,93-0,97 (m, 2H), 0,00 (s, 9H) .

[00549] **Etapa 2:** 3-[4-Bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridina

[00550] Una mezcla de 3-(4-bromo-2-prop-1-in-1-il-1,3-tiazol-5-il)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol (0,514 g, 1,29 mmol), yoduro de 1-aminopiridinio (0,343 g, 1,54 mmol) y carbonato de potasio (0,231 g, 1,67 mmol) en N,N-dimetilformamida (8,0 mL, 1,0E2 mmol) se agitó a rt durante 29 horas. La mezcla se inactivó con agua helada (80 mL) luego se extrajo con EtOAc 3 veces. La solución EtOAc combinada se lavó con agua, salmuera, se secó con Na_2SO_4, filtró y purificó por cromatografía en columna (SiO2, elución con 0-100% de EtOAc en hexano) para

proporcionar un producto sólido. (0,410 g, 64,8% de rendimiento). LCMS: (FA) ES^+ 491, 493. ^1H RMN (400MHz, $CDCl_3$) δ:8,43–8,46 (m, 2H), 8,32 (s, 1H), 7,39–7,42 (m, 1H), 6,90–6,93 (m, 1H, 5,57 (m, 2H), 3,72–3,76 (m, 2H), 2,76 (s, 3H), 0,96–1,00 (m, 2H),0,00 (s, 9H) .

[00551] **Etapa 3:** 3-[4-(4-Clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-*a*]piridina

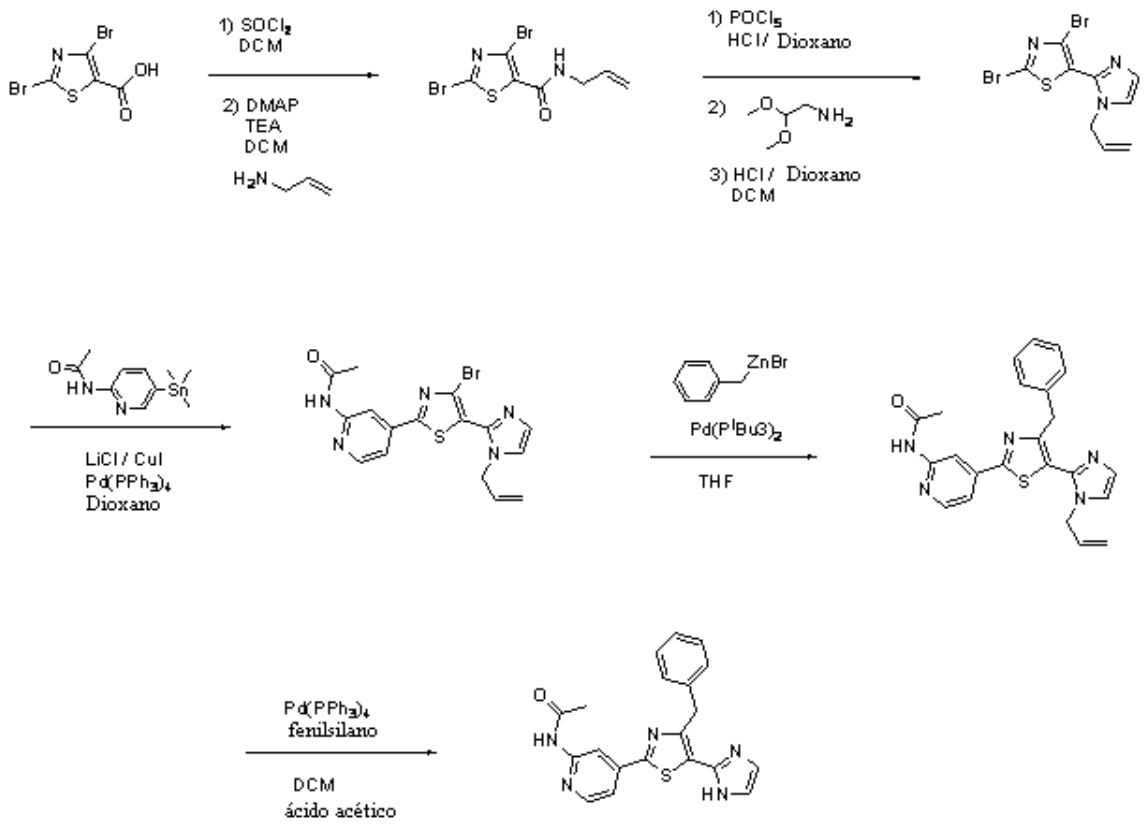
[00552] A una solución de 3-[4-bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-*a*]piridina (0,200 g, 0,407 mmol) en tetrahidrofurano (2,8 mL) se añadieron cloruro de 4-clorobencilzinc (0,50M solución en tetrahidrofurano, 1,63 mL, 0,814 mmol) y bis(tri-t-butilfosfina)paladio(0) (0,0156 g, 0,0305 mmol) bajo argón. La solución se agitó a 60°C durante 3 horas. La reacción estaba incompleta por LCMS, de modo que se añadió cloruro de 4-clorobencilzinc adicional (solución 0,50 M en tetrahidrofurano, 1,0 mL, 0,5 mmol) luego la reacción se agitó a 60°C durante 3 horas adicionales. La reacción se enfrió a temperatura ambiente luego el solvente se evaporó al vacío. El residuo se purificó por cromatografía en columna (SiO2, elución con EtOAc en hexanos 10–100% de gradiente) para producir el compuesto del título (0,188 g, 86%). LCMS: (FA) ES^+, 538. ^1H RMN (400MHz, d_6–DMSO) δ: 8,87 (s, 1 H), 8,76–8,72 (m, 1H), 8,28–8,24 (m,1H), 7,54–7,48 (m, 1H), 7,44–7,40 (m, 2H), 7,35–7,30 (m, 2H), 7,09–7,03 (m, 1H), 5,58 (s, 2H), 4,63 (s, 2H), 3,68–3,62 (m, 2H), 2,66 (s, 3H), 0,91–0,84 (m, 2H), 0,050 (s, 9H).

[00553] **Etapa 4:** 3-[4-(4-Clorobencil)-5-(4*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-*a*]piridina (Compuesto **4**)

[00554] A una solución de 3-[4-(4-clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-*a*]piridina (0,182 g, 0,339 mmol) en diclorometano (3,3 mL) a temperatura ambiente se añadió ácido trifluoroacético (5,1 mL, 66 mmol). La mezcla luego se agitó a temperatura ambiente durante 3 horas. El solvente se evaporó y el exceso de ácido trifluoroacético se extrajo por mezcla azeotrópica con tolueno. El producto bruto se purificó por cromatografía en columna (SiO2, elución con hexano a 100% de acetato de etilo) para producir el compuesto del título (0,0884 g, 64%). LCMS: (FA) ES^+, 407. ^1H RMN (400MHz, d_6-DMSO) δ: 8,76-8,70 (m, 2H), 8,28-8,22 (m, 1H), 7,53-7,46 (m, 1H), 7,45-7,40 (m, 2H), 7,37-7,31 (m, 2H), 7,07-7,01 (m, 1H), 5,55-5,50 (m, 1H), 4,64 (s, 2H), 2,65 (s, 3H).

[00555] **Ejemplo 15: Síntesis de N-{4-[4-bencilo-5-(1H-imidazol-2-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (Compuesto 2)**

[00556]



[00557] **Etapa 1:** *N*-alil-2,4-dibromo-1,3-tiazol-5-carboxamida

[00558] A una solución de ácido 2,4-dibromo-1,3-tiazol-5-carboxílico (25,0 g, 87,1 mmol) en diclorometano (600 mL) at 0°C se añadió cloruro de tionilo (66,1 mL, 906 mmol) seguido por N,N-dimetilformamida (7,02 mL, 90,6 mmol). La mezcla se dejó calentar a temperatura ambiente y agitar durante 2 horas. El solvente se evaporó y el exceso de cloruro de tionilo se extrajo por mezcla azeotrópica con tolueno. El residuo se disolvió en diclorometano (600 mL) y se enfrió a 0°C, luego se añadió trietilamina (63,2 mL, 453 mmol) seguido

por 2-propen-1-amina (23,8 mL, 317 mmol) y N,N-dimetilaminopiridina (1,11 g, 9,06 mmol). La mezcla se dejó calentar a temperatura ambiente y se agitó durante 2 horas. La solución luego se diluyó con diclorometano y agua y las fases se separaron. La fase acuosa luego se extrajo con diclorometano dos veces, luego los extractos orgánicos combinados se lavaron con salmuera, secaron sulfato de sodio anhidro, se filtraron y concentraron al vacío. Se realizó la cromatografía en columna para producir el compuesto del título (14,3 g, 50%). LCMS: (FA) ES^+, 327. ^1H RMN (400MHz, d_4-metanol) δ: 5,97-5,85 (m, 1H), 5,32-5,24 (m, 1H), 5,20-5,14 (m, 1H), 4,02-3,95 (m, 2H).

[00559] **Etapa 2:** 5-(1-alil-1*H*-imidazol-2-il)-2,4-dibromo-1,3-tiazol

[00560] A una solución de *N*-alil-2,4-dibromo-1,3-tiazol-5-carboxamida (13,0 g, 39,9 mmol) en diclorometano (260 mL) se añadió pentacloruro de fósforo (9,93 g, 47,7 mmol) y ácido clorhídrico 4 M en dioxano (1,52 mL, 6,06 mmol). La reacción se calentó a 60°C durante 90 minutos bajo atmósfera de nitrógeno. La reacción se dejó enfriar a temperatura ambiente y luego aminoacetaldehído dimetil acetal (47,8 mL, 439 mmol) se añadió lentamente a través del condensador. La mezcla se calentó a 60°C durante 2 horas bajo atmósfera de nitrógeno luego se enfrió a temperatura ambiente, y se añadió agua (200 mL). Las fases se separaron y la fase orgánica se lavó con agua nuevamente (2 x 200 mL). Los extractos orgánicos se lavaron con salmuera, secaron con sulfato de sodio anhidro, filtraron y lavaron con

diclorometano (200 mL). A esta solución de diclorometano solución del intermediario se añadió ácido clorhídrico 4 M en dioxano (120 mL, 480 mmol) y la solución se agitó a 60°C durante 16 horas. La solución se decantó (dejando detrás un residuo negro oleoso sobre el balón) luego el solvente se evaporó y el residuo se diluyó con acetato de etilo y solución de bicarbonato de sodio saturada. Las fases se separaron y la fase acuosa se extrajo tres veces más con acetato de etilo. Los extractos orgánicos se lavaron con salmuera, secaron sulfato de sodio anhidro, se filtraron y concentraron al vacío. Se realizó la cromatografía en columna para producir el compuesto del título (8,04 g, 58%). LCMS: (FA) ES^+, 306 (grupo original menos alilo). ^{1}H RMN (300MHz, d_4-metanol) δ: 7,37–7,31 (m, 1H), 7,20–7,16 (m, 1H), 6,02–5,86 (m, 1H), 5,26–5,18 (m, 1H), 5,07–4,96 (m, 1H), 4,68–4,59 (m, 2H).

[00561] **Etapa 3:** Síntesis de *N*-{4-[5-(1-alil-1*H*-imidazol-2-il)-4-bromo-1,3-tiazol-2-il]piridin-2-il}acetamida

[00562] A una solución de 5-(1-alil-1*H*-imidazol-2-il)-2,4-dibromo-1,3-tiazol (5,00 g, 14,3 mmol) en 1,4-dioxano (133 mL) se añadió N-[4-(trimetilestannil)piridina-2-il]acetamida (5,14 g, 17,2 mmol), cloruro de litio (1,82 g, 43,0 mmol), yoduro de cobre (I) (0,818 g, 4,30 mmol) y tetrakis(trifenilfosfina)paladio(0) (1,24 g, 1,07 mmol). El balón se purgó con argón y luego la mezcla se calentó a 115°C durante 4 horas. La reacción se dejó enfriar a temperatura ambiente, y luego el solvente se evaporó al vacío. Se realizó la cromatografía en columna para

producir el compuesto del título (3,13 g, 54%). LCMS: (FA) ES^+, 406. ^1H RMN (400MHz, d_6–DMSO) δ: 10,77 (s, 1H), 8,66–8,61 (m, 1H), 8,49–8,44 (m, 1H), 7,61–7,56 (m, 1H), 7,49–7,45 (m, 1H), 5,98–5,87 (m, 1H), 5,19–5,12 (m, 1H), 4,95–4,88 (m, 1H), 4,70–4,64 (m, 2H), 2,13 (s, 3H).

[00563] **Etapa 4:** Síntesis de N-{4-[5-(1-alil-1H-imidazol-2-il)-4-bencilo-1,3-tiazol-2-il]piridin-2-il}acetamida

[00564] A una solución de *N*-{4-[5-(1-alil-1*H*-imidazol-2-il)-4-bromo-1,3-tiazol-2-il]piridin-2-il}acetamida (0,0500 g, 0,124 mmol) en tetrahidrofurano (0,86 mL) se añadió bromuro de bencilzinc (solución 0,50 M en tetrahidrofurano, 0,495 mL, 0,247 mmol) y bis(tri-t-butilfosfina)paladio(0) (0,00474 g, 0,00928 mmol) bajo argón. La solución se agitó a 60°C durante 2 horas luego se enfrió a temperatura ambiente. El solvente se evaporó al vacío. Se realizó la cromatografía en columna para producir el compuesto del título (0,0110 g, 21%). LCMS: (FA) ES^+, 416. ^1H RMN (400MHz, d_4–metanol) δ: 8,70–8,65 (m, 1 H), 8,41–8,36 (m, 1H), 7,66–7,61 (m ,1H), 7,34–7,05 (m, 7H), 5,81–5,70 (m, 1H), 5,16–5,10 (m, 1H), 4,95–4,88 (m, 1H), 4,38–4,33 (m, 2H), 4,13 (s, 2H), 2,20 (s, 3H).

[00565] **Etapa 5:** Síntesis de N-{4-[4-bencilo-5-(1H-imidazol-2-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (Compuesto **2**)

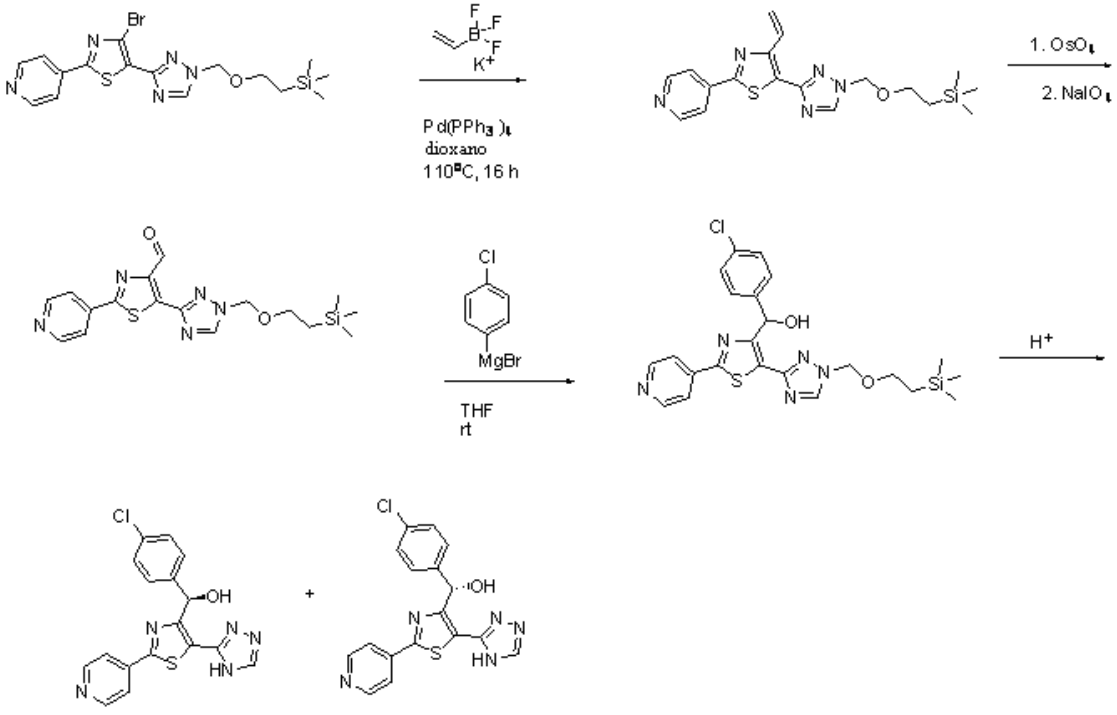
[00566] A una solución de N-{4-[5-(1-alil-1H-imidazol-2-il)-4-bencilo-1,3-tiazol-2-il]piridin-2-il}acetamida (0,210 g, 0,0505 mmol) en diclorometano (0,38 mL) y ácido acético (0,13 mL) se añadió

tetrakis(trifenilfosfina)paladio(0) (0,00292 g, 0,00253 mmol) seguido por fenilsilano (0,0318 mL, 0,258 mmol). La solución se agitó a 40°C durante 3 horas. La solución se enfrió a temperatura ambiente luego concentró al vacío y se diluyó con acetato de etilo y solución de bicarbonato de sodio saturada. Las fases se separaron y la fase acuosa se extrajo tres veces más con acetato de etilo. Los extractos orgánicos se lavaron con salmuera, secaron sulfato de sodio anhidro, se filtraron y concentraron al vacío. Se realizó la cromatografía en columna para producir el compuesto del título (0,0100 g, 53%). LCMS: (FA) ES^+, 376. ^{1}H RMN (400MHz, d_4–metanol) δ: 8,67–8,63 (m, 1H), 8,38–8,35 (m, 1H), 7,63–7,59 (m, 1H), 7,25–7,07 (m, 7H), 4,42 (s, 2H), 2,20 (s, 3H).

[00567] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 15:

24	LCMS: (FA) ES+ 390
67	LCMS: (FA) ES+ 410, 412.
73	LCMS: (FA) ES+ 410, 412.

[00568] Ejemplo 16: Síntesis de (4–clorofenil)[2–piridin–4–il–5–(1H–1,2,4–triazol–3–il)–1,3–tiazol–4–il]metanol (Compuestos 19 y 70)



[00569] **Etapa 1:** 4-[5-(1-{[2-(Trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-4-vinil-1,3-tiazol-2-il]piridina.

[00570] En un tubo sellado se añadió viniltrifluoroborato de potasio (1,34 g, 10,0 mmol), 1,4-dioxano (21,0 mL, 269 mmol), 4-[4-bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]piridina (2,0 g, 4,6 mmol) y carbonato de sodio 2 M en agua (9,10 mL, 18,2 mmol). La reacción se desgasificó con nitrógeno durante 15 min luego se añadió tetrakis(trifenilfosfina)paladio(0) (527 mg, 0,456 mmol). El tubo se selló y la reacción se calentó en un baño de aceite a 110°C con agitación durante la noche. La reacción solución se enfrió a temperatura ambiente, se añadieron agua (10 mL) y EtOAc (10 mL), y las fases

orgánicas combinadas se lavaron con salmuera, secaron $MgSO_4$, se filtraron y concentraron a presión reducida. El residuo obtenido se purificó por cromatografía en columna (SiO_2, elución con 0–10 % MeOH en DCM) para dar el compuesto del título como un sólido amarillo (1,34 g 81%). LCMS: (FA) ES^+, 386. ^1H RMN (400 MHz, *d6*–DMSO) δ:8,92 (s, 1H), δ 8,74–8,76 (dd, *J* = 1,75 Hz, *J* = 1,5 Hz 2H), 7,96–7,98 (dd, *J* = 1,75 Hz, 2H), 6,34–6,40 (dd, *J* = 2,3 Hz, 1 2H), 5,62–5,65 (dd, *J* = 2,3 Hz, 1H), 5,60 (s, br, 2H), 3,63–3,68 (m, 2H), 0,86–0,90 (m, 2H), –0,04 (s, 9H).

[00571] **Etapa 2:** 2–Piridin–4–il–5–(1–{[2–(trimetilsilil)etoxi]metil}–1H–1,2,4–triazol–3–il)–1,3–tiazol–4–carbaldehído

[00572] A una solución de 4–[5–(1–{[2–(trimetilsilil)etoxi]metil}–1H–1,2,4–triazol–3–il)–4–vinil–1,3–tiazol–2–il]piridina (1,43 g, 2,60 mmol) en una mezcla 3:1 de 1,4–dioxano (17,5 mL, 224,6 mmol) y agua (5,8 mL, 324,25 mmol) se añadió 2,6–lutidina (1,50 mL, 12,98 mmol) y la mezcla se enfrió a 0°C. Se añadió metaperyodato de sodio (2,80 g, 12,98 mmol) seguido por la adición de 4% de tetróxido de osmio en agua (0,50 mL, 0,080 mmol) y la mezcla de reacción se calentó lentamente a temperatura ambiente y se dejó agitar durante la noche. se añadió agua (10 mL). El precipitado amarillo resultante se recolectó por filtración, se lavó con agua, éter y MeOH. El filtrado se concentró a presión reducida y se secó a alto vacío para dar el compuesto del título (1,0 g, rendimiento 99%). LCMS: (FA) ES^+, 388. ^1H RMN (400 MHz, d_6–DMSO) δ: 10,70(s, 1H), δ:9,05 (s, 1H), 8,79–8,80

(dd, *J* = 1,5 Hz, 2H), 7,98–8,0 (dd, *J* = 1,5 Hz, *J* = 1,7 Hz, 2H), 5,64–5,66 (s, br, 2H), 3,64–3,68 (m, 2H), 0,870–0,90(m, 2H), –0,03 (s, 9H).

[00573] **Etapa 3:** (4–Clorofenil)[2–piridin–4–il–5–(1–{[2–(trimetilsilil)etoxi]metil}–1H–1,2,4–triazol–3–il)–1,3–tiazol–4–il]metanol

[00574] A una solución de 2–piridin–4–il–5–(1–{[2–(trimetilsilil)etoxi]metil}–1H–1,2,4–triazol–3–il)–1,3–tiazol–4–carbaldehído (280,0 mg, 0,722 mmol) en tetrahidrofurano (4,0 mL, 40 mmol), se añadió bromuro de 4–clorofenil magnesio 1 M en éter (4,0 mL, 4 mmol) y la mezcla se agitó durante 40 min a rt. Después de completar la reacción se añadieron una solución acuosa de 5% NH_4Cl (10 mL) y EtOAc (10 mL) y la mezcla bifásica resultante se agitó vigorosamente durante 15 min luego la fase acuosa se descartó. La fase orgánica se lavó con salmuera (5 mL) luego se secó con $MgSO_4$ anhidro. Los materiales insolubles se extrajeron por filtración y el filtrado se concentró a presión reducida. El residuo obtenido se purificó por cromatografía en columna (SiO_2, elución con 20–80% de EtOAc en hexano) para dar el compuesto del título como un sólido blanco (230 mg, 73,6%). LCMS: (FA) ES^+, 500. ^1H RMN (400 MHz, d_6–DMSO) δ:8,96 (s, 1H), δ 8,70–8,72 (dd, *J* = 1,75 Hz, 2H), 7,87–7,89 (dd, *J* = 1,75, 2H), 7,32–7,37(m, 2H), 7,55–7,58(m, 3H), 6,85–6,87(d, *J* = 5,5 Hz , 1H) , 6,15–6,17(d, *J* = 5,5 Hz , 1H) , 5,6 (s, br, 2H), 3,65–3,67 (m, 2H), 0,850–0,90(m, 2H), –0,05 (s, 9H).

[00575] **Etapa 4:** (4-Clorofenil)[2-piridin-4-il-5-(1H-1,2,4-triazol-3-il)-1,3-tiazol-4-il]metanol.

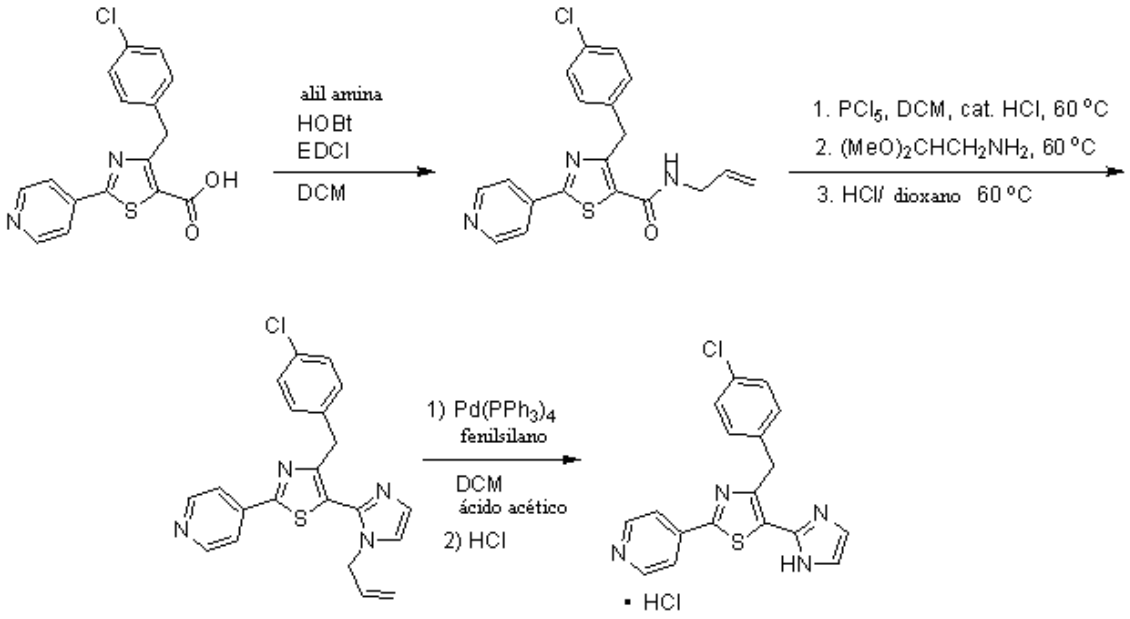
[00576] (4-Clorofenil)[2-piridin-4-il-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-4-il]metanol(266,0 mg, 0,530 mmol) se disolvió en cloruro de metileno (3,0 mL, 47 mmol). se añadió ácido trifluoroacético (3,0 mL, 39 mmol) y la solución se agitó a rt durante la noche. Después de completar la reacción, se añadió $NaHCO_3$ saturado y la reacción se agitó a rt durante 20 min, luego se añadió EtOAc (5 mL), la fase orgánica se separó, se lavó con salmuera, se secó con $MgSO_4$, se filtró, concentró y el residuo obtenido se purificó por cromatografía en columna (SiO_2, elución con 2-20% de MeOH en DCM) para dar el compuesto del título como un sólido blanco (200 mg). Los isómeros racémicos se separaron por HPLC preparativa quiral para producir **17** (34 mg, 12,7%) (pico 1, tiempo de ret 13,04 min). LCMS: (FA) ES^+, 370. ^1H RMN (400 MHz, d_6-DMSO) δ: 8,76(s, 1H), 8,69-8,71 (dd, J = 1,5 Hz, 2H), 7,86-7,88 (dd, J = 1,5, 2H), 7,55-7,58(d, , J = 8,5 Hz, 2H), 7,34-7,38(d, J = 8,5 Hz, 2H), 6,84-6,86 (s, br, 1H) y **70** (34,8 mg, 13,0%) (peak 2, ret. time 13,2 min). LCMS: (FA) ES^+, 370. ^1H RMN (400 MHz, d_6-DMSO) δ: 8,68-8,72(m, 3H), 7,86-7,88 (dd, J = 1,69 Hz , J = 1,5 Hz , 2H), 7,54-7,58(d, , J = 8,47 Hz, 2H), 7,34-7,38(d, J = 8,47 Hz, 2H), 6,81-6,82 (s, br, 1H).

[00577] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 16:

149	LCMS: (AA) ES+ 451, 453, 455
168	LCMS: (FA) ES+ 418, 420
238	LCMS: (AA) ES+ 427, 429
265	LCMS: (AA) ES+ 431, 433
278	LCMS: (AA) ES+ 451, 453, 455
282	LCMS: (FA) ES+ 418, 420
285	LCMS: (AA) ES+ 431, 433

[00578]

[00579] **Ejemplo 17: Síntesis de 4-(4-clorobencil)-5-(1H-imidazol-2-il)-2-(piridin-4-il)tiazol (Compuesto 15)**



[00580] **Etapa 1: N**-Alil-4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxamida

[00581] A una solución agitada de ácido 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxílico (220 mg, 0,665 mmol) en DCM (4,05 mL) se añadió HOBT (98,8 mg, 0,732 mmol) y EDCI (204 mg, 1,06 mmol) a temperatura ambiente y la mezcla se agitó durante 30 min. A la solución se añadió 2-propen-1-amina (0,200 mL, 2,66 mmol) luego la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con DCM (10 mL) y se lavó con agua (3 mL) y salmuera (2 mL), luego se secó con $MgSO_4$, se filtró y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→75/25) para dar 150 mg del compuesto del título como un sólido amarillo (61 % de rendimiento). LC/MS (FA) ES+ 370. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,74-8,72 (m, 2H), 7,79-7,77 (m, 2H), 7,35-7,32 (m, 2H), 7,27-7,25 (m, 2H), 5,94-5,80 (m + bs, 2H), 5,25-5,20 (m, 2H), 4,48 (s, 2H), 4,06-4,02 (m, 2H).

[00582] **Etapa 2: 5**-(1-Alil-1H-imidazol-2-il)-4-(4-clorobencil)-2-(piridin-4-il)tiazol

[00583] A una solución de N-alil-4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxamida (150 mg, 0,406 mmol) en DCM (2,64 mL) se añadió pentacloruro de fósforo (101 mg, 0,485 mmol) y ácido clorhídrico 4 M en 1,4-dioxano (0,0154 mL, 0,0614 mmol) y la mezcla se calentó a 60 °C durante 1,5 h. La reacción se enfrió a temperatura ambiente y se añadió aminoacetaldehído

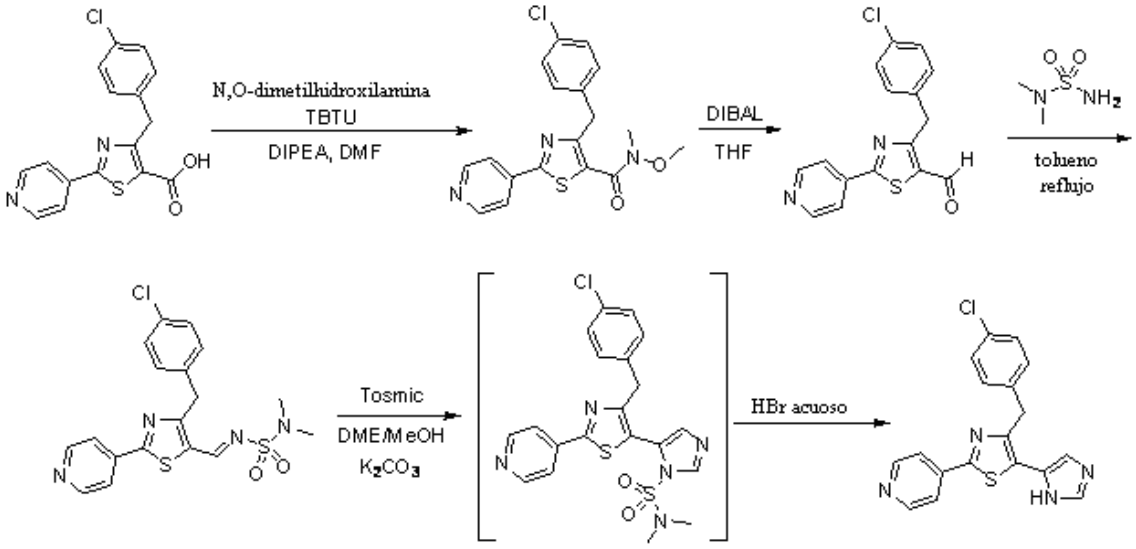
dimetil acetal (0,486 mL, 4,46 mmol). La mezcla resultante se calentó a 60°C durante 2 h. La mezcla se enfrió a temperatura ambiente, se diluyó con DCM (10 mL), se lavó con agua (2 x 2 mL) y salmuera (2 mL), se secó con sulfato de sodio, se filtró y concentró al vacío. El residuo se tomó en DCM (3,0 mL) y se añadió ácido clorhídrico 4 M en 1,4-dioxano (0,608 mL, 2,43 mmol) y la mezcla se agitó a 60°C durante la noche. La reacción se enfrió y concentró al vacío. El residuo se tomó en acetato de etilo (20 mL) y bicarbonato de sodio saturado (5 mL). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (5 mL). Las fases orgánicas combinadas se secaron en MgSO4, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (metanol/DCM = 0/100→5/95) para dar 99 mg del compuesto del título (62 % de rendimiento). LC/MS (FA) ES+ 393. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,72-8,70 (m, 2H), 7,80-7,72 (m, 2H), 7,26 (m, 1H), 7,22-7,14 (m, 4H), 7,06 (m, 1H), 5,84-5,71 (m, 1H), 5,23-5,19 (m, 1H), 5,01-4,96 (m, 1H), 4,38-4,34 (m, 2H), 4,20 (s, 2H).

[00584] **Etapa 3:** 4-(4-Clorobencil)-5-(1H-imidazol-2-il)-2-(piridin-4-il)tiazol, sal clorhidrato (Compuesto **15**)

[00585] A una solución de 5-(1-alil-1H-imidazol-2-il)-4-(4-clorobencil)-2-(piridin-4-il)tiazol (99,0 mg, 0,252 mmol) y tetrakis(trifenilfosfina)paladio (14,6 mg, 0,0126 mmol) en DCM (3,38 mL) se añadió ácido acético (0,623 mL, 11,0 mmol) y fenilsilano (0,158 mL,

1,28 mmol) y la mezcla se agitó durante 2 h a 40°C. La mezcla de reacción se evaporó para extraer los productos volátiles y se añadió DCM (10 mL). A esta solución se añadió bicarbonato de sodio saturado (4 mL) y la mezcla resultante se agitó durante 30 min. La mezcla se extrajo con DCM (3 x 10 mL) y las fases DCM combinadas se lavaron con salmuera. Las fases orgánicas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (metanol/DCM = 0/100→10/90) para dar 57 mg del compuesto del título como un sólido amarillo (64 % de rendimiento). La sal de HCl se obtuvo de la siguiente manera. A una mezcla de la base libre (57 mg, 0,162 mmol) en etanol (5 mL) se añadió HCl 1,0 M en éter (0,178 mL, 0,178 mmol) y la mezcla se agitó durante 2 horas luego concentró al vacío. El residuo se tomó en un mínimo de metanol, y acetonitrilo se añadió para dar un precipitado. Se añadió éter y el precipitado se filtró, se lavó con éter y se secó para dar el compuesto del título como un sólido anaranjado. LC/MS (FA) ES+ 353. ^{1}H RMN (400 MHz, d_6–DMSO) δ: 8,78–8,74 (m, 2H), 7,96–7,91 (m, 2H), 7,48–7,43 (m, 2H), 7,34–7,28 (m, 4H), 4,51 (s, 2H).

[00586] Ejemplo 18: Síntesis de 4–(4–clorobencil)–5–(1H–imidazol–5–il)–2–(piridin–4–il)tiazol (Compuesto 66)



[00587] **Etapa 1:** 4-(4-Clorobencil)-N-metoxi-N-metil-2-(piridin-4-il)tiazol-5-carboxamida

[00588] A una solución de ácido 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxílico (850 mg, 2,57 mmol) en DMF (11,9 mL) se añadió clorhidrato de N,O-dimetilhidroxilamina (852 mg, 8,74 mmol), HATU (1,95 g, 5,14 mmol) y diisopropiletilamina (2,42 mL, 13,9 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La reacción se diluyó con agua (30 mL) y se extrajo con acetato de etilo (2 x 25 mL). Las fases orgánicas combinadas se lavaron con agua (3 x 30 mL), se secaron con $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→80/20) para dar 775 mg del compuesto del título como un sólido amarillo (80 % de rendimiento). LC/MS (FA) ES+ 374. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,72-8,70 (m, 2H), 7,84-7,82 (m, 2H), 7,37-7,34 (m, 2H), 7,25-7,22 (m, 2H). 4,56 (s, 2H), 3,70 (s, 3H), 3,37 (s, 3H).

[00589] **Etapa 2:** Preparación de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carbaldehído

[00590] A una solución de 4-(4-clorobencil)-N-metoxi-N-metil-2-(piridin-4-il)tiazol-5-carboxamida (1,13 g, 3,02 mmol) en THF (36,8 mL) at -50°C se añadió hidruro de diisobutilaluminio 1,0 M en hexano (15,1 mL, 15,1 mmol) y la solución resultante se agitó a -50°C a -30°C durante 2 horas. La reacción se inactivó con cloruro de amonio saturado (10 mL) y se dejó calentar a temperatura ambiente. Se añadió agua (25 mL) y la mezcla se extrajo con acetato de etilo (2 x 40 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→70/30) para dar 699 mg del compuesto del título como un sólido blanco (73 % de rendimiento). LC/MS (FA) ES+ 315. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 10,16 (s, 1H), 8,78-8,76 (m, 2H), 7,85-7,83 (m, 2H), 7,30-7,25 (m, 4H), 4,47 (s, 2H).

[00591] **Etapa 3:** N'-{(1E)-[4-(4-clorobencil)-2-piridin-4-il-1,3-tiazol-5-il]metilen}-N,N-dimetilsulfamida

[00592] Una solución de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carbaldehído (186 mg, 0,591 mmol) y N,N-dimetilsulfonamida ((75,6 mg, 0,608 mmol) (preparada de acuerdo con Li, *Tetrahedron Letters*, 50(19), 2232-2235) en tolueno (5,0 mL) se sometió a reflujo durante la noche usando una trampa de Dean Stark para la mezcla azeotrópica con agua. La reacción se

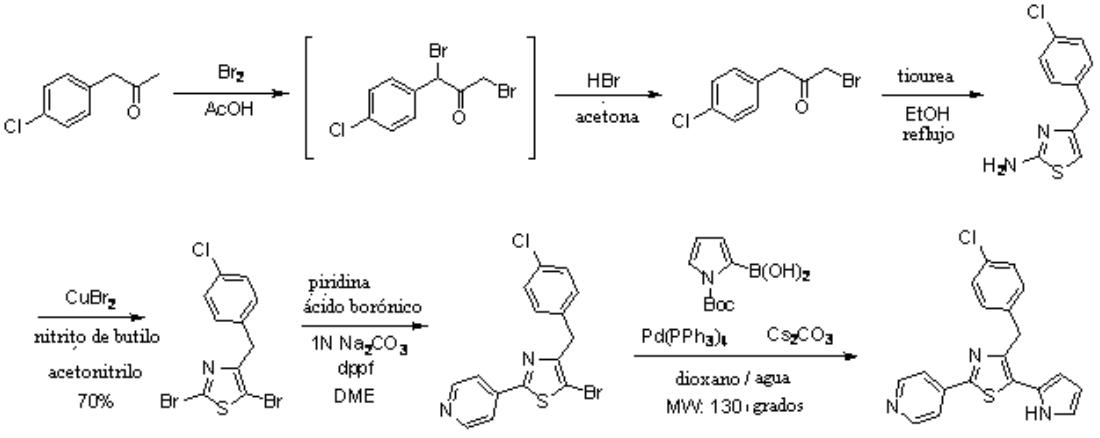
enfrió y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→60/40) para dar 699 mg del compuesto del título como un sólido amarillo (60% de rendimiento). LC/MS (FA) ES+ 421. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 9,08 (s, 1H), 8,78–8,76 (m, 2H), 7,84–7,82 (m, 2H), 7,32–7,22 (m, 4H), 4,38 (s, 2H), 2,86 (s, 6H).

[00593] **Etapa 4:** 5-(4-(4-Clorobencil)-2-(piridin-4-il)tiazol-5-il)-N,N-dimetil-1H-imidazol-1-sulfonamida y 4-(4-clorobencil)-5-(1H-imidazol-5-il)-2-(piridin-4-il)tiazol (Compuesto **66**).

[00594] Una solución de N'-{(1E)-[4-(4-clorobencil)-2-piridin-4-il-1,3-tiazol-5-il]metilene}-N,N-dimetilsulfamida (148 mg, 0,352 mmol), isocianuro de p-tolilsulfonilmetilo (75,5 mg, 0,387 mmol) y carbonato de potasio (146 mg, 1,05 mmol) en DME (2,50 mL) se calentó a 78°C durante 2 horas. La reacción se diluyó con DCM (10 mL) y agua (5 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (5 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (metanol/DCM = 0/100→15/85) para dar 50 mg de 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-N,N-dimetil-1H-imidazol-1-sulfonamida. LC/MS (FA) ES+ 460. (También se obtuvo algo del producto desprotegido, 4-(4-clorobencil)-5-(1H-imidazol-5-il)-2-(piridin-4-il)tiazol (19 mg). Este material se combinó con el material obtenido en la siguiente etapa de desprotección.)

Una solución de 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-N,N-dimetil-1H-imidazole-1-sulfonamida (50 mg, 0,109 mmol) en 48% HBr en agua (3,0 mL) se calentó a 90°C durante 2,5 horas. La solución enfriada se tomó en DCM (20 mL) y bicarbonato de sodio saturado (20 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (20 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. A este material bruto se añadieron los 19 mg del material desprotegido obtenido en la etapa previa. El material combinado se purificó por cromatografía en gel de sílice (metanol/DCM = 0/100→15/85) para dar 34 mg del compuesto del título como un sólido blanco (27 % de rendimiento). LC/MS (FA) ES+ 353. ^{1}H RMN (300 MHz, d_4-MeOH) δ: 8,63-8,61 (m, 2H), 7,93-7,91 (m, 2H), 7,80 (d, 1H, J = 1,1 Hz), 7,30-7,19 (m, 5H), 4,35 (s, 2H).

[00595] Ejemplo 19: Síntesis de 4-(4-clorobencil)-2-(piridin-4-il)-5-(1H-pirrol-2-il)tiazol (Compuesto 22)



[00596] Etapa 1: 1-Bromo-3-(4-clorofenil)propan-2-ona

[00597] A una solución de 1-(4-clorofenil)propan-2-ona (25,0 g, 148 mmol) en ácido acético (37,9 mL) se añadió 48% HBr acuoso (19,0 mL, 168 mmol). Una solución de bromo (16,3 mL, 316 mmol) en ácido acético (63,2 mL) luego se añadió durante 10 minutos y la solución resultante se agitó durante 4 horas a temperatura ambiente. Se añadió acetona (190 mL) y la solución resultante se agitó a temperatura ambiente durante 3 días. La reacción se concentró al vacío y el residuo se tomó en DCM (300 mL) y salmuera (100 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (100 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/hexanos = 0/100→15/85) para dar 25,4 gramos del compuesto del título como un sólido gris oscuro (69% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ: 7,34-7,31 (m, 2H), 7,18-7,15 (m, 2H), 3,94 (s, 2H), 3,91 (2, 2H).

[00598] **Etapa 2:** 4-(4-Clorobencil)tiazol-2-amina

[00599] Una mezcla de 1-bromo-3-(4-clorofenil)propan-2-ona (25,4 gramos, 103 mmol) y tiourea (8,59 g, 113 mmol) en etanol (1,51 L) se calentó a 85°C durante 2 horas. La reacción se enfrió y concentró al vacío y el residuo se tomó en acetato de etilo (300 mL) y bicarbonato de sodio saturado (100 mL). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (100 mL). Las fases orgánicas combinadas se lavaron con salmuera (50 mL), se secaron con $MgSO_4$, se filtraron

y concentraron al vacío. El residuo se recristalizó en acetato de etilo/hexanos para dar 19,9 gramos del compuesto del título como un polvo canela (86% de rendimiento). LC/MS (FA) ES+ 225. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 7,29–7,24 (m, 2H), 7,20–7,15 (m, 2H), 6,04 (m, 1H), 5,00 (bs, m, 2H), 3,83 (s, 2H).

[00600] **Etapa 3:** 2,5–Dibromo–4–(4–clorobencil)tiazol

[00601] A una mezcla de 4–(4–clorobencil)tiazol–2–amina (6,90 g, 30,7 mmol) en acetonitrilo (367 mL) se añadió bromuro de cobre (II) (10,3 gramos, 46,0 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 4 horas. Se añadió nitrito de butilo (5,21 mL, 46,0 mmol) y la mezcla se agitó a temperatura ambiente durante 30 minutos. La reacción se concentró al vacío y el residuo se suspendió en DCM (250 mL) durante 30 minutos. La mezcla se filtró a través de Celite y se lavó con DCM (50 mL). El filtrado se concentró al vacío y el residuo se purificó por cromatografía en gel de sílice (acetato de etilo/hexanos = 0/100→10/90) para dar 8,47 gramos del compuesto del título como un aceite anaranjado (75 % de rendimiento). LC/MS (FA) ES+ 368, 370. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 7,30–7,18 (m, 4H), 4,03 (s, 2H).

[00602] **Etapa 4:** 5–Bromo–4–(4–clorobencil)–2–(piridin–4–il)tiazol

[00603] A una solución de 2,5–dibromo–4–(4–clorobencil)tiazol (12,9 gramos, 35,1 mmol) en DME (365 mL) se añadió ácido piridin–4–borónico (5,61 g, 45,6

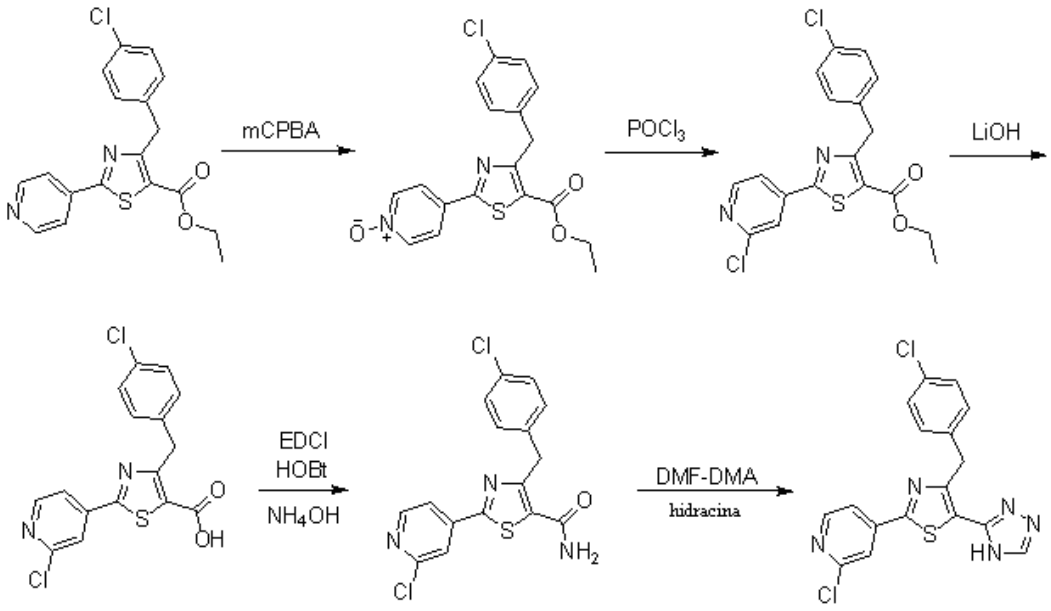
mmol), carbonato de sodio 1 M (70,2 mL, 70,2 mmol), y $PdCl_2$(dppf) (2,89 g, 3,51 mmol). La reacción se desgasificó con argón y se agitó a 85°C durante la noche. La reacción se enfrió y se tomó en acetato de etilo (400 mL) y bicarbonato de sodio saturado (200 mL). Los producto insolubles se filtraron a través de celite y el lecho se lavó con acetato de etilo (100 mL). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (100 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→70/30) seguido por otra cromatografía en gel de sílice (acetato de etilo/hexanos = 0/100→100/0) para dar 3,3 gramos del compuesto del título como un sólido marrón (26% de rendimiento). LC/MS (FA) ES+ 365, 367. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,70–8,67 (m, 2H), 7,70–7,67 (m, 2H), 7,28–7,26 (m, 4H), 4,13 (s, 2H).

[00604] **Etapa 5:** 4-(4-Clorobencil)-2-(piridin-4-il)-5-(1H-pirrol-2-il)tiazol (Compuesto **22**).

[00605] A una solución de 5-bromo-4-(4-clorobencil)-2-(piridin-4-il)tiazol (94,0 mg, 0,257 mmol) en 4:1 dioxano:agua (3,0 mL) se añadió ácido 1-(t-butoxicarbonil)pirrol-2-borónico (57 mg, 0,27 mmol), carbonato de cesio (251 mg, 0,771 mmol), y tetrakis(trifenilfosfina)paladio(0) (30 mg, 0,026 mmol). La solución se desgasificó con argón y se calentó en un reactor de microondas a 130°C durante 105 minutos. La reacción se concentró al vacío y el residuo se tomó en

DCM (25 mL) y agua (10 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (2 x 10 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 0/100→80/20) seguido por HPLC purificación (ácido fórmico método) para dar 26 mg del compuesto del título como un sólido amarillo (29 % de rendimiento). LC/MS (FA) ES+ 352. ^{1}H RMN (300 MHz, d_4-MeOH) δ: 8,62-8,60 (m, 2H), 7,90-7,88 (m, 2H), 7,66-7,55 (m, 1H), 7,26-7,24 (m, 2H), 7,20-7,17 (m, 2H), 6,92 (dd, 1H, J = 2,7, 1,5 Hz), 6,32 (dd, 1H, J = 3,5, 1,5 Hz), 6,21 (dd, 1H, J = 3,5, 2,7 Hz), 4,28 (s, 2H).

[00606] Ejemplo 20: Síntesis de 4-(4-clorobencil)-2-(2-cloropiridin-4-il)-5-(4H-1,2,4-triazol-3-il)tiazol (Compuesto 47)



[00607] **Etapa 1:** 1-óxido de 4-(4-(4-Clorobencil)-5-(metoxicarbonil)tiazol-2-il)piridina 1-óxido

[00608] A una solución de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboxilato de etilo (430 mg, 1,20 mmol) en DMF (6,0 mL) se añadió mCPBA (322 mg, 1,44 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. A la reacción se añadió DCM (30 mL) y bicarbonato de sodio saturado (25 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (20 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/DCM = 50/50→100/0) para dar 449 mg del compuesto del título como un sólido blanco (100 % de rendimiento). LC/MS (FA) ES+ 375. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,23-8,20 (m, 2H), 7,84-7,81 (m, 2H), 7,33-7,23 (m, 4H), 4,51 (s, 2H), 4,38 (q, 2H, J = 7,2 Hz), 1,39 (t, 3H, J = 7,2 Hz).

[00609] **Etapa 2:** 4-(4-clorobencil)-2-(2-cloropiridin-4-il)tiazol-5-carboxilato de etilo

[00610] Una solución de 1-óxido de 4-(4-(4-clorobencil)-5-(metoxicarbonil)tiazol-2-il)piridina (334 mg, 0,891 mmol) en cloruro de fosforilo (1,66 mL, 17,8 mmol) se calentó a 100°C durante 2 horas. La reacción se enfrió y se vertió en hielo y bicarbonato de sodio saturado (50 mL). La mezcla se extrajo con acetato de etilo (2 x 40 mL) y las fases orgánicas combinadas se lavaron con agua (20 mL), salmuera (10 mL) y se secó con

$MgSO_4$, se filtró y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (DCM/hexanos = 50/50→100/0) para dar 191 mg del compuesto del título como un sólido blanco (54% de rendimiento). LC/MS (FA) ES+ 393, 395. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,49 (dd, 1H, J = 5,3, 0,7 Hz), 7,88 (dd, 1H, J = 1,5, 0,7 Hz), 7,71 (dd, 1H, J = 5,3, 1,5 Hz), 7,36–7,31 (m, 2H), 7,27–7,23 (m, 2H), 4,53 (s, 2H), 4,39 (q, 2H, J = 7,2 Hz), 1,40 (t, 3H, J = 7,2 Hz).

[00611] **Etapa 3:** ácido 4-(4-Clorobencil)-2-(2-cloropiridin-4-il)tiazol-5-carboxílico

[00612] A una solución de 4-(4-clorobencil)-2-(2-cloropiridin-4-il)tiazol-5-carboxilato de etilo (199 mg, 0,506 mmol) en THF (2,84 mL) y agua (1,42 mL) se añadió LiOH 1,0 M (0,658 mL, 0,658 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La mezcla se acidificó a pH = 4 con HCl 1 N. Los sólidos precipitados se filtraron, se lavó con agua y secó para dar 179 mg del compuesto del título como un sólido blanco. (96 % de rendimiento). LC/MS (FA) ES+ 365, 367.

[00613] **Etapa 4:** 4-(4-Clorobencil)-2-(2-cloropiridin-4-il)tiazol-5-carboxamida

[00614] A una mezcla de ácido 4-(4-clorobencil)-2-(2-cloropiridin-4-il)tiazol-5-carboxílico (179 mg, 0,490 mmol) en DCM (27,5 mL) se añadió EDCI (282 mg, 1,47 mmol) y hidrato de 1-hidroxibenzotriazol (150 mg, 0,980 mmol) y la solución se agitó durante 10 minutos. Se añadió hidróxido de amonio 28% (2,12 mL, 24,5

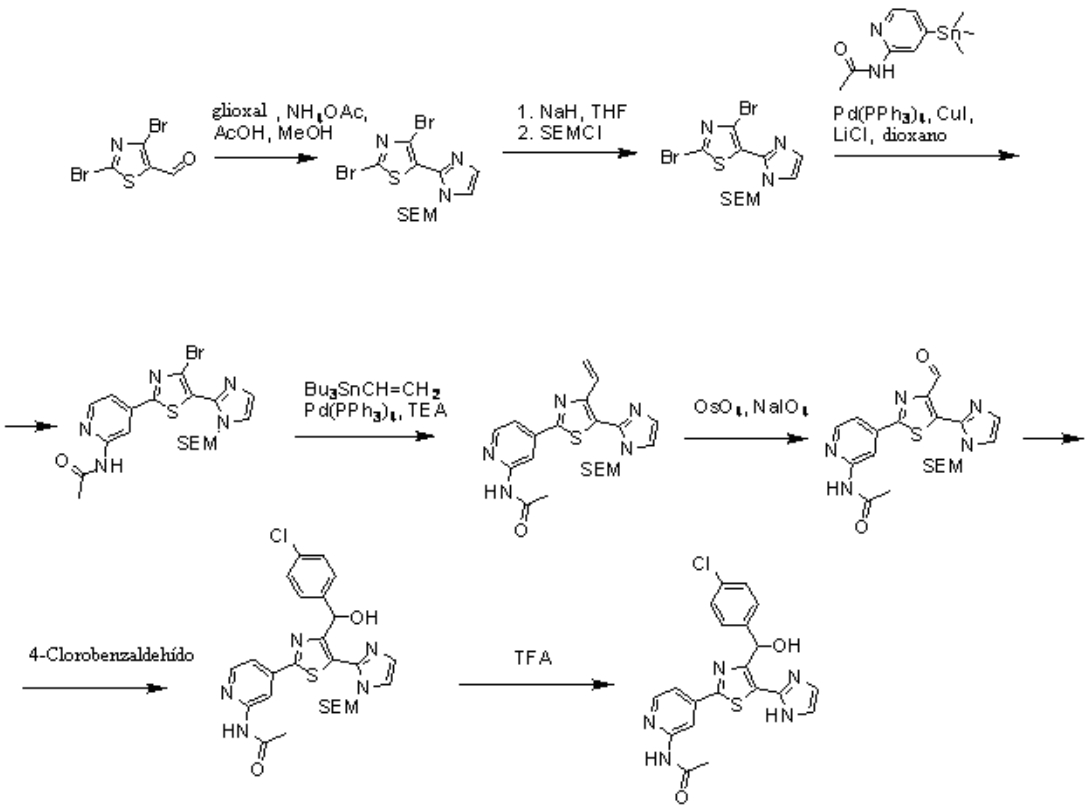
mmol) y la mezcla resultante se agitó a temperatura ambiente durante la noche. Se añadió agua (20 mL) y la mezcla se extrajo con DCM (2 x 25 mL). Las fases orgánicas combinadas se secaron en MgSO4, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (metanol/DCM = 0/100→15/85) para dar 121 mg del compuesto del título como un sólido blanco (67 % de rendimiento). LC/MS (FA) ES+ 364, 366. ^{1}H RMN (400 MHz, d_6–DMSO) δ: 8,54 (dd, 1H, J = 5,2, 0,7 Hz), 8,02 (bs, 1H), 7,91 (dd, 1H, J = 1,5, 0,7 Hz), 7,84 (dd, 1H, J = 5,2, 1,5 Hz), 7,79 (bs, 1H), 7,36–7,29 (m, 4H), 4,43 (s, 2H).

[00615] **Etapa 5:** 4–(4–Clorobencil)–2–(2–cloropiridin–4–il)–5–(4H–1,2,4–triazol–3–il)tiazol (Compuesto **47**).

[00616] Una solución de 4–(4–clorobencil)–2–(2–cloropiridin–4–il)tiazol–5–carboxamida (128 mg, 0,351 mmol) y 1,1–dimetoxi–N,N–dimetilmetanamina (0,467 mL, 3,51 mmol) en tolueno (3,75 mL) se calentó a 100 °C durante 1 hora. La reacción se enfrió y concentró al vacío para dar el intermediario, 4–(4–clorobencil)–2–(2–cloropiridin–4–il)–N–((dimetilamino)metilen)tiazol–5–carboxamida, como un sólido. LC/MS (FA) ES+ 419, 421. El intermediario se disolvió en ácido acético (3,60 mL). Se añadió hidrato de hidracina (0,0855 mL, 1,76 mmol) y la solución resultante se calentó a 90°C durante 2 horas. La mezcla se enfrió y concentró al vacío, y el residuo se destiló azeotrópicamente con tolueno. El residuo se suspendió en DCM (30 mL) y bicarbonato de sodio saturado

(20 mL). Algunos sólidos no disueltos se filtraron para dar un lote del producto deseado. Las fases del filtrado se separaron y la fase acuosa se extrajo con DCM (2 x 20 mL). Las fases orgánicas combinadas se secaron en MgSO4, se filtraron y concentraron al vacío para dar otro lote del producto deseado. Los dos lotes del producto se combinaron y se purificaron por cromatografía en gel de sílice (metanol/DCM = 0/100→20/80) para dar 85 mg del compuesto del título cmo un sólido beige (62% de rendimiento). LC/MS (FA) ES+ 388, 390. ^{1}H RMN (300 MHz, d_6–DMSO) δ: 14,48 (bs, 1H), 8,76 (s, 1H), 8,54–8,51 (m, 1H), 7,96–7,95 (m, 1H), 7,92–7,89 (m, 1H), 7,38–7,30 (m, 4H), 4,65 (s, 2H).

[00617] Ejemplo 21: Síntesis de N–{4–[4–[(4–clorofenil)(hidroxi)metil]–5–(1H–imidazol–2–il)–1,3–tiazol– 2–il]piridin–2–il}acetamida (Compuesto 60)



[00618] **Etapa 1:** 2,4-Dibromo-5-(1H-imidazol-2-il)tiazol

[00619] Una mezcla de 2,4-dibromo-tiazol-5-carbaldehído (14,8 g, 54,6 mmol), dihidrato de glioxal trímero (22,96 g, 109,2 mmol) y acetato de amonio (25,26 g, 327,8 mmol) en MeOH (450 mL) y ácido acético (31,06 mL) se agitó a rt durante la noche. La mezcla de reacción se concentró al vacío a una mezcla líquida espesa. El ácido acético restantes se extrajo por destilación azeotrópica con tolueno (3 x 100 mL) para proporcionar un sólido marrón oscuro. La mezcla se purificó por cromatografía en columna en gel de sílice (0 a 25% de EtOAc en hexanos) para dar el producto puro (9,12 g,

54%). LCMS: (AA) ES+, 310, 312. ^{1}H RMN (400 MHz, d_6–DMSO) δ: 12,50 (br, 1H), 7,21 (br, 2H).

[00620] **Etapa 2:** 2,4–Dibromo–5–(1–((2–(trimetilsilil)etoxi)metil)–1H–imidazol–2–il)tiazol

[00621] A una mezcla de hidruro de sodio (2,89 g, 72,2 mmol) en THF (431 mL) se añadió 2,4–dibromo–5–(1H–imidazol–2–il)tiazol (18,8 g, 60,9 mmol) en THF (60 mL) at 0 °C . Después de agitar 30 min, se añadió lentamente cloruro de 2–(trimetilsilil)etoximetilo (11,8 mL, 66,9 mmol) en THF (24 mL) a 0 °C . Después de 30 min a esta temperatura, la reacción se inactivó por la adición de MeOH (20 mL). El solvente se evaporó y el residuo se purificó por cromatografía en columna en gel de sílice (0 a 25% de EtOAc en hexanos). El producto se obtuvo como aceite incoloro (21,8 g, 81,6%). LCMS: (AA) ES+, 440, 442. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 7,24 (dd, 2H), 5,27 (s, 2H), 3,39 (t, 2H), 0,85 (t, 2H), –0,03(s, 9H).

[00622] **Etapa 3:** N–(4–(4–Bromo–5–(1–((2–(trimetilsilil)etoxi)metil)–1H–imidazol–2–il)tiazol–2–il)piridin–2–il)acetamida

[00623] Una mezcla de 2,4–dibromo–5–(1–((2–(trimetilsilil)etoxi)metil)–1H–imidazol–2–il)tiazol (13,6 g, 31,0 mmol), N–[4–(trimetilstannil)piridin–2–il]acetamida (11,1 g, 37,2 mmol), tetrakis(trifenilfosfina)paladio(0) (1,792 g, 1,550 mmol), yoduro de cobre (1,77 g, 9,30 mmol) y cloruro de litio (3,94 g, 93,0 mmol) en 1,4–dioxano (569 mL) se desgasificó con argón. La mezcla se sometió a sonicación durante 20 min y luego se calentó a 120°C durante 5 h. El

solvente se evaporó y la mezcla de reacción bruta se purificó por cromatografía ISCO (0 a 3% de MeOH en DCM). El producto se obtuvo como un sólido anaranjado (10,1 g, 66,0%). LCMS: (AA) ES+, 494, 496. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,65 (s, 1H), 8,44 (br, 1H), 8,34 (d, 1H), 7,60 (dd, 1H), 7,30 (d, 2H), 5,30 (s, 2H), 3,40 (t, 2H), 2,25 (s, 3H), 0,86 (t, 2H), -0,05 (s, 9H).

[00624] **Etapa 4:** N-{4-[5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-imidazol-2-il)-4-vinil-1,3-tiazol-2-il]piridin-2-il}acetamida

[00625] N-(4-(4-bromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol-2-il)piridin-2-il)acetamida (0,80 g, 1,6 mmol) y tetrakis(trifenilfosfina)paladio(0) (0,187 g, 0,162 mmol) se colocaron en un vial de microondas y se selló bajo atmósfera de argón. Se añadieron trietilamina (7,0 mL, 50 mM), THF (7 mL) y tributiletenil estannano (0,708 mL, 2,43 mmol) y la mezcla se irradió a 95°C durante 3 horas. El solvente se evaporó y el residuo se purificó usando cromatografía en columna en gel de sílice (0 a 60% de EA en hexano) para dar el compuesto del título (0,65 g, 72%). LCMS: (FA) ES+, 442. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,80 (s, 1H), 8,41–8,31 (m, 1H), 8,09 (s, 1H), 7,70–7,40 (m, 3H), 6,81 (dd, J = 17,2, 10,7 Hz, 1H), 6,38 (dd, J = 17,2, 1,9 Hz, 1H), 5,54 (dd, J = 10,7, 1,9 Hz, 1H), 5,27 (s, 2H), 3,48–3,34 (m, 2H), 2,25 (s, 3H), 0,90–0,84 (m, 2 H), -0,04 (s, 9 H).

[00626] **Etapa 5:** N-{4-[4-formil-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-imidazol-2-il)-1,3-tiazol-2-il]piridin-2-il}acetamida

[00627] N-{4-[5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-imidazol-2-il)-4-vinil-1,3-tiazol-2-il]piridin-2-il}acetamida (0,650 g, 1,47 mmol) se disolvió en tetrahidrofurano (20 mL) y agua (10 mL) a temperatura ambiente y se añadió tetraóxido de osmio 0,157 M en agua (93 uL, 0,014 mmol). La mezcla se agitó a temperatura ambiente durante 5 minutos. Luego se añadió en porciones mataperyodato de sodio (0,661 g, 3,09 mmol) durante 20 minutos y la mezcla se agitó a temperatura ambiente durante la noche. Los sólidos se extrajeron por filtración y se lavaron con THF (2 x 50 mL) y acetato de etilo (2 x 5 mL). El filtrado se extrajo con acetato de etilo (3 x 100 mL). Los extractos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, se filtraron y concentraron a presión reducida. El material bruto se purificó por cromatografía en gel de sílice (0 a 30% de acetato de etilo en hexanos) para proporcionar el compuesto del título (0,25 g, 38%). LCMS: (FA) ES+, 444. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,75 (s, 1H), 10,21 (s, 1H), 8,41 (d, J = 5,18 Hz, 1H), 8,20–8,07 (m, 1H), 7,76 (dd, J = 5,21, 1,58 Hz, 1H), 7,30 (dd, J = 2,87, 1,21 Hz, 2H), 5,32 (s, 2H), 3,50–3,33 (m, 2H), 2,26 (s, 3H), 0,93–0,78 (m, 2H), –0,04 (s, 9H).

[00628] **Etapa 6:** N-{4-[4-[(4-clorofenil)(hidroxi)metil]-5-(1-{[2-

(trimetilsilil)etoxi]metil}-1H-imidazol-2-il)-1,3-tiazol-2-il]piridin-2-il}acetamida

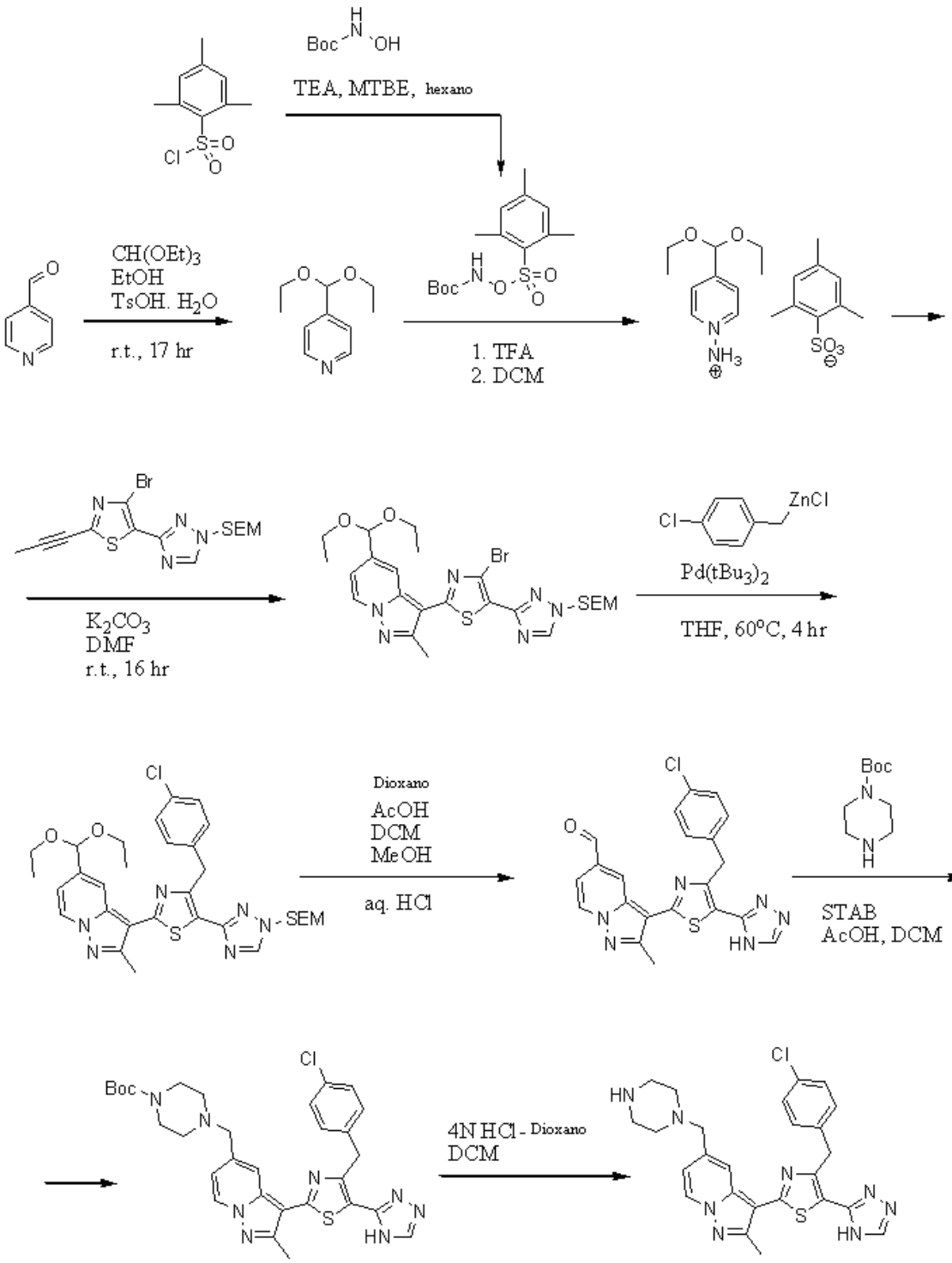
[00629] N-{4-[4-formil-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-imidazol-2-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (0,250 g, 0,564 mmol) se disolvió en tetrahidrofurano (20 mL) y se enfrió a 0°C. se añadió bromuro de 1,0M 4-clorofenilmagnesio en éter (1,41 mL, 1,41 mmol) y la solución se agitó a 0°C durante 30 minutos. La reacción se inactivó por la adición de MeOH (10 mL), y se evaporó a presión reducida. El residuo se purificó usando cromatografía en columna (20 a 100% de acetato de etilo en hexano) para dar el compuesto del título (0,150 g, 48%). LCMS: (FA) ES+, 556, 558. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,69 (s, 1H), 8,34 (d, J = 5,23 Hz, 1H), 8,21 (s, 1H), 7,65 (dd, J = 5,23, 1,55 Hz, 1H), 7,31 (d, J = 8,28 Hz, 2H), 7,21-7,16 (m, 3H), 7,07 (d, J = 1,31 Hz, 1H), 6,26-6,15 (m, 1H), 5,30 (s, 1H), 3,46-3,36 (m, 2H), 2,24 (s, 3H), 0,94-0,84 (m, 2H), -0,02 (s, 9H).

[00630] **Etapa 7:** N-{4-[4-[(4-clorofenil)(hidroxi)metil]-5-(1H-imidazol-2-il)-1,3-tiazol- 2-il]piridin-2-il}acetamida (Compuesto 60)

[00631] N-{4-[4-[(4-clorofenil)(hidroxi)metil]-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-imidazol-2-il)-1,3-tiazol-2-il]piridin-2-il}acetamida (0,120 g, 0,216 mmol) se disolvió en DCM (5 mL) y se añadió ácido trifluoroacético (5,0 mL, 65 mmol). La mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó, se destiló azeotrópicamente con tolueno y se purificó usando

cromatografía en columna en gel de sílice (0 a 10% de MeOH en DCM) para dar el compuesto del título (0,050 g, 50%). LCMS: (FA) ES+, 426, 428. ^{1}H RMN (400 MHz, d_4-metanol) δ: 8,68 (s, 1H), 8,38 (d, J = 5,24 Hz, 1H), 7,64 (dd, J = 5,25, 1,60 Hz, 1H), 7,45-7,37 (m, 2H), 7,30-7,23 (m, 2H), 7,25-7,09 (m, 2H), 6,37 (s, 1H), 2,20 (s, 3H).

[00632] Ejemplo 22: Síntesis de 3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metil-5-(piperazin-1-ilmetil)pirazolo[1,5-a]piridina (Compuesto 72)


TEA, MTBE, hexano
CH(OEt)3
EtOH
TsOH. H2O
r.t., 17 hr
1. TFA
2. DCM
K2CO3
DMF
r.t., 16 hr
Pd(tBu3)2
THF, 60°C, 4 hr
Dioxano
AcOH
DCM
MeOH
aq. HCl
STAB
AcOH, DCM
4N HCl - Dioxano
DCM
SEM

[00633] **Etapa 1:** 4-(Dietoximetil)piridina:

[00634] Se disolvió monohidrato del ácido p-toluensulfónico (11,8 g, 62,0 mmol) en etanol seco (80 mL) a rt. Se añadió 4-Piridincarboxaldehído (4,71 mL, 50,0 mmol), seguido por ortoformiato de etilo (20,79 mL, 125,0 mmol). La mezcla se agitó a rt durante 17 horas. La mezcla se concentró y el residuo se alcalinizó con solución acuosa saturada de $NaHCO_3$ a pH 8, se extrajo con EtOAc (150 mL), se lavó con salmuera, se secó con Na_2SO_4, se filtró, evaporó, y secó bajo alto vacío para dar un producto líquido. (9,06 g, yield 97,2%). LCMS: (FA) ES^+ 182. ^1H RMN (400MHz, $CDCl_3$) δ: 8,60-8,62 (m, 2H), 7,38-7,40 (m, 2H), 5,50 (s, 1H), 3,53-3,62 (m, 4H), 1,23-1,27 (m, 6H).

[00635] **Etapa 1A:** N-ter-Butoxicarbonil-O-(mesitilsulfonil)hidroxilamina

[00636] Se disolvieron ter-Butil-N-hidroxicarbamato (5,00 g, 37,6 mmol) y cloruro de mesitilensulfonilo (8,21 g, 37,6 mmol) en 2-metoxi-2-metilpropano (90 mL), purgado con nitrógeno y enfriado en un baño de hielo a una temperatura interna de 1°C. Se añadió trietilamina (5,34 mL, 38,3 mmol) gota a gota durante 25 min, durante el tiempo que la temperatura aumenta a 6°C. La mezcla se agitó con enfriamiento durante 2 horas, en el tiempo en la temperatura interna de reacción fue 8°C. La suspensión se filtró y los sólidos se lavaron con 2-metoxi-2-metilpropano (60 mL). El filtrado se concentró a ~20 mL de volumen, se diluyó

con hexano (70 mL) y se dejó decantar a rt durante 30 min. El sólido cristalino resultante se recolectó por filtración y se lavó con hexano (20 mL). El agua madre se evaporó, se diluyó con hexano (50 mL), y se dejó decantar, dando una segunda cosecha de cristales. Los sólidos recolectados combinados se secaron al vacío durante 1 hora para dar un producto cristalino blanco (11,06 g, rendimiento 93,4%). LCMS: (AA) ES^+ 316 y 333 para M^++NH_3. ^1H RMN (400MHz, $CDCl_3$) δ: 7,54 (s, 1H), 6,99 (s, 2H), 2,68 (s, 6H), 2,32 (s, 3H), 1,31 (s, 9H).

[00637] **Etapa 2:** 2,4,6-trimetilbencensulfonato de 1-Amino-4-(dietoximetil)piridinio

[00638] El ácido trifluoroacético (12,0 mL, 156 mmol) se enfrió en un baño de hielo. N-ter butoxicarbonil-O-(mesitilsulfonil)hidroxilamina (7,91 g, 25,1 mmol) se añadió en porciones durante 15 min. La mezcla se agitó con enfriamiento durante 2 horas luego se añadieron ~50 g de hielo, seguido por ~100 mL de agua helada. El sólido blanco resultante se recolectó por filtración y se lavó con agua hasta que los lavados tuvieron pH ~6. El sólido secó al aire durante 15 min para proporcionar un intermediario todavía húmedo (6,25 g). El sólido luego se disolvió en cloruro de metileno (160 mL, 2500 mmol), se secó con Na_2SO_4, y se filtró. El filtrado se enfrió en un baño de hielo y una solución de 4-(dietoximetil)piridina (5,91 g, 32,6 mmol) en cloruro de metileno seco (20 mL, 300 mmol) se añadió lentamente durante 10 min. El baño de hielo se retiró y la mezcla se agitó a rt durante 50 min. La mezcla se concentró a ~30

mL de volumen. El residuo oleoso se destiló azeotrópicamente con 15 mL de éter dietílico, luego el residuo se diluyó con 250 mL de éter dietílico y se enfrió en un baño de hielo durante 1 hora, luego se conservó en un congelador (–20°C) durante la noche. Apareció un residuo oleoso. La solución transparente decantó y el residuo oleoso se secó bajo alto vacío para dar una primera recolección del producto oleoso (2,15 g). La solución decantada se concentró para dar un residuo oleoso que se trituró con hexano (2 x 100 mL), luego se secó bajo alto vacío para dar una segunda cosecha de producto oleoso (6,15 g, rendimiento 79,7% para las 2 cosechas). LCMS: (FA) ES^+ 197; ES^- 199. ^1H RMN (400MHz, $CDCl_3$) δ: 9,00–9,05 (m, 4H), 7,69–7,71 (m, 2H),6,85 (s, 2H), 5,50 (s, 1H), 3,52–3,57 (m, 4H), 2,67 (s, 6H), 2,25 (s, 3H), 1,22–1,26 (m, 6H).

[00639] **Etapa 3:** 3-[4-Bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-5-(dietoximetil)-2-metilpirazolo[1,5-a]piridina

[00640] A una mezcla de 3-(4-bromo-2-prop-1-in-1-il-1,3-tiazol-5-il)-1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol [Preparado como se describió en el Ejemplo 14 (4,37 g, 10,9 mmol)] y carbonato de potasio (3,00 g, 21,7 mmol) en N,N-dimetilformamida seca (20,0 mL) se añadió una solución de 2,4,6-trimetilbencensulfonato de 1-amino-4-(dietoximetil)piridinio (6,37 g, 15,6 mmol) en N,N-dimetilformamida seca (20,0 mL) durante 10 min. La solución marrón oscura resultante se agitó a rt durante

40 horas. La mezcla se añadió a ~250 mL de agua helada con agitación, luego se extrajo con EtOAc (100 mL x 5) hasta que la fase acuosa se tornó en una solución transparente. Los extractos de EtOAc combinados se lavaron con agua, salmuera, se secaron con Na_2SO_4, filtraron y evaporaron. El producto bruto se purificó por cromatografía en columna en gel de sílice, usando EtOAc/hexano (0/100 a 50/50) como eluyente para dar un producto sólido (4,56g, 70,2%). LCMS: (FA) ES^+ 593, 595. ^1H RMN (400MHz, $CDCl_3$) δ: 8,46 (d, J = 2,01 Hz, 1H), 8,40–8,42 (d, J = 7,28 Hz, 1H), 8,32 (s, 2H), 7,05–7,08 (dd, J = 2,01, 7,03 Hz, 1H),5.57(s, 2H3,68–3,77 (m, 4H), 3,58–3,63 (m, 2H), 2,75 (s, 3H), 1,28–1,32 (m, 6H), 0,95–1,00 (m, 2H),0,02 (s, 9H)

[00641] **Etapa 4:** 3-[4-(4-Clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-5-(dietoximetil)-2-metilpirazolo[1,5-a]piridina

[00642] Una mezcla de 3-[4-bromo-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-5-(dietoximetil)-2-metilpirazolo[1,5-a]piridina (0,907 g, 1,53 mmol) y bis(tri-t-butilfosfina)paladio(0) (39,0 mg, 0,0764 mmol) en un vial de 40 mL se evacuaron en bajo vacío y se llenaron de nuevo con nitrógeno cuatro veces. Se añadió cloruro de 4-clorobencilzinc en tetrahidrofurano (0,50 M, 7,0 mL, 3,5 mmol) y la solución se evacuó nuevamente en bajo vacío y se llenó de nuevo con nitrógeno dos veces. La solución se calentó a 60°C durante 4 horas. La mezcla de reacción se enfrió a rt, se inactivó con agua, se ajustó a pH ~ 6 con

ácido acético, y se extrajo con EtOAc (2x). Las fases orgánicas se combinaron, se lavaron con agua, salmuera, se secaron con Na_2SO_4, filtraron y evaporaron para dar un residuo bruto que se purificó por cromatografía en columna en columna de gel de sílice usando EtOAc/hexano (0/100 a 40/60) como eluyente para dar un producto sólido (0,806 g, 85% puro por 1H-RMN, rendimiento 70,5%). LCMS: (FA) ES^+ 639, 641. ^1H RMN de pure fracción (400MHz, $CDCl_3$) δ: 8,36-8,39 (m, 2H), 8,27 (s, 1H), 7,45-7,47 (m, 2H), 7,23-7,25 (m, 2H), 6,99-7,01 (m, 1H),5,54 (s, 2H, 5,50 (s, 1H), 4,67 (s, 2H), 3,66-3,74 (m, 4H), 3,57-3,62 (m, 2H), 2,74 (s, 3H), 1,26-1,30 (m, 6H), 0,95-0,99 (m, 2H),0,00 (s, 9H).

[00643] **Etapa 5:** 3-[4-(4-Clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridina-5-carbaldehído

[00644] 3-[4-(4-Clorobencil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-5-(dietoximetil)-2-metilpirazolo[1,5-a]piridina (1,17 g, 1,83 mmol) se disolvió en 1,4-dioxano (45 mL) y se enfrió en un baño de agua. Se añadió ácido clorhídrico 12 M (15 mL) y la mezcla se agitó a rt durante 15 horas. Se añadió ácido acético (40 mL, 700 mmol) y la suspensión se agitó a rt durante 24 horas luego se calentó a 70° C durante 2 horas, luego se evaporó. El residuo sólido se agitó con ácido clorhídrico 1,00 M (100 mL) y metanol (120 mL) a rt durante 14 horas. La mezcla se evaporó en un evaporador rotatorio a 45°C a sequedad y luego se destiló azeotrópicamente con DCM para dar el producto bruto. El producto bruto se suspendió en

agua, se alcalinizó con $NaHCO_3$ a pH ~8, se extrajo con EtOAc (300 mL, 3 x 80 mL), se lavó con salmuera, se secó con Na_2SO_4, se filtró y evaporó para proporcionar un producto sólido amarillo (0,773 g, rendimiento 97,2%). LCMS: (FA) ES^+ 435, 437. ^1H RMN (400MHz, $CDCl_3$) δ: 10,84 (s, br, 1H), 9,99 (s, 1H), 8,75 (m, 1H), 8,43–8,46 (d, J = 7,28 Hz, 1H), 8,36 (s, 1H), 7,41–7,44 (d, J = 8,53 Hz, 2H), 7,32–7,35 (dd, J = 7,03, 2,01 Hz, 1H), 7,27–7,30 (d, J = 8,53 Hz, 2H), 4,69 (s, 2H), 2,79 (s, 3H).

[00645] **Etapa 6:** 4-({3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metil)piperazin-1-carboxilato de ter-Butilo

[00646] Una mezcla de 3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridina-5-carbaldehído (0,0563 g, 0,109 mmol), 1-piperazincarboxilato de ter-butilo (60,8 mg, 0,326 mmol) y ácido acético (0,0800 mL, 1,41 mmol) en cloruro de metileno seco (10 mL) se agitó a rt durante 15 min. Se añadió triacetoxiborohidruro de sodio (69,1 mg, 0,326 mmol) y la mezcla se agitó a rt durante 15 horas. La mezcla se lavó con solución saturada de $NaHCO_3$ y la fase acuosa se extrajo con DCM. El extracto de DCM se lavó con agua, salmuera, se secó con Na_2SO_4, filtró y evaporó para dar el producto bruto que se purificó por cromatografía en columna en gel de sílice usando MeOH/DCM (0/100 a 5/95) para dar el producto sólido (0,0464 g, rendimiento 70,5%). LCMS: (FA) ES^+ 605, 607; ES^- 603, 605. ^1H RMN (400MHz, $CDCl_3$ y d_4-metanol) δ: 8,23–8,25 (d, J = 7,03 Hz, 1H), 8,20 (s, 1H), 7,94 (s, 1H), 7,29–7,31 (d, J

= 8,28 Hz, 2H), 7,15–7,17 (d, J = 8,53 Hz, 2H), 6,86–6,89 (dd, J = 7,28, 1,76 Hz, 1H), 4,53 (s, 2H), 3,45 (s, 2H), 3,33–3,36 (m, 4H), 2,62 (s, 3H), 2,35 (s, br, 4H), 1,37 (s, 9H).

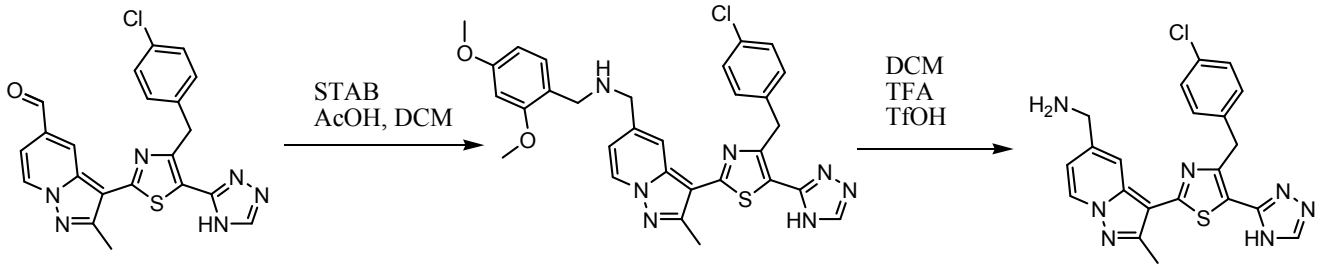
[00647] **Etapa 7:** 3-[4-(4-Clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metil-5-(piperazin-1-ilmetil)pirazolo[1,5-a]piridina (Compuesto **72**)

[00648] A una solución de 4-({3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metil)piperazine-1-carboxilato de ter-butilo (0,0435 g, 0,0719 mmol) en cloruro de metileno (2,0 mL) y metanol (2,0 mL) se añadió ácido clorhídrico 4 M en 1,4-dioxano (2,0 mL, 7,8 mmol). La mezcla se agitó a rt durante 5 horas luego se evaporó, se destiló azeotrópicamente con MeOH, y se secó bajo alto vacío para dar un sólido (~50 mg). El sólido se trituró con éter dietílico (10 ml x 2) luego se secó bajo alto vacío para dar el producto como un polvo amarillo pálido (0,0424 g, rendimiento 100%) como una sal bis HCl. LCMS: (FA) ES^+ 505, 507; ES^- 503, 505. ^{1}H RMN (400MHz, d_4-metanol) δ: 8,71 (s, 1H), 8,62–8,64 (d, J = 7,03 Hz, 1H), 8,41 (s, 1H), 7,39–7,41 (d, J = 8,78 Hz, 2H), 7,27–7,29 (d, J = 8,53 Hz, 2H), 7,20–7,23 (dd, J = 7,03, 2,01 Hz, 1H), 4,66 (s, 2H), 4,38 (s, 2H), 3,54 (s, br, 4H), 3,43 (s, br, 4H), 2,73 (s, 3H).

[00649] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 22:

31	LCMS: (FA) ES+ 570, 572.
32	LCMS: (FA) ES+ 526, 528.
38	LCMS: (FA) ES+ 493, 495.
54	LCMS: (FA) ES+ 479, 481.
61	LCMS: (FA) ES+ 519, 521.
82	LCMS: (FA) ES+ 579, 581.
83	LCMS: (FA) ES+ 569, 571.

[00650] **Ejemplo 23: Síntesis de 1-{3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metanamina (Compuesto 1)**



[00651] **Etapa 1:** 1-{3-[4-(4-Clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}-N-(2,4-dimetoxibencil)metanamina

[00652] A una suspensión de 3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridina-5-carbaldehído (0,300 g, 0,690 mmol) en ácido acético (0,20 mL, 3,5 mmol) y cloruro de metileno seco (10 mL, 200 mmol) se añadió 2,4-dimetoxibencilamina (0,207 mL, 1,38 mmol), seguido por triacetoxiborohidruro de sodio adicional (0,363 g, 1,71

mmol). La mezcla se agitó a rt durante 16 horas. La mezcla se alcalinizó con solución de $NaHCO_3$ a pH ~8 luego se extrajo con DCM. La solución DCM se lavó con agua. El producto bruto se purificó por cromatografía en columna (SiO2, elución con 0–100% de MeOH en DCM) para proporcionar un producto sólido (0,252 g, rendimiento 62%). LCMS: (FA) ES^+ 586, 588; ES^- 584, 586. ^1H RMN (400MHz, $CDCl_3$ y d_4–metanol) δ: 8,23–8,25 (d, J = 7,03 Hz, 1H), 8,18 (s, 1H), 8,01 (s, 1H), 7,28–7,30 (d, J = 8,53 Hz, 2H), 7,09–7,11 (d, J = 8,53 Hz, 2H), 7,01–7,03 (d, J = 8,28 Hz, 1H), 6,78–6,80 (d, J = 7,03 Hz, 1H), 6,33–6,37 (m, 2H), 4,53 (s, 2H), 3,65 (s, 2H), 3,64 (s, 6H), 3,61 (s, 2H), 2,61 (s, 3H).

[00653] **Etapa 2:** 1-{3-[4-(4-Clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metanamina (Compuesto **1**)

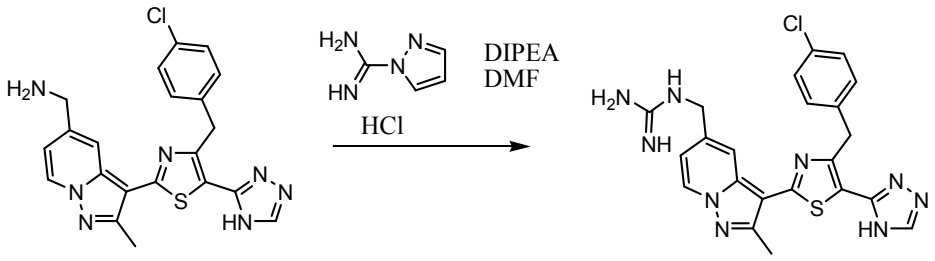
[00654] 1-{3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}-N-(2,4-dimetoxibencil)metanamina (0,257 g, 0,438 mmol) se disolvió en cloruro de metileno (6,0 mL) y ácido trifluoroacético (6,0 mL). Se añadió ácido trifluorometansulfónico (0,050 mL, 0,56 mmol) y la mezcla se calentó a 60°C durante 6 días. La mezcla se evaporó en un evaporador rotatorio, se destiló azeotrópicamente con EtOAc (3 x), y se evaporó para dar un residuo bruto. El residuo se suspendió en ~1 mL de MeOH y se diluyó con ~20 mL de Et_2O. El polvo resultante se recolectó por filtración y se secó bajo alto vacío para proporcionar un producto sólido rosado claro. El sólido se tomó en EtOAc / agua (20 mL / 10 mL) y se ajustó a pH ~8 con solución

de $NaHCO_3$. Las fases se separaron y la fase acuosa se extrajo con EtOAc (2x30 mL). La soluciones EtOAc combinadas se lavaron con agua, salmuera, se secaron con Na_2SO_4, y se filtraron. El filtrado se concentró a ~5 mL de volumen y el sólido precipitado se recolectó por filtración para dar una cosecha de producto puro (0,0069 g). El filtrado se evaporó luego se secó bajo alto vacío para proporcionar una segunda cosecha del producto sólido (0,171 g, rendimiento para las 2 cosechas 89,9%). LCMS: (FA) ES^+ 436, 438; ES^- 434, 436. ^1H RMN (400MHz, d_4-metanol) δ: 8,33-8,35 (d, J = 7,29 Hz, 1H), 8,24 (s, 1H), 8,09 (s, 1H), 7,31-7,33 (d, J = 8,78 Hz, 2H), 7,20-7,22 (d, J = 8,53 Hz, 2H), 6,98-7,00 (m, 1H), 4,59 (s, 2H), 4,06 (s, 2H), 2,67 (s, 3H).

[00655] El compuesto de la siguiente tabla se preparó a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 23:

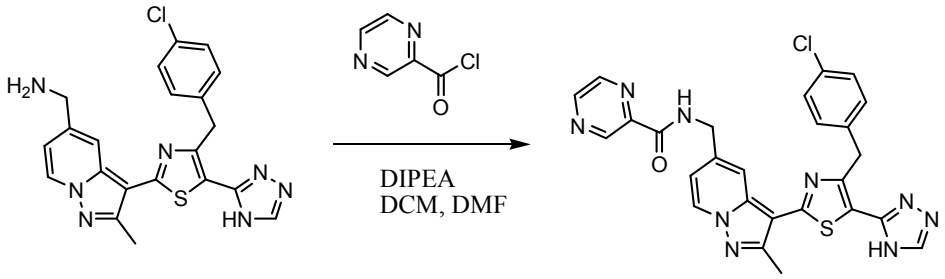
20	LCMS: (FA) ES+ 586, 588.

[00656] Ejemplo 24: Síntesis de N-({3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metil)guanidina (Compuesto 35)



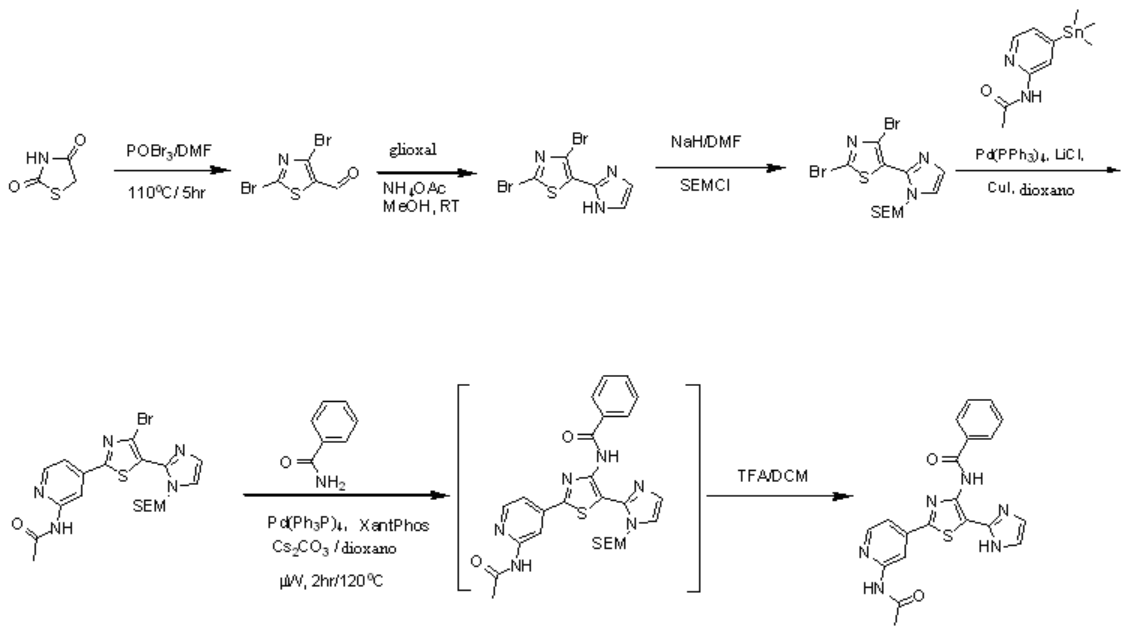
[00657] A una mezcla de 1-{3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metanamina (0,0250 g, 0,0553 mmol) y clorhidrato de 1H-pirazol-1-carboxamidina (8,20 mg, 0,0559 mmol) en N,N-dimetilformamida seca (0,50 mL) se añadió N,N-diisopropiletilamina (7,15 mg, 0,0553 mmol). La solución se agitó a rt durante 23 horas. La mezcla de reacción se diluyó con agua (15 mL) y se extrajo con EtOAc (5 x 15 mL). La solución EtOAc se lavó con salmuera, se secó con Na_2SO_4, se filtró y concentró en un evaporador rotatorio para dar un residuo bruto. El residuo se disolvió en ~0,2 mL de MeOH, luego se diluyó con ~5 mL de EtOAc. El sóido resultante se recolectó por filtración para dar un producto en polvo amarillo pálido (0,008 g, 30%). LCMS: (FA) ES^+ 478, 480; ES^- 476, 478. ^1H RMN (400MHz, $CDCl_3$ y d_4-metanol) δ: 8,25-8,27 (d, J = 7,28 Hz, 1H), 8,17 (s, 1H), 7,92 (s, 1H), 7,21-7,23 (d, J = 8,53 Hz, 2H), 7,08-7,10 (d, J = 8,28 Hz, 2H), 6,72-6,74 (dd, J = 7,28, 1,76 Hz, 1H), 4,48 (s, 2H), 4,30 (s, 2H), 2,57 (s, 3H).

[00658] **Ejemplo 25: Síntesis de N-({3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metil)pirazin-2-carboxamida (Compuesto 50)**



[00659] Una mezcla de 1-{3-[4-(4-clorobencil)-5-(4H-1,2,4-triazol-3-il)-1,3-tiazol-2-il]-2-metilpirazolo[1,5-a]piridin-5-il}metanamina (0,0222 g, 0,0491), cloruro de ácido pirazin-2-carboxílico (8,0 mg, 0,056 mmol) y N,N-diisopropiletilamina (10 mg, 0,08 mmol) en cloruro de metileno seco (5,0 mL) en N,N-dimetilformamida seca (1,0 mL) se sometió a sonicación durante 2 min. La mezcla se agitó a rt durante 22 horas. Se añadieron N,N-diisopropiletilamina (13 mg, 0,10 mmol) y cloruro de ácido pirazin-2-carboxílico (9,11 mg, 0,0639 mmol) y la mezcla se agitó a rt durante 3 días. La mezcla se inactivó con agua, luego se extrajo con DCM (3 x 30 mL). Las soluciones DCM combinadas se lavaron con agua, salmuera, se secaron con Na_2SO_4, filtraron y evaporaron para dar el producto bruto (80 mg). El producto bruto se purificó por HPLC para dar un producto sólido (0,0007 g, rendimiento 3%). LCMS: (AA) ES^+ 542, 544. ^1H RMN (400MHz, d_6-DMSO) δ: 9,72-9,74 (d, J = 6,53 Hz, 1H), 9,23 (s, 1H), 8,87 (s, 1H), 8,75 (s, 1H), 8,67-8,69 (d, J = 6,53 Hz, 1H), 8,63 (s, 1H), 8,22 (s, 1H), 7,24-7,30 (m, 4H), 7,03-7,05 (d, J = 7,28 Hz, 1H), 4,62-4,64 (d, J = 6,78 Hz, 2H), 4,47 (s, 2H), 2,63 (s, 3H).

[00660] **Ejemplo 26: Síntesis de N-(2-(2-acetamidopiridin-4-il)-5-(1H-imidazol-2-il)tiazol-4-il)benzamida (Compuesto 29)**



[00661] **Etapa 1:** 2,4-Dibromo-tiazol-5-carbaldehído

[00662] 2,4-Tiazolidinediona (3,50 g, 0,0299 mol) y oxibromuro de fósforo (42,76 g, 0,1491 mol) se colocaron en un balón de dos bocas y la mezcla sólida se mezcló bien. El balón se evacuó y se cargó con argón. Se añadió N,N-dimetilformamida (2,54 mL, 0,0329 mol) por medio de jeringa con agitación manual del balón en el mismo momento. La mezcla se agitó a rt durante 2 horas y luego se calienta lentamente a 105°C, hasta que cesó el desarrollo de bromuro de hidrógeno, (aproximadamente 4h). La reacción se enfrió a rt luego la mezcla se transfirió a un vaso de precipitado que contiene 200 g de hielo. La mezcla acuosa se agitó con DCM luego se filtró. La fase de DCM se separó y la fase acuosa se extrajo con DCM dos veces. Las fases de DCM se combinaron y se lavaron con solución de bicarbonato de sodio saturada, luego

salmuera, se secaron con sulfato de sodio anhidro, se filtraron y concentraron. La mezcla se cargó seca en gel de sílice y se purificó por cromatografía para proporcionar 2,4-dibromo-tiazol-5-carbaldehído (2,50g, 30,9%). LCMS (FA) ES+ 272, 274.

[00663] **Etapa 2:** 2,4-Dibromo-5-(1H-imidazol-2-il)tiazol

[00664] 2,4-Dibromo-tiazol-5-carbaldehído (14,8 g, 54,6 mmol), hexahidro-[1,4]dioxino[2,3-b][1,4]dioxine-2,3,6,7-tetraol (22,96 g, 109,2 mmol), y acetato de amonio (25,26 g, 327,8 mmol) se añadieron a un balón seguido por metanol (450 mL, 11000 mmol). La mezcla se agitó y se añadió ácido acético (31,06 mL, 546,3 mmol). La reacción se agitó durante la noche luego la mezcla de reacción se concentró bajo vacío para proporcionar una mezcla líquida espesa. Luego se añadió tolueno (100 mL) y reevaporó y este proceso se repitió varias veces para dar un sólido marrón oscuro. Se añadió metanol y la mezcla se cargó en gel de sílice. La purificación por cromatografía en columna en gel de sílice proporcionó 2,4-dibromo-5-(1H-imidazol-2-il)tiazol (9,12 g, 54%). LCMS (AA) ES+ 310, 312, 308.

[00665] **Etapa 3:** 2,4-Dibromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol

[00666] A una mezcla de hidruro de sodio (2,89 g, 72,2 mmol) en tetrahidrofurano (431 mL, 5310 mmol) se añadió 2,4-dibromo-5-(1H-imidazol-2-il)tiazol (18,81 g, 60,88 mmol) en tetrahidrofurano (60 mL, 700 mmol) a 0°C . La mezcla se agitó durante 30 min antes de

añadir lentamente cloruro de [β-(Trimetilsilil)etoxi]metilo (11,85 mL, 66,96 mmol) en tetrahidrofurano (24 mL, 3,0E2 mmol) a 0°C . La reacción se inactivó con MeOH. El solvente se evaporó y el residuo se purificó por cromatografía en columna en gel de sílice para proporcionar 2,4-dibromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol (13,6g, 81,7%). LCMS (AA) ES+ 440, 442.

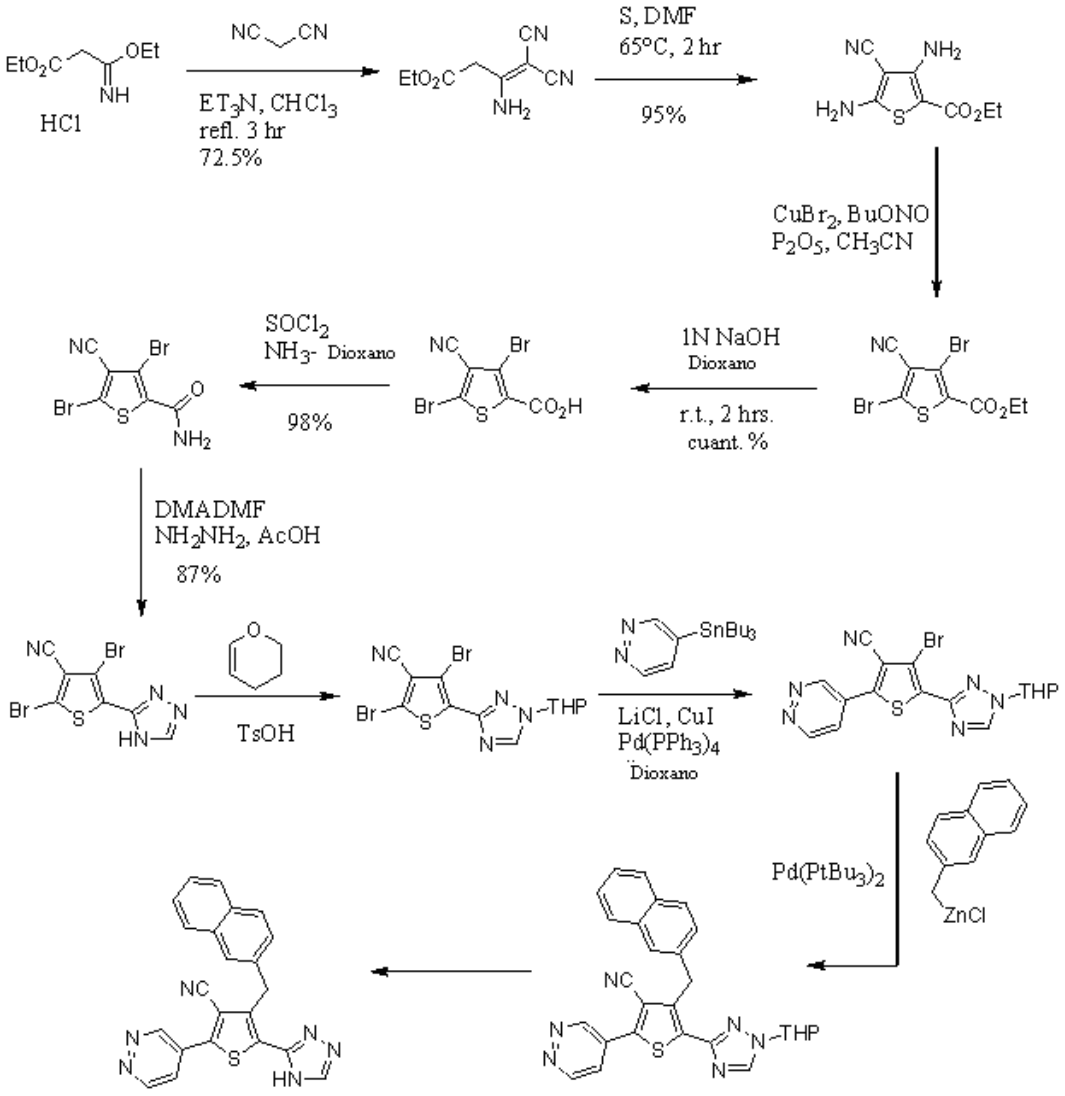
[00667] **Etapa 4:** N-(4-(4-bromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol-2-il)piridin-2-il)acetamida

[00668] Una mezcla de 2,4-dibromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol (13,62 g, 31,01 mmol), N-[4-(trimetilestannil)piridin-2-il]acetamida (11,1 g, 37,2 mmol), tetrakis(trifenilfosfina)paladio(0) (1,792 g, 1,550 mmol), yoduro de cobre (1,772 g, 9,302 mmol) y cloruro de litio (3,944 g, 93,02 mmol) en 1,4-dioxano (569 mL, 7290 mmol) se desgasificó y se cargó con argón tres veces. La mezcla se sometió a sonicación durante 20 min y luego se calentó a 120°C durante 5 horas. La mezcla de reacción se cargó seco en una columna de gel de sílice y se purificó por cromatografía para proporcionar N-(4-(4-bromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol-2-il)piridin-2-il)acetamida como un sólido anaranjado. LCMS (AA) ES+ 494, 496.

[00669] **Etapa 5:** N-(2-(2-acetamidopiridin-4-il)-5-(1H-imidazol-2-il)tiazol-4-il)benzamida (Compuesto **29**).

[00670] Una mezcla de N-(4-(4-bromo-5-(1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)tiazol-2-il)piridin-2-il)acetamida (80,9 mg, 0,164 mmol), benzamida (99,1 mg, 0,818 mmol), tris(dibencilideneacetona)dipaladio(0) (21,3 mg, 0,0233 mmol), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (39,9 mg, 0,0690 mmol) y carbonato de cesio (303 mg, 0,930 mmol) en 1,4-dioxano (7,66 mL, 98,2 mmol) se evacuó, luego se cargó con argón y luego se irradió con microonda a 130°C durante 3 horas. La mezcla de reacción se filtró y el filtrado se purificó por cromatografía en columna para proporcionar el intermediario deseado. LCMS (AA) ES+ 535, 536. Al anterio intermediario se añadieron cloruro de metileno (1,2 mL, 19 mmol) y ácido trifluoroacético (1,8 mL, 23 mmol). La mezcla se agitó a rt durante 2 horas. El exceso de ácido trifluoroacético y solvente se evaporó y el residuo se purificó por HPLC para proporcionar N-(2-(2-acetamidopiridin-4-il)-5-(1H-imidazol-2-il)tiazol-4-il)benzamida (11,3mg, 17,1%). LCMS (FA) ES+ 406, 407; ^{1}H RMN (300 MHz, d_4-metanol) δ: 8,67 (d, J = 0,45 Hz, 1H), 8,40 (d, J = 5,23 Hz, 1H), 8,17-8,07 (m, 2H), 7,84-7,78 (m, 1H), 7,59 (dd, J = 13,90, 7,27 Hz, 3H), 7,22 (s, 2H), 2,22 (s, 3H).

[00671] Ejemplo 27: Síntesis de 4-(2-naftilmetil)-2-piridazin-4-il-5-(4H-1,2,4-triazol-3-il)tiofeno-3-carbonitrilo (Compuesto 88)



[00672] **Etapa 1:** 3-amino-4,4-diciano-3-butenoato de etilo

[00673] Clorhidrato de 3-etoxi-3-iminopropionato de etilo (166 g, 721 mmol.) se suspendió en cloruro de metileno seco (400 mL, 6000 mmol). Se añadió malononitrilo (46,7 g, 707 mmol), seguido por trietilamina (1,00 mL, 721 mmol). La mezcla se calentó a reflujo durante 3 horas. La mezcla se enfrió a rt luego

se inactivó con 200 mL de agua. La fase orgánica separada se lavó con 2x200 mL de agua. Las fases acuosas combinadas se extrajeron con DCM (3 x 30 mL). Las fases orgánicas combinadas se lavaron con salmuera, secaron con Na_2SO_4 anhidro, se filtraron y concentraron a presión reducida. El residuo también se destiló azeotrópicamente con MTBE (2x200 mL) y acetato de etilo (70 mL). El residuo se diluyó con 70 mL de EtOAc. Un precipitado apareció y el sólido se recolectó por filtración y se lavó con ~20 mL de EtOAc hasta que el color rojo-rosado del sólido disminuyó para dar una primera cosecha del producto (32 g). El filtrado se concentró en el evaporador rotatorio y se secó bajo alto vacío a un peso de ~110 g. Apareció más precipitado después de que el filtrado concentrado se estacionó durante 1 hora. Se añadieron aproximadamente 50 mL de Et_2O y la mezcla se dejó decantar durante la noche. El precipitado resultante se recolectó por filtración y se lavó con Et_2O para proporcionar una segunda cosecha de producto sólido (20,59 g). El filtrado se concentró en un evaporador rotatorio para dar un residuo oleoso. La cromatografía en una columna de sílice usando EtOAc/hexano (gradiente corte de 0/100 a 50/50 luego permaneció 50/50 durante 100 min, con velocidad de flujo 120 mL/min) proporcionó una tercera cosecha de producto puro (39,3 g, rendimiento para todas las cosechas fue 72,5%). LCMS: (FA) ES- 178. ^{1}H RMN (400MHz, $CDCl_3$) δ: 7,57 (s, br, 1H), 6,33 (s, br, 1H),4,24-4,30 (q, 2H), 3,63 (s, 2H), 1,31-1,35 (t, 3H).

[00674] Etapa 2: 3,5-diamino-4-cianotiofeno-2-carboxilato de etilo

[00675] La mezcla de 3-amino-4,4-diciano-3-butenoato de etilo (91,9 g, 513 mmol) y azufre (16,4 g, 513 mmol) en N,N-dimetilformamida seca (200 mL, 3000 mmol) se enfrió en un baño de agua. Dietilamina (106 mL, 1020 mmol) se añadió lentamente, durante el tiempo en que la temperatura de reacción interna aumentó a 43°C. La solución marrón oscuro luego se enfrió en baño de hielo a rt (22°C) luego el baño de hielo se retiró. La mezcla se agitó a rt durante 3 horas. La mezcla se vertió en agua helada (~1,4 L) y la suspensión resultante se dejó decantar durante la noche. El sólido se recolectó por filtración y se lavó con 200 mL de agua por completo para dar un sólido húmedo. El sólido se agitó con 1,5 L de EtOAc a rt durante la noche, luego se filtró. El filtrado (bicapa de EtOAc-agua) se separó. La torta sólida se disolvió en 1,2 L de EtOAc. Las soluciones de EtOAc combinadas se lavaron con salmuera, secaron con Na_2SO_4 anhidro, filtraron, evaporaron en rotavap y se secaron bajo alto vacío durante la noche para dar un producto de polvo seco (102,6 g, rendimiento 94,7%). LCMS: (FA) ES+ 212, ES- 210. ^{1}H RMN (400MHz, $CDCl_3$ y *d4*-metanol) δ: 4,14 (m, 2H), 1,21-1,25 (t, 3H).

[00676] **Etapa 3:** 3,5-dibromo-4-cianotiofeno-2-carboxilato de etilo

[00677] Se disolvió 3,5-diamino-4-cianotiofeno-2-carboxilato de etilo (25,0 g, 118 mmol) en acetonitrilo (500 mL, 10000 mmol). Se añadió bromuro de cobre (II) (105,7 g, 473,4 mmol), seguido por pentóxido de fósforo (6,72 g, 23,7 mmol). La mezcla se agitó a

temperatura ambiente durante 30 min, luego se enfrió a 0°C. Se añadió lentamente nitrito de butilo (56,4 mL, 473,4 mmol). Después de completar la adición, la mezcla se calentó a reflujo durante 1 h, luego se enfrió a temperatura ambiente. La mezcla de reacción se vertió en 500 mL de solución de HCl 4 N, luego se extrajo con 500 mL de DCM dos veces. El material insoluble se filtró de la fase orgánica. El filtrado orgánico se secó con MgSO4, y se filtró. El filtrado se concentró y se purificó por cromatografía en columna en gel de sílice, usando el eluyente de 0–6% de acetato de etilo en hexano. Las fracciones que contienen el producto se recolectaron y concentraron para dar una suspensión. El sólido se recolectó por filtración para proporcionar un producto puro (14,45 g, rendimiento 36,0%). ^{1}H RMN (400 MHz, $CDCl_3$) δ:4,37–4,42 (q, 2H), 1,38–1,41 (t, 3H).

[00678] **Etapa 4:** ácido 3,5–dibromo–4–cianotiofeno–2–carboxílico

[00679] Se disolvió 3,5–dibromo–4–cianotiofeno–2–carboxilato de etilo (6,54 g, 0,0193 mol) en una mezcla de tetrahidrofurano (40,0 mL, 0,493 mol) y metanol (20,0 mL, 0,494 mol), luego se añadió hidróxido de sodio en agua (1,0 M, 60,0 mL, 0,0600 mol) a 0°C. La solución resultante se calentó a rt y se agitó durante 20 min. La mezcla se neutralizó con ácido clorhídrico en agua (4,0 M, 20 mL, 0,080 mol) y se extrajo con 80 mL de DCM dos veces. Las fases orgánicas combinadas se lavaron con 30 mL de agua, se evaporó al vacío para producir un producto sólido blanco (5,96 g, rendimiento 99,4%). LCMS: (FA) ES–, 307, 309, 311.

[00680] **Etapa 5:** 3,5-Dibromo-4-cianotiofeno-2-carboxamida

[00681] Se añadió 3,5-dibromo-4-cianotiofeno-2-carboxílico (5,90 g, 18,6 mmol) a una solución de cloruro de tionilo (27,1 mL, 371 mmol) en acetonitrilo (40,0 mL, 766 mmol). La mezcla se sometió a reflujo durante 30 min luego se enfrió a rt. El solvente se evaporó al vacío a sequedad para producir un sólido amarillo claro. Se añadió cloruro de metileno (100 mL, 2000 mmol) para disolver el sólido, luego la solución se enfrió a 0°C. Bajo atmósfera de nitrógeno, se añadió lentamente una solución de 0,500 M amoníaco en 1,4-dioxano (111,5 mL, 55,7 mmol), y la mezcla se llevó a temperatura ambiente durante 1 h. La mezcla se evaporó al vacío para dar un residuo sólido. Se añadieron 100 mL de HCl 1 N y la suspensión se agitó durante 1 h a temperatura ambiente. El producto sólido se recolectó por filtración y se secó bajo alto vacío para dar el producto (5,64 g, rendimiento 98%). LCMS: (FA) ES-, 308, 310, 312.

[00682] **Etapa 6:** 2,4-Dibromo-5-(4H-1,2,4-triazol-3-il)tiofeno-3-carbonitrilo

[00683] 3,5-Dibromo-4-cianotiofeno-2-carboxamida (5,90 g, 19,0 mmol) se suspendió en tolueno seco (250 mL, 2300 mmol). Se añadió 1,1-dimetoxi-N,N-dimetilmetanamina (10,1 mL, 76,1 mmol) y la mezcla se calentó a 90°C durante 1 hora. La mezcla se enfrió a rt luego se evaporó con rotavap a sequedad para dar un intermediario bruto. El intermediario se suspendió en ácido acético (150 mL, 2600 mmol).Se añadió hidrato de

hidracina (5,78 mL, 76,1 mmol) gota a gota y la temperatura se elevó a 55°C. La mezcla se agitó a la misma temperatura durante 2 horas. La suspensión luego se evaporó para eliminar la mayor parte de ácido acético. El sólido resultante se recolectó por filtración y se secó al vacío para dar un producto (5,54 g, rendimiento 87,2%). LCMS: (FA) ES-, 331, 333, 335. ^{1}H RMN (300 MHz, *d6*-dmso) δ:14,2 (s, br, 1H), 8,65 (s, 1H).

[00684] **Etapa 7:** 2,4-Dibromo-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo

[00685] 2,4-Dibromo-5-(4H-1,2,4-triazol-3-il)tiofeno-3-carbonitrilo (0,80 g, 2,4 mmol) se colocó en un balón de 500 mL y se añadió tetrahidrofurano (50 mL, 600 mmol). A la solución resultante se añadieron dihidropirano (1,31 mL, 14,4 mmol) y monohidrato de ácido p-toluensulfónico (0,683 g, 3,59 mmol). La mezcla se agitó durante 3 h a rt. La solución luego se vertió en 20 mL de agua y se extrajo con 40 mL de acetato de etilo dos veces. Las fases orgánicas combinadas se evaporaron evaporó al vacío. El residuo se purificó por cromatografía en columna usando 0-35% de EtOAc en hexano para proporcionar un producto sólido (0,842 g, rendimiento 84%). LCMS: (AA) ES+, 417, 419, 421. ^{1}H RMN (300MHz, $CDCl_3$) δ: 8,38 (s, 1H), 5,55-5,60 (m, 1H), 4,06-4,10 (m, 1H), 3,68-3,78 (m, 1H), 2,15-2,28 (m, 1H), 2,01-2,13 (m, 2H), 1,66-1,80 (m, 3H).

[00686] **Etapa 8:** 4-Bromo-2-piridazin-4-il-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo

[00687] Una mezcla de 2,4-dibromo-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo (0,248 g, 0,594 mmol), 4-(tributilestannil)piridazina (2,30 mg, 0,624 mmol), yoduro de cobre(I) (34,0 mg, 0,178 mmol), cloruro de litio (75,6 mg, 1,78 mmol) y tetrakis(trifenilfosfina)paladio(0) (34,3 mg, 0,0297 mmol) en 1,4-dioxanos seco (5,0 mL, 64 mmol) se sometió a sonicación bajo atmósfera de nitrógeno durante 2 min luego se calentó en un vial tapado a 130°C en máquina de microondas durante 20 min. La suspensión se enfrió a rt, se diluyó con 20% de MeOH/DCM (~100 mL), se trató con 12 g de gel de sílice luego se evaporó con rotavap y se secó bajo alto vacío. El gel de sílice recubierto se cromatografió en una columna de sílice que eluye con MeOH/DCM (0/100 a 5/95) para proporcionar un producto sólido (0,143 g, rendimiento 57,7%). LCMS: (AA) ES+, 417, 419. ^{1}H RMN (300MHz, $CDCl_3$) δ: 9,55 (s, 1H), 9,37-9,39 (m, 1H), 8,40 (s, 1H), 7,69-8,00 (m, 1H), 5,55-5,60 (m, 1H), 4,08-4,13 (m, 1H), 3,73-3,81 (m, 1H), 2,18-2,30 (m, 1H), 2,03-2,16 (m, 2H), 1,68-1,82 (m, 3H).

[00688] **Etapa 9:** 4-(2-Naftilmetil)-2-piridazin-4-il-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo.

[00689] Bis(tri-t-butilfosfina)paladio(0) (4,92 mg, 0,00963 mmol), 4-bromo-2-piridazin-4-il-5-[1-

(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo (0,0402 g, 0,0963 mmol), bromuro de 2-naftilmetilzinc en tetrahidrofurano (0,50M, 0,578 mL, 0,289 mmol) y tetrahidrofurano (4,0 mL, 49 mmol) se añadieron a un tubo de microondas. El tubo se selló bajo atmósfera de nitrógeno y se calentó a 70°C durante 2 h, luego se enfrió a rt. La mezcla se concentró al vacío y el residuo se purificó por cromatografía en una columna de gel de sílice que eluye con 0-100% de EtOAc en hexano para proporcionar un producto sólido (0,0332 g, rendimiento 72 %). LCMS: (AA) ES+, 479. ^{1}H RMN (300MHz, *d4*-metanol) δ: 9,63 (s, 1H), 9,28-9,35 (m, 1H), 8,68 (s, 1H), 8,13-8,15 (m, 1H), 7,69-8,00 (m, 4H), 7,37-7,48 (m, 3H), 5,62-5,66 (m, 1H), 3,94-4,08 (m, 1H), 3,69-3,80 (m, 1H), 3,30 (s, 2H), 2,07-2,22 (m, 1H), 1,95-2,07 (m, 2H), 1,61-1,79 (m, 3H).

[00690] **Etapa 10:** 4-(2-naftilmetil)-2-piridazin-4-il-5-(4H-1,2,4-triazol-3-il)tiofeno-3-carbonitrilo (Compuesto **88**)

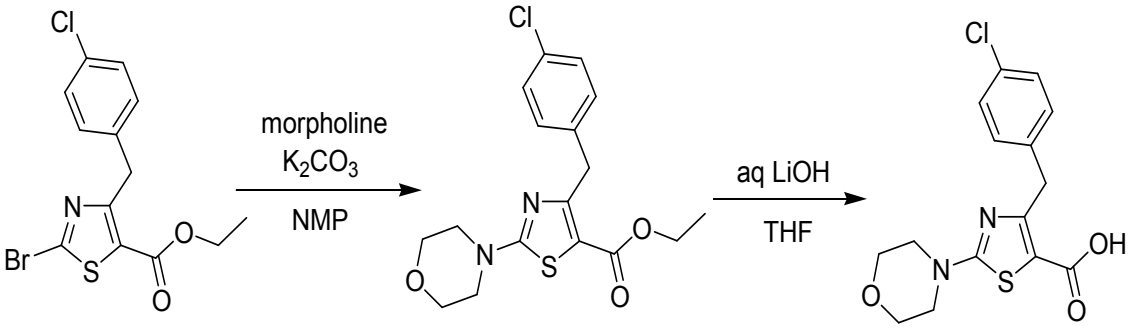
[00691] Se disolvió 4-(2-Naftilmetil)-2-piridazin-4-il-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo (0,03178 g, 0,06641 mmol) en metanol (3,00 mL, 74,0 mmol). se añadió HCl en agua (12 M, 3,00 mL, 36,0 mmol). La solución se calentó a 50°C durante 60 min luego se enfrió a rt. La mezcla se evaporó al vacío para eliminar la mayor parte de metanol. Al residuo se añadieron 30 mL de solución de bicarbonato de sodio saturada, se extrajo con 40 mL de acetato de etilo dos veces. Las fases de EtOAc combinadas se lavaron con 20 mL de agua luego se concentró al vacío. El sólido

cristalino resultante se recolectó por filtración para proporcionar un producto puro (0,0158 g, rendimiento 60,3%). LCMS: (AA) ES+ 395. ^{1}H RMN (300MHz, *d4*–metanol) δ: 9,60 (s, 1H), 9,27–9,29 (m, 1H), 8,47 (s, 1H), 8,09–8,11 (m, 1H), 7,69–7,77 (m, 4H), 7,37–7,47 (m, 3H), 3,30 (s, 2H).

[00692] El compuesto de la siguiente tabla se preparó a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 27:

89	LCMS: (FA) ES+ 379, 381.

[00693] Ejemplo 28: Síntesis de 4–(4–clorobencil)–2–morfolinotiazol–5–carboxílico (Compuesto 91)



[00694] Etapa 1, Preparación de 4–(4–clorobencil)–2–morfolinotiazol–5–carboxilato de etilo.

[00695] A una solución de 2–bromo–4–(4–clorobencil)tiazol–5–carboxilato de etilo (4,19 g, 11,6 mmol, preparado como se describió en el Ejemplo 10) en N–metilpirrolidinona (12,2 mL) se añadió carbonato de potasio (3,21 g, 23,2 mmol) y morfolina (1,52 mL, 17,4 mmol) y la mezcla resultante se calentó a 130 grados durante 90 minutos. La reacción se enfrió y los productos

volátiles se extrajeron por concentración a 65 grados bajo vacío con bomba de aceite. El residuo se tomó en DCM (100 mL) y agua (50 mL). Las fases se separaron y la fase acuosa se extrajo con DCM (50 mL). Las fases DCM combinadas se secaron en $MgSO_4$, se filtraron y concentraron para dar el producto bruto, que se purificó por cromatografía en gel de sílice (acetato de etilo/hexano = 0/100→35/65) para dar 3,44 g del compuesto del título como un sólido blanco. (80 % de rendimiento). LC/MS (FA) ES+ 367. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 7,32–7,27 (m, 2H), 7,24–7,20 (m, 2H), 4,28 (s, 2H), 4,27 (q, 2H, J = 7,2 Hz), 3,80–3,76 (m, 4H), 3,53–3,48 (m, 4H), 1,32 (t, 3H, J = 7,2 Hz).

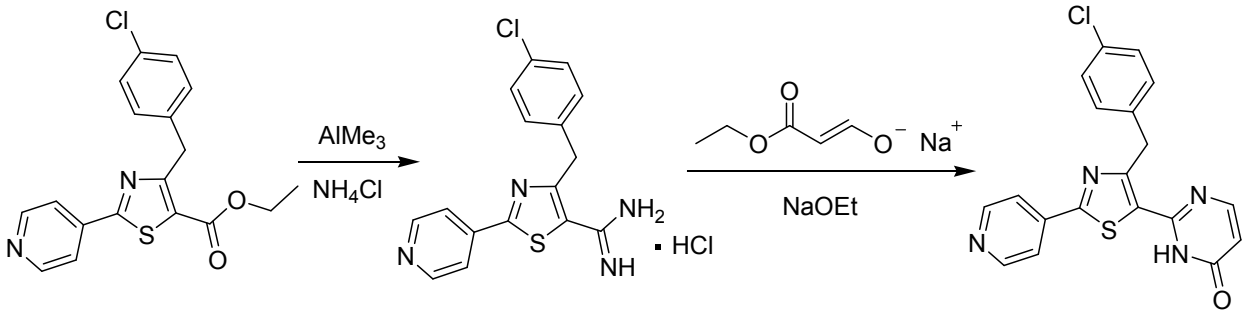
[00696] Etapa 2, Preparación de ácido 4–(4–clorobencil)–2–morfolinotiazol–5–carboxílico.

(Compuesto 91)

[00697] A una solución de 4–(4–clorobencil)–2–morfolinotiazol–5–carboxilato de etilo (3,44 g, 9,38 mmol) en THF (53 mL) se añadió agua (26 mL) y LiOH 1 N (28,2 mL, 28,2 mmol) y la mezcla resultante se calentó a 40 grados durante la noche. La reacción se enfrió, se acidificó con HCl 1 N, y se extrajo con acetato de etilo (3 x 50 mL). Las fases de acetato de etilo combinadas se secaron en $MgSO_4$, se filtraron y concentraron para dar el producto bruto, que se purificó por cromatografía en gel de sílice (metanol/DCM = 0/100→20/80). La recristalización en acetato de etilo/hexanos dio 1,3 g del compuesto del título como un sólido blanco. (41 % de rendimiento). LC/MS (FA) ES+ 339.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 12,74 (s, 1H), 7,33-7,30 (m, 2H), 7,26-7,23 (m, 2H), 4,21 (s, 2H), 3,67-3,64 (m, 4H), 3,42-3,40 (m, 4H).

[00698] Ejemplo 29: Síntesis de 2-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)pirimidin-4(3H)-ona (Compuesto 92)



[00699] Etapa 1, Preparación de clorhidrato de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboximidamida

[00700] A una suspensión de cloruro de amonio (2,25 g, 42,1 mmol) en tolueno (21,0 mL) en un baño de hielo se añadió trimetilaluminio 2,0 M en tolueno (21,1 mL, 42,2 mmol) gota a gota (desarrollo de gas). La mezcla luego se agitó a temperatura ambiente durante 30 minutos, durante el tiempo en que se disolvieron los sólidos. Se añadió 4-(4-clorobencil)-2-morfolinotiazol-5-carboxilato de etilo (4,11 g, 11,4 mmol) en una porción y la solución resultante se calentó lentamente a 110 °C durante 1 hora, luego se mantuvo a 110 °C durante 2,5 horas. La reacción se dejó enfriar a temperatura ambiente durante la noche. La reacción se vertió en una suspensión de gel de sílice (10 gramos) en cloroformo (100 mL) y se agitó 10 minutos. Se añadió metanol (20 mL) (se produce

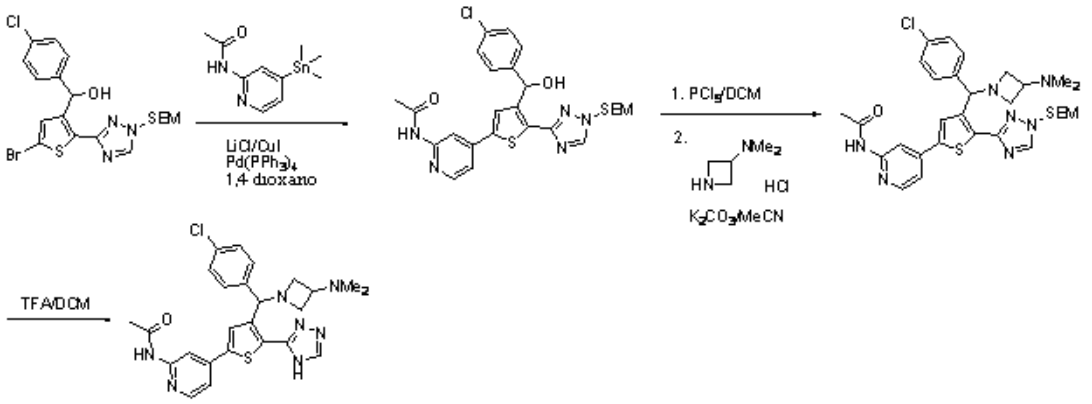
burbujeo), y la mezcla se filtró a través de un lecho de gel de sílice corto en un embudo de vidrio sinterizado, que eluye con 1:1 metanol/cloroformo para eliminar el producto. El filtrado se concentró para dar el producto bruto, que se purificó por cromatografía en gel de sílice (metanol/cloroformo = 50/50) para dar 1,9 g del compuesto del título como un sólido amarillo claro, que es la sal de HCl. (45% de rendimiento). (También se recuperaron 1,6 gramos (45%) de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carbonitrilo) LC/MS (FA) ES+ 329. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 9,73, (bs, 4H), 8,76-8,74 (m, 2H), 7,90-7,88 (m, 2H), 7,39-7,35 (m, 2H), 7,31-7,27 (m, 2H), 4,30 (s, 2H).

[00701] Etapa 2, Preparación de 2-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)pirimidin-4(3H)-ona (Compuesto 92)

[00702] A una solución de clorhidrato de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboximidamida (188 mg, 0,515 mmol) en etanol (8,0 mL) se añadió 21% de etóxido de sodio en etanol (0,192 mL, 0,515 mmol) y etenolato de 2-etoxicarbonil sódico (284 mg, 2,06 mmol) (preparado como en J. Med. Chem., (2001), 44(17), 2695-2700), y la reacción se calentó a reflujo durante la noche. La reacción se enfrió y concentró. El residuo se suspendió en DCM (15 mL) y agua (15 mL) durante 20 minutos. Los sólidos se filtraron, se secaron y purificaron por cromatografía en gel de sílice (metanol/DCM = 0/100→15/85) para dar el producto. La HPLC proporcionó 23 mg del compuesto del título como un

sólido amarillo. (12 % de rendimiento). LC/MS (FA) ES+ 381. ^{1}H RMN (300 MHz, DMSO-d_6) δ: 8,72-8,60 (m, 2H), 8,41 (d, 1 H, J = 5,7 Hz), 7,88-7,85 (m, 2H), 7,40-7,36 (m, 2H), 7,32-7,28 (m, 2H), 6,58 (d, 1H, J = 5,7 Hz), 4,80 (s, 2H).

[00703] Ejemplo 30: Síntesis de N-{4-[4-{(4-clorofenil)[3-(dimetilamino)azetidin-1-il]metil}-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (Compuesto 181)



[00704] Etapa 1: Preparación de N-{4-[4-[(4-clorofenil)(hidroxi)metil]-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida

[00705] Una mezcla de [5-bromo-2-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-3-tienil](4-clorofenil)metanol (3,07 g, 5,52 mmol)) (sintetizado de manera análoga a la que se describe en Ejemplo 2), N-[4-(trimetilstannil)piridin-2-il]acetamida (1,81 g, 6,07 mmol), tetrakis(trifenilfosfina)paladio(0) (319 mg, 0,28 mmol), yoduro de cobre (315 mg, 1,65 mmol) y cloruro de litio (702 mg, 16,5 mmol) en 1,4-dioxano

(25,0 mL) se agitó a 100 °C durante 2 horas bajo atmósfera de nitrógeno. La reacción se enfrió a temperatura ambiente y se concentró con celite. La mezcla bruta se purificó por cromatografía en columna (SiO_2, eluyente con metanol en diclorometano, 0–5% de gradiente) para proporcionar un sólido amarillo (2,48 g, 80%). LCMS: (AA) ES+ 556, 558; 1H RMN (400 MHz, $CDCl_3$) δ: 8,48 (br s, 1H), 8,43 (br s, 1H), 8,25 (s, 1H), 8,19 (d, J = 5,6 Hz, 1H), 7,41 (d, J = 8,4 Hz, 2H), 7,33–7,24 (m, 2H), 7,19 (s, 1H), 7,16 (dd, J = 1,2, 5,6 Hz, 1H), 6,22 (s, 1H), 6,05 (br s, 1 H), 5,51 (s, 2H), 3,66 (t, J = 8,4 Hz, 2H), 2,22 (s, 3H), 0,94 (t, J = 8,4 Hz, 2H), −0,01 (s, 9H).

[00706] Etapa 2: Preparación de N–{4–[4–{(4–clorofenil)[3–(dimetilamino)azetidin–1–il]metil}–5–(1–{[2–(trimetilsilil)etoxi]metil}–1H–1,2,4–triazol–3–il)–2–tienil]piridin–2–il}acetamida

[00707] A una solución de N–{4–[4–[(4–clorofenil)(hidroxi)metil]–5–(1–{[2–(trimetilsilil)etoxi]metil}–1H–1,2,4–triazol–3–il)–2–tienil]piridin–2–il}acetamida (100 mg, 0,18 mmol) en diclorometano (2,00 mL) se añadió pentacloruro de fósforo (112 mg, 0,54 mmol) a temperatura ambiente. La mezcla se agitó durante 15 min y luego se añadió agua (10 mL). La mezcla se agitó vigorosamente durante 10 min. Las fases se separaron y la fase acuosa se extrajo con diclorometano dos veces.Las fases orgánicas combinadas se lavaron con solución saturada de $NaHCO_3$, se secaron con Na_2SO_4, se filtraron y concentraron al vacío para dar un intermediario como un sólido amarillo. Este intermediario se disolvió en acetonitrilo (1,66 mL) y c se añadieron

carbonato de potasio (124 mg, 0,90 mmol) y clorhidrato de 1-azetidin-3-il-dimetilamina (130 mg, 0,54 mmol). La mezcla se agitó a 80 °C durante 5 horas. Después del enfriamiento a temperatura ambiente, la mezcla se diluyó con diclorometano y se filtró a través de un filtro de vidrio. El filtrado se concentró al vacío y el residuo se purificó por cromatografía en columna (SiO_2, elución con metanol en diclorometano, gradiente 0-10%) para proporcionar a producto sólido (103 mg, 52,3%). LCMS: (AA) ES+ 638, 640; 1H RMN (400 MHz, $CDCl_3$) δ: 8,48 (s, 1H), 8,26 (s, 1H), 8,22 (d, J = 5,2 Hz, 1H), 8,10 (s, 1H), 7,80 (s, 1H), 7,62 (d, J = 8,4 Hz, 2H), 7,25-7,21 (m 3H), 5,61 (s, 1H), 5,56 (s, 2H), 3,72 (dd, J = 8,8, 7,6 Hz, 2H), 3,43-3,32 (m, 2H), 2,93-2,80 (m, 3H), 2,24 (s, 3H), 2,06 (s, 6H), 0,99 (dd, J = 8,8, 7,6 Hz, 2H), 0,02 (s, 9H).

[00708] Etapa 3: Preparación de N-{4-[4-{(4-clorofenil)[3-(dimetilamino)azetidin-1-il]metil}-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (Compuesto 181)

[00709] Se disolvió N-{4-[4-{(4-clorofenil)[3-(dimetilamino)azetidin-1-il]metil}-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (60 mg, 0,094 mmol) en diclorometano (1,19 mL) y se añadió ácido trifluoroacético (0,30 mL, 3,85 mmol). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se concentró al vacío y se distribuyó entre EtOAc y solución saturada de $NaHCO_3$. La fase acuosa se extrajo con EtOAc

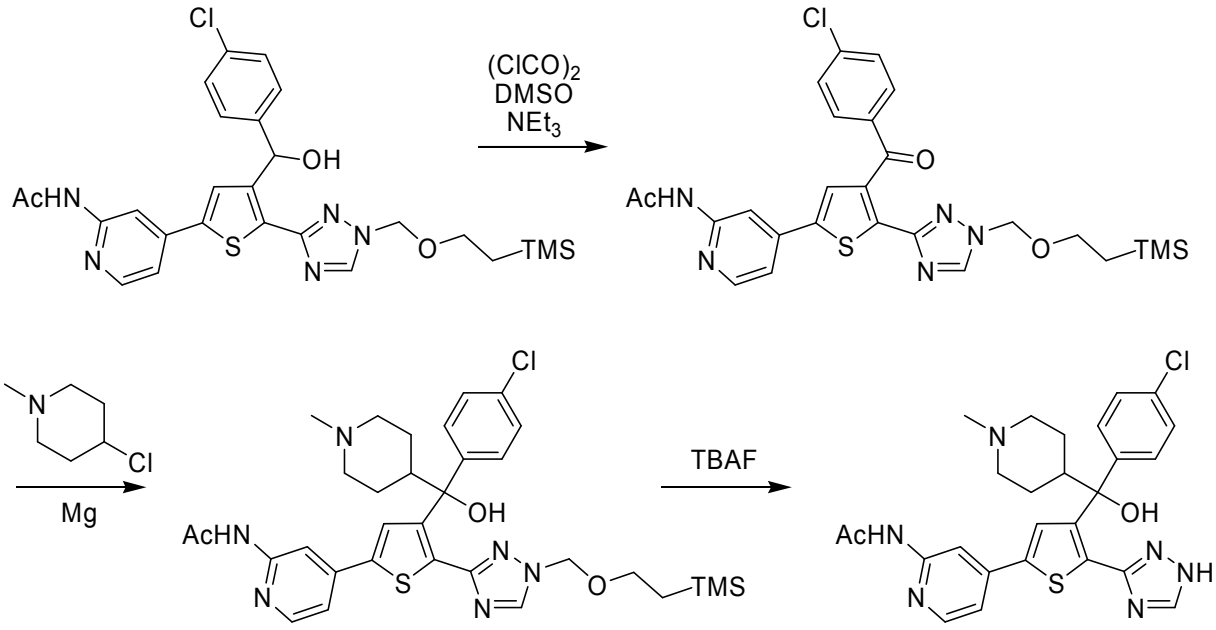
dos veces. Las fases orgánicas combinadas se secaron en Na_2SO_4, se filtraron y concentraron. El residuo se purificó por cromatografía en columna (SiO_2, elución con metanol en diclorometano, gradiente de 0–20%) para proporcionar el compuesto del título como un sólido blanco (34,2 mg, 71,6%). LCMS: (AA) ES+ 508, 510; 1H RMN (400 MHz, *d*$_4$–metanol): 8,51 (s, 1H), 8,39 (s, 1H), 8,24 (br s, 1H), 7,78 (s, 1H), 7,59 (d, J = 8,4 Hz, 2H), 7,32 (br s, 1H), 7,26 (d, J = 8,4 Hz, 2H), 5,71 (s, 1H), 3,45–3,36 (m, 2H), 3,00–2,83 (m, 3H), 2,19 (s, 3H), 2,06 (s, 6H).

[00710] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 30:

129	LCMS: (AA) ES+ 494, 496.
144	LCMS: (AA) ES+ 508, 510.
157	LCMS: (AA) ES+ 576, 578.
160	LCMS: (AA) ES+ 508, 510.
170	LCMS: (AA) ES+ 494, 496.
172	LCMS: (AA) ES+ 479.
189	LCMS: (AA) ES+ 450, 452.
211	LCMS: (AA) ES+ 451, 453.
218	LCMS: (AA) ES+ 519, 521.
222	LCMS: (AA) ES+ 522, 524.
223	LCMS: (AA) ES+ 509, 511.
226	LCMS: (AA) ES+ 469, 471.
227	LCMS: (AA) ES+ 463, 465.
230	LCMS: (AA) ES+ 479, 481.
244	LCMS: (FA) ES+ 467, 469.

245	LCMS: (AA) ES+ 536, 538.
250	LCMS: (AA) ES+ 408, 410.
269	LCMS: (AA) ES+ 509, 511.
274	LCMS: (AA) ES+ 494, 496.
277	LCMS: (AA) ES+ 494, 496.

[00711] **Ejemplo 31: Síntesis de N-(4-{4-[(4-clorofenil)(hidroxi)(1-metilpiperidin-4-il)metil]-5-(4H-1,2,4-triazol-3-il)-2-tienil}piridin-2-il)acetamida (Compuesto 237)**



[00712] **Etapa1**: Una solución de cloruro de oxalilo (63,1 uL, 0,746 mmol) en cloruro de metileno (1,50 mL, 23,4 mmol) se enfrió a -78 °C. A esta solución se añadió dimetilsulfóxido (65,1 uL, 0,918 mmol) en cloruro de metileno (1,00 mL) gota a gota. La reacción se agitó durante 10 min bajo atmósfera de nitrógeno. A esta mezcla se añadió una solución de N-{4-[4-[(4-

clorofenil)(hidroxi)metil]-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (319 mg, 0,574 mmol) en cloruro de metileno (1,50 mL) gota a gota. En 1 hr, se añadió gota a gota trietilamina (0,400 mL, 2,87 mmol) a la reacción y la mezcla resultante se calentó a rt. En 1 hr, la solución se diluyó con CH_2Cl_2 y se lavó con agua. La fase acuosa se extrajo con CH_2Cl_2(x2). Las fases orgánica combinada se lavaron con solución saturada de $NaHCO_3$(aq), se secaron y concentraron para proporcionar N-{4-[4-(4-clorobenzoil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1, 2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida como un sólido amarillo (325 mg, cuantitativa). LCMS: (AA) 554, 556; ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,56 – 8,47 (s, 1H), 8,32 – 8,24 (m, 1H), 8,11 – 8,03 (s, 1H), 8,03 – 7,92 (s, 1H), 7,87 – 7,77 (m, 2H), 7,63 – 7,57 (s, 1H), 7,42 – 7,32 (m, 3H), 5,37 – 5,32 (s, 2H), 3,53 – 3,40 (t, *J* = 8,1 Hz, 2H), 2,27 – 2,19 (s, 3H), 0,94 – 0,80 (t, *J* = 8,1 Hz, 2H), 0,02 – -0,04 (s, 9H).

[00713] **Etapa2**: Un balón de 25 mL cargado con virutas de magnesio (23,0 mg, 0,947 mmol) se secó a la llama. Al balón se añadió tetrahidrofurano (1,00 mL) y una gota de 1,2-dibromoetano. La mezcla se calentó a 45 °C durante 10 min y se enfrió a rt. A la mezcla se añadió 4-cloro-N-metilpiperidina (126 mg, 0,947 mmol). La reacción se agitó a 35 °C bajo atmósfera de nitrógeno durante 12 hrs. La mezcla se tornó turbia, y las virutas de magnesio finalmente desaparecieron, a medida que la reacción progresó. A una solución de N-{4-[4-(4-

clorobenzoil)-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (113 mg, 0,204 mmol) en tetrahidrofurano (1,00 mL) se añadió gota a gota la solución de reactivo de Grignard pre-preparada a 0 °C. En 3 horas, la reacción se calentó a rt. En otras 3 horas, la reacción se inactivó con agua y se distribuyó entre solución saturada de $NaHCO_3$(aq) y EtOAc. La fase acuosa se extrajo con EtOAc(x2). La fase orgánica combinada se secó y concentró. La purificación en una columna de gel de sílice (gradiente de elución, 1-20% de MeOH) proporcionó N-(4-{4-[(4-clorofenil)(hidroxi)(1-metilpiperidin-4-il)metil]-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil}piridin-2-il)acetamida como un sólido amarillo (59,0 mg, 44,3% de rendimiento). LCMS: (AA) ES+ 653, 655; ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,77 – 8,66 (s, 1H), 8,60 – 8,49 (s, 1H), 8,31 – 8,23 (d, *J* = 5,3 Hz, 1H), 8,15 – 8,08 (m, 2H), 7,66 – 7,60 (s, 1H), 7,34 – 7,23 (m, 3H), 7,17 – 7,08 (d, *J* = 8,7 Hz, 2H), 5,45 – 5,38 (s, 2H), 3,63 – 3,51 (m, 2H), 3,49 – 3,44 (s, 3H), 3,02 – 2,90 (d, *J* = 10,8 Hz, 1H), 2,90 – 2,78 (d, *J* = 11,2 Hz, 1H), 2,28 – 2,20 (m, 4H), 2,20 – 2,09 (m, 1H), 2,07 – 1,95 (m, 1H), 1,96 – 1,78 (m, 2H), 1,76 – 1,58 (qd, *J* = 12,7, 3,8 Hz, 1H), 1,16 – 1,07 (d, *J* = 12,5 Hz, 1H), 0,99 – 0,85 (m, 2H), 0,02 – -0,04 (s, 9H).

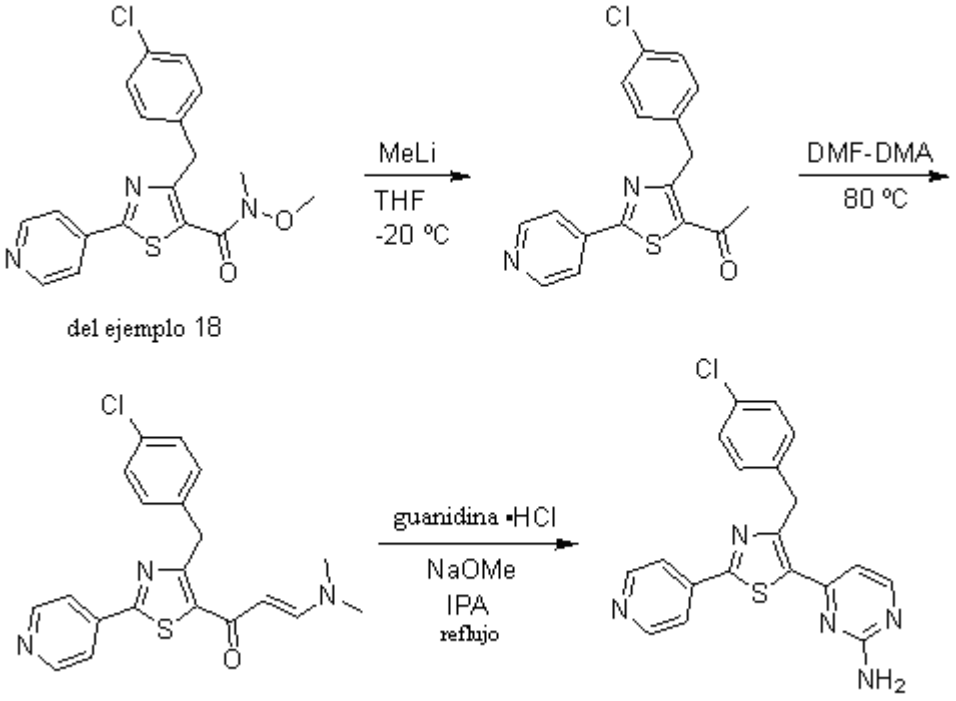
[00714] **Etapa3:** Un tubo de microonda de 5 mL se cargó con N-(4-{4-[(4-clorofenil)(hidroxi)(1-metilpiperidin-4-il)metil]-5-(1-{[2-(trimetilsilil)etoxi]metil}-1H-1,2,4-triazol-3-il)-2-tienil}piridin-2-il)acetamida (10,0 mg, 0,0153 mmol) y

tetrahidrofurano (0,500 mL, 6,16 mmol). A la solución se añadió 1,00 M de fluoruro de tetra-n-butilamonio en tetrahidrofurano (61,2 uL). El tubo se selló y se calentó a 80 °C en un baño de aceite durante 4 horas. La mezcla resultante se enfrió a rt y se distribuyó entre solución saturada de $NaHCO_3$(aq) y EtOAc. La fase acuosa se extrajo con EtOAc(x2). La fase orgánica combinada se secó y concentró. La purificación en HPLC (fase inversa, AA) proporcionó N-(4-{4-[(4-clorofenil)(hidroxi)(1-metilpiperidin-4-il)metil]-5-(4H-1,2,4-triazol-3-il)-2-tienil}piridin-2-il)acetamida como un sólido blanco. (2,0mg, 25% de rendimiento) LCMS (AA) ES+ 523, 525; ^{1}H RMN (400 MHz, MeOD) δ 8,50 – 8,42 (s, 1H), 8,41 – 8,36 (s, 1H), 8,36 – 8,29 (d, *J* = 5,3 Hz, 1H), 7,92 – 7,83 (s, 1H), 7,50 – 7,43 (m, 1H), 7,43 – 7,34 (d, *J* = 8,6 Hz, 2H), 7,25 – 7,14 (d, *J* = 8,6 Hz, 2H), 2,91 – 2,76 (m, 1H), 2,65-2,55 (m, 4H), 2,26 – 2,15 (s, 3H), 2,11 – 2,01 (m, 2H), 1,88 – 1,72 (m, 2H), 1,70 – 1,57 (s, 1H), 1,47 – 1,35 (dd, *J* = 15,0, 7,4 Hz, 1H), 1,31 – 1,20 (m, 2H).

[00715] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 31:

145	LCMS: (AA) ES+ 511, 513
225	LCMS: (AA) ES+ 493, 495.
273	LCMS: (AA) ES+ 508, 510.

[00716] Ejemplo 32: Síntesis de 4-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)pirimidin-2-amina (Compuesto 150)



[00717] Etapa 1, Preparación de 1-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)etanona

[00718] A una solución de 4-(4-clorobencil)-N-metoxi-N-metil-2-(piridin-4-il)tiazol-5-carboxamida (1,79 g, 4,79 mmol) en THF (97 mL) at -20 °C se añadió una solución de MeLi 1,60 M en éter (4,19 mL, 6,70 mmol). La reacción se agitó durante 30 minutos a -20 °C. Una porción adicional de solución de MeLi 1,60 M en éter (0,838 mL, 1,34 mmol) se añadió y la reacción se agitó durante 30 minutos más a -20 °C. La reacción se inactivó por la adición de cloruro de amonio saturado (25 mL) seguido por agua (35 mL). La mezcla se extrajo con acetato de etilo (2 x 150 mL) y las fases orgánicas combinadas se secaron, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de

sílice (EA/DCM = 0/100→80/20) para dar 1,27 g (81 % de rendimiento) del compuesto del título como un sólido amarillo claro. LC/MS (FA) ES+ 329, 331. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,75–8,73 (m, 2H), 7,83–7,81 (m, 2H), 7,34–7,31 (m, 2H). 7,26–7,23 (m, 2H), 4,53 (s, 2H), 2,59 (s, 3H).

[00719] Etapa 2, Preparación de (E)–1–(4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–il)–3–(dimetilamino)prop–2–en–1–ona

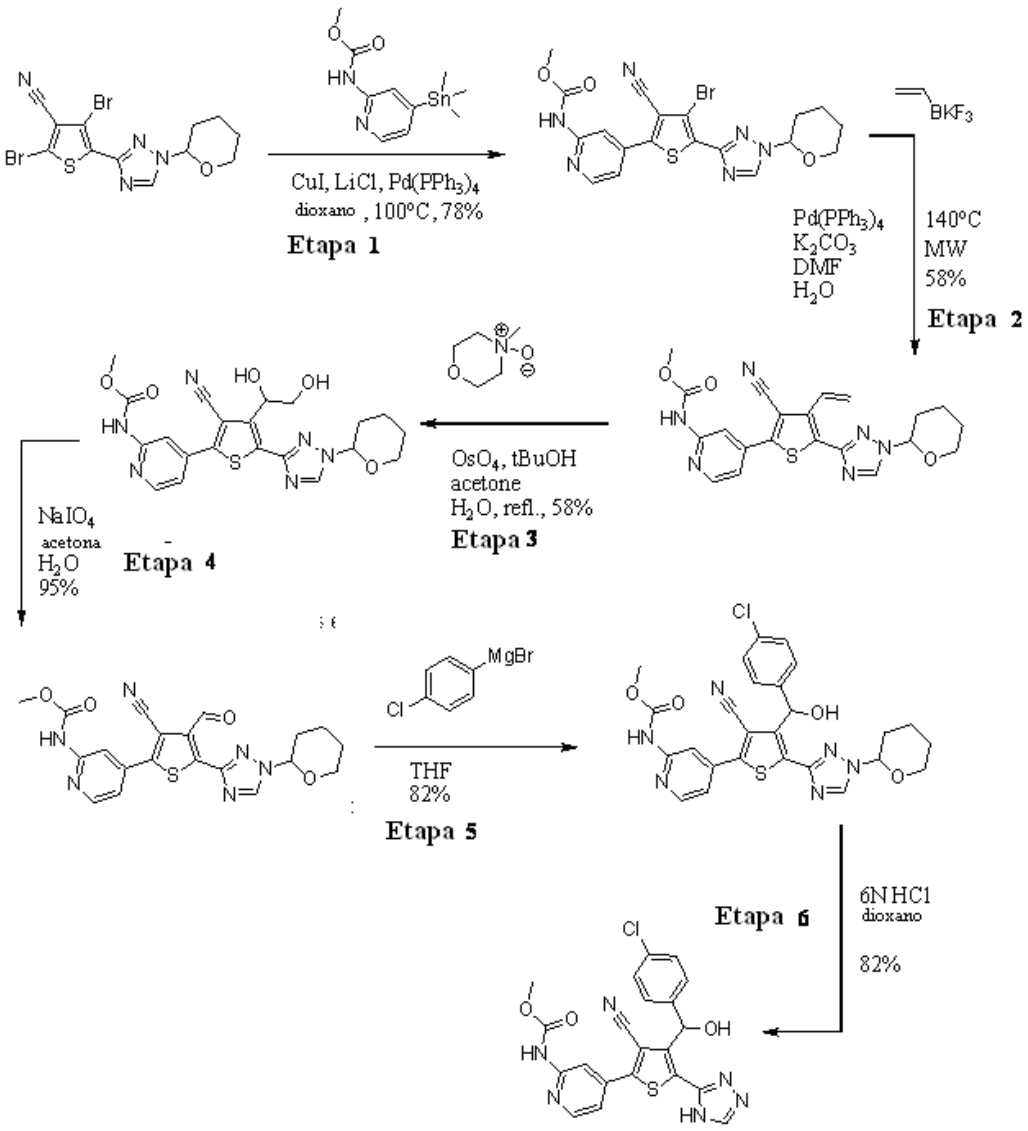
[00720] Una solución de 1–(4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–il)etanona (370 mg, 1,12 mmol) en 1,1–dimetoxi–N,N–dimetilmetanamina (10,0 mL, 75,3 mmol) se calentó a 80 grados durante 6 horas. La reacción se enfrió y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (EA/DCM = 0/100→100/0) para dar 389 mg (90 % de rendimiento) del compuesto del título como un sólido amarillo. LC/MS (FA) ES+ 384, 386. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,70–8,68 (m, 2H), 7,81–7,75 (m, 3H), 7,36–7,33 (m, 2H), 7,26–7,24 (m, 2H), 5,41 (d, 1H, J = 12,3 Hz), 4,55 (s, 2H), 3,16 (s, 3H), 2,88 (s, 3H).

[00721] Etapa 3, Preparación de 4–(4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–il)pirimidin–2–amina

[00722] A una solución de (E)–1–(4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–il)–3–(dimetilamino)prop–2–en–1–ona (93,0 mg, 0,242 mmol) en alcohol isopropílico (1,0 mL) se añadió clorhidrato de guanidina (34,7 mg, 0,363 mmol) y etóxido de sodio (65,4 mg, 1,21 mmol) y la mezcla resultante se calentó a

reflujo durante 3 días. La reacción se enfrió y concentró al vacío. El residuo se suspendió en DCM (10 mL) y agua (10 mL). Los sólidos no disueltos se filtraron. Este material se purificó por cromatografía inversa preparativa para dar 57 mg (62% de rendimiento) del compuesto del título como un sólido blanco. LC/MS (FA) ES+ 380, 382. ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,73-8,71 (m, 2H), 8,31 (d, 1H, J = 5,1 Hz), 7,88-7,86 (m, 2H), 7,36-7,30 (m, 4H), 6,86 (bs, 2H), 6,84 (d, 1H, J = 5,1 Hz), 4,56 (s, 2H).

[00723] Ejemplo 33: Síntesis de {4-[4-[(4-clorofenil)(hidroxi)metil]-3-ciano-5-(4H-1,2,4-triazol- 3-il)-2-tienil]piridin-2-il}carbamato de metilo (Compuesto 195)



[00724] **Etapa 1: (4-{4-bromo-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo**

[00725] Una mezcla de 2,4-dibromo-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo (1,27 g, 3,05 mmol), [4-(trimetilestannil)piridin-2-il]carbamato de metilo (0,960 g, 3,05 mmol), cloruro de litio (0,388 g, 9,14 mmol),

yoduro de cobre (0,174 g, 0,914 mmol) y tetrakis(trifenilfosfino)platino (0) (0,190 g, 0,152 mmol) en 1,4-dioxanos anhidro (45 mL) se desgasificó por la evacuación al vacío y relleno con N_2 4 veces, luego se calentó a 100°C bajo N_2 durante 8 horas, luego se enfrió a temperatura ambiente. La suspensión se filtró y se lavó con dioxano. El sólido se suspendió en 20% de MeOH en DCM (300 mL), y se lavó con agua (2X). La suspensión orgánica se concentró en un evaporador a rotatorio para dar un residuo sólido. El residuo se agitó en DMF/DCM (10 mL / 10 mL) a temperatura ambiente durante 20 min, se filtró y se lavó con DCM para dar un producto sólido (1,16 g, rendimiento 77,8%). LC/MS: (FA) ES+ 489, 491. ^{1}H RMN (400MHz, *d*$_4$-MeOH /*d*-cloroformo) δ8,26-8,35 (m, 3H), 7,34 (m, 1H), 5,48 (m, 1H), 4,00 (m, 1H), 3,73 (s, 3H), 3,64-3,69 (m, 1H), 1,97-2,14 (m, 3H), 1,58-1,68 (m, 3H).

[00726] Etapa 2: (4-{3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-4-vinil-2-tienil}piridin-2-il)carbamato de metilo

[00727] Una mezcla de (4-{4-bromo-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo (1,14 g, 2,33 mmol), viniltrifluoroborato de potasio (0,624 g, 4,66 mmol), tetrakis(trifenilfosfina)platino (0) (0,145 g, 0,116 mmol) y carbonato de potasio (0,967 g, 7,00 mmol) en N,N-dimetilformamida (14,0 mL) y agua (5,0 mL) en un vial de microondas se calentó bajo atmósfera de nitrógeno a 140°C en un microondas durante 15 min. La mezcla se enfrió a temperatura ambiente, se inactivó con agua, se extrajo con DCM, se lavó con agua luego

salmuera, se secó con Na_2SO_4, filtró, y se evaporó en rotavap para dar el producto bruto. La purificación en una columna de gel de sílice usando MeOH/DCM (0/100 a 5/95) proporcionó el producto deseado (1,16 g, con PF3 y O=PF3 contaminado) con Rf en TLC (MeOH/DCM 5/95) de 0,4, y producto de-carbamida (0,627 g, rendimiento 58%). LC/MS: (FA) ES+ 437. ^{1}H RMN (400MHz, *d*-cloroformo) δ8,52 (s, 1H), 8,45 (s, 1H), 8,41 (m, 1H), 8,33 (s, 1H), 7,51-7,59 (m, 1H), 7,46 - 7,49 (m, 1H), 6,28-6,33 (m, 1H), 5,66-5,69 (m, 1H), 5,51-5,54 (m, 1H), 4,09-4,12 (m, 1H), 3,86 (s, 3H), 3,75-3,78 (m, 1H), 2,00-2,20 (m, 3H), 1,68-1,77 (m, 3H).

[00728] Etapa 3: (4-{3-ciano-4-(1,2-dihidroxietil)-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo

[00729] A la suspensión de (4-{3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-4-vinil-2-tienil}piridin-2-il)carbamato de metilo (0,625 g, 1,34 mmol) en alcohol ter-butílico (3,0 mL) y acetona (30 mL) se añadió N-metilmorfolina N-óxido (0,315 g, 2,69 mmol), seguido por agua (1,0 mL) luego 0,157 M de tetraóxido de osmio en agua (0,257 mL, 0,0404 mmol). La suspensión amarilla pálida se agitó a temperatura ambiente durante 17 horas. N-metilmorfolina N-óxido (0,315 g, 2,69 mmol) se añadió y la suspensión se agitó durante 3 más horas, luego se calentó a reflujo durante 7 horas. La mezcla se enfrió a temperatura ambiente, se sometió a evaporación con rotavapor y se destiló azeotrópicamente con MeOH para dar un residuo bruto sólido. El sólido bruto se disolvió parcialmente en DCM-

MeOH, recubrió en gel de sílice, se evaporó en rotavapor y cromatografió en una columna de gel de sílice usando una elución de MeOH/DCM (0/100 a 5/95) para proporcionar a producto sólido (0,365 g, rendimiento 57,6%). LC/MS: (FA) ES+ 471; ES-469. ^{1}H RMN (400MHz, *d*-cloroformo/*d4*-metanol) δ 8,35 (m, 2H), 8,30 (m, 1H), 7,40 (m, 1H), 5,47-5,49 (m, 1H), 5,31-5,33 (m, 1H), 4,03-4,07 (m, 1H), 3,87 (m, 1H), 3,79 (s, 3H), 3,71-3,81 (m, 2H), 2,13 (m, 1H), 2,00-2,02 (m, 2H), 1,65-1,70 (m, 3H).

[00730] Etapa 4: (4-{3-ciano-4-formil-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol- 3-il]-2-tienil}piridin-2-il)carbamato de metilo

[00731] Se disolvió (4-{3-ciano-4-(1,2-dihidroxietil)-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo (0,362 g, 0,769 mmol) en acetona (40 mL) y agua (10 mL). Se añadió metaperyodato de sodio (0,494 g, 2,31 mmol) y la mezcla se agitó a temperatura ambiente durante 6 horas. Se añadió metaperyodato de sodio (0,329 g, 1,54 mmol) y la mezcla se agitó durante 16 horas más. La mezcla se concentró en rotavapor. El residuo se trituró con agua, se filtró y lavó por completo con agua, luego se secó en un liofilizador para dar un producto sólido seco (0,320 g, rendimiento 94,8%). LC/MS: (FA) ES+ 439. ^{1}H RMN (400MHz, *d6*-dmso) δ10,67 (s, 1H), 10,57 (s, 1H), 9,05 (s, 1H), 8,49 (m, 1H), 8,28 (s, 1H), 7,50 (m, 1H), 5,69-5,73 (m, 1H), 3,94-3,98 (m, 1H), 3,73 (s, 3H), 3,66-3,71 (m, 1H), 1,93-2,12 (m, 3H), 1,58-1,71 (m, 3H).

[00732] Etapa 5: (4-{4-[(4-clorofenil)(hidroxi)metil]-3-ciano-5-[1-(tetrahidro- 2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo

[00733] A una suspensión de (4-{3-ciano-4-formil-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo (0,1077 g, 0,2456 mmol) en tetrahidrofurano anhidro (6,0 mL) se enfrió con baño de hielo se añadió lentamente 1,0 M de bromuro de 4-clorofenilmagnesio en éter(2,50 mL, 2,50 mmol). La solución transparente resultante se agitó con enfriamiento durante 30 min, luego la mezcla se inactivó con metanol (0,5 mL), luego con ácido acético (148 mg, 2,46 mmol) . La mezcla se calentó a temperatura ambiente, luego se evaporó por rotavapor para dar el producto bruto, que se cromatografió en una columna de gel de sílice usando MeOH/DCM (0/100 a 3/97) para proporcionar un producto sólido (0,116 g, rendimiento 82%). LC/MS: (FA) ES+ 551; ES- 549, . ^{1}H RMN (400MHz, *d*-cloroformo/*d4*-metanol) δ 8,36 (s, 1H), 8,29 (m, 2H), 7,43 (m, 1H), 7,34 (m, 2H), 7,19 (m, 2H), 6,37 (s, 1H), 5,41-5,46 (m, 1H), 3,99-4,04 (m, 1H), 3,79 (s, 3H), 3,68-3,72 (m, 1H), 2,13 (m, 1H), 1,97-2,00 (m, 2H), 1,55-1,70 (m, br, 3H).

[00734] Etapa 6: {4-[4-[(4-clorofenil)(hidroxi)metil]-3-ciano-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}carbamato de metilo

[00735] A una suspensión de (4-{4-[(4-clorofenil)(hidroxi)metil]-3-ciano-5-[1-(tetrahidro-2H-

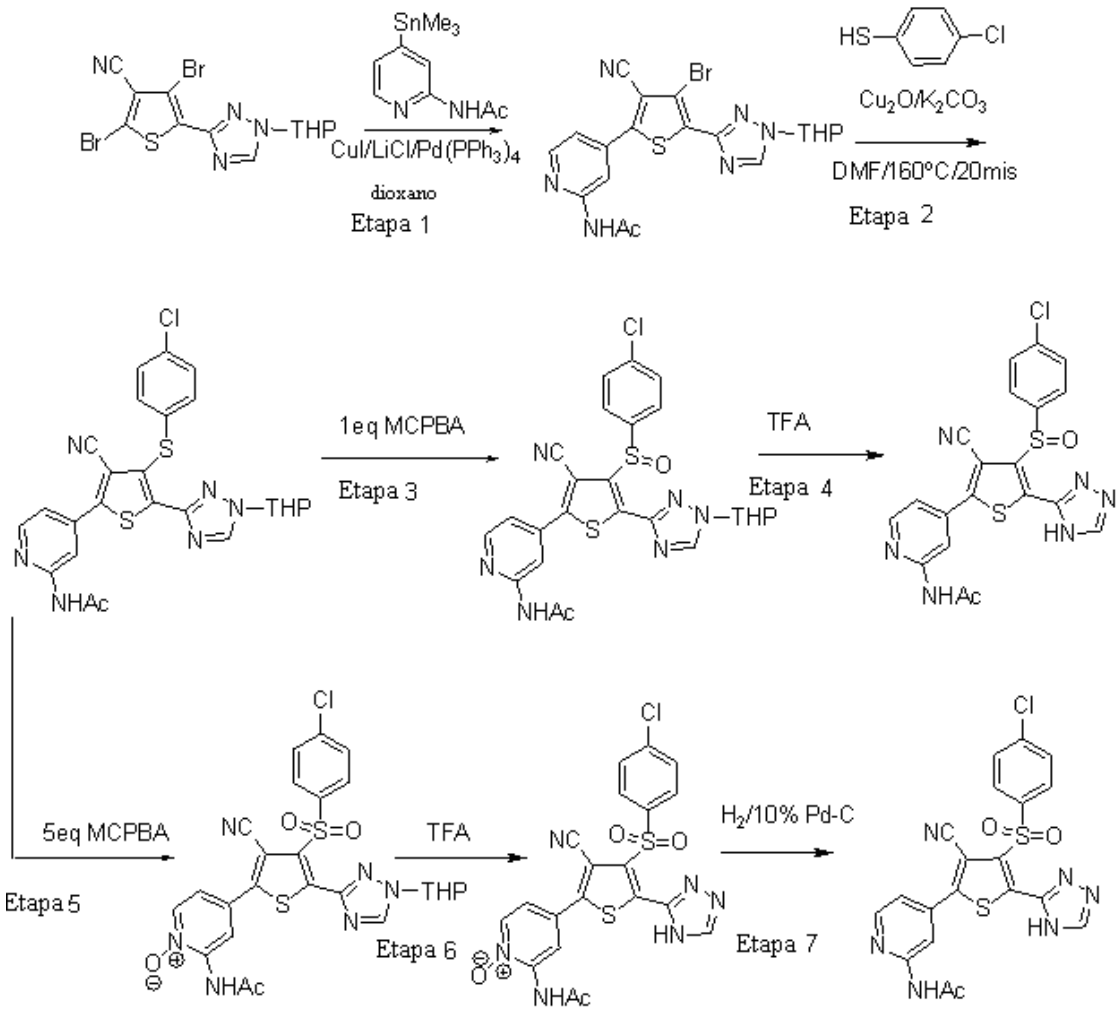
piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)carbamato de metilo (0,0450 g, 0,0817 mmol) en 1,4-dioxano (4,0 mL, 51 mmol) y enfriada en un baño de hielo se añadió ácido clorhídrico 6,0 M en agua (4,0 mL, 24 mmol). La solución resultante se llevó a temperatura ambiente. Se añadió hexano (5,0 mL) y la mezcla bifásica se agitó durante 4 horas. El hexano se separó y la fase acuosa se lavó con hexano dos veces. La fase acuosa se concentró en un rotavapor a ~ la mitad de volumen, se diluyó con hielo y agua, se alcalinizó con solución saturada acuosa de $NaHCO_3$ a pH ~ 7,5, se extrajo con EtOAc (4 x). Las soluciones de EtOAc combinadas se lavaron con salmuera, secaron Na_2SO_4, se filtraron y evaporaron por rotavapor para dar un sólido bruto. El sólido bruto se cromatografió en una columna de gel de sílice usando MeOH/DCM (0/100 a 5/95) para proporcionar un producto sólido (33 mg, rendimiento 82 %). LC/MS: (FA) ES+ 467, 469. ^{1}H RMN (400MHz, *d6*-dmso) δ 10,50 (s, 1H), 8,82 (s, 1H), 8,41 (m, 1H), 8,20 (s, 1H), 7,57 (m, 2H), 7,39 (m, 3H), 7,06 (s, 1H), 6,59 (s, br, 1H), 3,69 (s, 3H).

[00736] Los compuestos de la siguiente tabla se prepararon a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 33:

153	LCMS: (AA) ES+ 468.
165	LCMS: (AA) ES+ 451, 453.

[00737] Ejemplo 34: Síntesis de N-{4-[4-[(4-clorofenil)sulfinil]-3-ciano-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (Compuesto 131) y N-

{4-[4-[(4-clorofenil)sulfonil]-3-ciano-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (Compuesto 140)



[00738] Etapa 1: N-(4-{4-bromo-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)acetamida

[00739] Una mezcla de 2,4-dibromo-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]tiofeno-3-carbonitrilo (1,3809 g, 3,3027 mmol), [B] N-[4-

(trimetilstannil)-piridin-2-il]acetamida (987,38 mg, 3,3028 mmol), yoduro de cobre (188,70 mg, 0,99082 mmol), cloruro de litio (420,04 mg, 9,9082 mmol) y tetrakis(trifenilfosfina)-paladio(0) (190,82 mg, 0,16514 mmol) en 1,4-Dioxano seco (20,0 mL) se sometió a sonicación bajo N_2 durante 2 min, luego se calentó en un vial tapado a 130°C en máquina de microondas durante 20 min. La suspensión se enfrió a temperatura ambiente, y el residuo se purificó usando cromatografía en gel de sílice. El eluyente fue 40-100% de acetato de etilo en hexano, proporcionando un producto sólido (0,8802g, rendimiento 56,3%) LCMS: (AA) ES+ 473, 475. 1H RMN (300MHz, CDCl3) **δ:** 8,61 (s, 1H), 8,41 (d, 1H), 8,39 (s, 1H), 8,10 (s, 1H), 7,53 (d, 1H), 5,55-5,60 (dd, 1H), 4,06-4,10 (m, 1H), 3,68-3,78 (m, 1H), 2,35 (s, 3H), 2,15-2,28 (m, 1H), 2,01-2,13 (m, 2H), 1,66-1,80 (m, 3H).

[00740] **Etapa 2:** N-(4-{4-[(4-clorofenil)sulfanil]-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)acetamida

[00741] N-(4-{4-bromo-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)acetamida (0,2601 g, 0,5495 mmol), óxido de cobre (I) e (0,1572 g, 1,099 mmol), 4-clorobencenotiol (0,3179 g, 2,198 mmol) y carbonato de potasio (0,2278 g, 1,648 mmol) se añadieron a un vial de microondas seguido por DMF (15,00 mL). La reacción se irradió at 150 °C durante 15 min. El sólido se filtró y se lavó con DCM. La solución se diluyó con 80 ml agua, y se extrajo con 100 ml DCM durante dos veces. La fase

orgánica se concentró, y se purificó por columna. El eluyente fue 50-100% acetato de etilo en hexano para producir a producto sólido (0,224 g, rendimiento 76,0%) LCMS: (AA) ES+ 537, 539. 1H RMN (300MHz, CDCl3) **δ:** 8,59 (s, 1H), 8,37 (d, 1H), 8,36 (s, 1H), 8,03 (s, 1H), 7,53 (d, 1H), 7,32 (d, 2H), 7,22 (d, 2H), 5,50-5,55 (dd, 1H), 4,02-4,08 (m, 1H), 3,68-3,78 (m, 1H), 2,25 (s, 3H), 2,10-2,18 (m, 1H), 2,00-2,07 (m, 2H), 1,66-1,80 (m, 3H).

[00742] **Etapa 3:** N-(4-(4-(4-clorofenilsulfinil)-3-ciano-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-2-il)piridin-2-il)acetamida

[00743] N-(4-{4-[(4-clorofenil)sulfanil]-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)acetamida (0,0575 g, 0,107 mmol) se disolvió en cloruro de metileno (5,00 mL), seguido por la adición de ácido m-cloroperbenzoico (0,0194 g, 0,112 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La solución se concentró, y se purificó por cromatografía en columna. El eluyente fue 50-100% de acetato de etilo en hexano para producir un producto sólido (0,0324g, 54,7%) LCMS: (AA) ES+ 553, 555. 1H RMN (300MHz, CDCl3) **δ:** 8,47 (m, 2H), 8,41 (s, 1H), 8,36 (d, 1H), 8,06 (dd, 2H), 7,46 (dd, 2H), 7,45 (d, 1H), 5,53-5,59 (dd, 1H), 4,08-4,16 (m, 1H), 3,73-3,81 (m, 1H), 2,25 (s, 3H), 2,10-2,18 (m, 1H), 2,00-2,07 (m, 2H), 1,69-1,80 (m, 3H).

[00744] **Etapa 4:** N-{4-[4-[(4-clorofenil)sulfinil]-3-ciano-5-(4H-1,2,4-triazol-3-il)-2-tienil]piridin-2-il}acetamida (Compuesto **131**)

[00745] N-(4-(4-(4-clorofenilsulfinil)-3-ciano-5-(1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il)tiofen-2-il)piridin-2-il)acetamida (0,0315 g, 0,0570 mmol) se disolvió en TFA (5,00 mL, 64,9 mmol). La mezcla se agitó a temperatura ambiente durante 1 hr, y el solvente se evaporó. Se añadieron 10 ml de DCM para redisolver el material seguido por la adición de trietilamina (1 mL). El solvente se evaporó off, y la mezcla se purificó por columna en gel de sílice. El eluyente fue 0-6% de metanol en hexano para producir un producto sólido (0,0112g, rendimiento 41,9%) LCMS: (AA) ES+ 469, 471. 1H RMN (300MHz, MeOD) **δ:** 8,65 (s, 1H), 8,51 (s, 1H), 8,42 (d, 1H), 8,06 (d, 2H), 7,58 (d, 2H), 7,44 (dd, 1H), 2,25 (s, 3H).

[00746] **Etapa 5:** N-(4-{4-[(4-clorofenil)sulfonil]-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}-1-oxidopiridin-2-il)acetamida

[00747] N-(4-{4-[(4-clorofenil)sulfanil]-3-ciano-5-[1-(tetrahidro-2H-piran-2-il)-1H-1,2,4-triazol-3-il]-2-tienil}piridin-2-il)acetamida (0,0698 g, 0,130 mmol) se disolvió en cloruro de metileno (6,00 mL) seguido por la adición de ácido m-cloroperbenzoico (0,08971 g, 0,5199 mmol). La mezcla se agitó durante 30 min a temperatura ambiente. El solvente se evaporó, y el residuo se purificó por cromatografía en columna. El

eluyente fue 0–7% de metanol en acetato de etilo para producir a producto sólido (0,0654 g, rendimiento 86,0%) LCMS: (AA) ES+ 585, 587. 1H RMN (300MHz, CDCl3) **δ:** 8,76 (s, 1H), 8,41 (s, 1H), 8,37 (d, 2H), 8,26 (d, 1H), 7,50 (d, 2H), 7,43 (d, 1H), 5,50–5,57 (dd, 1H), 4,03–4,10 (m, 1H), 3,70–3,78 (m, 1H), 2,25 (s, 3H), 2,10–2,18 (m, 1H), 2,00–2,07 (m, 2H), 1,69–1,80 (m, 3H).

[00748] **Etapa 6:** N–{4–[4–[(4–clorofenil)sulfonil]–3–ciano–5–(4H–1,2,4–triazol–3–il)–2–tienil]–1–oxidopiridin–2–il}acetamida

[00749] N–(4–{4–[(4–clorofenil)sulfonil]–3–ciano–5–[1–(tetrahidro–2H–piran–2–il)–1H–1,2,4–triazol–3–il]–2–tienil}–1–oxidopiridin–2–il)acetamida (0,0742 g, 0,127 mmol) se disolvió en ácido trifluoroacético (4,00 mL, 51,9 mmol). La mezcla se agitó a temperatura ambiente durante 4 horas, el solvente se evaporó y el residuo se purificó por HPLC para producir a producto sólido (0,0421 g, rendimiento 66,3%) LCMS: (AA) ES+ 501, 503. 1H RMN (300MHz, MeOD) **δ:** 8,90 (s, 1H), 8,60 (s, 1H), 8,43 (d, 1H), 8,35 (d, 2H), 7,67 (d, 2H), 7,59 (d, 1H), 2,28 (s, 3H).

[00750] **Etapa 7:** N–{4–[4–[(4–clorofenil)sulfonil]–3–ciano–5–(4H–1,2,4–triazol–3–il)–2–tienil]piridin–2–il}acetamida (Compuesto **140**)

[00751] N–{4–[4–[(4–clorofenil)sulfonil]–3–ciano–5–(4H–1,2,4–triazol–3–il)–2–tienil]–1–oxidopiridin–2–il}acetamida (0,0229 g, 0,0457 mmol) se disolvió en metanol (3,00 mL), seguido por la adición de 10% Pd–C (5 mg). El balón se cargó con hidrógeno a 40

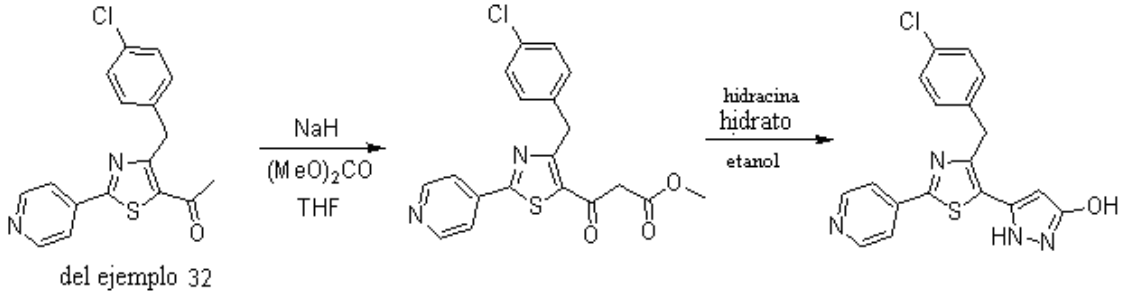
psi, y la suspensión se agitó a temperatura ambiente durante la noche. El sólido se filtró, y el residuo se concentró seguido por purificación by cromatografía en columna. El eluyente fue 0–8% de metanol en acetato de etilo para producir a producto sólido (0,0142 g, rendimiento 64,0%). LCMS: (AA) ES+ 485, 487. 1H RMN (300MHz, MeOD) **δ:** 8,60 (s, 1H), 8,53 (s, 1H), 8,45 (d, 1H), 8,35 (d, 2H), 7,66 (d, 2H), 7,48 (d, 1H), 2,20 (s, 3H).

[00752] El compuesto de la siguiente tabla se preparó a partir de los materiales iniciales apropiados con un método análogo al del Ejemplo 34:

166	LCMS: (AA) ES+ 454

[00753]

[00754] Ejemplo 35: Síntesis de 5–(4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–il)–1H–pirazol–3–ol (Compuesto 178)



[00755] Etapa 1, Preparación de 3–(4–(4–clorobencil)–2–(piridin–4–il)tiazol–5–il)–3–oxopropanoato de etilo

[00756] A un matraz que contiene 60% de NaH en aceite mineral (213 mg, 5,32 mmol) bajo nitrógeno se añadió THF (31,7 mL) y dimetil éster del ácido

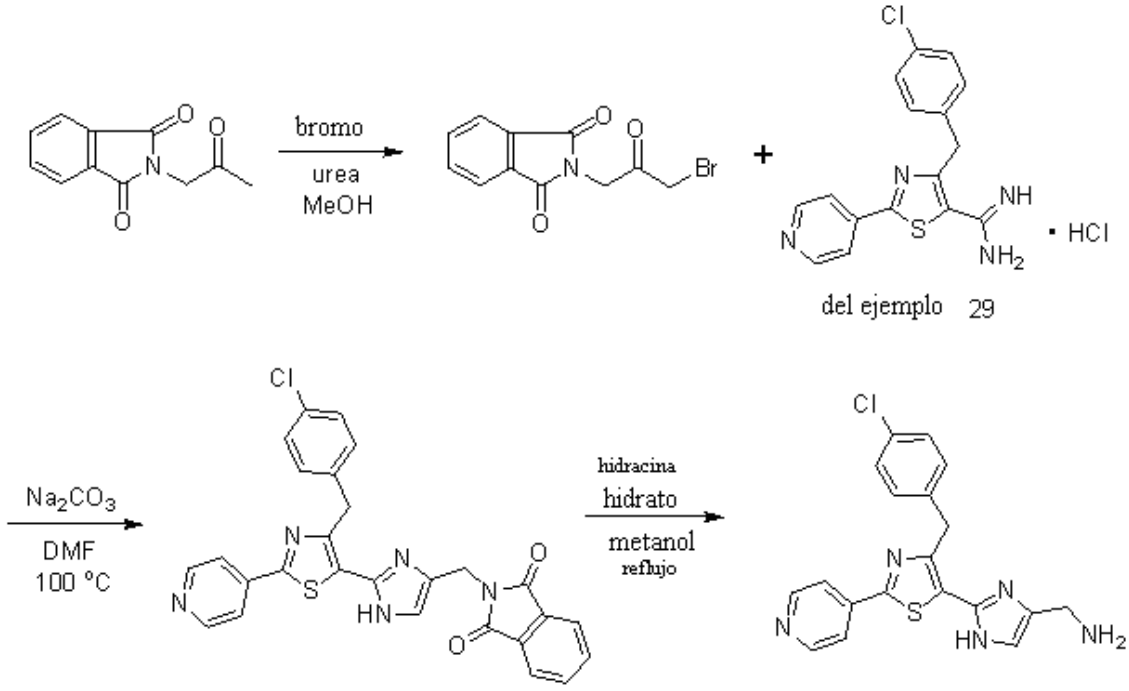
carbónico (0,448 mL, 5,32 mmol). La mezcla se calentó a 60 grados y luego se añadió una solución de 1-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)etanona (875 mg, 2,66 mmol) en THF (12,7 mL). La mezcla se calentó a 60 grados durante 1 hora. La reacción se enfrió y se inactivó con metanol (5 mL), luego NH_4Cl saturado (10 mL). Los solventes orgánicos se concentraron al vacío, y el residuo acuoso se diluyó con agua (10 mL) y se extrajo con acetato de etilo (2 x 20 mL). Las fases orgánicas combinadas se secaron, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (EA/DCM = 0/100→40/60) para dar 253 mg (25 % de rendimiento) del compuesto del título como un aceite. LC/MS (FA) ES+ 387, 389. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 8,76-8,74 (m, 2H), 7,83-7,81 (m, 2H), 7,35-7,32 (m, 2H), 7,26-7,23 (m, 2H), 4,53 (s, 2H), 3,89 (s, 2H), 3,77 (s, 3H).

[00757] Etapa 2, Preparación de 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-pirazol-3-ol

[00758] A una solución de 3-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-3-oxopropanoato de etilo (253 mg, 0,631 mmol) en etanol (16 mL) se añadió hidrato de hidracina (0,123 mL, 2,52 mmol) y la solución resultante se calentó a 80 grados durante 3 horas. La reacción se enfrió y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (MeOH/DCM = 0/100→10/90) para dar 118 mg de el producto. Este material se purificó por cromatografía de fase inversa preparativa para dar 63 mg (27 % de rendimiento) del compuesto del título como un sólido blanco. LC/MS (FA)

ES+ 369, 371. ^{1}H RMN (300 MHz, DMSO-d_6) δ: 12,44 (bs, 1H), 8,68 (bs, 2H), 7,83-7,81 (m, 2H), 7,35-7,32 (m, 2H), 7,27-7,24 (m, 2H), 5,60 (s, 1H), 4,34 (s, 2H).

[00759] Ejemplo 36: Síntesis de (2-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-imidazol-4-il)metanamina (Compuesto 255)



[00760] Etapa 1, Preparación de 2-(3-bromo-2-oxopropil)isoindoline-1,3-diona

[00761] A una solución de ftalimidoacetona (4,04 g, 19,9 mmol) en metanol (100 mL) se añadió urea (1,19 g, 19,9 mmol) y bromo (3,18 g, 19,9 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La reacción se concentró al vacío y el residuo se tomó en DCM (150 mL) y agua (50 mL). Las fases se separaron y la fase orgánica se secó, se filtró y concentró al vacío. El residuo se purificó

por cromatografía en gel de sílice (EA/hexanos = 0/100→50/50) para dar 159 mg (3% de rendimiento) del compuesto del título. ^{1}H RMN (300 MHz, $CDCl_3$) δ: 7,90–7,86 (m, 2H), 7,79–7,73 (m, 2H), 4,78 (s, 2H), 4,01 (s, 2H).

[00762] Etapa 2, Preparación de 2-((2-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-imidazol-4-il)metil)isoindoline-1,3-diona

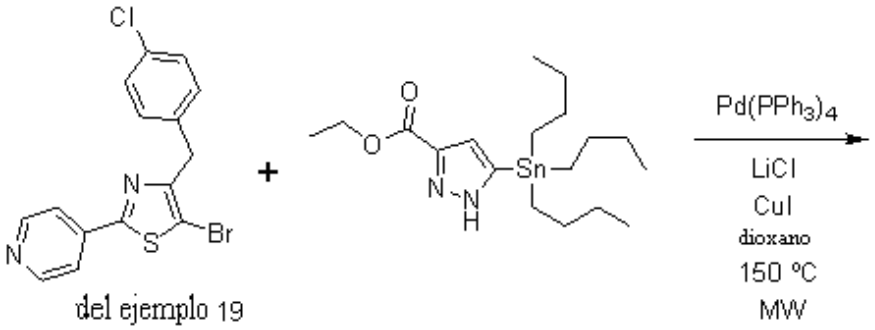
[00763] A una mezcla de clorhidrato de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboximidamida (112 mg, 0,306 mmol) en DMF (2,96 mL) se añadió carbonato de sodio (162 mg, 1,53 mmol) y 2-(3-bromo-2-oxopropil)isoindoline-1,3-diona (95,0 mg, 0,337 mmol) y la mezcla resultante se calentó a 100 grados durante 4 horas. La reacción se enfrió y se tomó en acetato de etilo (30 mL) y agua (5 mL). Las fases se separaron y la fase orgánica se lavó con agua (3 x 5 mL). La fase orgánica se secó, se filtró y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (MeOH/DCM = 0/100→10/90) para dar 47 mg (30% de rendimiento) del compuesto del título. LC/MS (FA) ES+ 512. 514. ^{1}H RMN (300 MHz, DMSO-d_6) δ: 12,67 (bs, 1H), 8,69–8,67 (m, 2H), 7,91–7,79 (m, 6H), 7,27–7,24 (m, 3H), 7,11–7,08 (m, 2H), 4,77 (s, 2H), 4,45 (s, 2H).

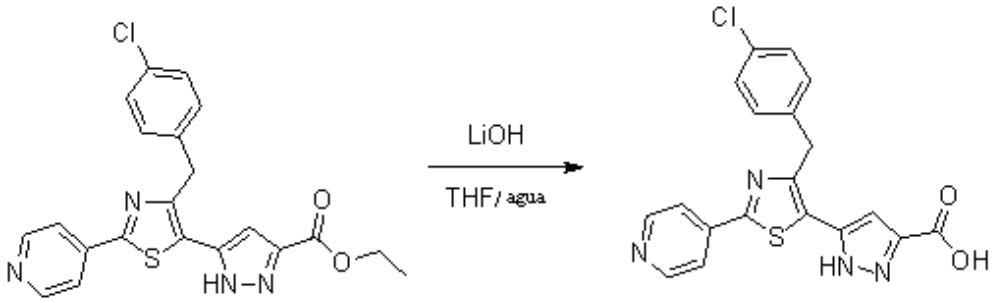
[00764] Etapa 3, Preparación de (2-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-imidazol-4-il)metanamina

[00765] A una solución de 2-((2-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-imidazol-4-il)metil)isoindolino-1,3-diona (45 mg, 0,0879 mmol) en

metanol (2,0 mL) se añadió hidrato de hidracina (,0086 mL, 0,176 mmol) y la solución resultante se calentó a reflujo durante 1 hora. La reacción se enfrió y concentró al vacío. El residuo se tomó en acetato de etilo y agua. Las fases se separaron y la fase orgánica se secó, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (MeOH/DCM = 0/100→40/60) para dar 13 mg (39% de rendimiento) del compuesto del título. LC/MS (FA) ES+ 382, 384. ^{1}H RMN (300 MHz, MeOH-d_4) δ: 8,71-8,68 (m, 2H), 7,82-7,80 (m, 2H), 7,35 -7,29 (m, 4H), 7,22 (s, 1H), 4,53 (s, 2H), 3,86 (s, 2H).

[00766] Ejemplo 37: Síntesis de ácido 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-pirazol-3-carboxílico (Compuesto 262)





[00767] Etapa 1, Preparación del 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-pirazol-3-carboxilato de etilo

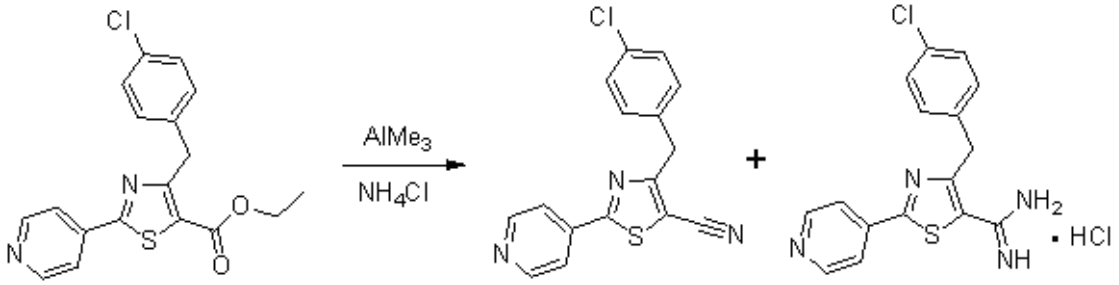
[00768] Una mezcla desgasificada con argón de 5-bromo-4-(4-clorobencil)-2-(piridin-4-il)tiazol (583 mg, 1,59 mmol), 5-(tributilstannil)-1H-pirazol-3-carboxilato de etilo (456 mg, 1,06 mmol), tetrakis(trifenilfosfina)paladio(0) (61,4 mg, 0,0531 mmol), yoduro de cobre (60,7 mg, 0,319 mmol), y cloruro de litio (135 mg, 3,19 mmol) en dioxano (7,46 mL) se calentó en una microondas a 150 grados durante 30 minutos. La mezcla de reacción se suspendió en acetato de etilo (100 mL) y agua (2 mL) y la mezcla se filtró y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (EA/DCM = 0/100→100/0) para dar el producto bruto. Este material se purificó por cromatografía de fase inversa preparativa para dar 55 mg (12% de rendimiento) del compuesto del título como un sólido blanco. LC/MS (FA) ES+ 425, 427. ^{1}H RMN (300 MHz, DMSO-d_6) δ: 8,71-8,69 (m, 2H), 7,85-7,83 (m, 2H), 7,36-7,33 (m, 2H), 7,28-7,25 (m, 2H), 7,09 (s, 1H), 4,41 (s, 2H), 4,34 (q, 1H, J = 7,2 Hz), 1,31 (t, 1H, J = 7,2 Hz).

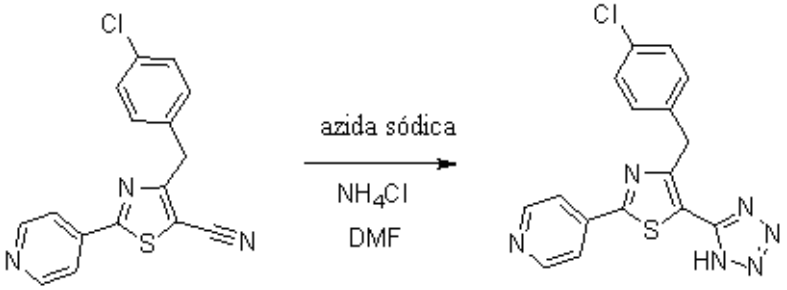
[00769] Etapa 2, Preparación de ácido 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-pirazol-3-carboxílico

[00770] Una solución de 5-(4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-il)-1H-pirazol-3-carboxilato de etilo (16,1 mg, 0,0379 mmol) en THF (0,50 mL) se trató con LiOH acuoso 1,0 M (0,0568 mL, 0568 mmol)

y la solución se agitó a 40 grados durante 3 días. La reacción luego se calentó a 65 grados durante 6 horas. La mezcla de reacción se enfrió y acidificó con HCl 1 N. La solución se extrajo con EA (3 x 25 mL) y las fases orgánicas combinadas se secaron, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía de fase inversa preparativa para dar 1 mg (7 % de rendimiento) del compuesto del título como un sólido blanco. LC/MS (FA) ES+ 397, 399.

[00771] Ejemplo 38: Síntesis de 4-(4-clorobencil)-2-(piridin-4-il)-5-(1H-tetrazol-5-il)tiazol (Compuesto 190)





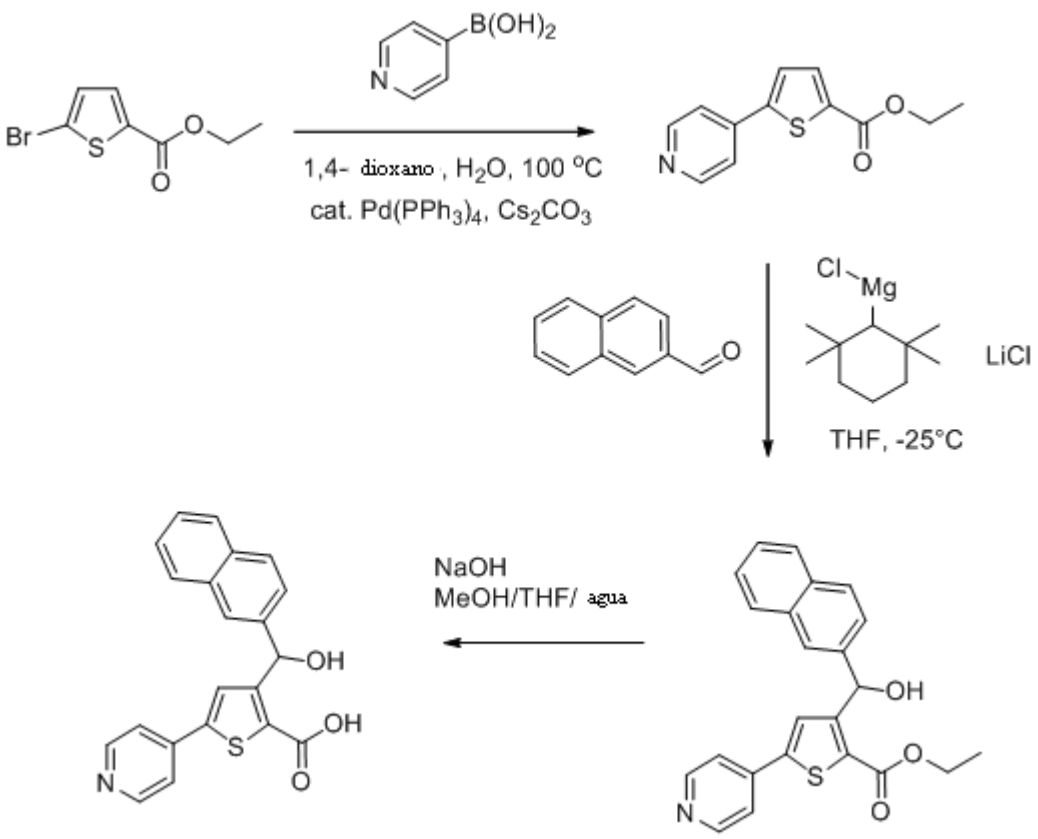
[00772] Etapa 1, Preparación de clorhidrato de 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carboximidamida y 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carbonitrilo

[00773] A una suspensión de cloruro de amonio (2,25 g, 42,1 mmol) en tolueno (21,0 mL) en un baño de hielo se añadió trimetilaluminio 2,0 M en tolueno (21,1 mL, 42,2 mmol) gota a gota (se observó desarrollo de gas). La mezcla luego se agitó a temperatura ambiente durante 30 minutos, durante el tiempo en que los sólidos se disolvieron. Se añadió 4-(4-clorobencil)-2-morfolinotiazol-5-carboxilato de etilo (4,11 g, 11,4 mmol) en una porción y la solución resultante se calentó lentamente a 110 °C durante 1 hora, luego se mantuvo a 110 °C durante 2,5 horas. La reacción se dejó enfriar a temperatura ambiente durante la noche. La reacción se vertió en una suspensión de gel de sílice (10 gramos) en cloroformo (100 mL) y se agitó 10 minutos. Se añadió metanol (20 mL) (se produjo burbujeo), y la mezcla se filtró a través de un lecho corto de gel de sílice en un embudo de vidrio sinterizado, eluyendo con 1:1 metanol/cloroformo para extraer el producto. El filtrado se concentró para dar el producto bruto, que se purificó por cromatografía en gel de sílice (MeOH/DCM = 0/100→50/0) para dar 1,6 gramos (45% de rendimiento) del nitrilo, que eluyó primero, y 1,9 g (45% de rendimiento) de la guanidina, que es la sal de HCl. Guanidina: LC/MS (FA) ES+ 329. 331. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 9,73, (bs, 4H), 8,76-8,74 (m, 2H), 7,90-7,88 (m, 2H), 7,39-7,35 (m, 2H), 7,31-7,27 (m, 2H), 4,30 (s, 2H). Nitrilo: LC/MS (FA) ES+ 312, 314. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 8,77-8,75 (m, 2H), 7,78-7,76 (m, 2H), 7,34-7,29 (m, 4H), 4,29 (s, 2H).

[00774] Etapa 2, Preparación de 4-(4-clorobencil)-2-(piridin-4-il)-5-(1H-tetrazol-5-il)tiazol

[00775] A una solución 4-(4-clorobencil)-2-(piridin-4-il)tiazol-5-carbonitrilo (167 mg, 0,536 mmol) en DMF (3,5 mL) se añadió azida sódica(104 mg, 1,61 mmol) y cloruro de amonio (86 mg, 1,61 mmol) y la mezcla resultante se calentó a 100 grados durante la noche. La reacción se enfrió y se tomó en acetato de etilo y agua. La fase acuosa se concentró al vacío, y el residuo se purificó por cromatografía en gel de sílice (MeOH/DCM = 0/100→10/90) para dar 9 mg (5% de rendimiento) del compuesto del título. LC/MS (FA) ES+ 355, 357. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 8,74-8,73 (m, 2H), 7,93-7,92 (m, 2H), 7,38-7,32 (m, 4H), 4,62 (s, 2H).

[00776] Ejemplo 39: Preparación de ácido 3-[hidroxi(2-naftil)metil]-5-piridin-4-iltiofeno-2-carboxílico (Compuesto 205)



[00777] **Etapa 1:** 5-piridin-4-iltiofeno-2-carboxilato de etilo

[00778] Una mezcla de 5-bromotiofeno-2-carboxilato de etilo (1,560 g, 6,65 mmol), ácido piridin-4-borónico (0,98 g, 7,98 mmol), tetrakis(trifenilfosfina)paladio(0) (768 mg, 0,665 mmol) y carbonato de cesio (6,50 g, 19,9 mmol) en 1,4-dioxano (20 mL) y agua (3,35 mL) se agitó y se calentó a 100° C bajo atmósfera de nitrógeno durante la noche. La reacción fue anaranjada claro transparente con una pequeña cantidad de una segunda fase líquida en la parte inferior del balón. Se tomó una alícuota, se inactivó en agua, y se extrajo con acetato de etilo. Una TLC en gel de sílice (1:1 DCM:hexano) indicó que todo el material inicial ha

sido consumido. Se observa un nuevo producto mayor con Rf ~0,4. La reacción se enfrió a temperatura ambiente luego se inactivó en agua agitada y se extrajo con acetato de etilo. Los extractos de acetato de etilo se lavaron con salina, se secaron con sulfato de sodio, filtraron y se evaporaron para dejar el producto bruto como un sólido blancuzco. El producto bruto se disolvió en DCM mínimo luego se purificó por cromatografía en columna en gel de sílice (gradiente 100% de DCM a 50% de acetato de etilo) para proporcionar el producto 1,02 g (66% de rendimiento) como sólido blanco. LC/MS (FA) ES+ 234. ^{1}H RMN (400 MHz, DMSO) δ 8,68 – 8,60 (m, 2H), 7,91 – 7,83 (m, 2H), 7,78 – 7,71 (m, 2H), 4,37 – 4,27 (d, *J* = 7,1 Hz, 2H), 1,35 – 1,27 (t, *J* = 7,1 Hz, 3H).

[00779] **Etapa 2:** 3-[hidroxi(2-naftil)metil]-5-piridin-4-iltiofeno-2-carboxilato de etilo

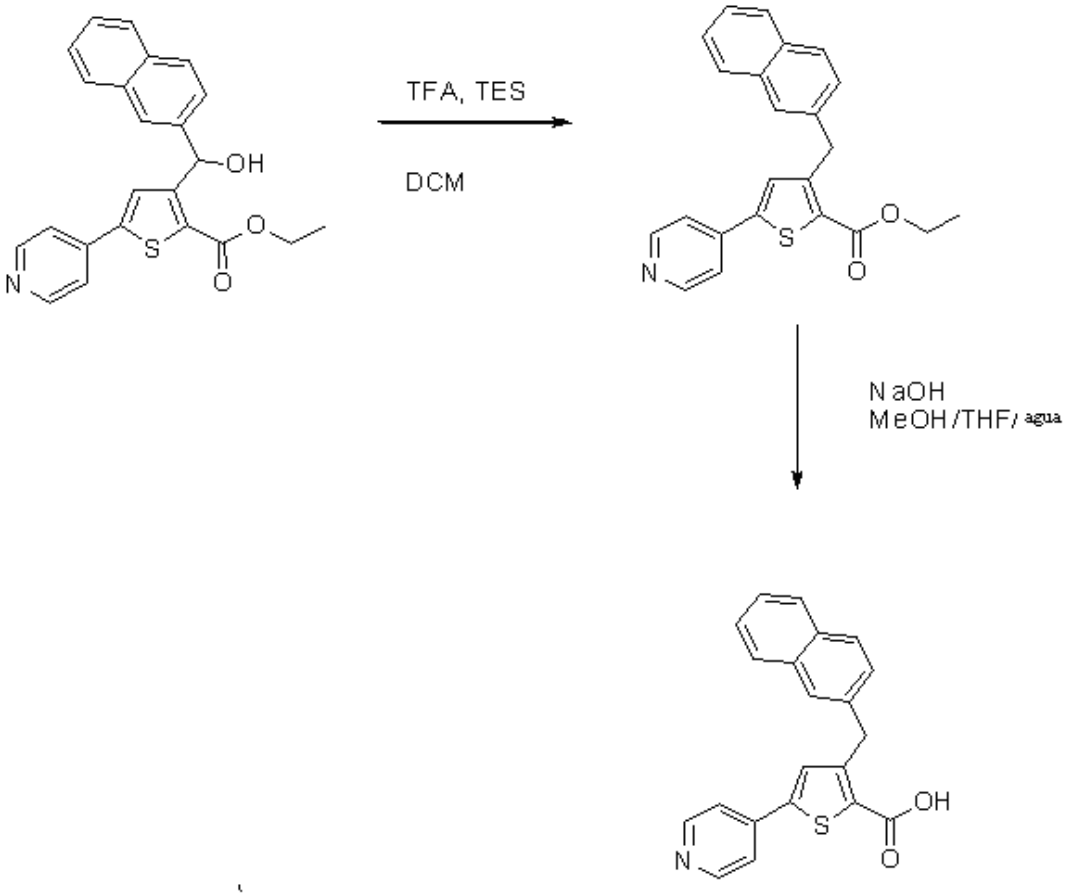
[00780] Un matraz lavado con nitrógeno, seco, equipado con barra agitadora y tabique separador se cargó con 2,2,6,6-cloruro de tetrametilpiperidinilmagnesio•cloruro de litio en tetrahidrofurano (1,0M, 1,21 mL, 1,21 mmol). El balón se enfrió a -25° C y una solución de 5-piridin-4-iltiofeno-2-carboxilato de etilo (0,257 g, 1,10 mmol) en tetrahidrofurano (1,0 mL, 12 mmol) se añadió gota a gota con agitación. La solución anaranjada rojizo oscuro resultante se agitó a -25° C durante 30 minutos. Luego se añadió gota a gota 2-Naftaslencarboxaldehído (0,172 g, 1,10 mmol) (como una solución en 1,5 ml de THF) - la mezcla de reacción se volvió púrpura. La reacción se

agitó a −25° durante 5 minutos, luego el baño refrigerante se eliminó y la reacción se dejó calentar a temperatura ambiente con agitación. Una alícuota se extrajo la reacción y se inactivó en solución saturada de NH4Cl, luego se extrajo con acetato de etilo. Ua LCMS de este extracto indicó que todo el material de partida se ha consumido y que el pico mayor tenía masa correcta para el producto deseado. La reacción se inactivó por la adición gota a gota de una solución saturada de cloruro de amonio (5 ml). La mezcla amarillo-anaranjada resultante e transfirió a un embudo de separación y se diluyó adicionalmente con agua y acetato de etilo. La fase orgánica se separó y la fase acuosa se extrajo adicionalmente con acetato de etilo. Los extractos se combinaron, se lavaron con salina, se secaron y se evaporó para dejar el producto bruto como un aceite anaranjado que se disolvió en diclorometano mínimo luego se purificó por cromatografía en columna en gel de sílice (gradiente 100% de DCM a 5% de MeOH en acetato de etilo) para proporcionar el producto de 210 mg (49% de rendimiento) como una espuma blanca. LC/MS (FA) ES+ 390. ^{1}H RMN (400 MHz, DMSO) δ 8,63 – 8,58 (dd, *J* = 4,6, 1,6 Hz, 2H), 8,04 – 8,00 (s, 1H), 8,00 – 7,96 (s, 1H), 7,87 – 7,81 (d, *J* = 8,7 Hz, 3H), 7,76 – 7,71 (dd, *J* = 4,6, 1,7 Hz, 2H), 7,62 – 7,58 (d, *J* = 1,6 Hz, 1H), 7,50 – 7,45 (t, *J* = 3,0 Hz, 2H), 6,74 – 6,69 (d, *J* = 4,2 Hz, 1H), 6,33 – 6,28 (d, *J* = 4,2 Hz, 1H), 4,37 – 4,31 (dd, *J* = 7,1, 4,3 Hz, 2H), 1,35 – 1,27 (t, *J* = 7,1 Hz, 3H).

[00781] **Etapa 3:** Ácido 3-[Hidroxi(2-naftil)metil]-5-piridin-4-iltiofeno-2-carboxílico (Compuesto 205)

[00782] 3-[hidroxi(2-naftil)metil]-5-piridin-4-iltiofeno-2-carboxilato de etilo (70,0 mg, 0,180 mmol) se colocó en un balón equipado con barra agitadora. Se añadieron tetrahidrofurano (2,00 mL), metanol (1,00 mL), y agua (1,50 mL) con agitación – todos los sólidos se disolvieron. Se añadió hidróxido de sodio (1,0 M, 1,50 mL, 1,50 mmol) en una sola porción y la solución resultante se agitó bajo atmósfera de nitrógeno durante la noche, lo que produce una solución amarilla claro transparente. La reacción se inactivó en agua y el pH de la mezcla se ajustó al pH a ~6-6,5 con solución de bicarbonato de sodio. La mezcla se extrajo con acetato de etilo, los extractos se combinaron y luego se evaporó por rotovapor para dejar el producto bruto como un sólido amarillo claro. El producto bruto se purificó por HPLC para producir 9 mg (14% de rendimiento) de producto como polvo amarillo pálido. LC/MS (FA) ES+ 362. ^{1}H RMN (400 MHz, DMSO) δ 8,60 – 8,51 (d, *J* = 6,1 Hz, 2H), 7,98 – 7,94 (s, 2H), 7,91 – 7,75 (m, 4H), 7,68 – 7,58 (m, 3H), 7,53 – 7,37 (m, 2H), 6,64 – 6,36 (s, 1H).

[00783] Ejemplo 40: Preparación de ácido 3-(2-naftilmetil)-5-piridin-4-iltiofeno-2-carboxílico (Compuesto 210)



[00784] **Etapa 1:** 5-piridin-4-iltiofeno-2-carboxilato de etilo

[00785] Se combinaron 3-[hidroxi(2-naftil)metil]-5-piridin-4-iltiofeno-2-carboxilato de etilo (118,0 mg, 0,3030 mmol), cloruro de metileno (2,4 mL), ácido trifluoroacético (140,0 uL, 1,818 mmol), y trietilsilano (84,7 uL, 0,530 mmol) en un balón equipado con barra agitadora. La reacción se agitó durante la noche a temperatura ambiente bajo atmósfera de nitrógeno. Una alícuota se tomó de la reacción, inactivó e agua, se alcalinizó con carbonato de sodio, y se extrajo con acetato de etilo. El análisis de TLC (2:1 acetato de etilo:DCM) indicó que el éster inicial fue ~50%

convertido en un producto Rf ligeramente superior. Se añadieron ácido trifluoroacético adicional (300 uL, 4 mmol) y trietilsilano (200 uL, 1 mmol) y la reacción se agitó a temperatura ambiente bajo atmósfera de nitrógeno durante otras 4 horas. El análisis de LCMS mostró un pico mayor con correcta ES+ para el producto con una pequeña cantidad de SM restante. La reacción se inactivó en agua, se alcalinizó, y extrajo en acetato de etilo. El extracto se lavó con salina, se secó con sulfato de sodio, se filtró y se evaporó para dejar el producto bruto como un aceite. El producto bruto se disolvió en DCM mínimo luego se purificó por cromatografía en columna en gel de sílice (gradiente 100% DCM a 50% de acetato de etilo) para proporcionar el producto 86 mg (76% de rendimiento) como un sólido blanco. LC/MS (FA) ES+ 374. ^{1}H RMN (400 MHz, DMSO) δ 8,64 – 8,55 (m, 2H), 7,90 – 7,80 (m, 4H), 7,80 – 7,75 (s, 1H), 7,73 – 7,66 (m, 2H), 7,52 – 7,40 (m, 3H), 4,57 – 4,49 (s, 2H), 4,39 – 4,27 (q, J = 7,1 Hz, 2H), 1,35 – 1,25 (t, J = 7,1 Hz, 3H).

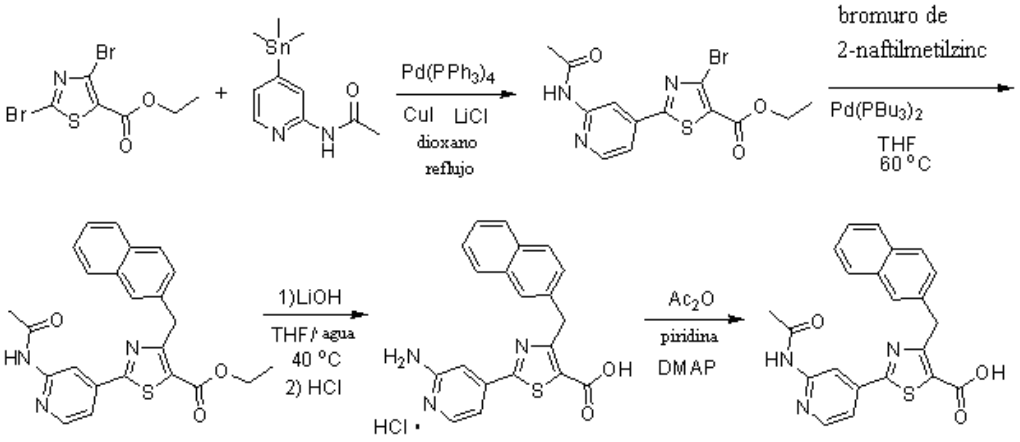
[00786] Etapa 2: ácido 3-(2-naftilmetil)-5-piridin-4-iltiofeno-2-carboxílico (Compuesto 210)

[00787] Se colocó 3-(2-naftilmetil)-5-piridin-4-iltiofeno-2-carboxilato de etilo (80,0 mg, 0,214 mmol) en un balón equipado con barra agitadora. Se añadieron metanol (3 mL, 70 mmol) y tetrahidrofurano (3 mL, 40 mmol) seguido por agua (2 mL, 100 mmol). La solución resultante se agitó y hidróxido de sodio en agua (1,0 M, 0,643 mL, 0,643 mmol) se añadió. El balón se selló y se agitó durante la noche a rt. La LCMS de una alícuota indicó que todo el material inicial se ha

consumido para dar un solo producto con la masa correcta para el producto deseado. A la reacción en agitación se añadió ~30 mL de agua y unos pocos mL de solución salina. La mezcla se agitó y acidificó a pH ~ 1 con HCl 1 N – se formó un precipitado gelatinoso. La mezcla se agitó rápidamente y se añadió éter dietílico (10 mL) – el precipitado se volvió más granular y se suspendió la mayor parte en la fase orgánica. La mezcla de inactivación se agitó a temperatura ambiente durante ~30 minutos luego el sólido se recolectó en un embudo sinterizado, se lavó bien con agua luego éter dietílico, luego se secó al vacío para dar el producto 60 mg (81% de rendimiento) como un polvo blanco. LC/MS (FA) ES+ 346. ^{1}H RMN (400 MHz, DMSO) δ 13,62 – 13,20 (s, 1H), 8,63 – 8,52 (dd, *J* = 4,7, 1,5 Hz, 2H), 7,91 – 7,80 (m, 3H), 7,80 – 7,72 (d, *J* = 3,0 Hz, 2H), 7,70 – 7,63 (dd, *J* = 4,6, 1,5 Hz, 2H), 7,53 – 7,40 (m, 3H), 4,57 – 4,48 (s, 2H).

[00788] Ejemplo 41: Síntesis de ácido 2-(2-acetamidopiridin-4-il)-4-(naftalen-2-ilmetil)tiazol-5-carboxílico (Compuesto 177)

[00789]



[00790] Etapa 1, Preparación de 2-(2-acetamidopiridin-4-il)-4-bromotiazol-5-carboxilato de etilo

[00791] Una mezcla de 2,4-dibromotiazol-5-carboxilato de etilo (0,500 g, 1,59 mmol), N-(4-(trimetilstannil)piridin-2-il)acetamida (0,569 g, 1,90 mmol), tetrakis(trifenilfosfina)paladio(0) (91,7 mg, 0,0794 mmol), yoduro de cobre (I) (90,7 mg, 0,476 mmol), y cloruro de litio (202 mg, 4,76 mmol) en dioxano (29,1 mL) se desgasificó con nitrógeno y se calentó a reflujo durante 1 hr. La reacción se enfrió y concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/hexano = 0/100→50/50) para dar 312 mg del compuesto del título. (44 % de rendimiento). LC/MS (FA) ES+ 370, 372. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 8,71 (s, 1H), 8,39 (d, 1H, J = 5,2 Hz), 8,25 (bs, 1H), 7,68 (dd, 1H, J = 5,2, 1,6 Hz), 4,41 (q, 2H, J = 7,2 Hz), 2,26 (s, 3H), 1,41 (t, 3H, J = 7,2 Hz).

[00792] Etapa 2, Preparación de 2-(2-acetamidopiridin-4-il)-4-(naftalen-2-ilmetil)tiazol-5-carboxilato de etilo

[00793] A una mezcla de 2-(2-acetamidopiridin-4-il)-4-bromotiazol-5-carboxilato de etilo (190 mg, 0,510 mmol) y bis(tri-t-butilfosfina)paladio(0) (65,6 mg, 0,128 mmol) bajo nitrógeno se añadió una solución 0,500 M de bromuro de 2-naftilmetilzinc en THF (3,60 mL, 1,80 mmol). La reacción se agitó a temperatura ambiente durante 5 minutos, luego at 60 grados durante 1 hora. Otra porción de bis(tri-t-butilfosfina)paladio(0) (60,0 mg, 0,117 mmol) se añadió, seguida por otra porción de solución 0,500 M de bromuro de 2-naftilmetilzinc en THF (3,00 mL, 1,50 mmol), y la reacción se calentó a 60 grados durante unos 45 minutos adicionales. La reacción se enfrió a temperatura ambiente y se inactivó con cloruro de amonio saturado (10 mL). La mezcla se extrajo con acetato de etilo (2 x 20 mL) y las fases orgánicas combinadas se secaron en MgSO4, se filtraron y concentraron al vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/hexano = 0/100→100/0) para dar 100 mg del compuesto del título. (40 % de rendimiento). LC/MS (FA) ES+ 432.

[00794] Etapa 3, Preparación de ácido 2-(2-aminopiridin-4-il)-4-(nafthalen-2-ilmetil)tiazol-5-carboxílico, sal HCl

[00795] A una mezcla de 2-(2-acetamidopiridin-4-il)-4-(nafthalen-2-ilmetil)tiazol-5-

carboxilato de etilo (100 mg, 0,232 mmol) en THF (2,00 mL) se añadió LiOH 1,0 M acuoso (2,32 mL, 2,32 mmol) y la mezcla resultante se calentó a 40 grados durante 3 días. La mezcla se acidificó con HCl 1N y el precipitado resultante se filtró y se secó para dar los 85 mg de la sal HCl bruta (100% de rendimiento) que se usó como tal en la próxima etapa. LC/MS (FA) ES+ 362.\

Etapa 4, Preparación de ácido 2-(2-acetamidopiridin-4-il)-4-(nafthalen-2-ilmetil)tiazol-5-carboxílico

Una solución de ácido (2-aminopiridin-4-il)-4-(nafthalen-2-ilmetil)tiazol-5-carboxílico, sal HCl (85,0 mg, 0,214 mmol) en anhídrido acético (1,15 mL, 12,2 mmol) y piridina (0,300 mL, 3,71 mmol) se añadió DMAP (0,30 mg, 0,0024 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La reacción se concentró al vacío y el residuo se purificó por cromatografía en gel de sílice (MeOH/DCM = 0/100→40/60) para dar 20 mg del compuesto del título (23 % de rendimiento). LC/MS (FA) ES+ 404. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 13,84 (bs, 1H), 10,7 1 (s, 1H), 8,63 (s, 1H), 8,41 (d, 1H, J = 5,2 Hz), 7,86-7,82 (m, 3H), 7,76 (s, 1H), 7,57 (dd, 1H, J = 5,2, 1,2 Hz), 7,49-7,42 (m, 3H), 4,70 (s, 2H), 2,10 (s, 3H).

[00796] Se utilizaron los siguientes métodos analíticos para los ejemplos de abajo:

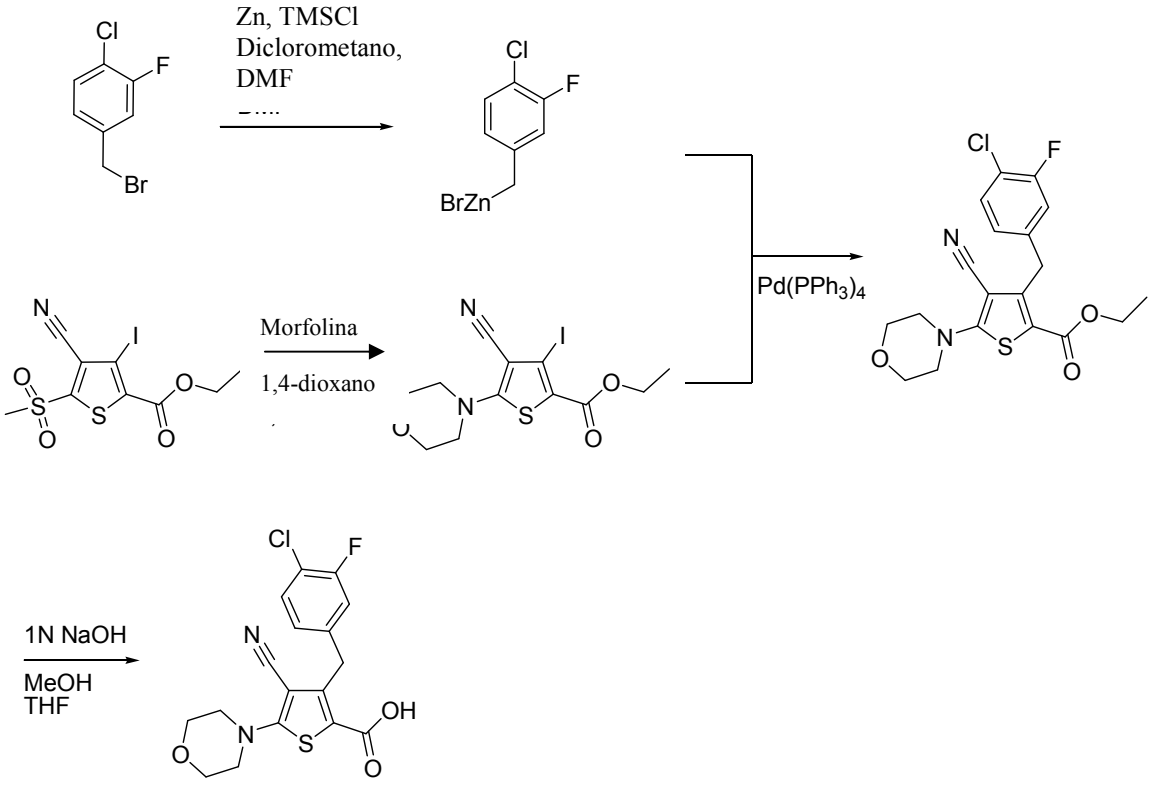
[00797] Se corrieron los espectros LCMS sobre una columna Phenominex Luna de 5□m C18 50 × 4.6 mm sobre una Hewlett-Packard HP1100 utilizando los siguientes gradientes:

- Método del ácido fórmico (FA): Acetonitrilo que contiene 0 a 100 por ciento de ácido fórmico al 0,1% en agua (2,5 ml/min. durante una corrida de 3 minutos).
- Método de acetato de amonio (AA): Acetonitrilo que contiene 0 a 100 por ciento de acetato de amonio 10 mM en agua (2,5 ml/min. durante una corrida de 3 minutos).

[00798] Los isómeros quirales se separaron utilizando HPLC quiral sobre una columna Chiralpak IC 250x25 mm 5 micrones utilizando hexano/etanol/dietilamina o hexano/alcohol isopropílico/ dietilamina como fase móvil. Las configuraciones absolutas de los isómeros separados eran desconocidas, las estructuras se asignaron en forma arbitraria.

[00799] Los espectros de RMN se muestran mediante RMN de protones, con tetrametilsilano como el estándar interno y utilizando un espectrómetro de 300 MHz Broker Avance equipado con una sonda QNP de 5 mm y un espectómetro de 400 MHz Broker Avance II equipado con una sonda QNP de 5 mm para la medición; los valores δ se expresan en ppm.

[00800] **Ejemplo 42: Síntesis del ácido 3-(4-cloro-3-fluorobencil)-4-ciano-5-morfolin-4-iltiofeno-2-carboxílico (Compuesto 94).**



[00801] **Paso 1:** 4-ciano-3-yodo-5-morfolin-4-iltiofeno-2-carboxilato de etilo.

[00802] A un RBF de 500 ml que contiene 4-ciano-3-yodo-5-(metilsulfonil)tiofeno-2-carboxilato de etilo (17,20 g, 44,65 mmoles, preparado como en WO 2009154741) se agregó 1,4 dioxano anhidro (172,0 ml, 2204 mmoles). A la suspensión resultante se agrego morfolina (8,177 ml, 93,77 mmoles). Un condensador de reflujo se unió y la suspensión heterogénea de color rosa/naranja se calentó hasta la temperatura de baño de 90°C y se dejó agitar. Enseguida de iniciar el calentamiento, la mezcla de reacción se tornó una solución homogénea color rojo cereza. La reacción se agito durante 16 horas a 90°C. A continuación la reacción se enfrió hasta temperatura ambiente y se diluyó con agua (100 ml). La mezcla se filtro y el sólido se seco al vacío a 40°C durante 5 días para dar 4-ciano-3-yodo-5-morfolin-4-iltiofeno-2-

carboxilato de etilo (14,3 gramos, 82% de rendimiento). LCMS: (FA) ES+ 393; ^{1}H RMN (400 MHz, DMSO) δ 4,24 (q, *J* = 7,1, 2H), 3,78 – 3,70 (m, 4H), 3,63 – 3,57 (m, 4H), 1,26 (t, *J* = 7,1, 3H).

[00803] **Paso 2:** 3-(4-cloro-3-fluorobencil)-4-ciano-5-morfolin-4-iltiofeno-2-carboxilato de etilo.

[00804] En un recipiente de centelleo secado a la llama, a una suspensión de zinc (0,0998 g, 1,53 mmoles) en N,N-dimetilformamida (1,36 ml, 17,6 mmoles) se agregaron 1,2-dibromoetano (0,003279 ml, 0,03805 mmoles) y clorotrimetilsilano (0,004830 ml, 0,03805 mmoles). Se agitó a temperatura ambiente durante 15 minutos, en cuyo momento se agregó una solución de 3-fluoro-4-clorobencilbromuro (0,341 g, 1,53 mmoles) en N,N-dimetilformamida (1,36 ml, 17,6 mmoles). La suspensión resultante se agitó a temperatura ambiente durante 16 horas. Un recipiente de centelleo que contiene 4-ciano-3-yodo-5-morfolin-4-iltiofeno-2-carboxilato de etilo (199 mg, 0,507 mmoles y bis(tri-t-butilfosfina)paladio(0) (12,96 mg, 0,02537 mmoles) se purgó mediante vacío/retrollenado con argón. A esto se agregó la solución de organozinc de arriba, y la solución resultante se agitó a 45°C durante 6 horas, en cuyo momento la LC/MS mostró conversión completa a un único nuevo pico con masa que representa el producto deseado. La mezcla de reacción se transfirió a un embudo separador que contiene $NaHCO_3$ saturado (ac., 10 ml) y agua (10 ml), y luego se diluyó con EtOAc (40 ml). Las capas se separaron, y la capa acuosa se extrajo 2 x 30 ml con EtOAc. Las capas orgánicas combinadas se lavaron 1 x salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron al vacío para dar 3-(4-cloro-3-fluorobencil)-4-ciano-5-morfolin-4-iltiofeno-2-carboxilato de etilo bruto en forma de un aceite

de color marrón que se utilizó sin purificación posterior. LCMS: (FA) ES+ 409, 411

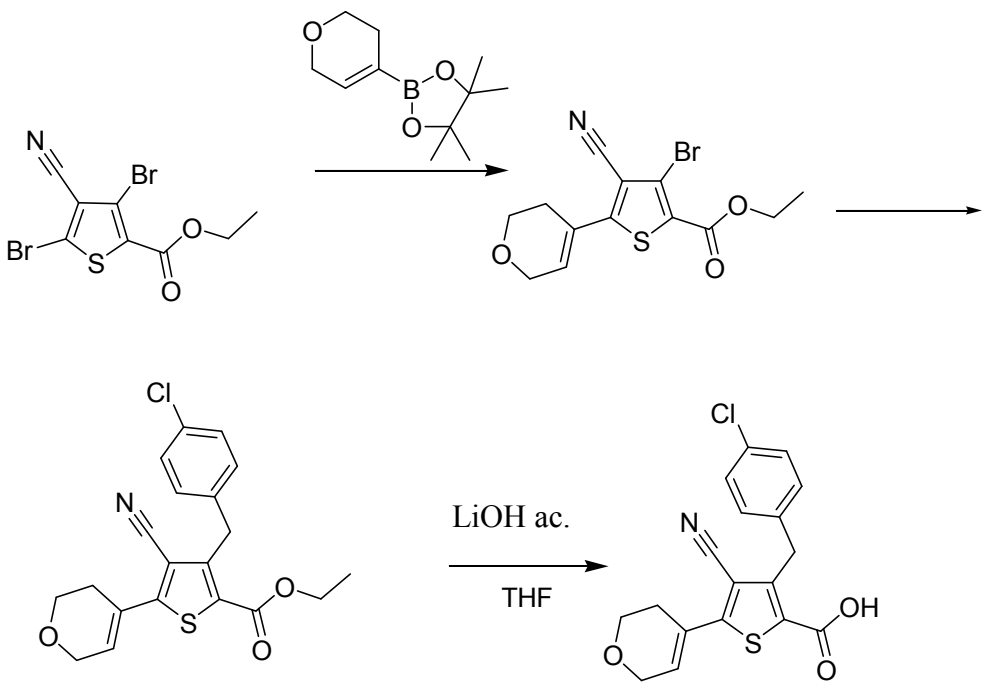
[00805] **Paso 3:** Ácido 3-(4-cloro-3-fluorobencil)-4-ciano-5-morfolin-4-iltiofeno-2-carboxílico (Compuesto 94).

[00806] A una solución de 3-(4-cloro-3-fluorobencil)-4-ciano-5-morfolin-4-iltiofeno-2-carboxilato de etilo en tetrahidrofurano (5,64 ml, 69,6 mmoles) se agregó metanol (2,5 ml, 62 mmoles) e hidróxido de sodio 1 M en agua (4,23 ml, 4,23 mmoles) y la suspensión resultante se agitó a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 16 horas. Los volátiles se eliminaron a continuación al vacío, y el residuo se diluyó con EtOAc (30 ml). Posteriormente la mezcla se transfirió aun embudo separador que contiene HCl 1N (5,0 ml) y agua (10 ml), en cuyo momento el pH de la capa acuosa se midió a ~2,0. Las capas se separaron, y la capa acuosa se extrajo 3 x 20 ml con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. El residuo resultante se adsorbió hasta celite, y el sólido resultante se coloco en un cartucho de carga seca y se purifico mediante cromatografía de columna (elución de gradiente, 0-5% MeOH:CH_2Cl_2) para dar el ácido 3-(4-cloro-3-fluorobencil)-4-ciano-5-morfolin-4-iltiofeno-2-carboxílico (94) en forma de un sólido de color blanco (0,128 g, rendimiento 66,3%). LCMS: (FA) ES+ 381, 383; ^{1}H RMN (400 MHz, DMSO) δ 13,25 (s, 1H), 7,52 (dd, *J* = 8,1, 8,1, 1H), 7,22 (dd, *J* = 1,9, 10,5, 1H), 7,05 (dd, *J* = 1,5, 8,3, 1H), 4,31 (s, 2H), 3,80 – 3,65 (dd, *J* = 4,5, 5,2, 4H), 3,59 – 3,47 (dd, *J* = 4,5, 5,2, 4H).

[00807] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 42.

96	LC/MS: (FA) ES- 395, 397
97	LC/MS: (AA) ES+ 347
102	LC/MS: (FA) ES- 411
105	LC/MS: (AA) ES+ 359
106	LC/MS: (FA) ES- 405, 407
107	LC/MS: (FA) ES- 381
108	LC/MS: (FA) ES+ 393, 395
112	LC/MS: (FA) ES+ 379
115	LC/MS: (FA) ES+ 354
116	LC/MS: (FA) ES+ 363
117	LC/MS: (FA) ES- 391, 393
122	LC/MS: (FA) ES- 391, 393
123	LC/MS: (FA) ES+ 381
124	LC/MS: (FA) ES- 395, 397
125	LC/MS: (FA) ES+ 393, 395
126	LC/MS: (FA) ES- 397, 399
127	LC/MS: (FA) ES- 409, 411
300	LC/MS: (FA) ES- 397

[00808] **Ejemplo 43: Síntesis del ácido 3-(4-clorobencil)-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxílico (Compuesto 95).**



[00809] **Paso 1:** 3-bromo-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxilato de etilo.

[00810] Aun recipiente de microondas que contiene una suspensión de 3,5-dibromo-4-cianotiofen-2-carboxilato de etilo (300,0 mg, 0,8849 mmoles, preparado como en MPI10-008P1M) y pinacol éster del ácido 3,6-dihidro-2h-piran-4-borónico (204 mg, 0,973 mmoles) en 1,4 dioxano (8,98 ml, 115 mmoles) y agua (0,925 ml, 51,3 mmoles) se agregaron tetrakis(trifenilfosfina)paladio(0) (102 mg, 0,0885 mmoles) y carbonato de cesio (865 mg, 2,65 mmoles). El recipiente se cerró, se desgasificó mediante burbujeo de argón durante10 minutos, y a continuación se calentó a 100°C con agitación durante 24 horas. La reacción se enfrió a continuación hasta temperatura ambiente y se divido entre EtOAc y agua. Las capas se separaron, y la capa acuosa se extrajo 2 x con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se

filtraron y se concentraron al vacío. El residuo se sometió a cromatografía de columna en forma de una solución en DCM (columna de 40 g, elución de gradiente 0 hasta 25% de EtOAc/hexanos) para dar 3-bromo-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxilato de etilo en forma de un sólido de color blanco (183 mg, rendimiento 63%). LCMS: (FA) ES+ 342, 344; ^{1}H RMN (400 MHz, DMSO) δ 6,86 – 6,79 (m, 1H), 4,36 – 4,27 (m, 4H), 3,82 (dd, *J* = 5,4, 5,4, 2H), 2,53 (ddd, *J* = 2,1, 4,9, 10,0, 2H), 1,30 (dd, *J* = 7,1, 7,1, 3H).

[00811] **Paso 2:** 3-(4-clorobencil)-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxilato de etilo.

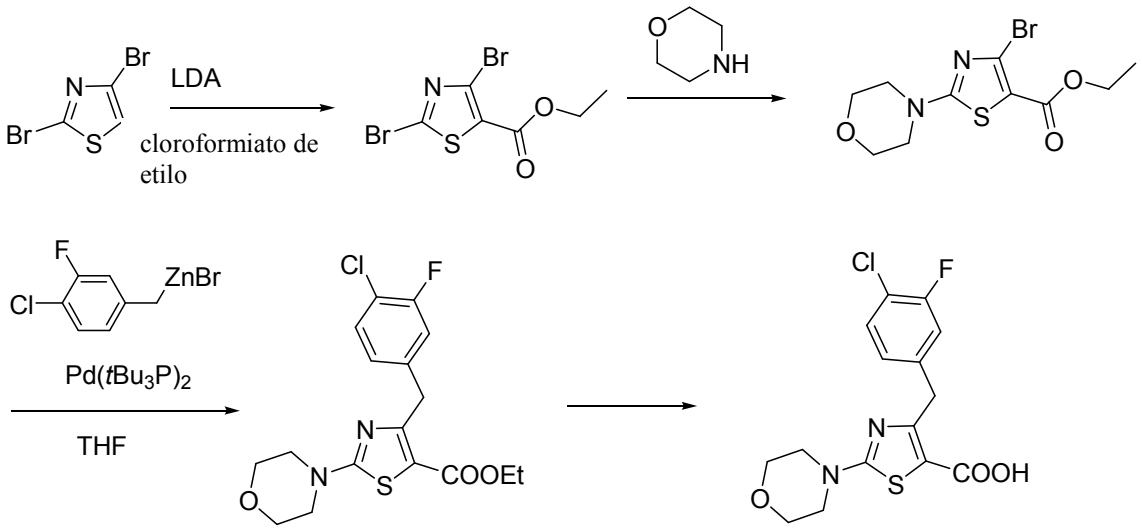
[00812] En un recipiente de reacción que puede cerrarse, 3-bromo-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxilato de etilo (180,0 mg, 0,5260 mmoles) y una vaina agitadora se azeotropearon con tolueno 3x y se secaron a alto vacío durante toda la noche. Al recipiente se agregó bis(tri-t-butilfosfina)paladio(0) (26,88 mg, 0,05260 mmoles). El recipiente se evacuo y a continuación se retrollenó con argón 2X, en cuyo momento se agrego mediante jeringa 4-clorobencilzinc cloruro como una solución 0,50M en tetrahidrofurano (3,682 ml, 1,841 mmoles). La reacción se calentó con agitación a 60°C durante 2 horas. La reacción se enfrió hasta temperatura ambiente y a continuación se diluyó con EtOAc y NH_4Cl acuoso saturado. La mezcla se transfirió aun embudo separador, las capas se separaron, y la capa acuosa se extrajo 2x con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron a través de un taco de celite, y se concentraron al vacío para dar un aceite de color amarillo. El residuo se disolvió en DCM y se cargo sobre una columna ISCO de 40 g (elución de gradiente: 0-25% de EtOAc/hexanos) para dar 3-(4-

clorobencil)-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxilato de etilo (92 mg, 43,6%) en forma de un sólido de color amarillo. LC/MS: (AA) ES- 386, 388; ^{1}H RMN (400 MHz, DMSO) δ 7,38 – 7,33 (m, 2H), 7,22 (m, 2H), 6,80 – 6,76 (m, 1H), 4,40 (s, 2H), 4,34 – 4,24 (m, 4H), 3,80 (dd, *J* = 5,4, 5,4, 2H), 2,52 (dd, *J* = 2,2, 5,0, 2H), 1,26 (dd, *J* = 7,1, 7,1, 3H).

[00813] **Paso 3:** 3-(4-clorobencil)-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxílico (Compuesto 95).

[00814] A un matraz de base redonda que contiene 3-(4-clorobencil)-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxilato de etilo (43,0 mg, 0,111 mmoles) se agregaron tetrahidrofurano (1,23 ml, 15,2 mmoles), hidróxido de sodio (1,0N en agua, 0,925 ml, 0,925 mmoles), y metanol (0,617 ml, 15,2 mmoles). La mezcla se agitó a temperatura ambiente durante toda la noche. La reacción se templó mediante la adición de HCl 1N en agua (2 ml), a continuación se diluyó con EtOAc y se transfirió al embudo separador. Las capas se separaron, y la capa acuosa se extrajo 2 x con EtOAc. Los orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, y se filtraron, adsorbido hasta celite (10 ml). La cromatografía de columna (40 g de columna ISCO, elución de gradiente 0-8% de MeOH/DCM dio ácido 3-(4-clorobencil)-4-ciano-5-(3,6-dihidro-2H-piran-4-il)tiofen-2-carboxílico (95) (25 mg, 63%) en forma de un sólido de color blanco. LC/MS: (FA) ES- 358, 360; ^{1}H RMN (400 MHz, DMSO) δ 14,04 (br s, 1H), 7,33 (d, *J* = 8,5, 2H), 7,26 (d, *J* = 8,5, 2H), 6,64 (s, 1H), 4,43 (s, 2H), 4,24 (d, *J* = 2,9, 2H), 3,79 (dd, *J* = 5,4, 5,4, 2H), 3,32 (br s, 2H).

[00815] **Ejemplo 44: Síntesis del ácido 4-(4-cloro-3-fluorobencil)-2-morfolin-4-il-1,3-tiazol-5-carboxílico (Compuesto 118).**



[00816] **Paso 1:** 2,4-dibromo-1,3-tiazol-5-carboxilato de etilo.

[00817] En un RBF de 2 cuellos de 50 ml equipado con septo, una solución de N,N-diisopropilamina (0,04374 g, 0,4322 mmoles) en tetrahidrofurano (1,33 ml, 16,4 mmoles) en atmósfera de argón se enfrió a -78°C, en cuyo punto se agregó n-butillitio (2,50 M en hexano, 0,1647 ml, 0,4116 mmoles) gota a gota y la solución resultante se agitó durante30 minutos a -78°C. A la solución anterior se agregó gota a gota una solución de 2,4-dibromotiazol (0,100 g, 0,412 mmoles) en tetrahidrofurano (1,33 ml, 16,4 mmoles) a -78°C y esta solución se agitó durante 30 min. A -78°C. A continuación, se agregó cloroformiato de etilo (0,07872 ml, 0,8233 mmoles) gota a gota a -78°C y la mezcla se agitó durante 30 minutos. La reacción se templó por la adición de agua (20 ml), las capas se separaron, y la capa acuosa se extrajo con acetato de etilo (3 x 20 ml). Las capas orgánicas

combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (columna Analogix de 12g, elución de gradiente 5% a 10% de EtOAc en hexano) para dar 2,4-dibromo-1,3-tiazol-5-carboxilato de etilo (60 mg, rendimiento 46%). LC/MS: (FA) ES+ 314, 316, 318; ^{1}H RMN (400 MHz, CDCl3) δ 4,37 (q, *J* = 7,1, 2H), 1,44 – 1,33 (m, 3H).

[00818] **Paso 2:** 4-bromo-2-morfolin-4-il-1,3-tiazol-5-carboxilato de etilo.

[00819] En un recipiente de reacción que puede cerrarse, a una suspensión de 2,4-dibromo-1,3-tiazol-5-carboxilato de etilo (2,90 g, 9,21 mmoles, preparado como en WO 2005026149) y carbonato de cesio (9,00 g, 27,6 mmoles) en tetrahidrofurano (24,3 ml, 299 mmoles) se agregó morfolina (0,883 ml, 10,1 mmoles), en cuyo momento el recipiente se cerró y la mezcla se calentó con agitación a 90°C durante 4 horas. La mezcla de reacción se diluyó con EtOAc y el agua y se transfirió a un embudo separador. Las capas se separaron, y la capa orgánica se lavó con agua, se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo se sometió a cromatografía de columna (elución de gradiente, 0 a 50% de EA en hexanos) para dar 4-bromo-2-morfolin-4-il-1,3-tiazol-5-carboxilato de etilo (2,4 g, rendimiento 81%) en forma de un sólido de color blanco. LC/MS: (FA) ES+ 321, 323; ^{1}H RMN (300 MHz, CDCl3) δ 4,30 (dd, *J* = 7,1, 7,1, 2H), 3,82 – 3,75 (m, 4H), 3,58 – 3,50 (m, 4H), 1,34 (dd, *J* = 7,1, 7,1, 3H).

[00820] **Paso 3:** **4**-(4-cloro-3-fluorobencil)-2-morfolin-4-il-1,3-tiazol-5-carboxilato de etilo.

[00821] En un matraz de base redonda secado a la llama de 50 ml, una suspensión de zinc (0,183 g, 0,00280 moles), clorotrimetilsilano (8,9 ul, 0,000070 moles) y 1,2-dibromoetano (6,0 ul, 0,000070 moles) en N,N-dimetilformamida (2,4 ml, 0,031 moles) se agitó durante 15 minutos. A esto se agregó una solución de 3-fluoro-4-clorobencilbromuro (0,626 g, 0,00280 moles) en N,N-dimetilformamida (4,8 ml, 0,062 moles), y la suspensión resultante se agitó durante toda la noche a temperatura ambiente. A un matraz de base redonda secado a la llama de 50 ml que contiene 4-bromo-2-morfolin-4-il-1,3-tiazol-5-carboxilato de etilo (0,300 g, 0,000934 moles) y bis(tri-t-butilfosfina)paladio(0) (36 mg, 0,000070 moles) se agregó la solución de organozinc anterior, y la reacción se calentó con agitación a 60°C durante 60 min. La reacción se templó con cloruro de amonio saturado, y a continuación se transfirió a un embudo separador que contiene agua (10 ml) y EtOAc (40 ml). Las capas se separaron, y la capa acuosa se extrajo 2 x 30 ml con EtOAc. Las capas orgánicas combinadas se lavaron 1 x salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. El residuo resultante se disolvió en DCM, se adsorbió en gel de sílice y se purificó mediante cromatografía de columna (columna Isco 24 g, elución de gradiente, 0-50% de EtOAc/ hexanos) para dar 4-(4-cloro-3-fluorobencil)-2-morfolin-4-il-1,3-tiazol-5-carboxilato de etilo (245 mg, rendimiento 68,2%).

[00822] **Paso 4:** Ácido 4-(4-cloro-3-fluorobencil)-2-morfolin-4-il-1,3-tiazol-5-carboxílico (Compuesto 118).

[00823] En un matraz de base redonda de 50 ml se combinaron 4-(4-cloro-3-fluorobencil)-2-morfolin-4-il-1,3-tiazol-5-carboxilato de etilo (0,245 g, 0,000637 moles),

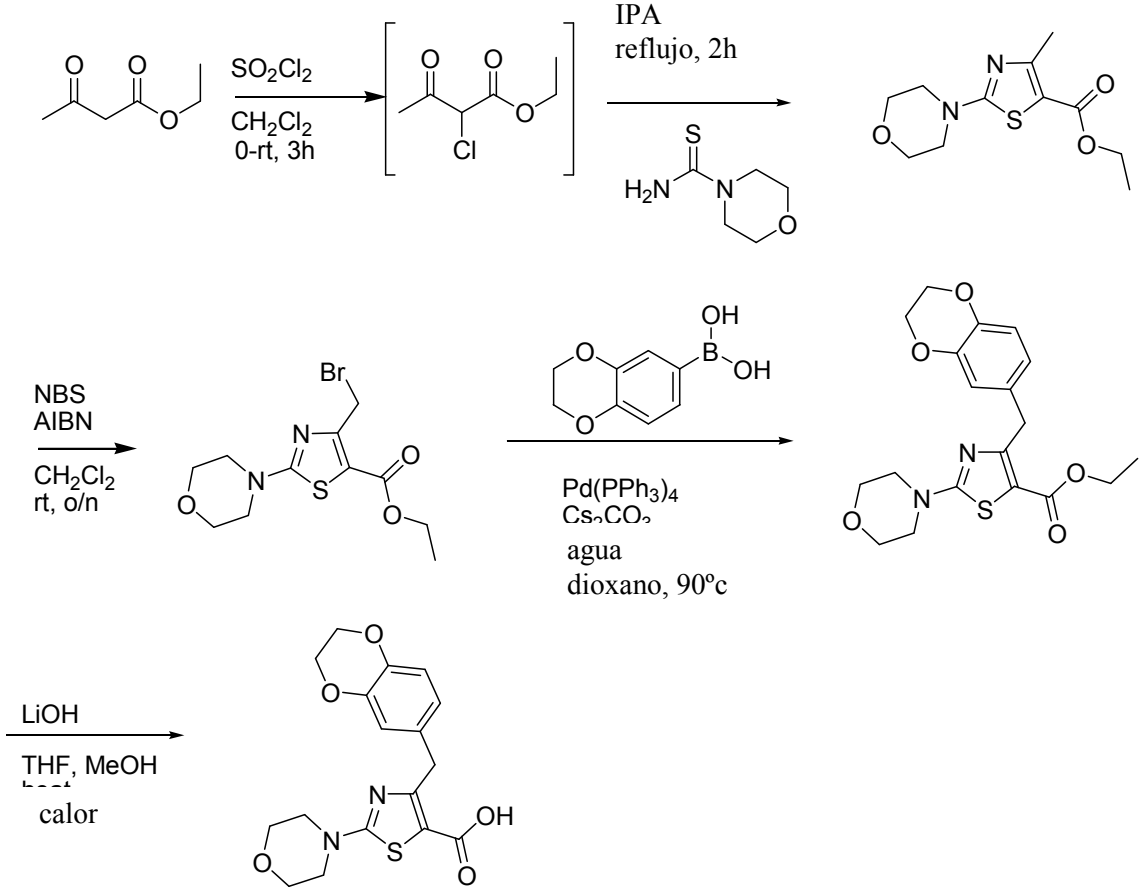
tetrahidrofurano (5,49 ml, 0,0677 moles) y una solución de hidróxido de litio (2,0 M en agua, 3,18 ml, 0,00637 moles). La mezcla se calentó a 80°C con agitación durante 2 días, y a continuación se enfrió hasta temperatura ambiente y se diluyó con agua. La mezcla de reacción se ajustó cuidadosamente hasta pH 5 mediante la adición de HCl 1N y se transfirió a un embudo separador que contiene EtOAc (40 ml). Las capas se separaron, y la capa acuosa se extrajo 2 x 30 ml con EtOAc. Las capas orgánicas combinadas se lavaron 1 x salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío para dar un sólido de color blanco, el cual se disolvió en DCM y se adsorbió sobre gel de sílice. La cromatografió de columna (columna de 4 g, elución de gradiente 0-20% de MeOH en DCM) luego dio el ácido 4-(4-cloro-3-fluorobencil)-2-morfolin-4-il-1,3-tiazol-5-carboxílico (118) (31 mg, 14%). LC/MS: (FA) ES+ 357, 359; ^{1}H RMN (400 MHz, DMSO) δ 12,79 (s, 1H), 7,48 (t, *J* = 8,1, 1H), 7,24 (dd, *J* = 1,9, 10,5, 1H), 7,08 (dd, *J* = 1,5, 8,3, 1H), 4,24 (s, 2H), 3,71 – 3,62 (m, 4H), 3,46 – 3,38 (m, 4H).

[00824] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 44.

91	LC/MS: (FA) ES+ 339
93	LC/MS: (FA) ES+ 330
98	LC/MS: (FA) ES+ 355
101	LC/MS: (FA) ES+ 357, 359
103	LC/MS: (FA) ES+ 335
104	LC/MS: (FA) ES+ 373, 375, 377
109	LC/MS: (FA) ES+ 389
111	LC/MS: (FA) ES+ 373
114	LC/MS: (FA) ES+ 373, 375, 377

119	LC/MS: (FA) ES+ 323
120	LC/MS: (FA) ES+ 369, 371

[00825] **Ejemplo 45: Síntesis del ácido 4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico (Compuesto 110).**



[00826] **Paso 1:** Ácido butanoico, 2-cloro-3-oxo-, etil éster.

[00827] En un matraz de base redonda de 500 ml, a una solución de etil éster del ácido 3-oxobutanoico (7,69 ml, 60,3 mmoles) en cloruro de metileno (150 ml, 2300 mmoles) a 0°C se agregó lentamente cloruro de sulfurilo (6,30 ml, 77,8 mmoles). La mezcla se agitó durante 3 horas, y luego

se templó con $NaHCO_3$ saturado. La mezcla se transfirió aun embudo separador, las capas se separaron. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío para dar el ácido butanoico, 2-cloro-3-oxo-, etil éster que se utilizó inmediatamente sin purificación posterior.

[00828] **Paso 2:** 4-metil-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo.

[00829] En un matraz de base redonda de 100 ml, a una solución de ácido butanoico, 2-cloro-3-oxo-, etil éster (11,2 g, 68,4 mmoles) en alcohol isopropílico (250 ml, 3300 mmoles) se agregó morfolina-4-carbotioicacidamida (10,0 g, 68,4 mmoles). La mezcla se agitó a reflujo durante 1 hora, y a continuación se agitó a temperatura ambiente durante 3 días. Los volátiles se eliminaron al vacío, y el residuo resultante se disolvió en acetato de etilo y se diluyó con bicarbonato de sodio acuoso saturado. La mezcla se transfirió aun embudo separador, las capas se separaron, y la capa orgánica se secó sobre Na2SO4, se filtró y se concentró al vacío. El producto bruto se disolvió en DCM, se adsorbió en gel de sílice y se purificó mediante cromatografía de columna (columna Isco 120 g, elución de gradiente, 0-100% de EtOAc/ hexanos) para dar 4-metil-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (14,51 g, rendimiento para dos pasos, 82%). LC/MS: (FA) ES+ 257, 259; ^{1}H RMN (400 MHz, CDCl3) δ 4,26 (dd, *J* = 7,1, 7,1, 2H), 3,87 – 3,67 (m, 4H), 3,59 – 3,42 (m, 4H), 2,55 (s, 3H), 1,33 (dd, *J* = 7,1, 7,1, 3H).

[00830] **Paso 3:** 4-(bromometil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo.

[00831] A un matraz de base redonda que contiene una solución de 4-metil-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (14,50 g, 56,57 mmoles) en cloruro de metileno (400 ml, 6000 mmoles) se agregaron N-bromosuccinimida (10,07 g, 56,57 mmoles) y 2,2'-azo-bis-isobutironitrilo (464 mg, 2,83 mmoles). La mezcla se agitó a reflujo durante toda la noche. La reacción se templó mediante la adición del 10% de bisulfito de sodio acuoso (20 g en 200 ml de agua) y se agitó durante 20 minutos. La mezcla se transfirió aun embudo separador, las capas se separaron, y la capa acuosa se extrajo 2x DCM. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. El residuo resultante se disolvió en DCM y se adsorbió sobre gel de sílice. La purificación mediante cromatografía de columna (columna Isco de 220 g, elución de gradiente 0-10% de EtOAc en 1:1 DCM:hexanos) dio 4-(bromometil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (13,5 g, rendimiento 71,1%). LC/MS: (FA) ES+ 335, 337; ^{1}H RMN (300 MHz, CDCl3) δ 4,76 (s, 2H), 4,30 (dd, *J* = 7,1, 7,1, 2H), 3,88 – 3,72 (m, 4H), 3,62 – 3,49 (m, 4H), 1,35 (dd, *J* = 7,1, 7,1, 3H).

[00832] **Paso 4:** 4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo.

[00833] El 4-(bromometil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (109,4 mg, 0,326 mmoles), ácido 1,4-benzodioxano-6-borónico (91,0 mg, 0,506 mmoles), tetrakis(trifenilfosfina)paladio (0) (43,0 mg, 0,0372 mmoles), carbonato de cesio (430 mg, 1,3 mmoles), 1,4-dioxano (2,19 ml, 28,0 mmoles) y agua (43,8 ul, 2,43 mmoles) se combinaron en un recipiente equipado con una barra de agitación. El recipiente se cerró y la atmósfera se reemplazó con nitrógeno. El

recipiente se sonicó durante 1 minuto, luego se calentó a 90°C (temperatura del bloque de calentamiento) con agitación durante 1 hora. La reacción se enfrió hasta temperatura ambiente, el recipiente se abrió y el contenido se templó en solución salina para agitación. La mezcla templada se transfirió a un embudo separador y se extrajo dos veces con acetato de etilo. Los extractos se combinaron, se lavaron con solución salina, se secaron sobre sulfato de sodio, se filtraron, y se concentraron al vacío para dar un aceite de color naranja. El residuo bruto se purificó por cromatografía de gel de sílice (elución de gradiente: acetato de etilo/hexano a partir de 0/100 a 100/0) para dar 4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (60 mg, 47% de rendimiento) en forma de un polvo de color blanco. LC/MS (FA) ES+ 391; ^{1}H RMN (300 MHz, DMSO-d6) δ: 6,67-6,74 (m, 3H), 4,20 (q, 2H, J = 7,1 Hz), 4,17 (s, 4H), 4,07 (s, 2H), 3,69-3,65 (m, 4H), 3,46-3,43 (m, 4H), 1,24 (t, 3H, J = 7,1 Hz).

[00834] **Paso 5:** Ácido 4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico (Compuesto 110).

[00835] Se colocó 4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (58,0 mg, 0,000148 moles) en un matraz de base redonda de 50 ml equipado con una barra de agitación. Se agregaron tetrahidrofurano (2,25 ml, 0,0277 moles) y metanol (0,50 ml, 0,012 moles) y la mezcla se agitó para dar una solución transparente. Una solución de hidróxido de litio en agua (2,0M, 0,750 ml, 0,00150 moles) se agregó en una porción única, dando por resultado una solución de color amarillo pálido la cual se agitó a temperatura ambiente en atmósfera de

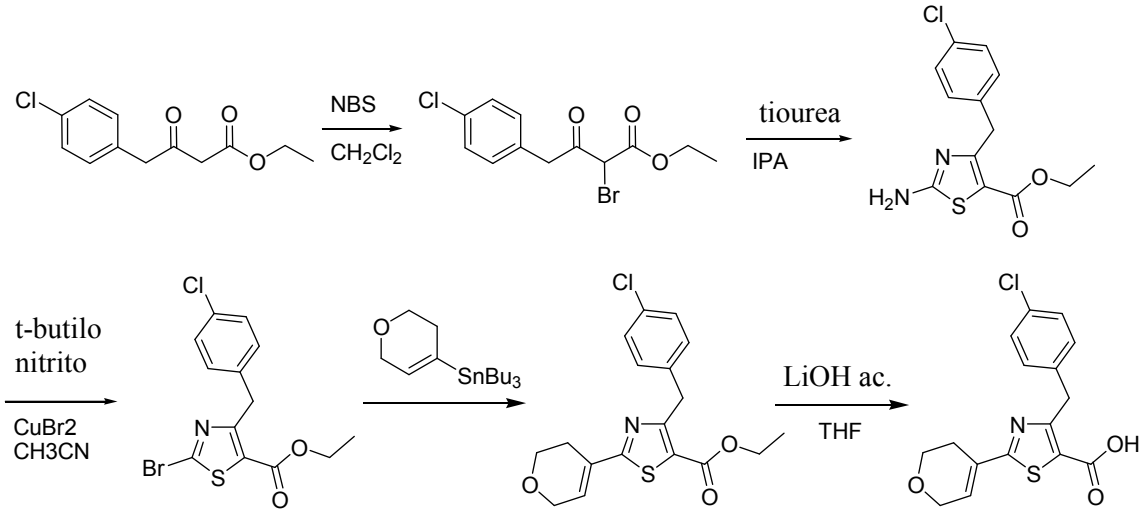
nitrógeno durante 15 minutos. A continuación la reacción se calentó a reflujo durante 2,5 horas, se enfrió hasta temperatura ambiente, y se diluyó con agua (~25 ml) para dar una solución de color gris levemente transparente, la cual se dejó agitar a temperatura ambiente durante toda la noche en una atmósfera de nitrógeno. Se agregó lentamente HCl 1N (~1,8ml) a la solución en agitación para bajar el pH hasta ~3 (papel de pH) donde se formó un precipitado de color blanco. La mezcla se agitó durante ~15 minutos, en cuyo momento el sólido se recolectó sobre un embudo filtrante, se lavó con agua, y se secó sobre el embudo con vacío local en una corriente de nitrógeno durante varias horas para dar el ácido 4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico (110) (45 mg, 84% de rendimiento) en forma de un polvo levemente gris. LC/MS (FA) ES+ 363; ^{1}H RMN (300 MHz, DMSO) δ 12,65 (s, 1H), 6,76 – 6,64 (m, 3H), 4,17 (s, 4H), 4,08 (s, 2H), 3,77 – 3,61 (m, 4H), 3,51 – 3,34 (m, 4H).

[00836] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 45.

99	LC/MS: (FA) ES+ 357, 359
128	LC/MS: (AA) ES+ 373
286	LC/MS: (FA) ES+ 361
288	LC/MS: (AA) ES+ 385
289	LC/MS: (FA) ES+ 376
290	LC/MS: (FA) ES+ 391, 393, 395
292	LC/MS: (AA) ES+ 356
299	LC/MS: (AA) ES+ 373
302	LC/MS: (FA) ES+ 358
303	LC/MS: (FA) ES+ 439, 441
310	LC/MS: (AA) ES+ 373

314	LC/MS: (AA) ES+ 373
318	LC/MS: (FA) ES+ 398
319	LC/MS: (AA) ES+ 373
325	LC/MS: (FA) ES+ 380
328	LC/MS: (FA) ES+ 344
335	LC/MS: (AA) ES+ 385
338	LC/MS: (AA) ES+ 373
339	LC/MS: (FA) ES+ 365
340	LC/MS: (AA) ES+ 373
341	LC/MS: (AA) ES+ 345
344	LC/MS: (AA) ES+ 356

[00837] **Ejemplo 46: Síntesis del ácido 4-(4-clorobencil)-2-(3,6-dihidro-2H-piran-4-il)-1,3-tiazol-5-carboxílico (Compuesto 100).**



[00838] **Paso 1:** 2-bromo-4-(4-clorofenil)-3-oxobutanoato de etilo.

[00839] En un matraz de base redonda de 250 ml, a una solución de 4-(4-clorofenil)-3-oxobutanoato de etilo (4,04 g, 16,8 mmoles) en cloruro de metileno (100 ml, 2000 mmoles) se agregó N-bromosuccinimida (3,13 g, 17,6 mmoles) y la mezcla se agitó

durante 3 horas a temperatura ambiente. La reacción se templó mediante la adición de una solución acuosa al 10% de $NaHSO_3$ (50 ml), y la mezcla bisfásica resultante se agitó vigorosamente durante 15 minutos. La mezcla de reacción se transfirió aun embudo separador, las capas se separaron, y la capa acuosa se extrajo con CH_2Cl_2 (30 mL). Las capas orgánicas combinadas se lavaron con una solución acuosa saturada de $NaHCO_3$ (50 ml), se secaron sobre $MgSO_4$ anhidro, se filtraron, y se concentraron al vacío para dar 2-bromo-4-(4-clorofenil)-3-oxobutanoato de etilo (5,23 g, rendimiento 97,5%) en forma de un aceite de color amarillo que se utilizó sin purificación posterior. LC/MS (FA) ES- 317, 319, 321.

[00840] **Paso 2:** 2-amino-4-(4-clorobencil)-1,3-tiazol-5-carboxilato de etilo.

[00841] En un matraz de base redonda de 100 ml, a una solución de 2-bromo-4-(4-clorofenil)-3-oxobutanoato de etilo (990 mg, 3,1 mmoles) en alcohol isopropílico (20 ml, 300 mmoles) se agregó tiourea (590 mg, 7,8 mmoles) y la mezcla resultante se agitó a reflujo durante 16 horas. La mezcla se dejó enfriar hasta temperatura ambiente y a continuación se concentró bajo presión reducida El residuo se suspendió en EtOAc (50 ml), y luego se lavó con una solución acuosa saturada de $NaHCO_3$ (50 ml), salmuera (50 ml). La capa orgánica se sobre $MgSO_4$ anhidro, se filtró, y se concentró al vacío para dar 2-amino-4-(4-clorobencil)-1,3-tiazol-5-carboxilato de etilo (900 mg, rendimiento >99%), en forma de un sólido amarillento que se utilizó sin purificación posterior. LC/MS (FA) ES+ 297, 299.

[00842] **Paso 3:** 2-bromo-4-(4-clorobencil)-1,3-tiazol-5-carboxilato de etilo.

[00843] En un matraz de base redonda de 250 ml, a una solución de 2-amino-4-(4-clorobencil)-1,3-tiazol-5-carboxilato de etilo (786 mg, 2,65 mmoles) en acetonitrilo (75 ml, 1400 mmoles) se agregó bromuro de cobre (II) (963 mg, 4,31 mmoles). La suspensión se agitó a temperatura ambiente durante 15 minutos para dar una solución de color verde. A la mezcla se agregó nitrito de ter-butilo (0,630 ml, 5,30 mmoles) y la reacción se calentó posteriormente con agitación a 70°C durante 1,5 horas. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y a continuación se concentró bajo presión reducida El residuo se purificó por cromatografía de columna (columna de 80 gramos, elución de gradiente 10% a 50% de EtOAc/hexanos) para dar 2-bromo-4-(4-clorobencil)-1,3-tiazol-5-carboxilato de etilo (820 mg, rendimiento 86%) en forma de un jarabe de color amarillo. LC/MS (FA) ES+ 360, 362, 364; ^{1}H RMN (400 MHz, CDCl3) δ 7,33 – 7,20 (m, 4H), 4,44 (s, 2H), 4,34 (dd, *J* = 7,1, 7,1, 2H), 1,36 (dd, *J* = 7,1, 7,1, 3H).

[00844] **Paso 4:** 4-(4-clorobencil)-2-(3,6-dihidro-2H-piran-4-il)-1,3-tiazol-5-carboxilato de etilo.

[00845] Una mezcla de 2-bromo-4-(4-clorobencil)-1,3-tiazol-5-carboxilato de etilo (289 mg, 0,802 mmoles), tributil(3,6-dihidro-2H-piran-4-il)estannano (332 mg, 0,890 mmoles), tetrakis(trifenilfosfina)paladio (0) (46,4 mg, 0,0401 mmoles), cloruro de litio (1,20E2 mg, 2,82 mmoles) y yoduro de cobre (I) (45,8 mg, 0,241 mmoles) en 1,4-dioxano seco (6,26 ml, 80,2 mmoles) se desgasificó al vacío y se retrollenó con argón cuatro veces, y a continuación se calentó en argón a reflujo durante 3 horas. La mezcla se filtró a través de celite, lavando con 10% de MeOH en DCM. Los volátiles se eliminaron al vacío, y el residuo se adsorbió a

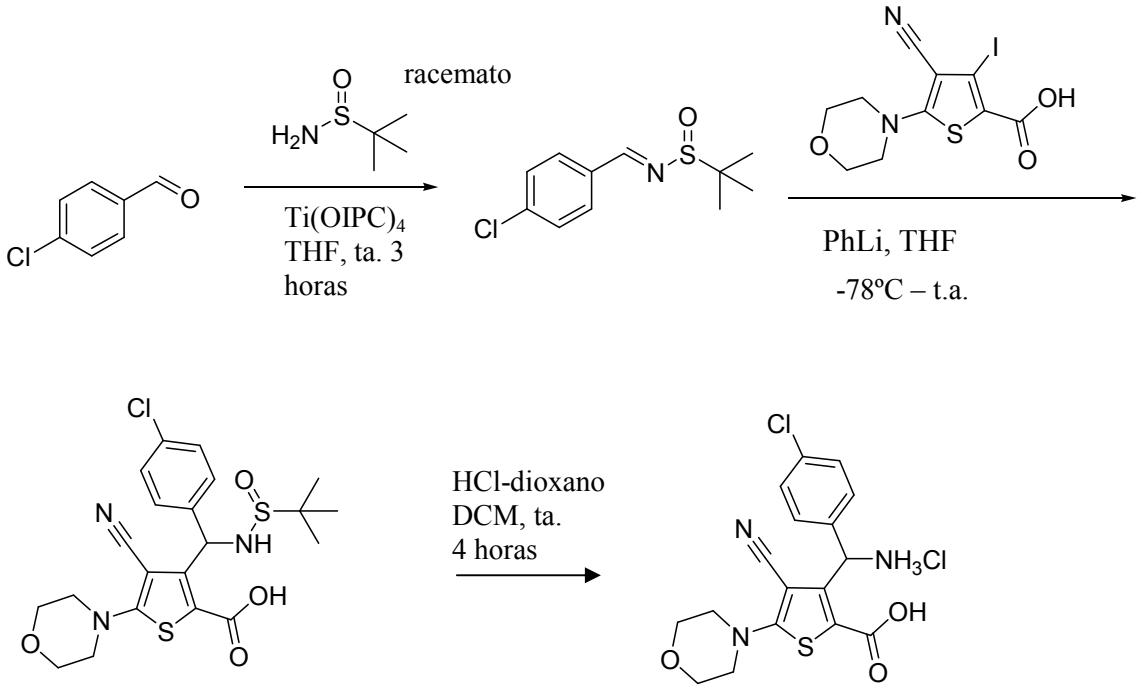
gel de sílice mediante la concentración de una solución de DCM a la cual se había agregado gel de sílice. La cromatografía de columna (elución de gradiente, 0 a 20% de EA en hexanos) dio 4-(4-clorobencil)-2-(3,6-dihidro-2H-piran-4-il)-1,3-tiazol-5-carboxilato de etilo (113 mg, 38,9%) en forma de un sólido de color blanco. ^{1}H RMN (300 MHz, DMSO) δ 7,35 - 7,31 (m, 2H), 7,27 - 7,23 (m, 2H), 6,86 - 6,83 (m, 1H), 4,40 (s, 2H), 4,29 (q, J = 6,9, 2H), 4,25 – 4,22 (m, 2H), 3,78 (t, J = 5,4, 2H), 2,51 – 2,46 (m, 2H), 1,27 (t, J = 6,9 Hz, 3H).

[00846] **Paso 5:** Ácido 4-(4-clorobencil)-2-(3,6-dihidro-2H-piran-4-il)-1,3-tiazol-5-carboxílico (Compuesto 100).

[00847] En un matraz de base redonda equipado con una barra de agitación, una solución de 4-(4-clorobencil)-2-(3,6-dihidro-2H-piran-4-il)-1,3-tiazol-5-carboxilato de etilo (109 mg, 0,300 mmoles) en tetrahidrofurano (3,33 ml, 41,1 mmoles) y metanol (1,67 ml, 41,1 mmoles) se trató con hidróxido de litio (1,0 M en agua, 2,40 ml, 2,40 mmoles). La mezcla se agitó a temperatura ambiente durante toda la noche. El pH se ajustó hasta ~3 mediante la adición de solución de HCl acuoso 1N, y la reacción luego se diluyó con EtOAc y se transfirió al embudo separador. Las capas se separaron, y la capa acuosa se extrajo 2 x con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. La cromatografía de columna (elución de gradiente, 0 a 10 % de de MeOH en DCM) dio el ácido 4-(4-clorobencil)-2-(3,6-dihidro-2H-piran-4-il)-1,3-tiazol-5-carboxílico (100) (53 mg, rendimiento 53%) en forma de un polvo de color blanco. LCMS: (FA) ES+ 336; ^{1}H RMN (400 MHz, DMSO) δ 13,52 (bs, 1H), 7,35 – 7,31 (m, 2H), 7,27-7,23 (m,

2H), 6,82 – 6,79 (m, 1H), 4,40 (s, 2H), 4,24 – 4,22 (m, 2H), 3,77 (t, J = 5,4, 2H), 2,50 – 2,45 (m, 2H).

[00848] Ejemplo 47: Síntesis del clorhidrato del ácido 3-[amino(4-clorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico (Compuesto 113).



[00849] Paso 1: N-[(E)-(4-clorofenil)metileno]-2-metilpropan-2-sulfinamida.

[00850] A una solución de 4-clorobenzaldehído (2,88 g, 20,5 mmoles), (S)-(-)-2-metil-2-propanosulfinamida (1,40 g, 11,6 mmoles), y (R)-(+)-2-metil-2-propanosulfinamida (1,40 g, 11,6 mmoles) en tetrahidrofurano anhidro (30,0 ml) en atmósfera de nitrógeno se agregó tetraisopropóxido de titanio (6,00 ml, 20,3 mmoles) gota a gota. La solución transparente se agitó a temperatura ambiente durante 3 horas. Se agregaron cloruro de metileno (200 ml) y agua (2,0 ml) y la mezcla se agitó a temperatura ambiente durante 1 hora. La suspensión se filtró a

través de celite y se lavó con DCM. El filtrado se concentró al vacío y se purificó por cromatografía de columna (elución de gradiente: 0-20% EtOAc/hexano) para dar N-[(E)-(4-clorofenil)metileno]-2-metilpropan-2-sulfinamida (3,93 g, rendimiento 78,7%). LCMS: (FA) ES+ 244; ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,55 (s, 1H), 7,78-7,80 (d, 2H, J = 8,53 Hz), 7,44-7,47(d, 2H, J = 8,53 Hz), 1,26 (s, 9H).

[00851] **Paso 2:** Ácido 3-{[(ter-butilsulfinil)amino](4-clorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico.

[00852] Se suspendió el ácido 4-ciano-3-yodo-5-morfolin-4-iltiofeno-2-carboxílico (1,44 g, 3,96 mmoles, preparado como en WO2009/154741) en tetrahidrofurano anhidro (80,0 ml, 986 mmoles), se sonicó en atmósfera de nitrógeno durante 10 minutos, y se enfrió en un baño de acetona-hielo seco durante 10 minutos. Se agregó fenillitio (1,8 M en n-butil éter, 8,81 ml, 15,9 mmoles) gota a gota durante 7 minutos. La suspensión se agitó con enfriamiento durante 5 minutos, en cuyo momento el baño de enfriamiento se eliminó y la suspensión se agitó sin enfriamiento durante 7 minutos. La mezcla de reacción se reenfrió en un baño de acetona-hielo seco durante 10 minutos, en cuyo momento una solución de N-[(E)-(4-clorofenil)metileno]-2-metilpropan-2-sulfinamida (2,91 g, 11,9 mmoles) en tetrahidrofurano anhidro (20,0 ml, 246 mmoles) se agregó gota a gota durante 8 minutos, y la mezcla se agitó con enfriamiento durante 30 minutos. La mezcla se templó con metanol (5,0 ml, 120 mmoles) y luego ácido acético (1,0 ml, 18 mmoles), y se dejó entibiar hasta temperatura ambiente. Los volátiles se eliminaron al vacío, y el residuo resultante se diluyó con agua y EtOAc. Las capas se separaron, y la capa acuosa se extrajo con 2 x EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. La purificación mediante

cromatografía de columna (elución de gradiente: AcOH/MeOH/DCM, 0/0/100 a 0.5/4.5/95) dio el ácido 3-{[(ter-butilsulfinil)amino](4-clorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico en forma de una mezcla de diastereómeros. Diastereómero principal: 1,19 g, rendimiento 62,2%. (FA) ES+ 482; ES- 480; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,31-7,33 (m, 2H), 7,15-7,17(m, 2H), 6,14 (br s, 2H), 3,87-3,89 (m, 4H), 3,60-3,63 (m, 4H), 1,21 (s, 9H). Diastereómero menor: (0,292 g, rendimiento 15,3%). (FA) ES+ 482; ES- 480; ^{1}H RMN (400 MHz, CDCl3) δ 7,26-7,34 (m, 4H), 6,29-6,38 (m, br, 2H), 3,84-3,86 (m, 4H), 3,56-3,60 (m, 4H), 1,35 (s, 9H).

[00853] **Paso 3:** Clorhidrato del ácido 3-[amino(4-clorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico (Compuesto 113).

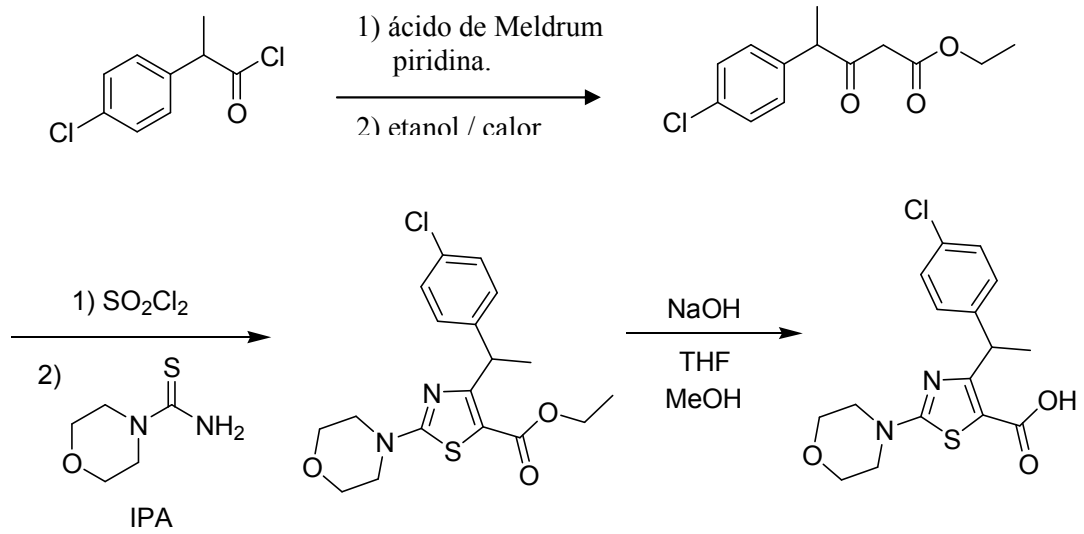
[00854] A una solución del ácido 3-{[(ter-butilsulfinil)amino](4-clorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico (1,46 g, 3,03 mmoles) en cloruro de metileno (25,0 ml) se agregó lentamente ácido clorhídrico (4M en 1,4-dioxano, 15,0 ml), y la suspensión resultante se agitó a temperatura ambiente durante 1 hora. La suspensión se filtró a través de un embudo poroso fino. El sólido recolectado se lavó con DCM y se secó al vacío para dar clorhidrato del ácido 3-[amino(4-clorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico (113) (1,10 g, rendimiento 86,5%) en forma de un polvo de color blanco. LCMS: (FA) ES+ 378; ES- 376; ^{1}H RMN (400 MHz, CD3OD) δ 7,44-7,90 (m, 4H), 5,84 (s, 1H), 3,81-3,84 (m, 4H), 3,64-3,67 (m, 4H).

[00855] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 47.

291	LC/MS: (FA) ES+ 412, 413; ES- 410, 412
317	LC/MS: (FA) ES- 454, 456

323	LCMS: (FA) ES+ 498; ES- 496
342	LC/MS: (FA) ES+ 516, 518; ES- 514, 516
353	LC/MS: (FA) ES+ 420
354	LC/MS: (FA) ES+ 452
357	LC/MS: (FA) ES+ 394; ES- 392

[00856] Ejemplo 48: Síntesis del ácido 4-[1-(4-clorofenil)etil]-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico (Compuesto 121).



[00857] Paso 1: 4-(4-clorofenil)-3-oxopentanoato de etilo.

[00858] En un matraz de base redonda, a una suspensión de 2,2-dimetil-1,3-dioxano-4,6-diona (ácido de Meldrum, 2,91 g, 20,2 mmoles) en cloruro de metileno (11,3 ml, 177 mmoles) a -10°C (temp. interna) se agregó piridina (4,00 ml, 49,5 mmoles) durante 10 minutos. A la solución transparente resultante a -10°C, se agregó gota a gota una solución de 2-(4-clorofenil)propanoíl cloruro (4,10 g, 20,2 mmoles) en cloruro de metileno (7,93 ml, 124 mmoles) durante 1 hora. La mezcla de reacción se agitó durante 1 hora a -10°C, y a continuación durante 1 hora a temperatura ambiente. La mezcla se vertió en ácido clorhídrico (2,00M en agua, 45,3 ml, 90,6 mmoles) y hielo, las capas se separaron, y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con HCl 1N y salmuera, se secaron sobre $MgSO_4$ anhidro,

se filtraron y se concentraron al vacío. Al residuo bruto se agregó etanol (39,6 ml, 679 mmoles) y la mezcla se calentó a reflujo (89 grados de temperatura de baño) durante 3 horas. Después de enfriar hasta temperatura ambiente, los volátiles se eliminaron al vacío. El residuo se adsorbió sobre sílice utilizando DCM y se purificó mediante cromatografía de columna (elución de gradiente: 0 a 20% de EtOAc/hexanos para dar 4-(4-clorofenil)-3-oxopentanoato de etilo (2,94g, 92%) en forma de un aceite de color amarillo. LCMS: (FA) ES+ 255; ^{1}H RMN (400 MHz, DMSO) δ 7,34 - 7,30 (m, 2H), 7,17 – 7,13 (m, 2H), 4,16 – 4,09 (m, 2H), 3,90 (q, J = 7,2, 1H), 3,40 (d, J = 15,6, 1H), 3,30 (d, J = 15,6, 1H), 1,40 (d, J = 6,8, 3H), 1,23 (t, J = 7,2, 3H).

[00859] **Paso 2:** 4-[1-(4-clorofenil)etil]-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo.

[00860] A una solución de 4-(4-clorofenil)-3-oxopentanoato de etilo (1,78 g, 6,99 mmoles) en cloruro de metileno (22,4 ml, 349 mmoles) a 0°C se agregó cloruro de sulfurilo (566 ul, 6,99 mmoles) y la mezcla se agitó durante toda la noche a temperatura ambiente. La reacción se templó con una solución acuosa saturada de $NaHCO_3$ y se transfirió hasta un embudo separador. Las capas se separaron, y la capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ anhidro, se filtró y se concentró al vacío. El residuo resultante se utilizó inmediatamente sin purificación posterior
En un matraz de base redonda, a una solución del residuo bruto del anterior en alcohol isopropílico (50,3 ml, 657 mmoles), se agregó morfolin-4-carbotioicacidamida (1,44 g, 9,86 mmoles). La mezcla de reacción se calentó con agitación a 90°C durante 90 minutos. Los volátiles se eliminaron al vacío y el residuo se redisolvió en DCM y se trató con $NaHCO_3$ acuoso saturado con agitación durante 30 minutos. Las capas se separaron, y la capa acuosa se extrajo con DCM. Las capas orgánicas combinadas se lavaron con salmuera, se

secaron sobre Mg_2SO_4, se filtraron y se concentraron al vacío. La purificación mediante cromatografía de columna (elución de gradiente: 0 a 25% de EtOAc en hexanos) dio 4-[1-(4-clorofenil)etil]-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (1,45 g, 57,9%) en forma de un sólido de color blanco. LCMS: (FA) ES+ 381; ^{1}H RMN (400 MHz, DMSO) δ 7,41 – 7,37 (m, 2H), 7,24 – 7,21 (m, 2H), 5,12 (q, J = 7,2 , 1H), 4,33 – 4,20 (m, 2H), 3,81 – 3,78 (m, 4H), 3,57 – 3,48 (m, 4H), 1,57 (d, J = 6,8, 3H), 1,33 (t, J = 7,2, 3H).

[00861] **Paso 3:** Ácido 4-[1-(4-clorofenil)etil]-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico (Compuesto 121). A una solución de 4-[1-(4-clorofenil)etil]-2-(morfolin-4-il)-1,3-tiazol-5-carboxilato de etilo (1,42 g, 0,00373 moles) en tetrahidrofurano (30,2 ml, 0,373 moles) y metanol (6,04 ml, 0,149 moles) se agregó hidróxido de sodio (1,0N en agua, 29,8 ml, 0,0298 moles), y la mezcla nubosa resultante se calentó a 65°C durante 5 horas. La reacción se enfrió hasta temperatura ambiente, se diluyó con agua, y se ajustó hasta pH 3,0 mediante la adición de HCl acuoso 1N. La mezcla se transfirió aun embudo separador y las capas se separaron. La capa acuosa se extrajo con EtOAc, y las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío para dar el ácido 4-[1-(4-clorofenil)etil]-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico (121) (1,21 g, rendimiento 92%) en forma de un sólido de color blanco. LCMS: (FA) ES+ 353; ^{1}H RMN (400 MHz, DMSO) δ 12,70 (bs, 1H), 7,37 – 7,34 (m, 2H), 7,33 – 7,30 (m, 2H), 5,09 (q, J = 7,2, 1H), 3,69 – 3,76 (m, 4H), 3,48 – 3,39 (m, 4H), 1,49 (d, J = 6,8, 3H).

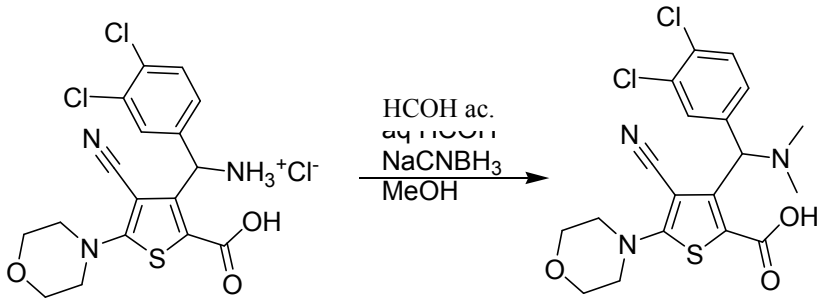
[00862] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 48.

304	LC/MS: (AA) ES+ 381, 383

332	LC/MS: (AA) ES+ 387, 389

[00863]

[00864] Ejemplo 49: Síntesis del ácido 4-ciano-3-[(3,4-diclorofenil)(dimetilamino)metil]-5-(morfolin-4-il)tiofen-2-carboxílico (Compuesto 362).



[00865] Paso 1: Ácido 4-ciano-3-[(3,4-diclorofenil)(dimetilamino)metil]-5-(morfolin-4-il)tiofen-2-carboxílico.

[00866] A una suspensión del ácido 3-[amino(4-diclorofenil)metil]-4-ciano-5-(morfolin-4-il)tiofeno-2-carboxílico •HCl (186,0 mg, 0,4145 mmoles, preparado de acuerdo con el ejemplo 6) en metanol (8,09 ml, 0,101 moles) se agregó 10 M de formaldehído en agua (74,00 ul, 0,9119 mmoles), y cianoborohidruro de sodio (130 mg, 2,07 mmoles). Se agitó a temperatura ambiente en argón durante 16 horas. Se agregó 10 M de formaldehído en solución acuosa (74,00 ul, 0,919 mmoles) y cianoborohidruro de sodio (0,130 g, 2,07 mmoles) y se agitó a temperatura ambiente durante 72 horas. Se templó la reacción con solución de bicarbonato de sodio acuoso saturado, se agregó EtOAc, las capas se separaron, se extrajeron nuevamente con EtOAc, los orgánicos se combinaron, se lavaron con bicarbonato de sodio saturado, salmuera, se secaron sobre Na_2SO_4, se filtraron, se agregó celite al filtrado, y se concentró al vacío. La purificación de carga seca mediante cromatografía de columna de gel de sílice (elución de gradiente: 100% de DCM hasta 8% de MeOH en DCM) dio el ácido 4-ciano-3-[(3,4-

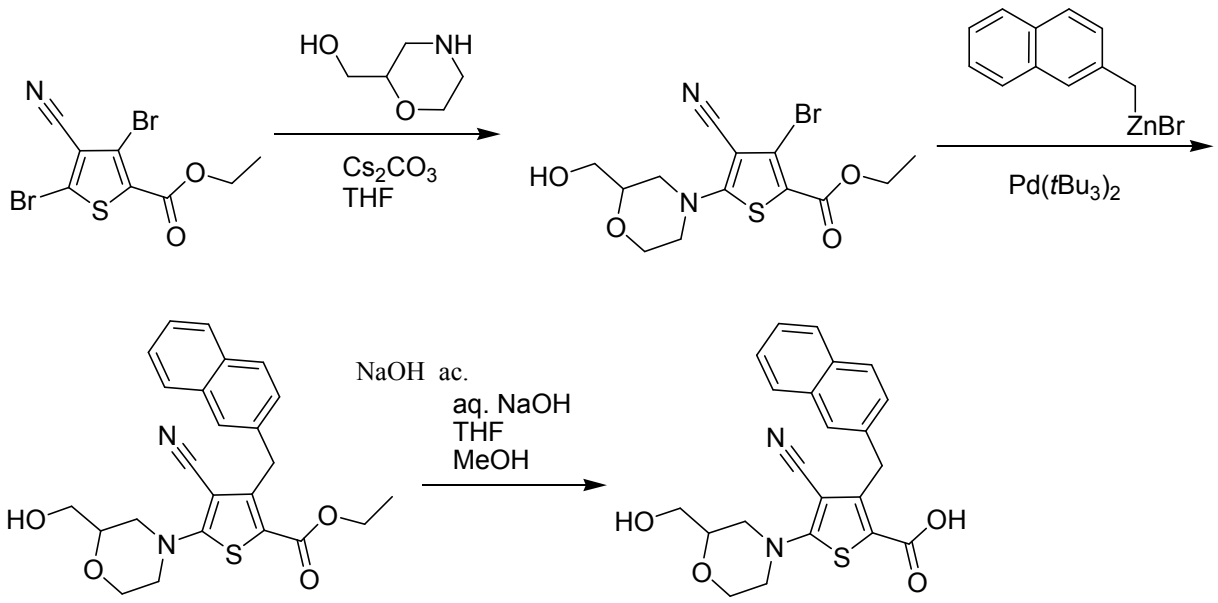
diclorofenil)(dimetilamino)metil]-5-(morfolin-4-il)tiofen- 2-carboxílico racémico (134 mg, 68%) en forma de un sólido blancuzco. LC/MS: (FA) 440, 442, 444; ^{1}H RMN (400 MHz, DMSO) δ 7,80-7,76 (m, 2 H), 7,53 (dd, *J* = 8,4, 2,1 Hz, 1H), 5,26 (s, 1H), 3,74 – 3,64 (m, 4H), 3,53 – 3,38 (m, 4H), 2,76 (s, 3H), 2,42 (s, 3H). Se combinó con otro lote de 134 mg de racemato para HPLC quiral para obtener enantiómeros puros. Se purificó sobre IC 4.6X250 mm con 90/10/0.1 HEX/ETOH/DEA 10 uL. Inyección a 1,0 ml/min. durante 50 min. CD AT 254 nm para obtener enantiómeros separados como las sales de dietilamina. Cada compuesto Pico1 y Pico2 se disolvieron en forma separada en agua, se acidificaron hasta pH de 2 con solución de HCl 1N acuoso, se extrajeron con EtOAc, 3x, se combinaron los orgánicos y se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, se concentraron al vacío, se agregó agua, se liofilizó, durante toda la noche para recuperar el compuesto principal. Pico 1 (103 mg, sólido de color tostado, general 27% de rendimiento) LC/MS: (FA) 440, 442, 444; ^{1}H RMN (400 MHz, DMSO) δ 7,80-7,76 (m, 2 H), 7,53 (dd, *J* = 8,4, 2,1 Hz, 1H), 5,26 (s, 1H), 3,74 – 3,64 (m, 4H), 3,53 – 3,38 (m, 4H), 2,76 (s, 3H), 2,42 (s, 3H). Pico 2 (80 mg, sólido de color beige, general 20% de rendimiento) LC/MS: (FA) 440, 442, 444; ^{1}H RMN (400 MHz, DMSO) δ 7,80-7,76 (m, 2 H), 7,53 (dd, *J* = 8,4, 2,1 Hz, 1H), 5,26 (s, 1H), 3,74 – 3,64 (m, 4H), 3,53 – 3,38 (m, 4H), 2,76 (s, 3H), 2,42 (s, 3H).

[00867] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 49.

336	LC/MS: (FA) ES+ 440, 442, 444
351	LC/MS: (FA) ES+ 406, 408

[00868] **Ejemplo 50:** Síntesis del ácido 4-ciano-5-[2-(hidroximetil)morfolin-4-il]-3-(2-naftilmetil)tiofeno-2-carboxílico (Compuesto

297).



[00869] Paso 1: 3-bromo-4-ciano-5-(2-hidroximetil)morfolin-4-il]tiofen-2-carboxilato de etilo.

[00870] Se combinaron 3,5-dibromo-4-cianotiofen-2-carboxilato de etilo (0,360 g, 1,06 mmoles), carbonato de cesio (1,05 g, 3,21 mmoles), 2-hidroximetilmorfolina (137 mg, 1,17 mmoles), y tetrahidrofurano (4,5 ml, 36 mmoles) en un recipiente de presión de 15 ml equipado con una barra de agitación. El recipiente se cerró, y el rxn se calentó a 90°C con agitación durante 4 horas. La reacción se enfrió hasta temperatura ambiente. El rxn se vertió en agua /solución salina. El recipiente de reacción se lavó con agua adicional, luego acetato de etilo, y estos se agregaron al templado el cual luego se transfirió a un embudo separador. La capa acuosa se extrajo 3X con EtOAc. Los extractos se combinaron, se lavaron con solución salina, se secaron sobre Na_2SO_4, se filtraron, se agregó celite, se concentraron al vacío, y se secaron a alto vacío 30 minutos. Se purificó la carga seca mediante cromatografía de gel de sílice (elución de gradiente: 0-60% EtOAc/hexanos) para dar 163 mg de sólido (41% de rendimiento). ^{1}H RMN (400 MHz, DMSO) δ 4,91 (t, *J* = 5,7 Hz, 1H), 4,25 (q, *J* = 7,1

Hz, 2H), 3,99-3,92 (m, 3 H), 3,69-3,58 (m, 2 H), 3,50 (dt, *J* = 10,5, 5,2 Hz, 1H), 3,41 (dt, *J* = 11,5, 5,8 Hz, 1H), 3,37 – 3,27 (m, 1H, en pico de H2O),3,15 – 3,08 (m, 1H), 1,26 (t, *J* = 7,1 Hz, 3H).

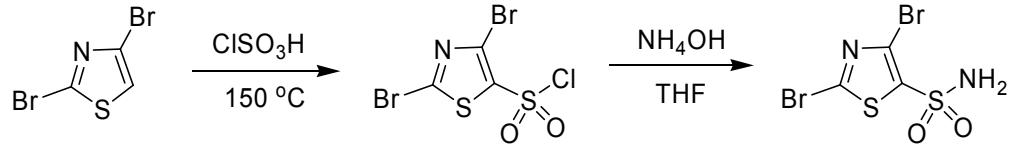
[00871] Paso 2: 4-ciano-5-[2-(hidroximetil)morfolin-4-il]-3-(2-naftilmetil)tiofeno-2-carboxilato de etilo y ácido 4-ciano-5-[2-(hidroximetil)morfolin-4-il]-3-(2-naftilmetil)tiofen-2-carboxílico

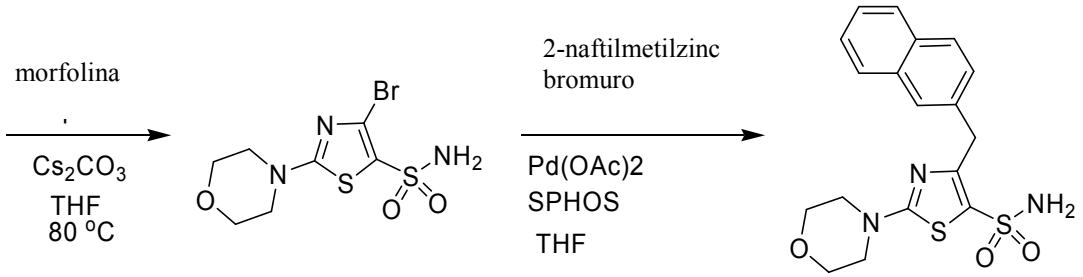
[00872] Se combinaron bis(tri-t-butilfosfina)paladio(0) (16,44 mg, 0,03218 mmoles) y 3-bromo-4-ciano-5-(2-hidroximetil)morfolin-4-il]tiofen-2-carboxilato de etilo (161,0 mg, 0,4290 mmoles) en un matraz de base redonda seco equipado con una barra de agitación y septo. Se evacuó/ rellenó con argón 3X, luego se agregó solución 0,50 M de 2-naftilmetilzinc bromuro en tetrahidrofurano (1,72 ml, 0,858 mmoles) mediante una jeringa para dar una solución de color marrón. La reacción se agitó a temperatura ambiente durante 5 minutos, luego a 60°C durante 1,5 horas. Se agregó bis(tri-t-butilfosfina)paladio(0) (38,4 mg, 0,0751 mmoles) y se agregó solución 0,50 M de 2-naftilmetilzinc bromuro en tetrahidrofurano (1,29 ml, 0,644 mmoles), se desgasificó 2x y se inundó con argón, se calentó a 60°C 1 hora. La reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc, y luego se templó con solución de NH4Cl saturado. Se transfirió la mezcla templada a un embudo separador, se separaron las capas, y se extrajo la capa acuosa una vez más con EtOAc, se combinaron los orgánicos, se lavaron con salmuera, se secaron sobre Na2SO4, se filtraron, y se concentraron al vacío. Se agregó EtOAc y celite, se rotovapeó, se secó a alta vacío 3 minutos. Se purificó la carga seca en columna ISCO de 40 g (elución de gradiente: 0-55% EtOAc/hexanos) para obtener 119 mg de aceite de color amarillo (64% de rendimiento). LC/MS (AA) ES+437.

[00873] A 4-ciano-5-[2-(hidroximetil)morfolin-4-il]-3-(2-naftilmetil)tiofeno-2-carboxilato de etilo (0,116 g, 0,266 mmoles) en un rbf equipado con una barra de agitación se agregó

tetrahidrofurano (2,96 ml, 36,4 mmoles) y 1,000 M de hidróxido de sodio en agua (2,22 ml, 2,22 mmoles) y metanol (1,48 ml, 36,5 mmoles). La mezcla de color amarillo resultante se agitó a temperatura ambiente durante 16 horas. La reacción se templó con la adición de 2,5 ml de HCl 1N en agua hasta pH de 2, y se agregó EtOAc. Se transfirió al embudo separador, se separaron las capas, se extrajo la capa acuosa 2x con EtOAc, se combinaron los orgánicos, se lavaron con salmuera, se secaron sobre Na2SO4, se filtraron, se agregó celite, y se concentró al vacío. Se purificó la carga seca mediante cromatografía de gel de sílice sobre una columna ISCO de 40 g (elución de gradiente 0-20% de MeOH/ DCM) para dar 66 mg de sólido de color blanco (61% de rendimiento). LC/MS (FA) ES+409; ES-407; ^{1}H RMN (400 MHz, DMSO) δ 13,45 (br s, 1H), 7,88-7,77 (m, 3 H), 4,7 Hz, 3H), 7,69 (s, 1H), 7,51 – 7,42 (m, 3H), 4,87 (s, 1H), 4,57 – 4,47 (m, 2H), 3,94-3,77 (m, 3 H), 3,65-3,53 (m, 2 H), 3,60 – 3,52 (m, 1H), 3,47 (dd, *J* = 11,3, 5,0 Hz, 1H), 3,37 (dd, *J* = 11,3, 5,8 Hz, 1H, superpone con pico de H_2O), 3,15 (td, *J* = 12,1, 3,4 Hz, 1H), 2,99 – 2,89 (m, 1H).

[00874] Ejemplo 10: Síntesis de 2-morfolino-4-(naftalen-2-ilmetil)tiazol-5-sulfonamida (Compuesto 329)





[00875] Paso 1. Preparación de 2,4-dibromotiazol-5-sulfonil cloruro

[00876] A un matraz que contiene ácido clorosulfónico (51,0 ml, 767 mmoles) se agregó 2,4-dibromotiazol (10,2 g, 42,0 mmoles) con agitación durante 15 minutos. La solución resultante se calentó hasta 150 grados durante toda la noche. La reacción se templó vertiendo cuidadosa y lentamente sobre hielo (500 ml). El precipitador resultante se extrajo con acetato de etilo (2 x 200 ml) y las capas orgánicas combinadas se lavaron con agua, se secaron y se concentraron al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (acetato de etilo:hexano = 0/100→15/85) para dar 8,1 g (56 % de rendimiento) del compuesto del título en forma de un aceite de color amarillo el cual se solidificó parcialmente. ^{13}C RMN (400 MHz, $CDCl_3$) δ: 145.04, 138.78, 131.81.

[00877] **Paso 2. Preparación de 2,4-dibromotiazol-5-sulfonamida**

[00878] A una mezcla de 2,4-dibromotiazol-5-sulfonil cloruro (3,17 g, 9,28 mmoles) en THF (51,4 ml) se agregó 33% de NH_4OH acuoso (24,1 ml, 278 mmoles) y la reacción se agitó a temperatura ambiente durante 30 minutos. La mezcla se concentró al vacío y el residuo se colocó en acetato de etilo (100 ml) y agua (100 ml). La capa acuosa se extrajo con acetato de etilo (50 ml) y las capas orgánicas combinadas se lavaron con agua (50 ml) y salmuera (50 ml), a continuación se as capas orgánicas combinadas se lavaron con agua. El residuo se purificó por cromatografía de columna de gel de sílice (acetato de etilo/DCM = 0/100→20/80) para dar 1,7 g (57 % de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 321, 323, 325. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 8,33 (s, 2H).

[00879] **Paso 3. Preparación de 4-bromo-2-morfolinotiazol-5-sulfonamida**

[00880] Una mezcla de 2,4-dibromotiazol-5-sulfonamida (0,515 g, 1,60 mmoles), morfolina (0,153 ml, 1,76 mmoles), THF (4,22 ml) y carbonato de cesio (1,56 g, 4,80 mmoles) en un tubo cerrado se

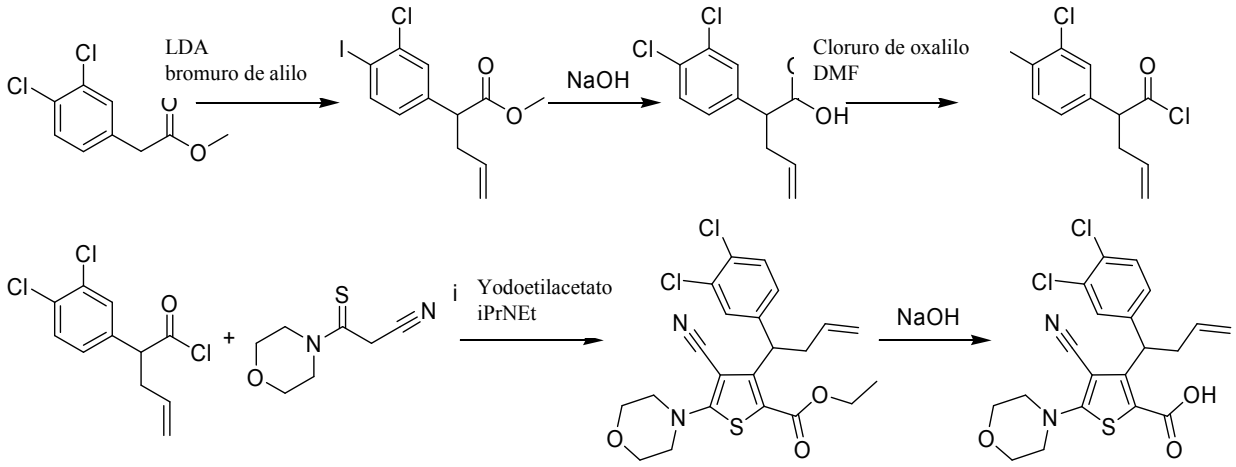
calentó hasta 80 grados durante 4 horas. La reacción enfriada se concentró al vacío y el residuo se colocó en acetato de etilo (50 ml) y agua (25 ml). Las capas se separaron, y la capa orgánica se lavó con agua (15 ml), se secó y se concentró al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (acetato de etilo/DCM = 0/100→50/50) para dar 230 mg (44 % de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 328, 330. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,76 (s, 2H), 3,69-3,66 (m, 4H), 3,43-3,40 (m, 4H).

[00881] Paso 4. Preparación de 2-morfolino-4-(naftalen-2-ilmetil)tiazol-5-sulfonamida

[00882] A un matraz seco se agregó 4-bromo-2-morfolinotiazol-5-sulfonamida (194 mg, 0,591 mmoles), THF (4,79 ml), paladio(II) acetato (1,33 mg, 0,00591 mmoles) y diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (4,85 mg, 0,0118 mmoles). La mezcla se agitó durante 5 minutos, y una solución 0,500 M de 2-naftilmetilzinc bromuro en THF (4,14 ml, 2,04 mmoles) se agregó a continuación gota a gota durante 30 minutos. La reacción se agitó a temperatura ambiente durante 1 hora y se templó con cloruro de amonio saturado (10 ml). La reacción se extrajo con acetato de etilo (2 x 25 ml) y las capas orgánicas combinadas se lavaron con agua, se secaron y se concentraron al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (acetato de etilo/DCM = 0/100→40/60) el cual dio una mezcla del producto deseado con 4-bromo-2-morfolinotiazol-5-sulfonamida residual. Este material se purificó por cromatografía de fase inversa preparativa para dar 51 mg (22% de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 390. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,85-7,77 (m, 4H), 7,71 (bs, 2H), 7,50-7,42 (m, 3H), 4,25 (s, 2H), 3,64-3,61 (m, 4H), 3,35-3,32 (m, 4H).

[00883]

[00884] Ejemplo 51: Síntesis de 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen-2-carboxilato (Compuesto 355).



[00885] Paso 1: A una solución de N,N-diisopropilamina (1,79 ml, 12,8 mmoles) en tetrahidrofurano (10,0 ml, 123 mmoles) se agregó 2,50 M de n-butillitio en hexano (4,68 ml, 11,7 mmoles) gota a gota a 0°C. La solución se agitó en una atmósfera de nitrógeno durante 10 min. y luego se enfrió hasta -78°C. Una solución de 3,4-diclorofenilacetato de metilo (2,27 g, 10,4 mmoles) en tetrahidrofurano (10,0 ml) se agregó a la solución de LDA gota a gota mediante cánula. Después de 10 minutos de agitación, la reacción se entibió hasta 0°C durante 1 hora. La solución se retro enfrió hasta -78°C, y se agregó bromuro de alilo (2,24 ml, 25,9 mmoles) en una porción. En 10 minutos, la reacción se retro entibió hasta 0°C. Después de 1 hora de agitación, la reacción se templó con solución de NH_4Cl saturado y se extrajo con EtOAc (x3). La capa orgánica combinada se secó y se concentró para dar un aceite de color naranja. La purificación posterior sobre columna de gel de sílice (elución de gradiente, 0-10% de EtOAc/hexanos) dio 2-(3,4-diclorofenil)pent-4-enoato de metilo en forma de un aceite incoloro (2,47 g, 92,0% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,43 – 7,37 (m, 2H), 7,18 – 7,12 (dd, *J* = 8,3, 2,1 Hz,

1H), 5,73 – 5,60 (ddt, *J* = 17,1, 10,2, 6,8 Hz, 1H), 5,12 – 4,98 (m, 2H), 3,70 – 3,64 (s, 3H), 3,63 – 3,55 (t, *J* = 7,8 Hz, 1H), 2,85 – 2,71 (m, 1H), 2,55 – 2,43 (m, 1H).

[00886] **Paso 2:** A una solución de 2-(3,4-diclorofenil)pent-4-enoato de metilo (2,47 g, 9,53 mmoles) en tetrahidrofurano (15,0 ml) se agregó una solución de monohidrato de hidróxido de litio (2,00 g, 47,6 mmoles) en agua (15,0 ml). La mezcla se agitó vigorosamente a temperatura ambiente durante 12 horas. La mezcla resultante se acidificó mediante la adición de 12,0 M de ácido clorhídrico en agua (3,97 ml, 47,6 mmoles) a 0°C, y se extrajo con EtOAc (x3). La capa orgánica combinada se secó y se concentró para dar el ácido 2-(3,4-diclorofenil)pent-4-enoico en forma de un jarabe de color amarillo (2,65 g, cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,45 – 7,35 (m, 2H), 7,21 – 7,11 (dd, *J* = 8,3, 2,1 Hz, 1H), 5,76 – 5,59 (ddt, *J* = 17,0, 10,2, 6,8 Hz, 1H), 5,14 – 4,99 (m, 2H), 3,65 – 3,56 (t, *J* = 7,7 Hz, 1H), 2,88 – 2,74 (dt, *J* = 14,8, 7,5 Hz, 1H), 2,58 – 2,43 (dt, *J* = 14,3, 6,9 Hz, 1H).

[00887] **Paso 3:** A una solución del ácido 2-(3,4-diclorofenil)pent-4-enoico (2,34 g, 9,53 mmoles) en cloruro de metileno (25,0 ml) se agregó cloruro de oxalilo (1,61 ml, 19,0 mmoles) seguido de N,N-dimetilformamida (73,8 ul, 0,953 mmoles). Después de 1 hora de agitación a temperatura ambiente, la solución se concentró para dar 2-(3,4-diclorofenil)pent-4-enoil cloruro en forma de un aceite de color amarillo (2,70 g, cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,49 – 7,42 (d, *J* = 8,3 Hz, 1H), 7,40 – 7,36 (d, *J* = 2,2 Hz, 1H), 7,17 – 7,10 (dd, *J* = 8,3, 2,2 Hz, 1H), 5,73 – 5,57 (ddt, *J* = 17,1, 10,2, 6,9 Hz, 1H), 5,15 – 5,06 (m, 2H), 4,06 – 3,97 (t, *J* = 7,6 Hz, 1H), 2,97 – 2,83 (m, 1H), 2,61 – 2,49 (m, 1H).

[00888] **Paso 4:** A una solución de 2-(3,4-diclorofenil)pent-4-enoil cloruro (2,51 g, 9,53 mmoles) y 3-morfolin-4-il-3-tioxopropanonitrilo (1,62 g, 9,53 mmoles) en acetonitrilo (40,0 ml) en un matraz de base redonda de 100 ml se agregó N,N-

diisopropiletilamiina (1,82 ml, 10,5 mmoles), y la solución de color naranja/rojo profundo resultante se agitó a temperatura ambiente durante 1 hora. A la mezcla resultante se agregó N,N-diisopropiletilamina (4,15 ml, 23,8 mmoles) y a continuación yodoacetato de etilo (1,24 ml, 10,5 mmoles). El matraz se ajustó con condensador de reflujó y la reacción se calentó a reflujo durante 48 horas. La mezcla se concentró y se distribuyó entre solución saturada de $NaHCO_3$ (aq) y EtOAc. La capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se lavó con salmuera, se secó y se concentró para dar un jarabe de color oscuro. La purificación sobre columna de gel de sílice (elución de gradiente 3-30% de EtOAc/hexanos dio 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (704 mg, 15,9% de rendimiento). LCMS: (AA) ES+ 465, 467, 469; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,49 – 7,42 (m, 1H), 7,41 – 7,33 (m, 1H), 7,31 – 7,27 (m, 1H), 5,82 – 5,66 (ddt, J = 17,2, 10,1, 6,8 Hz, 1H), 5,62 – 5,50 (t, J = 8,2 Hz, 1H), 5,16 – 5,08 (dd, J = 17,1, 1,6 Hz, 1H), 5,04 – 4,94 (dd, J = 10,2, 1,5 Hz, 1H), 4,35 – 4,27 (q, J = 7,1 Hz, 2H), 3,86 – 3,78 (m, 4H), 3,59 – 3,48 (m, 4H), 3,10 – 2,99 (h, J = 6,9 Hz, 2H), 1,40 – 1,31 (m, 3H).

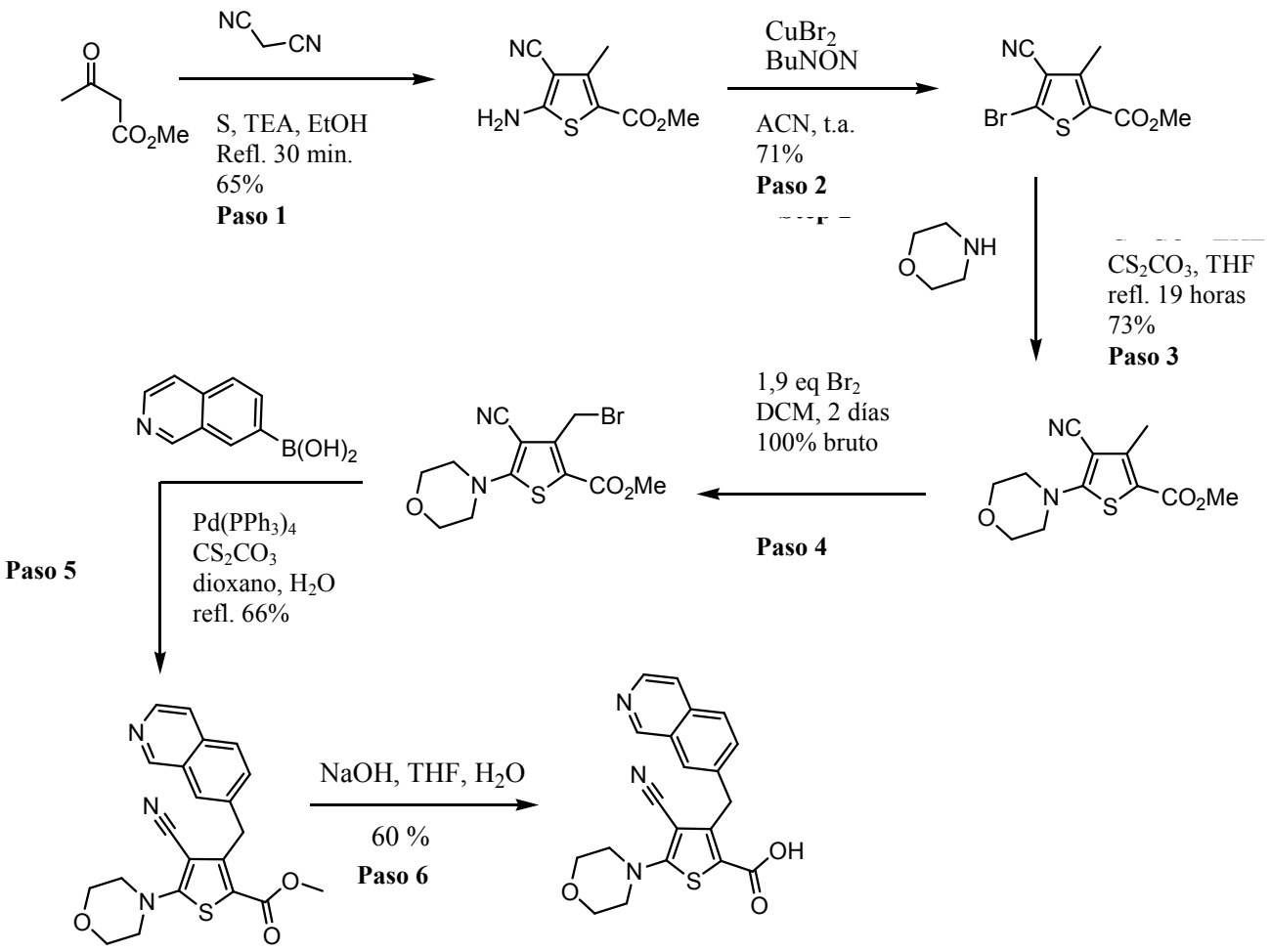
[00889] Paso 5: A una solución de 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen- -2-carboxilato de etilo (0,211 g, 0,453 mmoles) en tetrahidrofurano (8,00 ml) se agregó 1,000 M de hidróxido de sodio en agua (10,0 ml) y metanol (4,00 ml). La mezcla resultante se agitó a temperatura ambiente durante 3 horas Los volátiles se eliminaron a presión reducida, y la mezcla resultante se acidificó con solución de HCl conc. Hasta pH~2, y se extrajo con EtOAc (x3). La capa orgánica combinada se secó y se concentró para dar un jarabe de color púrpura. La purificación de la mezcla bruta sobre HPLC (AA, fase inversa) dio el ácido 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen-2-carboxílico en forma de un

sólido de color blanco (63 mg, 31,8% de rendimiento). LCMS: (AA) ES- 391, 393, 395; ^{1}H RMN (400 MHz, MeOD) δ 7,54 – 7,46 (d, J = 1,6 Hz, 1H), 7,45 – 7,35 (d, J = 8,4 Hz, 1H), 7,34 – 7,24 (dd, J = 8,4, 1,6 Hz, 1H), 5,88 – 5,68 (m, 2H), 5,16 – 5,05 (dd, J = 17,1, 1,7 Hz, 1H), 5,00 – 4,92 (m, 1H), 3,82 – 3,71 (t, J = 4,8 Hz, 4H), 3,51 – 3,40 (t, J = 4,8 Hz, 4H), 3,05 – 2,95 (m, 2H).

[00890] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 51.

307	LC/MS: (FA) ES- 412
308	LC/MS: (FA) ES- 413
321	LC/MS: (AA) ES+ 411, 413
326	LC/MS: (AA) ES+ 411
345	LC/MS: (FA) ES- 395
349	LC/MS: (FA) ES- 437
358	LC/MS: (FA) ES+ 399, 401
364	LC/MS: (FA) ES- 395
369	LC/MS: (AA) ES+ 411

[00891] Ejemplo 52: **Síntesis del ácido 4-ciano-3-(isoquinolin-7-ilmetil)-5-(morfolin-4-il)tiofen-2-carboxílico (Compuesto 309).**



[00892] **Paso 1: Etil éster del ácido 5-amino-4-ciano-3-metil-tiofen-2-carboxílico:**

[00893] A una solución de metil éster del ácido 3-oxobutanoico (8,25 ml, 76,4 mmoles), malonitrilo (5,05 g, 76,4 mmoles) y azufre (2,45 g, 76,4 mmoles) en etanol anhidro (100 ml, 2000 mmoles) se agregó trietilamina (10,7 ml, 76,8 mmoles). La mezcla se calentó a reflujo durante 30 min. La mezcla se enfrió hasta temperatura ambiente. El cristal resultante se recolectó por filtración y se lavó con MeOH, se secó al vacío para dar el producto (9,25 g, rendimiento 61,7%). LC/MS: (FA) ES- 195. ^{1}H RMN (400MHz, *d*-cloroformo) δ 5,13 (s, br, 2H), 3,82 (s, 3H), 2,52 (s, 3H).

[00894] **Paso 2: 5-bromo-4-ciano-3-metiltiofen-2-carboxilato de metilo:**

[00895] A una solución oscura de 5-amino-4-ciano-3-metiltiofen-2-carboxilato de metilo (6,65 g, 33,9 mmoles) y bromuro de cobre (I) (15,1 g, 67,8 mmoles) en acetonitrilo anhidro (260 ml) se agregó lentamente nitrito de butilo (7,26 ml, 61,0 mmoles) durante 8 minutos. La mezcla se agitó a temperatura ambiente durante 70 min. La mezcla se concentró en rotavapor para dar un residuo de color negro. El residuo se disolvió en DCM, se filtró a través de celite. El filtrado se rotavapeó con celite. El residuo recubierto con celite se cargó seco en una columna de gel de sílice y se cromatografió utilizando EtOAc/hexano (0/100 a 10/90) para dar un producto sólido de color blanco (6,29 g, rendimiento 71,4%). ^{1}H RMN (400MHz, *d*-cloroformo) δ 3,89 (s, 3H), 2,67 (s, 3H)

[00896] Paso 3: **4-ciano-3-metil-5-(morfolin-4-il)tiofen-2-carboxilato de metilo:**

[00897] Una mezcla de 5-bromo-4-ciano-3-metiltiofen-2-carboxilato de metilo (6,29 g, 24,2 mmoles), morfolina (2,53 g 29,0 mmoles) y carbonato de cesio (15,8 g, 48,4 mmoles) en tetrahidrofurano anhidro (110 ml) se calentó a reflujo durante 19 horas, y a continuación se enfrió hasta temperatura ambiente. La mezcla se filtró y se lavó con DCM. El filtrado se rotavapeó con celite. El celite recubierto se cargo seco en un cartucho de gel de sílice y se cromatografió utilizando MeOH/DCM (1/99) para dar un producto sólido de color blanco (4,70 g, rendimiento 73 %). LC/MS: (FA) ES$^+$ 267. ^{1}H RMN (400MHz, *d*-cloroformo) δ 3,85 (m, 4H), 3,82 (s, 3H), 3,58 (m, 4H), 2,56 (s, 3H).

[00898] Paso 4: **3-(bromometil)-4-ciano-5-(morfolin-4-il)tiofen-2-carboxilato de metilo:**

[00899] A la solución de 4-ciano-3-metil-5-(morfolin-4-il)tiofen-2-carboxilato de metilo (0,500 g, 1,88 mmoles) en cloruro de metileno anhidro (15 ml, 230 mmoles) se agregó una solución de bromo (0,409 g, 2,56 mmoles) en cloruro de metileno anhidro (5,0 ml, 78 mmoles). La mezcla se agitó a temperatura ambiente durante 4 días. La mezcla se evaporó a presión reducida y se secó al vacío para dar un producto bruto que se utilizó sin purificación posterior (0,658g, contenía 3,4% del material de partida, rendimiento del 96,6%). LC/MS: (FA) ES^+ 345, 347. ^1H RMN (400MHz, *d*-cloroformo) δ 4,83 (s, 2H), 3,87 (s, 3H), 3,85 (m, 4H), 3,62 (m, 4H).

[00900] **Paso 5: 4-ciano-3-(isoquinolin-7-ilmetil)-5-(morfolin-4-il)tiofen-2-carboxilato de metilo**

[00901] Una mezcla de 3-(bromometil)-4-ciano-5-(morfolin-4-il)tiofen-2-carboxilato de metilo (0,128 g, 0,371 mmoles), ácido isoquinolin-7-borónico (101 mg, 0,584 mmoles), tetrakis(trifenilfosfina)paladio(0) (21,4 mg, 0,0185 mmoles) y carbonato de cesio (0,242 g, 0,742 mmoles) se suspendió en 1,4-dioxano (8,0 ml, 100 mmoles) y agua (0,60 ml, 33 mmoles) en atmósfera de N_2 en un recipiente de 20 ml. El recipiente se tapó y se calentó hasta 90°C durante 1 hora. La mezcla se enfrió hasta temperatura ambiente y se concentró al vacío. El residuo se suspendió en DCM y se filtró sobre un taco de celite. El filtrado se cromatografió en una columna de gel de sílice utilizando MeOH/DCM (0/100 hasta 3/97) para dar un producto sólido (103 mg, 66,4 %). LC/MS: (FA) ES^+ 394. ^1H RMN (400MHz, *d*-cloroformo) δ 9,20 (s, 1H), 8,47 (d, J = 5,77 Hz, 1H), 7,87 (s, 1H), 7,73 (d, J = 5,77 Hz, 1H), 7,60 (d, J = 5,77 Hz, 1H), 7,44-7,48 (m, 1H), 4,60 (s, 2H), 3,86 (s, 3H), 3,84 (m, 4H), 3,59 (m, 4H).

[00902] **Paso 6: Ácido 4-ciano-3-(isoquinolin-7-ilmetil)-5-(morfolin-4-il)tiofen-2-carboxílico**

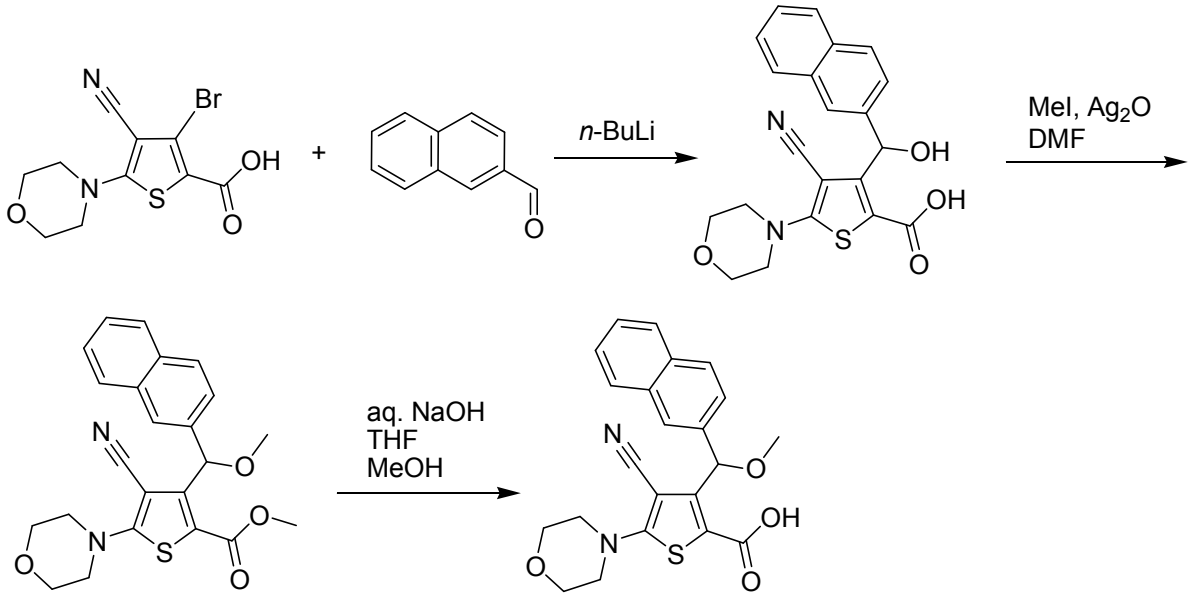
[00903] A la solución de 4-ciano-3-(isoquinolin-7-ilmetil)-5-(morfolin-4-il)tiofen-2-carboxilato de metilo (0,103 g, 0,246 mmoles) en tetrahidrofurano (15,0 ml, 185 mmoles) se agregó 1,00 M de hidróxido de sodio en agua (3,80 ml, 3,80 mmoles), seguido de agua (4,0 ml, 220 mmoles) y metanol (4,0 ml, 99 mmoles). La solución homogénea se agitó a temperatura ambiente durante 18 horas. Se agregó ácido acético (270 mg, 4,5 mmoles) y la mezcla se concentró en rotavapor. El residuo se disolvió en DCM-MeOH y a continuación se concentró con celite. La mezcla se cargo en un cartucho y se cromatografió en una columna de gel de sílice utilizando AcOH/MeOH/DCM (0/0/100 a0.5/4.5/95) para dar un producto sólido de color blanco (56,5 mg, rendimiento 60,3%). LC/MS: (FA) ES^+ 380; ES^- 378. ^{1}H RMN (400MHz, *d*-cloroformo) δ 9,23 (s, 1H), 8,45 (d, J = 5,77 Hz, 1H), 7,90 (d, J = 8,53 Hz, 1H), 7,84 (s, 1H), 7,76 (d, J = 5,77 Hz, 1H), 7,65 (dd, J = 8,53, 1,76 Hz, 1H), 4,53 (s, 2H), 3,72 (m, 4H), 3,52 (m, 4H).

[00904] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 52.

287	LC/MS: (AA) ES- 395
293	LC/MS: (AA) ES- 395
295	LC/MS: (AA) ES- 395
301	LC/MS: (AA) ES+ 409
305	LC/MS: (FA) ES- 381
311	LCMS: (FA) ES+ 385; ES- 383
312	LC/MS: (FA) ES+ 386, 388; ES- 384, 386
315	LC/MS: (FA) ES+ 397
324	LC/MS: (AA) ES- 395
330	LC/MS: (FA) ES+ 382; ES- 380
343	LC/MS: (AA) ES- 395

359	LC/MS: (FA) ES+ 402, 404; ES- 401, 403
361	LC/MS: (AA) ES+ 409

[00905] **Ejemplo 53: Ejemplo de síntesis 3:** Síntesis del ácido 4-ciano-3-[metoxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxílico (Compuesto 368).



[00906] **Paso 1: Ácido 4-ciano-3-[hidroxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxílico**

Una solución del ácido 3-bromo-4-ciano-5-morfolinotiofen-2-carboxílico (5,50 g, 17,3 mmoles) y 2-naftalenocarboxaldehído (8,12 g, 52,0 mmoles) en tetrahidrofurano (550 ml) se enfrió a -78°C durante 10 min., dando por resultado una suspensión de color blanco. Se agregó gota a gota 2,5M de n-butillitio en hexano (27,7 ml, 69,4 mmoles) gota a gota, dando por resultado una solución de color naranja. La solución se agitó a -78°C durante 10 min., luego el baño frío se eliminó y la solución de color naranja se agitó a temperatura ambiente durante 40 minutos. La solución se templó mediante la adición de metanol (21 ml) y ácido acético

(3,9 ml), y la mezcla resultante se dejó entibiar hasta temperatura ambiente O/N. La mezcla se combinó con una corrida previa sobre una escala de 2,86 g del ácido carboxílico, se concentró al vacío, y azeotropeó con tolueno (2x50 ml). El sólido bruto se disolvió en MeOH, se agregó celite, se rotavapeó, se secó sobre O/N a alto vacío. El producto bruto se purificó utilizando carga seca mediante cromatografía de gel de sílice sobre una columna ISCO de 330 g (elución de gradiente 0-20% de (10% de AcOH en MeOH) en DCM) para dar 15,2 g de sólido que contiene 37% en peso de AcOH, para un rendimiento total del 92%. LC/MS (AA) ES-393; ^{1}H RMN (400 MHz, DMSO) δ 10,86 (d, *J* = 9,9 Hz, 1H), 7,86-7,81 (m, 4H), 7,70 (dd, *J* = 8,6, 1,6 Hz, 1H), 7,51 – 7,42 (m, 2H), 5,69 (d, *J* = 9,4 Hz, 1H), 3,73 – 3,68 (m, 4H), 3,39 – 3,33 (m, 4H).

[00907] Paso 2: 4-ciano-3-[metoxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxilato de metilo

[00908] A un matraz de base redonda se agregó óxido de plata (I) (56,15 g, 0,2423 moles), ácido 4-ciano-3-[hidroxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxílico (15,17 g, 0,02423 moles), y N,N-dimetilformamida (66,2 ml), seguido de yoduro de metilo (53,7 ml, 0,863 moles). Se agregaron otros 10 ml de DMF, se sonicó hasta suspender/mezclar todo el sólido. La mezcla de reacción se agitó a temperatura ambiente durante 26 horas, luego se diluyó con EtOAc, se filtró a través de un taco de celite, se concentró el filtrado al vacío, se azeotropeó con tolueno (10x 10 ml), DCM (20 ml), se secó sobre bomba de alto vacío. El material bruto se utilizó directamente en el próximo paso. LC/MS (AA) ES+423, ES+Na+445; ^{1}H RMN (400 MHz, DMSO) δ 7,97 (s, 1H), 7,91-7,86 (m, 3H), 7,53 – 7,48 (m, 3H), 6,62 (s, 1H), 3,85 (s, 3H), 3,72 – 3,69 (m, 4H), 3,52-3,50 (m, 4 H), 3,43 (s, 3H).

[00909] Paso 3: Ácido 4-ciano-3-[metoxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxílico

[00910] A 4-ciano-3-[metoxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxilato de metilo (10,56 g, 25 mmoles) en un matraz de base redonda equipado con una barra de agitación se agregó tetrahidrofurano (278 ml) y 1,000 M de hidróxido de sodio en agua (208 ml, 208 mmoles). Se agregó metanol (139 ml) a la mezcla, y la mezcla de color amarillo resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se templó mediante la adición de una solución de HCl 1N acuoso para ajustar el pH hasta 2 y se agregó EtOAc. La mezcla se transfirió a un embudo separador, las capas se separaron, se extrajo la capa acuosa 2x con EtOAc, se combinaron los orgánicos, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, se agregó celite, se rotavapeó, se secó a alto vacío durante 45 minutos. El material bruto se purificó utilizando una carga seca sobre una columna ISCO de gel de sílice de 330 g (elución de gradiente: 0-20% MeOH/DCM) para obtener el producto en forma de un sólido de color beige impuro (9,8g). Se tomaron 2 g, se redisolvieron en DCM, se agregó celite, se rotavapeó, se secó a alto vacío 45 min., se repurificó esta porción del producto sobre una columna de gel de sílice ISCO de 120 g (elución de gradiente: 0-12% MeOH/DCM) para obtener 2,0 g de producto de espuma de color beige (racemato). LC/MS (FA) ES-407; ^{1}H RMN (400 MHz, DMSO) δ 13,57 (s, 1H), 7,96 (s, 1H), 7,89-7,86 (m, 3H), 7,53 – 7,46 (m, 3H), 6,68 (s, 1H), 3,73 – 3,67 (m, 4H), 3,50 – 3,45 (m, 4H), 3,43 (s, 3H). La separación enantiomérica de los enantiómeros se realizó mediante HPLC quiral sobre CHIRALPAK IC 4.6X250 mm con 85/5/10/0.1% de HEX/IPA/ETOH/DEA 10 uL. Inyección a 1,0 m/min. durante 50 minutos.

[00911] **Paso 4:** Ácido 4-ciano-3-[metoxi(2-naftil)metil]-5-(morfolin-4-il)tiofen-2-carboxílico•**Na**

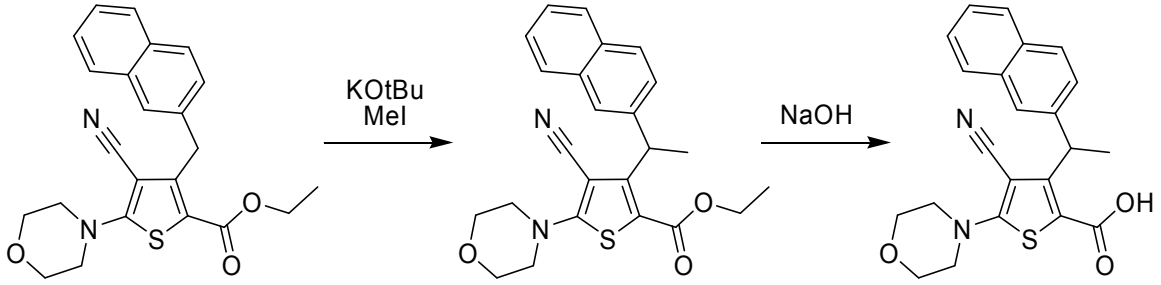
[00912] El ácido 4-ciano-3-[metoxi(2-naftilmetil]-5-(morfolin-4-il)tiofen-2-carboxílico (313,0 mg, 0,7663 mmoles) se suspendió en etanol (7,159 ml, 122,6 mmoles) y agua (2,071 ml, 114,9 mmoles) a

temperatura ambiente. Se agregó lentamente 1,030 M de hidróxido de sodio en agua (744,0 ul, 0,7663 mmoles) y la solución resultante se agitó durante 10 min. El solvente orgánico se eliminó al vacío. Se agregó 40 ml de agua, se liofilizó durante toda la noche para dar 322 mg de sólido de color ámbar (98% de rendimiento). LC/MS (FA) ES-407,5; ^{1}H NMR (400 MHz, DMSO) δ 7,99 (s, 1H), 7,88 – 7,76 (m, 3H), 7,61 (dd, *J* = 8,6, 1,3 Hz, 1H), 7,50 – 7,42 (m, 2H), 7,24 (s, 1H), 3,68 – 3,65 (m, 4H), 3,37 (s, 3H), 3,26-3,33 (m, 4H).

[00913] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 53.

337	LC/MS: (FA) ES- 407

[00914] **Ejemplo 54: Síntesis de 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftil)etil]tiofen-2-carboxilato de etilo (Compuesto 367).**



[00915] Paso 1: Un matraz de 1 litro se cargó con una barra de agitación con forma de huevo y 4-ciano-5-morfolin-4-il-3-(2-naftilmetil)tiofen-2-carboxilato de etilo (14,5 g, 35,7 mmoles). Al matraz se agregó N.N-dimetilformamida (240 ml) y la mezcla se evacuó y se purgó con nitrógeno (x3). Al matraz se agregó tetrahidrofurano (60 ml), y la mezcla se agitó hasta que se tornó una solución de color amarillo claro. La solución se enfrió hasta ~-25 °C en un baño de hielo seco-acetona (la temperatura se controló activamente mediante la adición lenta de hielo seco entre -30~-40 °C). Se

agregó gota a gota 1 M de ter-butóxido de potasio en tetrahidrofurano (42,8 ml) durante 3 minutos. La mezcla se volvió púrpura pesado inmediatamente. Después de la adición, la mezcla se agitó durante 10 min. a esta temperatura. Se agregó yoduro de metilo (11,1 ml, 178 mmoles) durante 1 minuto. Al finalizar la adición la mezcla se tornó de color rojo claro. Después de agitar la mezcla resultante a 0°C durante 10 minutos, la reacción se templó mediante la adición de 10 ml de agua. Todos los volátiles se eliminaron a presión reducida y la mezcla resultante se distribuyó entre salmuera y EtOAc. La capa acuosa se extrajo con EtOAc (x2). Las capas orgánicas combinadas se lavaron con 10% de solución de LiCl (aq), luego salmuera, se secaron y se concentraron para dar un jarabe de color amarillo. La purificación sobre columna de gel de sílice (elución de gradiente 5-20% de EtOAc/ hexanos) dio 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftil)etil]tiofen-2-carboxilato de etilo en forma de un sólido de color blanco (11,8g, 78,7% de rendimiento). LCMS: (AA) ES+ 421; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,90 – 7,82 (m, 2H), 7,82 – 7,70 (dd, *J* = 15,4, 8,1 Hz, 2H), 7,50 – 7,37 (m, 3H), 5,82 – 5,67 (q, *J* = 7,3 Hz, 1H), 4,40 – 4,25 (qd, *J* = 6,1, 5,0, 3,1 Hz, 2H), 3,86 – 3,72 (t, *J* = 4,8 Hz, 4H), 3,54 – 3,44 (t, *J* = 4,8 Hz, 4H), 1,95 – 1,85 (d, *J* = 7,3 Hz, 3H), 1,42 – 1,31 (t, *J* = 7,1 Hz, 3H).

[00916] Paso 2: Se agitó 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftil)etil]tiofen-2-carboxilato de etilo (13,3 g, 31,6 mmoles) en tetrahidrofurano (200 ml) y metanol (150 ml) hasta que la mezcla se tornó una solución transparente. A la solución se agregó 1,000 M de hidróxido de sodio en agua (158 ml). La mezcla turbia resultante se agitó vigorosamente a temperatura ambiente durante 12 horas. Los volátiles se eliminaron a presión reducida, y la solución

acuosa resultante se acidificó mediante la adición de 12,0 M de ácido clorhídrico en agua (15,9 ml, 191 mmoles) a 0°C, y luego se extrajo con EtOAc (x3). Las capas orgánicas combinada se lavaron con solución de HCl 1M, se secaron, y se concentraron para dar 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftil)etil]tiofen-2-carboxilato de etilo en forma de un sólido de color blanco (12,1g, 97,5% de rendimiento). Doscientos cincuenta gramos de la mezcla racémica se purificaron sobre HPLC de prep quiral para dar cada enantiómero (115 mg cada uno, >95% ee) (columna OJ, elución con 85/5/10/0.1% de hexano/iPrOH/EtOH/Et_2NH). LCMS: (AA) ES+ 393; ^{1}H RMN (400 MHz, MeOD) δ 7,85 – 7,76 (m, 3H), 7,76 – 7,71 (d, J = 8,6 Hz, 1H), 7,49 – 7,38 (m, 2H), 7,38 – 7,29 (dd, J = 8,5, 1,7 Hz, 1H), 5,90 – 5,74 (q, J = 7,3 Hz, 1H), 3,82 – 3,69 (m, 4H), 3,52 – 3,43 (dd, J = 5,8, 4,0 Hz, 4H), 1,91 – 1,80 (d, J = 7,3 Hz, 3H).

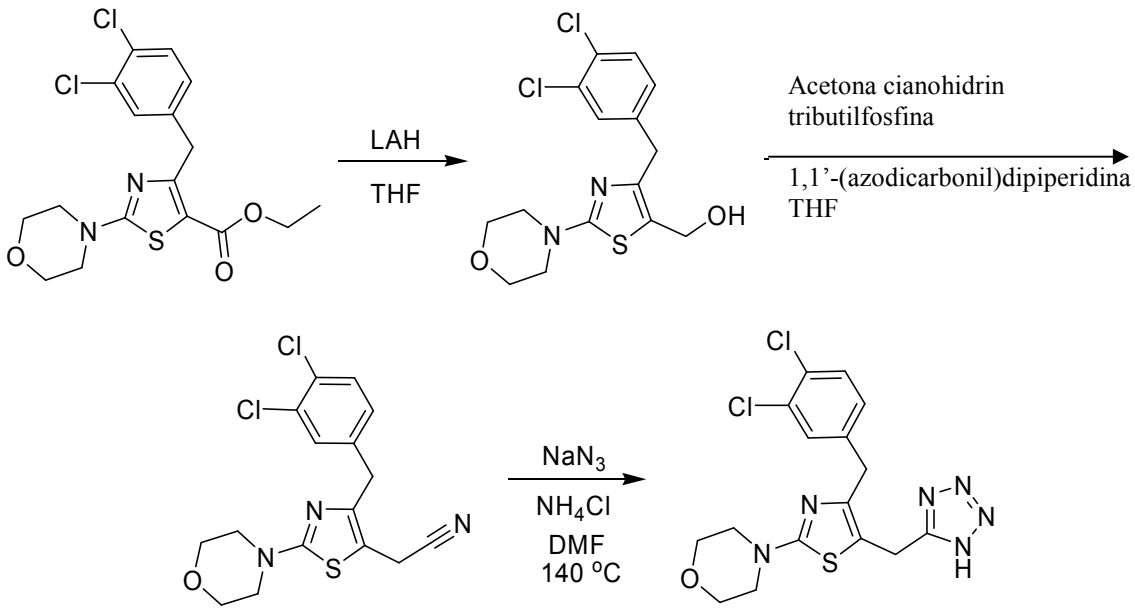
Paso 3: El enantiómero activo ácido 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftil)etil]tiofen-2-carboxílico (780 mg, 1,99 mmoles) se suspendió en etanol (10,0 ml, 171 mmoles). A la mezcla se agregó 1,030 M de hidróxido de sodio en agua (2,00 ml, 2,06 mmoles). La mezcla se revolvió y se sonicó hasta que se tornó homogénea. La solución se concentró para dar el ácido 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftil)etil]tiofen-2-carboxílico•Na en forma de un sólido de color amarillo (785 mg, 95% de rendimiento). LCMS: (AA) ES+ 393; ^{1}H RMN (400 MHz, MeOD) δ 7,85 – 7,72 (m, 3H), 7,72 – 7,66 (d, J = 8,6 Hz, 1H), 7,45 – 7,30 (ddd, J = 12,6, 4,9, 2,2 Hz, 3H), 6,20 – 6,06 (q, J = 7,0 Hz, 1H), 3,81 – 3,70 (t, J = 4,8 Hz, 4H), 3,40 – 3,32 (t, J = 4,8 Hz, 4H), 1,88 – 1,78 (d, J = 7,4 Hz, 3H).

[00917] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 54.

306	LC/MS: (FA) ES+ 423

313	LC/MS: (FA) ES+ 423
322	LC/MS: (FA) ES+ 425
333	LC/MS: (AA) ES+ 393
346	LC/MS: (FA) ES+ 369
363	LC/MS: (FA) ES+ 423
365	LC/MS: (FA) ES+ 425
366	LC/MS: (AA) ES- 409, 411, 413

[00918] Ejemplo 55: Síntesis de 4-(5-((1H-tetrazol-5-il)metil)-4-(3,4-diclorobencil)tiazol-2-il)morfolina (Compuesto 350).



[00919] Paso 1. Preparación de (4-(3,4-diclorobencil)-2-morfolinotiazol-5-il)metanol

[00920] A una solución de 4-(3,4-diclorobencil)-2-morfolinotiazol-5-carboxilato de etilo (4,92 g, 12,2 mmoles) en THF (100 ml) se agregó una solución 2,00 M de LAH en THF (12,9 ml, 25,8 mmoles) y la solución resultante se agitó durante 2 horas a temperatura ambiente. La reacción se templó agregando NH_4Cl saturado (26 ml) seguido de HCL 1M

(26 ml). A continuación se agregó agua (100 ml) y acetato de etilo (200 ml). Las capas se separaron, y la capa orgánica se lavó con salmuera (50 ml). La capa orgánica se secó y se concentró al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (acetato de etilo/DCM = 0/100→100/0) para dar 2,87 g (65 % de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 359, 361. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 7,34-7,31 (m, 2H), 7,09 (dd, 1H, J = 6,0, 2,0 Hz), 4,66 (d, 2H, J = 1,2 Hz), 3,84 (s, 2H), 3,79-3,77 (m, 4H), 3,42-3,39 (m, 4H).

[00921] **Paso 2. Preparación de 2-(4-(3,4-diclorobencil)-2-morfolinotiazol-5-il)acetonitrilo**

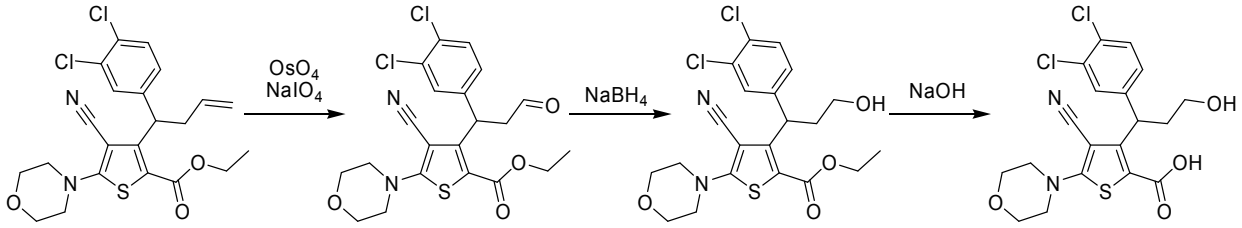
[00922] A una solución de (4-(3,4-diclorobencil)-2-morfolinotiazol-5-il)metanol (1,19 g, 3,31 mmoles) en THF (58,6 ml) se agregó cianohidrin acetona (0,454 ml, 4,97 mmoles), 1,1'-(azodicarbonil)dipiperidina (1,67 g, 6,62 mmoles) y tributilfosfina (1,65 ml, 6,62 mmoles) y la reacción se agitó durante 3 horas a temperatura ambiente. La reacción se concentró al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (acetato de etilo/DCM = 0/100→20/80) para dar 551 mg (45 % de rendimiento) del compuesto del título en forma de un sólido de color beige. LC/MS (FA) ES+ 368, 370. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 7,35 (d, 1H, J = 6,0 Hz), 7,32 (d, 1H, J = 2,0 Hz), 7,07 (dd, 1H, J = 6,0, 2,0 Hz), 3,82 (s, 2H), 3,80-3,77 (m, 4H), 3,66 (s, 2H), 3,42-3,40 (m, 4H).

[00923] **Paso 3. Preparación de 4-(5-((1H-tetrazol-5-il)metil)-4-(3,4-diclorobencil)tiazol-2-il)morfolina**

[00924] A una solución de 2-(4-(3,4-diclorobencil)-2-morfolinotiazol-5-il)acetonitrilo (87,0 mg, 0,236 mmoles) en DMF (0,74 ml) se agregó azida de sodio (21,6

mg, 0,332 mmoles) y NH_4Cl (17,8 mg, 9,53 mmoles) y la mezcla resultante se calentó hasta 140 grados durante toda la noche. Se agregaron más azida de sodio (43 mg, 0,66 mmoles) y NH_4Cl (36 mg, 19 mmoles) y la reacción se calentó hasta 120 grados durante toda la noche. La reacción se enfrió y se colocó en acetato de etilo (25 ml) y agua (5 ml). Las capas se separaron, y la capa orgánica se lavó con agua (3 x 5 ml).). La capa orgánica se secó y se concentró al vacío. El residuo se purificó por cromatografía de fase inversa preparativa para dar 5 mg (5% de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 411. 413. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,50 (d, 1H, J = 8,0 Hz), 7,46 (d, 1H, J = 2,0 Hz), 7,20 (dd, 1H, J = 8,0, 2,0 Hz), 4,41 (s, 2H), 3,88 (s, 2H), 3,65-3,62 (m, 4H), 3,32 (bs, 1H), 3,26-3,24 (m, 4H).

[00925] Ejemplo 56: Síntesis del ácido 4-ciano-3-[1-(3,4-diclorofenil)-3-hidroxipropil]-5-(morfolin-4-il)tiofen- -2-carboxílico (Compuesto 347).



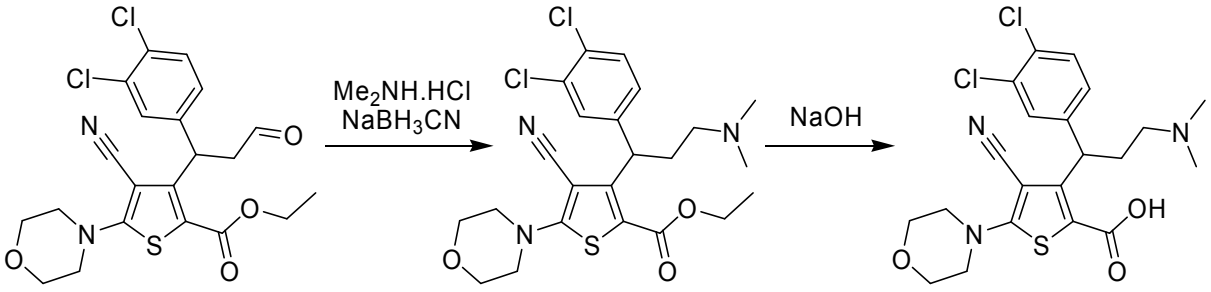
[00926] Paso 1: A una suspensión de 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen- -2-carboxilato de etilo (247 mg, 0,531 mmoles) en 1,4-dioxano (6,00 ml) y agua (2,00 ml) se agregó metaperiodato de sodio (454 mg, 2,12 mmoles), 2,6-lutidina (246 ul; 2,12 mmoles) y 4% de tetróxido de osmio en agua (4:96, tetraóxido de osmio:agua, 64,9 ul, 0,0106 mmoles). La reacción se agitó vigorosamente a temperatura ambiente durante 5 horas. La mezcla se filtró sobre un taco de celite y el sólido filtrado se enjuagó con EtOAc. El filtrado se lavó con solución de $NaHCO_3$ (ac) saturado

y la capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se lavó con solución de HCl 1N y salmuera, se secó, y se concentró. La purificación sobre columna de gel de sílice (elución de gradiente 5-50% de EtOAc/hexanos dio 4-ciano-3-[1-(3,4-diclorofenil)-3-oxopropil]-5-(morfolin-4-il)tiofen-2-carboxilato de etilo en forma de un jarabe de color amarillo (108 mg, 43,5% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,84 – 9,73 (d, J = 1,3 Hz, 1H), 7,48 – 7,42 (d, J = 2,1 Hz, 1H), 7,42 – 7,32 (d, J = 8,4 Hz, 1H), 7,30 – 7,18 (m, 1H), 6,06 – 5,94 (t, J = 7,7 Hz, 1H), 4,38 – 4,26 (q, J = 7,1 Hz, 2H), 3,86 – 3,77 (t, J = 4,9 Hz, 4H), 3,62 – 3,51 (dd, J = 5,7, 4,0 Hz, 4H), 3,50 – 3,42 (m, 2H), 1,41 – 1,29 (m, 3H).

[00927] Paso 2: A una solución de 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (50,0 mg, 0,107 mmoles) en etanol (1,00 ml) se agregó tetrahidroborato de sodio (4,05 mg, 0,107 mmoles). La mezcla se agitó a temperatura ambiente durante 1 hora. La reacción se templó con 1,00 M de ácido clorhídrico en agua (0,428 ml) y se distribuyó entre solución de $NaHCO_3$ (ac) saturado y EtOAc. La capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se secó y se concentró para dar un sólido de color blanco. La purificación sobre columna de gel de sílice (elución de gradiente 0-5% de MeOH) dio 4-ciano-3-[1-(3,4-diclorofenil)-3-hidroxipropil]-5-(morfolin-4-il)tiofen-2-carboxilato de etilo en forma de un jarabe incoloro (38 mg, 75,7% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,46 – 7,35 (dd, *J* = 5,2, 3,1 Hz, 2H), 7,30 – 7,19 (m, 1H), 5,65 – 5,52 (t, *J* = 8,0 Hz, 1H), 4,42 – 4,26 (q, *J* = 7,1 Hz, 2H), 3,85 – 3,77 (t, *J* = 4,9 Hz, 4H), 3,76 – 3,65 (ddt, *J* = 13,0, 9,0, 4,6 Hz, 1H), 3,57 – 3,44 (t, *J* = 4,8 Hz, 5H), 2,69 – 2,58 (dd, *J* = 8,4, 4,1 Hz, 1H), 2,56 – 2,43 (dt, *J* = 8,1, 4,9 Hz, 2H), 1,44 – 1,32 (t, *J* = 7,1 Hz, 3H).

[00928] **Paso 3:** A una solución de 4-ciano-3-[1-(3,4-diclorofenil)-3-hidroxipropil]-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (38,0 mg, 0,0810 mmoles) en tetrahidrofurano (1,00 ml) se agregó NaH 60% en aceite mineral (60:40, hidruro de sodio:aceite mineral, 3,56 mg, 0,0890 mmoles). La mezcla se calentó hasta 60°C durante 3 horas. La reacción se enfrió hasta temperatura ambiente y se distribuyó entre salmuera y EtOAc. La capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se lavó con salmuera, se secó y se concentró para dar un sólido de color amarillo. La purificación sobre HPLC (AA, fase inversa) dio el ácido 4-ciano-3-[1-(3,4-diclorofenil)-3-hidroxipropil]-5-(morfolin-4-il)tiofen-2-carboxílico en forma de un sólido de color blanco (6,5mg, 18,2% de rendimiento). LCMS: (AA) ES+ 441, 443, 445; ^{1}H RMN (400 MHz, MeOD) δ 7,50 – 7,45 (s, 1H), 7,45 – 7,37 (d, *J* = 8,4 Hz, 1H), 7,30 – 7,22 (m, 1H), 5,79 – 5,63 (m, 1H), 3,83 – 3,71 (t, *J* = 4,8 Hz, 4H), 3,60 – 3,50 (q, *J* = 6,9, 6,0 Hz, 2H), 3,50 – 3,41 (d, *J* = 3,2 Hz, 4H), 2,52 – 2,37 (m, 2H).

[00929] **Ejemplo 57: Síntesis del ácido 4-ciano-3-[1-(3,4-diclorofenil)-3-(dimetilamino)propil]-5-(morfolin4-il)tiofen- -2-carboxílico (Compuesto 331).**



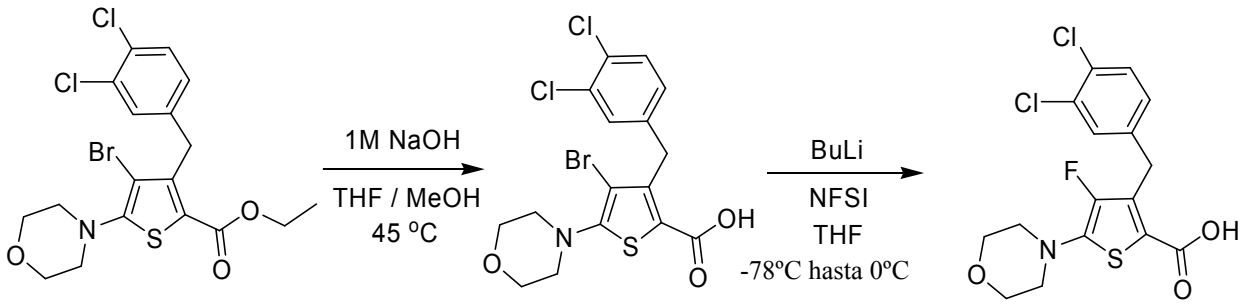
[00930] Paso 1: A una solución de 4-ciano-3-[1-(3,4-diclorofenil)but-3-en-1-il]-5-(morfolin-4-il)tiofen--2-carboxilato de etilo (38,0 mg, 0,0813 mmoles) (del ejemplo 56, paso 1) en metanol (1,00 ml) se agregó clorhidrato de

dimetilamina (9,94 mg, 0,122 mmoles), acetato de sodio (8,00 mg, 0,0976 mmoles), y cianoborohidruro de sodio (6,13 mg, 0,0976 mmoles) La reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se distribuyó entre solución de $NaHCO_3$ (ac) saturado y EtOAc. La capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se secó y se concentró. La purificación sobre columna de gel de sílice (elución de gradiente 0-15% de MeOH/CH_2Cl_2) dio 4-ciano-3-[1-(3,4-diclorofenil)-3-(dimetilamino)propil]-5-(morfolin-4-il)tiofen-2-carboxilato de etilo en forma de un jarabe de color amarillo (29,0 mg, 71,8% de rendimiento). LCMS: (AA) ES+ 496, 498, 500; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,52 – 7,44 (d, *J* = 1,9 Hz, 1H), 7,41 – 7,34 (m, 1H), 7,33 – 7,27 (m, 1H), 5,54 – 5,40 (t, *J* = 7,7 Hz, 1H), 4,38 – 4,27 (q, *J* = 7,1 Hz, 2H), 3,88 – 3,76 (t, *J* = 4,9 Hz, 4H), 3,58 – 3,49 (dd, *J* = 5,7, 4,0 Hz, 4H), 2,57 – 2,31 (m, 3H), 2,29 – 2,24 (s, 6H), 2,24 – 2,16 (m, 1H), 1,41 – 1,30 (t, *J* = 7,1 Hz, 3H).

[00931] Paso 2: A una solución de 4-ciano-3-[1-(3,4-diclorofenil)-3-(dimetilamino)propil]-5-(morfolin-4-il)tiofen- -2-carboxilato de etilo (29,0 mg, 0,0584mmoles) en metanol (0,500 ml) se agregó 1,030 M de hidróxido de sodio en agua (284 ul, 0,284 mmoles). La reacción se agitó a temperatura ambiente durante 2 días. La mezcla se neutralizó con 1,00 M de ácido clorhídrico e nagua (0,292 ml), se diluyó con 5 ml de agua y se extrajo con 10% de MeOH/$CHCl_3$ (x5). La capa orgánica combinada se secó y se concentró, y el jarabe/sólido de color blanco resultante se liofilizó para dar el ácido 4-ciano-3-[1-(3,4-diclorofenil)-3-(dimetilamino)propil]-5-(morfolin4-il)tiofen- -2-carboxílico en forma de un sólido de color blanco (26 mg, 95% de rendimiento). LCMS: (AA) ES+ 468, 470, 472; ^{1}H RMN (400 MHz, DMSO) δ 7,63 – 7,52 (d, *J* = 8,4 Hz, 1H), 7,44 – 7,37 (s, 1H),

7,15 – 7,02 (d, *J* = 8,1 Hz, 1H), 5,49 – 5,34 (d, *J* = 9,4 Hz, 1H), 3,73 – 3,63 (t, *J* = 4,8 Hz, 4H), 3,38 – 3,31 (dd, *J* = 6,2, 4,0 Hz, 4H), 3,13 – 2,97 (s, 1H), 2,85 – 2,73 (s, 1H), 2,72 – 2,60 (s, 6H), 2,56 – 2,52 (m, 1H).

[00932] Ejemplo 58: Síntesis del ácido 3-(3,4-diclorobencil)-4-fluoro-5-morfolinotiofen-2-carboxílico (compuesto 320)



del ejemplo 24

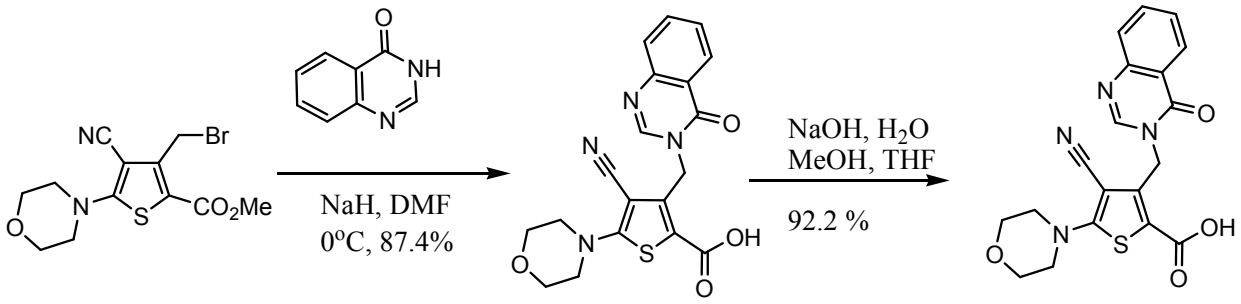
[00933] Paso 1. Preparación del ácido 4-bromo-3-(3,4-diclorobencil)-2-morfolinotiofen-2-carboxílico

[00934] A una solución de 4-bromo-3-(3,4-diclorobencil)-2-morfolinotiofen-2-carboxilato de etilo **(**109 mg, 0,227 mmoles) en THF (1,8 ml) y MeOH (0,37 ml) se agregó 1,00 M de NaOH acuoso (1,82 ml, 1,82 mmoles) y la mezcla resultante se agitó a 45°C durante toda la noche. La reacción se diluyó con agua (5 ml) y se acidificó hasta pH = 3 con HCl 1N. La mezcla se extrajo con acetato de etilo (2 x 20 ml), y las capas orgánicas combinadas se secaron, se filtraron, y se concentraron al vacío para dar 92 mg (90% de rendimiento) de un sólido de color blanco el cual se utilizó como está en el próximo paso. LC/MS (AA) ES+ 450, 452, 454. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 13,21 (bs, 1H), 7,52 (d, 1H, J = 8,0 Hz), 7,39 (d, 1H, 2,0 Hz), 7,09 (dd, 1H, J = 8,0, 2,0 Hz), 4,36 (s, 2H), 3,74-3,71 (m, 4H), 3,13-3,11 (m, 4H).

[00935] Paso 2. Preparación del ácido 3-(3,4-diclorobencil)-4-fluoro-5-morfolinotiofen-2-carboxílico

[00936] A una solución del ácido 4-bromo-3-(3,4-diclorobencil)-2-morfolinotiofen-2-carboxílico (89,0 mg, 0,197 mmoles) en THF (3,00 ml) en un baño de hielo seco /acetona se agregó 1,60 M de BuLi en hexanos (0,271 ml, 0,434 mmoles) y la solución resultante se agitó durante 10 minutos a -78°C. Una solución de N-fluoro-N-(fenilsulfonil)bencenosulfonamida (93,3 mg, 0,296 mmoles) en THF (0,70 ml) se agregó a continuación y la reacción se dejó entibiar hasta 0°C. La reacción se templó con NH_4Cl saturado (5 ml) y acetato de etilo (15 ml) se agregó posteriormente. Las capas se separaron y la capa acuosa se acidificó hasta pH = 3 con HCl 1N. La capa acuosa ácida se extrajo con acetato de etilo (2 x 20 ml) y las capas orgánicas combinadas se secaron, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (MeOH/DCM = 0/100→15/85) para dar 31 mg del producto. Este material se purificó por cromatografía de fase inversa preparativa para dar 9 mg (10 % de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 390, 392. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 13,04 (bs, 1H), 7,54 (d, 1H, J = 8,0 Hz), 7,44 (d, 1H, J = 1,6 Hz), 7,16 (dd, 1H, J = 8,0, 1,6 Hz), 4,21 (s, 2H), 3,71-3,68 (m, 4H), 3,14-3,12 (m, 4H).

[00937] Ejemplo 59: Síntesis del ácido 4-ciano-5-(morfolin-4-il)-3-[(4-oxoquinazolin-3(4H)-il)metil]tiofen-2-carboxílico (Compuesto 294).



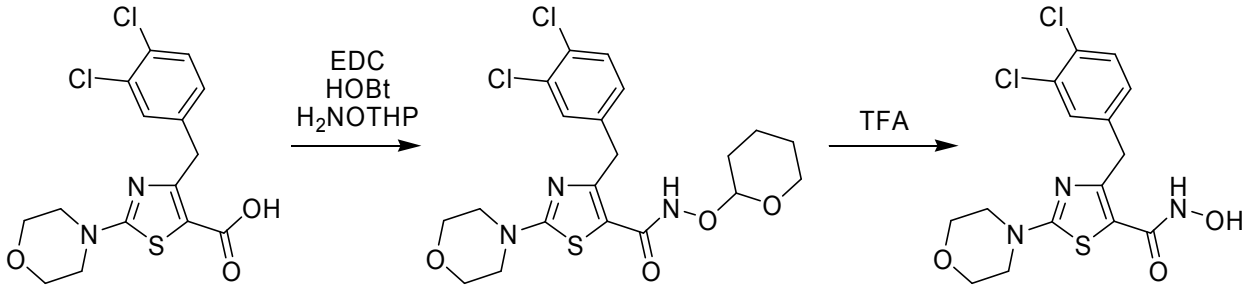
[00938] **Paso 1: 4-ciano-5-(morfolin-4-il)-3-[(4-oxoquinazolin-3(4H)-il)metil]tiofen-2-carboxilato de metilo.**

[00939] En atmósfera de N_2 se suspendió hidruro de sodio (23,0 mg, 0,910 mmoles) en N,N-dimetilformamida anhidra (3,0 ml, 39 mmoles), se enfrió con un baño de hielo y se agitó durante 10 min. Se agregó 4-hidroxiquinazolina (0,120 g, 0,821 mmoles) y la solución transparente se agitó a temperatura ambiente durante 10 min., se enfrió con un baño de hielo. Se agregó 3-(bromometil)-4-ciano-5-(morfolin-4-il)tiofen-2-carboxilato de metilo (0,203 g, 0,588 mmoles) y la solución rojiza-marrón se agitó con enfriamiento durante 40 min. La mezcla se templó con solución acuosa de NH4Cl saturado, se extrajo con EtOAc. La solución de EtOAc se lavó con agua (3x) luego salmuera, se secó sobre Na_2SO_4, se filtró, se rotavapeó para dar un sólido bruto. La cromatografía en una columna de gel de sílice utilizando MeOH/DCM (0/100 hasta 5/95) dio un producto sólido (0,211 g, 87,4%). LC/MS: (FA) ES^+ 411. ^1H RMN (400MHz, *d*-cloroformo) δ 8,30 (m, 1H), 8,26 (s, 1H),7,68-7,76 (m, 2H), 7,45-7,49 (m, 1H), 5,43 (s, 2H), 3,83-3,85 (m, 4H), 3,82 (s, 3H), 3,59-3,62 (m, 4H).

[00940] **Paso 2: Sal de sodio del ácido 4-ciano-5-(morfolin-4-il)-3-[(4-oxoquinazolin3(4H)-il)metil]tiofen2-carboxílico.**

[00941] Se disolvió 4-ciano-5-(morfolin-4-il)-3-[(4-oxoquinazolin-3(4H)-il)metil]tiofen-2-carboxilato de metilo (0,139 g, 0,339 mmoles) en tetrahidrofurano (15,0 m l), agua (2,0 ml) y metanol (5,0 ml). Se agregó 1,00 M de hidróxido de sodio en agua (1,0 ml, 1,0 mmoles) y la solución homogénea se agitó a temperatura ambiente durante 24 horas. La solución se concentró en rotavapor para dar un sólido bruto de color blanco, se disolvió en H2O/MEOH (1/10, ~ 20 mL) y se concentró en rotavapor hasta una suspensión de color blanco (columna ~ 2 mL). La suspensión se filtró para recolectar el sólido, se secó en el liofilizador para dar un producto sólido de color blanco (0,132 g, rendimiento 92,2 %). LC/MS: (FA) ES^+ 397; ES^- 395. ^1H RMN (400MHz, *d4*-metanol) δ 8,37 (s, 1H), 8,22 (d, J = 8,03 Hz, 1H),7,78-7,82 (m, 1H), 7,65 (d, J = 7,28 Hz, 1H), 7,51-7,55 (m, 1H), 5,99 (s, 2H), 3,78-3,81 (m, 4H), 3,47-3,50 (m, 4H).

[00942] **Ejemplo 60: Síntesis de 4-(3,4-diclorobencil)-N-hidroxi-2-(morfolin-4-il)-1,3-tiazol-5-carboxamida (Compuesto 298).**



[00943] **Paso 1:** A una suspensión del ácido 4-(3,4-diclorobencil)-N-hidroxi-2-(morfolin-4-il)-1,3-tiazol-5-carboxílico•Na(125 mg, 0,316 mmoles), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (72,8 mg, 0,380 mmoles), y 1-hidroxibenzotriazol (51,3 mg, 0,380 mmoles) en N,N-dimetilformamida (1,50 ml) se agrego O-tetrahidropiran-2-

il)hidroxilamina (55,6 mg, 0,474 mmoles). La reacción se agitó a temperatura ambiente durante 15 horas. La mezcla se distribuyó entre agua y EtOAc, y la capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se lavó con solución saturada de $NaHCO_3$ (ac) y 10% de solución de LiCl (ac) (x2), se secó sobre Na_2SO_4, y se concentró para dar 4-(3,4-diclorobencil)-N-hidroxi-2-(morfolin-4-il)-N-(tetrahidro-2H-piran-2-iloxi)-1,3-tiazol-5-carboxamida en forma de un sólido de color blanco (153 mg, cuantitativo). LCMS: (AA) ES+ 472, 474, 476; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,49 – 7,43 (d, *J* = 1,9 Hz, 1H), 7,30 – 7,26 (m, 1H), 7,26 – 7,17 (m, 1H), 5,01 – 4,89 (d, *J* = 2,8 Hz, 1H), 4,31 – 4,21 (m, 2H), 3,96 – 3,86 (td, *J* = 10,4, 9,1, 2,8 Hz, 1H), 3,80 – 3,70 (t, *J* = 4,9 Hz, 4H), 3,66 – 3,56 (m, 1H), 3,51 – 3,42 (t, *J* = 4,9 Hz, 4H), 1,90 – 1,73 (m, 3H), 1,69 – 1,49 (m, 3H).

[00944] Paso 2: A una solución de 4-(3,4-diclorobencil)-N-hidroxi-2-(morfolin-4-il)-N-(tetrahidro-2H-piran-2-iloxi)-1,3-tiazol-5-carboxamida (153 mg, 0,324 mmoles) en cloruro de metileno (1,50 ml) se agregó ácido trifluoroacético (1,50 ml, 19,5 mmoles). La reacción se agitó a temperatura ambiente durante 12 horas. La solución resultante se concentró y se distribuyó entre solución de $NaHCO_3$ (ac) saturado y CH_2Cl_2. La capa acuosa se extrajo con CH_2Cl_2(x2). La capa orgánica combinada se lavó con agua, se secó y se concentró La purificación sobre columna de gel de sílice (elución de gradiente, 0-8% de MeOH/CH_2Cl_2) dio 4-(3,4-diclorobencil)-N-hidroxi-2-(morfolin-4-il)-1,3-tiazol-5-carboxamida en forma de un sólido de color amarillo (53 mg, 42,1% de rendimiento). LCMS: (AA) ES+ 388, 390, 392; ^{1}H RMN (400 MHz, MeOD) δ 7,47 – 7,41 (d, *J* = 1,8 Hz, 1H), 7,38 – 7,29 (d, *J* = 8,3 Hz, 1H), 7,25 – 7,14 (dd, *J* = 8,3, 1,9 Hz, 1H),

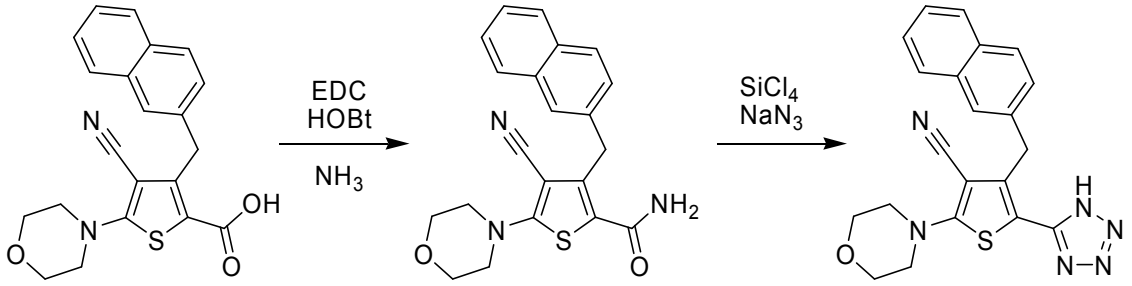
4,28 – 4,21 (s, 2H), 3,79 – 3,71 (t, *J* = 4,9 Hz, 4H), 3,50 – 3,43 (t, *J* = 4,9 Hz, 4H), 3,33 – 3,27 (t, *J* = 1,6 Hz, 1H).

[00945] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 60.

334	LC/MS: (AA) ES+ 354

[00946]

[00947] **Ejemplo 61: Síntesis de 2-(morfolin-4-il)-4-(2-naftilmetil)-5-(1H-tetrazol-5-il)tiofen-3-carbonitrilo (Compuesto 316)**

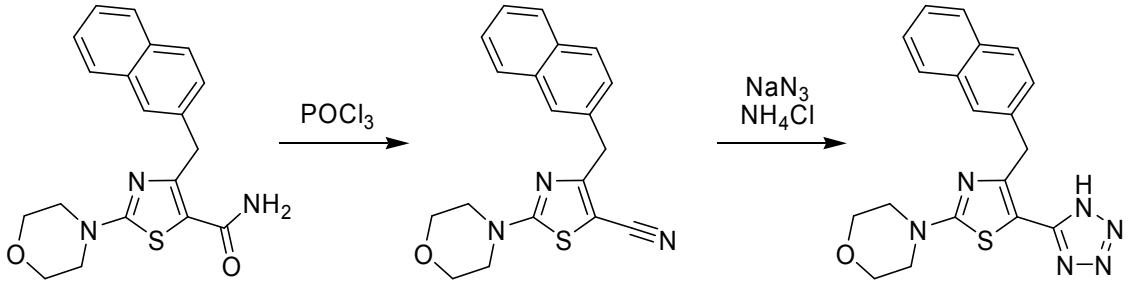


[00948] Paso 1: A una mezcla del ácido 4-ciano-5-morfolin-4-il-3-(2-naftilmetil)tiofeno-2-carboxílico•Na(255 mg, 0,637 mmoles) en N,N-dimetilformamida (6,00 ml) se agregó 1-hidroxibenzotriazol hidrato (117 mg, 0,764 mmoles), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (146 mg, 0,764 mmoles), y 0,500 M de amoníaco en 1,4-dioxano (3,18 ml, 1,59 mmoles). La reacción se agitó vigorosamente a temperatura ambiente durante 5 horas. La mezcla se distribuyó entre salmuera y EtOAc, y la capa acuosa se extrajo con EtOAc (x2). Las capas orgánicas combinadas se lavaron con 10% de solución de LiCl (ac) (x2), se secaron, y se concentraron para dar 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftilmetil]tiofen-2-carboxamida (compuesto 327) en forma de un sólido de color blanco (224 mg, 93,2% de rendimiento). LCMS: (AA) ES+ 378; ^{1}H RMN (400 MHz, DMSO) δ 7,89 – 7,76 (td, *J* = 11,0, 6,6 Hz, 3H), 7,68 – 7,62 (s, 1H), 7,51 – 7,44 (td, *J* =

6,8, 6,0, 3,7 Hz, 3H), 7,43 – 7,34 (m, 1H), 4,50 – 4,42 (s, 2H), 3,78 – 3,69 (t, *J* = 4,9 Hz, 4H), 3,50 – 3,40 (t, *J* = 4,9 Hz, 4H).

[00949] Paso 2: A una mezcla de azida de sodio (153 mg, 2,35 mmoles) en acetonitrilo (2,50 ml) en un tubo de microondas de 20 ml se agregó cloruro de silicio (IV) (89,9 ul, 0,783 mmoles). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 20 min., luego se agregó 4-ciano-5-(morfolin-4-il)-3-[1-(2-naftilmetil]tiofen-2-carboxamida (197 mg, 0,522 mmoles). El tubo se cerró y la reacción se calentó hasta 90°C durante 12 horas. La mezcla se enfrió y se distribuyó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se lavó con salmuera, se secó y se concentró para dar un jarabe de color púrpura. a purificación sobre HPLC (AA, fase inversa, AA) dio 2-(morfolin-4-il)-4-(2-naftilmetil)-5-(1H-tetrazol-5-il)tiofen-3-carbonitrilo en forma de un sólido de color amarillo (44 mg, 20,9% de rendimiento). LCMS: (AA) ES+ 403; ^{1}H RMN (400 MHz, MeOD) δ 7,78 – 7,73 (m, 1H), 7,73 – 7,67 (d, *J* = 7,8 Hz, 2H), 7,67 – 7,61 (s, 1H), 7,42 – 7,36 (m, 2H), 7,36 – 7,30 (m, 1H), 4,63 – 4,57 (s, 2H), 3,85 – 3,76 (t, *J* = 4,9 Hz, 4H), 3,57 – 3,48 (t, *J* = 4,8 Hz, 4H).

[00950] **Ejemplo 62: Síntesis de 2-[4-(2-naftilmetil)-5-(1H-tetrazol-5-il)-1,3-tiazol-2-il]morfolina (Compuesto 360)**



[00951] Paso 1: Una mezcla de 2-(morfolin-4-il)-4-(2-naftilmetil)-1,3-tiazol-5-carboxamida (229 mg, 0,648 mmoles) (para acoplamiento amida, véase el ejemplo 61 – paso 1) y cloruro de fosforilo (4,00 ml, 42,9 mmoles) se agitó a 80°C durante 30 min. La reacción se tornó lentamente homogénea. La solución resultante se concentró a presión reducida y se templó cuidadosamente con solución de NaOH 1N a 0°C. La mezcla resultante se distribuyó entre solución de NaOH 1N y EtOAc. La capa acuosa se extrajo con EtOAc. La capa orgánica combinada se secó y se concentró para dar 2-(morfolin-4-il)-4-(2-naftilmetil)-1,3-tiazol-5-carbonitrilo en forma de un sólido de color amarillo (213 mg, 98% de rendimiento). LCMS: (AA) ES+ 336; ^{1}H RMN (400 MHz, DMSO) δ 7,90 – 7,83 (dd, *J* = 9,0, 1,9 Hz, 3H), 7,80 – 7,72 (s, 1H), 7,53 – 7,46 (m, 2H), 7,46 – 7,38 (m, 1H), 4,18 – 4,09 (s, 2H), 3,70 – 3,60 (t, *J* = 4,9 Hz, 4H), 3,51 – 3,41 (t, *J* = 4,9 Hz, 4H).

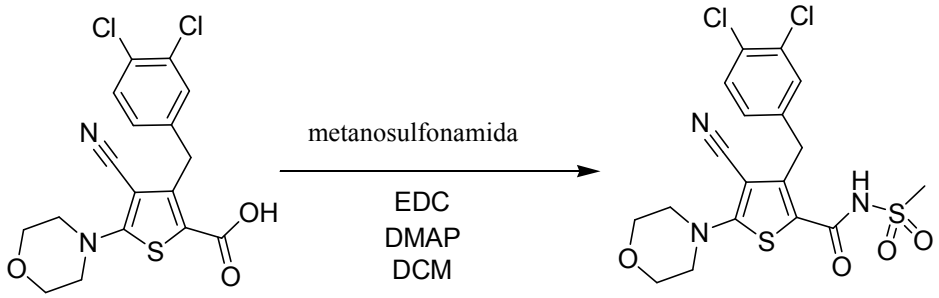
[00952] Paso 2: A una solución de 2-(morfolin-4-il)-4-(2-naftilmetil)-1,3-tiazol-5-carbonitrilo (213 mg, 0,635 mmoles) en N,N-dimetilformamida (3,00 ml) se agregó azida de sodio (61,9 mg, 0,952 mmoles) y cloruro de amonio (102 mg, 1,90 mmoles). La mezcla se calentó hasta 100°C y se agitó durante 24 horas. La mezcla resultante se enfrió hasta temperatura ambiente y se distribuyó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc (x2). La capa orgánica combinada se lavó con solución 10% de LiCl (ac) (x2), se secó, y se concentró. La purificación sobre HPLC (fase inversa, AA) dio 2-[4-(2-naftilmetil)-5-(1H-tetrazol-5-il)-1,3-tiazol-2-il]morfolina en forma de un sólido de color amarillo (105 mg, 43,7% de rendimiento). LCMS: (AA) ES+ 379; ^{1}H RMN (400 MHz, MeOD) δ 7,79 – 7,61 (m, 4H), 7,43 – 7,31 (m, 3H), 4,57 – 4,45 (s, 2H), 3,82 – 3,68 (t, *J* = 4,9 Hz, 4H), 3,53 – 3,43 (t, *J* = 4,9 Hz, 4H).

[00953] Los compuestos en la siguiente tabla se prepararon a partir de materiales de partida apropiados en un método análogo al del ejemplo 62.

356	LC/MS: (AA) ES+ 378

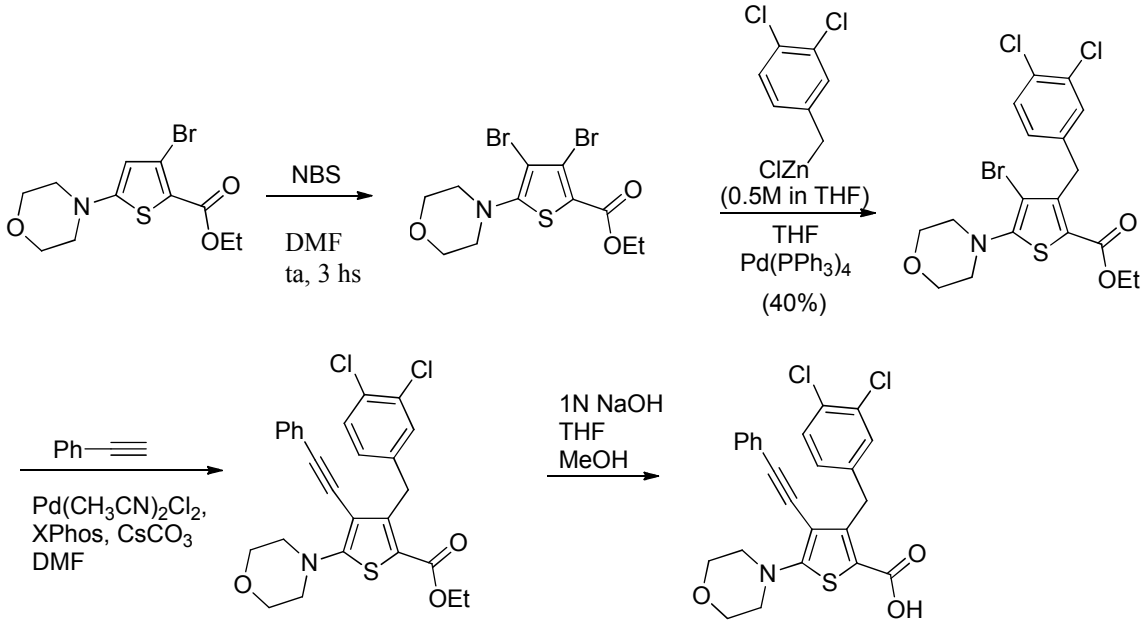
[00954]

[00955] **Ejemplo 63: Síntesis de 4-ciano-3-(3,4-diclorobencil)-N-(metilsulfonil)-5-morfolinotiofen-2-carboxamida (compuesto 352)**



[00956] A una mezcla del ácido 3-(3,4-diclorobencil)-5-morfolinotiofen-2-carboxílico (291 mg, 0,732 mmoles), en DCM (5,0 ml) se agregó metanosulfonamida (87,1 mg, 0,916 mmoles), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (176 mg, 0,916 mmoles), y N,N-dimetilaminopiridina (103 mg, 0,842 mmoles) y la solución resultante se agitó a temperatura ambiente durante toda la noche. La reacción se diluyó con DCM (10 ml), HCl 1N (3 ml) y con agua (3 ml). La capa orgánica se secó, se filtró y se concentró al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (MeOH/DCM = 0/100→20/80) para dar 250 mg del producto bruto. Este material se purificó por cromatografía de fase inversa preparativa para dar 70 mg (20 % de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 474, 476. ^{1}H RMN (400 MHz, MeOH-d_4) δ: 7,45 (d, 1H, J = 2,0 Hz)), 7,38 (d, 1H, J = 8,4 Hz), 7,25 (dd, 1H, J = 8,0, 2,0 Hz), 4,38 (s, 2H), 3,82-3,80 (m, 4H), 3,57-3,55 (m, 4H), 3,18 (s, 3H).

[00957] **Ejemplo 64: Síntesis del ácido 3-(3,4-diclorobencil)-5-(morfolin-4-il)-4-(feniletinil)tiofen-2-carboxílico (Compuesto 296).**



[00958] **Paso 1:** 3,4-dibromo-5-(morfolin-4-il)tiofen-2-carboxilato de etilo.

[00959] A una solución desgasificada de 3-bromo-5-morfolin-4-iltiofen-2-carboxilato de etilo (0,688 g, 2,15 mmoles) en DMF (14 ml, 180 mmoles) se agregó N-bromosuccinimida (0,7648 g, 4,297 mmoles) gota a gota en forma de una solución en DMF desgasificado (4,1 ml, 52 mmoles). La mezcla se envolvió en una lámina de metal para protegerla de la luz ambiental, y la reacción se agitó en argón a temperatura ambiente durante 2 horas. La mezcla de reacción se templó mediante la adición de solución de tiosulfato de sodio al 10% (10 ml) y luego se diluyó con EtOAc (30 ml). Las capas se separaron, y la capa acuosa se extrajo con EtOAc (10 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. Cromatografía flash (eluyente: 0-25% EtOAc:hexano) dio

3,4-dibromo-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (593 mg, rendimiento 69%). LCMS: (FA) ES+ 398, 400, 402; ^{1}H RMN (400 MHz, DMSO) δ 4,26 (q, J = 7,1 Hz, 2H), 3,75 (dd, J = 5,5, 3,8 Hz, 4H), 3,24 – 3,10 (m, 4H), 1,27 (t, J = 7,1 Hz, 3H).

[00960] **Paso 2:** 4-bromo-3-(3,4-diclorobencil)-5-(morfolin-4-il)tiofen-2-carboxilato de etilo

[00961] Un recipiente de reacción que puede cerrarse que contiene una suspensión de 3,4-dibromo-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (0,560 g, 1,40 mmoles), 0,500 M de 3,4-diclorobencilzinc cloruro en THF (3,368 ml, 1,684 mmoles) y THF (2,06 ml, 25,4 mmoles) se purgó mediante vacío/retrollenado con argón. A esta suspensión se agregó tetrakis(trifenilfosfina)paladio(0) (81,07 mg, 0,07016 mmoles), el recipiente se tapó, y la suspensión de color negro resultante se agitó a 95°C durante toda la noche. La mezcla de reacción se adsorbió hasta celite al vacío, y el sólido que se obtuvo de este modo se purificó mediante cromatografía de columna (eluyente: 0-15% EtOAc:hexano) para dar 4-bromo-3-(3,4-diclorobencil)-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (323 mg, 50%). LCMS: (FA) ES+ 478, 480, 482; ^{1}H RMN (400 MHz, DMSO) δ 7,53 (d, J = 8,3 Hz, 1H), 7,39 (d, J = 2,0 Hz, 1H), 7,07 (dd, J = 8,3, 2,1 Hz, 1H), 4,36 (s, 2H), 4,22 (q, J = 7,1 Hz, 2H), 3,75 – 3,70 (m, 4H), 3,17 – 3,12 (m, 4H), 1,22 (t, J = 7,1 Hz, 3H).

[00962] **Paso 3:** 3-(3,4-diclorobencil)-5-(morfolin-4-(feniletinil)-tiofen-2-carboxilato de etilo

[00963] A una suspensión de 4-bromo-3-(3,4-diclorobencil)-5-(morfolin-4-il)tiofen-2-carboxilato de etilo (0,125 g, 0,000222 moles),), XPhos (0,0172 g, 0,0000362 mol), CsCO3 (0,199 g, 0,000612 moles) y fenilacetileno (0,146 ml, 0,00133 moles) en DMF (1,2 mL, 0,015 mol) se agregó

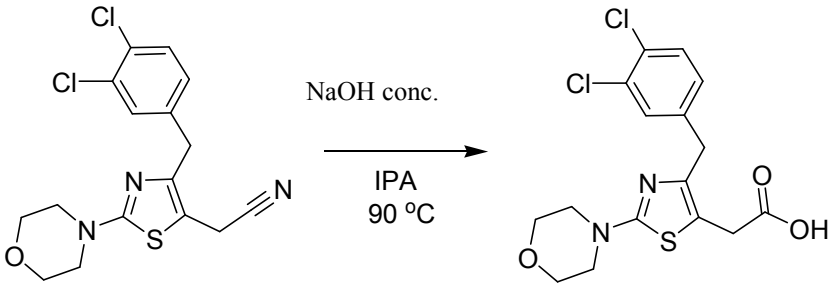
bis(acetonitrilo)paladio(II) cloruro (0,00288 g, 0,0000111 moles) y la mezcla se calentó a 50°C durante toda la noche. La mezcla de reacción se diluyó con EtOAc (30 ml) y agua (15 ml), y las capas se separaron. La capa acuosa se extrajo con EtOAc (2 x 15 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo bruto se purificó utilizando una carga seca sobre una columna de gel de sílice (eluyente: 0-30% EtOAc:hexano) para dar 3-(3,4-diclorobencil)-5-(morfolin-4-il)-4-(feniletinil)tiofen-2-carboxilato de etilo (45 mg, 40% de rendimiento). LCMS: (FA) ES+ 500, 501, 502; ^{1}H RMN (400 MHz, DMSO) δ 7,55 – 7,51 (m, 2H), 7,43 – 7,37 (m, 5H), 7,20 (dd, J = 8,3, 2,0 Hz, 1H), 4,38 (s, 2H), 4,22 (q, J = 7,1 Hz, 2H), 3,79 – 3,74 (m, 4H), 3,57 – 3,52 (m, 4H), 1,23 (t, J = 7,1 Hz, 3H).

[00964] **Paso 4:** Ácido 3-(3,4-diclorobencil)-5-(morfolin-4-il)-4-(feniletinil)-tiofen-2-carboxílico

[00965] A una suspensión de 3-(3,4-diclorobencil)-5-(morfolin-4-(feniletinil)-tiofen-2-carboxilato de etilo (0,041 g, 0,082 mmoles en THF (2,00 ml, 24,6 mmoles) y metanol (0,37 ml, 9,1 mmoles) se agregó 1,000 M de hidróxido de sodio en agua (1,684 ml, 1,684 mmoles) y la mezcla bifásica resultante se agitó a temperatura ambiente durante 2 días. El pH se ajustó cuidadosamente hasta 3,0 mediante la adición de HCl 1N (se monitoreó en tiempo real con un medidor de pH), y la mezcla de reacción se transfirió a un embudo separador. La mezcla se diluyó con EtOAc (40 ml) y agua (15 ml), y las capas se separaron. La capa acuosa se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas combinadas se lavaron con salmuera, luego se secaron sobre Na_2SO_4, y se concentraron. Cromatografía de columna (eluyente: 0-5% MeOH:DCM) dio el ácido 3-(3,4-diclorobencil)-5-(morfolin-4-il)-4-(feniletinil)tiofen-2-carboxílico (30 mg, 78% de rendimiento). LCMS: (FA) ES+ 472,

473, 474; ^{1}H RMN (400 MHz, DMSO) δ 12,92 (s, 1H), 7,55 – 7,50 (m, 2H), 7,43 – 7,34 (m, 5H), 7,21 (dd, J = 8,3, 2,0 Hz, 1H), 4,39 (s, 2H), 3,81 – 3,68 (m, 4H), 3,56 – 3,42 (m, 4H).

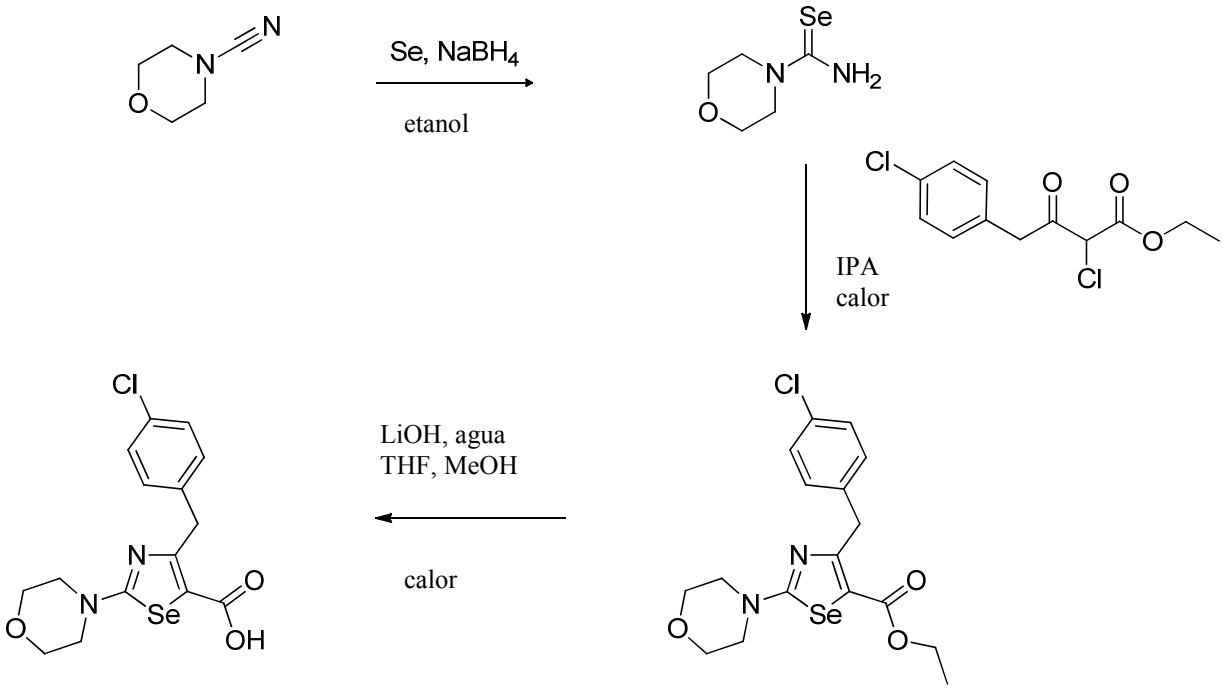
[00966] Ejemplo 65: Síntesis del ácido 2-(4-(3,4-diclorobencil)-2-morfolinotiazol-5-il)acético (compuesto 348)



del ejemplo 65 anterior

[00967] A una solución de 2-(4-(3,4-diclorobencil)-2-morfolinotiazol-5-il)acetonitrilo (165 mg, 0,448 mmoles) en IPA (4,88 ml) se agregó 50% de NaOH acuoso (1,68 ml, 44,8 mmoles) y la solución resultante se calentó hasta 90 grados durante 3 horas. La reacción se enfrió y se concentró al vacío. El residuo se acidificó con HCl 1N y se extrajo con acetato de etilo (2 x 25 ml). Las capas orgánicas se secaron, se filtraron y se concentraron al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (MeOH/DCM = 0/100→20/80) para dar 120 mg del producto. Este material se purificó por cromatografía de fase inversa preparativa para dar 16 mg (9 % de rendimiento) del compuesto del título en forma de un sólido de color blanco. LC/MS (FA) ES+ 387, 389. ^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,49 (d, 1H, J = 8,0 Hz), 7,47 (d, 1H, J = 2,0 Hz), 7,21 (dd, 1H, J = 8,0, 2,0 Hz), 3,78 (s, 2H), 3,67 (s, 2H), 3,66-3,63 (m, 4H), 3,26-3,24 (m, 4H).

[00968] **Ejemplo 66: Síntesis del ácido 4-(4-clorobencil)-2-morfolino-1,3-selenazol-5-carboxílico (compuesto 370)**



[00969] **Paso 1: Morfolina-4-carboxelenoamida**

[00970] En un matraz de base redonda equipado con una barra de agitación se agregaron metal de selenio (4,00 g, 49,4 mmoles) y etanol (50 ml). La mezcla se enfrió en un baño helado y se agitó en atmósfera de nitrógeno mientras se agregaba lentamente tetrahidroborato de sodio (2,01 g, 53,1 mmoles). El gas se evolucionó y el selenio se disolvió lentamente. Después que había cesado la evolución de gas, se agregó lentamente 4-morfolincarbonitrilo (2,77 g, 24,7 mmoles) seguido de clorhidrato de piridina (11,4 g, 98,7 mmoles). La mezcla oscura resultante se agitó durante toda la noche a temperatura ambiente. La mezcla de reacción grisácea se templó con agua (~250 ml) y la mezcla se agitó brevemente, luego se transfirió a un embudo separador. La mezcla se

extrajo con diclorometano (3x). Los extractos se combinaron, y se secaron sobre sulfato de sodio. Los insolubles se filtraron y el filtrado se evaporó para dejar un sólido de color rosa claro el cual se agitó con agua y luego se filtró. El sólido recolectado se lavó con acetato de etilo y los lavados se combinaron, luego se evaporaron para dejar 80 mg (2% de rendimiento) del producto en forma de un sólido color rosa claro. LC/MS (FA) ES+ 195. ^{1}H RMN (400 MHz, DMSO) δ 8,15 - 7,71 (br s, 2H), 3,94 - 3,61 (br s, 4H), 3,60 - 3,51 (t, J = 4,9 Hz, 4H).

[00971] **Paso 2: 4-(4-clorobencil)-2-morfolino-1,3-selenazol-5-carboxilato de etilo.**

[00972] En un matraz de base redonda se colocaron 2-cloro-4-(4-clorofenil)-3-oxobutanoato de etilo (84,4 mg, 0,3069 mmoles), alcohol isopropílico (5 ml), y morfolina-4-carboselenoamida (80,0 mg, 0,414 mmoles). La mezcla resultante se llevó a reflujo en una atmósfera de nitrógeno (todos los sólidos se disolvieron para dar una solución de color rosa pálido transparente). Después de aproximadamente 1 hora de reflujó, el análisis de TLC indicó que todos los materiales de partida habían sido consumido con la producción de un producto principal. La reacción se dejó enfriar hasta temperatura ambiente y agitar durante toda la noche. El solvente se eliminó en el rotovap luego el residuo se disolvió en diclorometano mínimo y se purificó por cromatografía de columna sobre gel de sílice (gradiente 100% de hexano a 35% de acetato de etilo) para dar 35 mg (28% de rendimiento) del producto en forma de un sólido de color blanco. LC/MS (FA) ES+ 413/415/417. ^{1}H RMN (400 MHz, DMSO) δ 7,37 - 7,23 (m, 4H), 4,25 - 4,14 (m, 4H), 3,72 - 3,62 (t, J = 4,9 Hz, 4H), 3,50 - 3,41 (t, J = 4,8 Hz, 4H), 1,27 - 1,20 (t, J = 7,1 Hz, 3H).

[00973] Paso 3: Ácido 4-(4-clorobencil)-2-morfolino-1,3-selenazol-5-carboxílico

[00974] El compuesto 4-(4-clorobencil)-2-(morfolin-4-il)-1,3-selenazol-5-carboxilato de etilo (35,0 mg, 0,0846 moles) se colocó en un matraz de base redonda equipado con una barra de agitación. Se agregaron tetrahidrofurano (1,00 ml) y metanol (0,1 moles) y la mezcla se agitó para dar una solución de color amarillo claro. Una solución de hidróxido de litio en agua (2,0 M, 0,423 ml, 0,846 mmoles) se agregó en una porción única, y la mezcla resultante se agitó en una atmósfera de nitrógeno a temperatura ambiente durante toda la noche. El análisis de LCMS de la reacción indicó que el material de partida todavía quedó; sólo una pequeña cantidad del mismo había sido hidrolizado al producto. Se agregaron tetrahidrofurano adicional (2 ml) e hidróxido de litio en agua (2,0 M, 0,423 ml, 0,846 mmoles) y la reacción se calentó durante toda la noche a 50°C en una atmósfera de nitrógeno. El análisis LCMS indicó que la reacción se completó en un 90%. La reacción se calentó a 60°C durante otras 8 horas. El análisis LCMS indicó hidrólisis completa. La reacción se enfrió hasta temperatura ambiente, se diluyó con 10 ml de solución salina, y se acidificó con ácido acético diluido con buena agitación. Se formó un precipitador de color blanco el cual se tornó granular con agitación. El producto se aisló sobre un embudo fritado, se lavó con agua, y se secó a 40°C durante toda la noche para dar 29,2 mg (89% de rendimiento) del producto en forma de un polvo de color blanco. LC/MS (FA) ES+ 385/387/389. ^{1}H RMN (400 MHz, DMSO) δ 12,73 – 12,44 (br s, 1H), 7,36 – 7,24 (m, 4H), 4,26 – 4,18 (s, 2H), 3,74 – 3,63 (t, *J* = 4,8 Hz, 4H), 3,49 – 3,39 (t, *J* = 4,7 Hz, 4H).

[00975] **Ejemplo de formulación 1 (cantidad por comprimido)**

(1)	Compuesto obtenido en el ejemplo 1	10,0 mg
(2)	lactosa	60,0 mg
(3)	almidón de maíz	35,0 mg
(4)	gelatina	3,0 mg
(5)	estearato de magnesio	2,0 mg

[00976] Una mezcla de 10,0 mg del compuesto que se obtuvo en el ejemplo 1, 60,0 mg de lactosa y 35,0 mg de almidón de maíz se granuló a través de un tamiz de malla de 1 mm utilizando 0,03 ml de una solución acuosa al 10% en peso de gelatina (3,0 mg de gelatina), después de lo cual los gránulos se secaron a 40°C y se filtraron nuevamente. Los gránulos obtenidos se mezclaron con 2,0 mg de estearato de magnesio y se comprimieron. Los comprimidos centrales se recubrieron con un recubrimiento de azúcar que contiene una suspensión de sacarosa, dióxido de titanio, talco y goma arábiga y se lustró con cera de abejas para dar los recubrimientos de azúcar.

[00977] **Ejemplo de formulación 2 (dosis por comprimido)**

(1)	Compuesto obtenido en el ejemplo 1	10,0 mg
(2)	lactosa	70,0 mg
(3)	almidón de maíz	50,0 mg
(4)	almidón soluble	7,0 mg
(5)	estearato de magnesio	3,0 mg

[00978] Se granularon 10,0 mg del compuesto que se obtuvo en el ejemplo 1 y 3,0 mg de estearato de magnesio utilizando 0,07 ml de una solución acuosa de almidón soluble (7,0 mg de almidón soluble), después de lo cual estos gránulos se secaron y se mezclaron con 70,0 mg de lactosa y

50,0 mg de almidón de maíz. Esta mezcla se comprimió para dar comprimidos.

[00979] **DATOS BIOLÓGICOS:**

[00980] **Ensayos enzimáticos de P13K y VPS34**

[00981] **Clonación, expresión, y purificación de P13Ks y VPS34**

[00982] Las subunidades catalíticas de las P13Ks se clonan dentro de o bien pDEST8(p110 alfa) o pDEST10(p110beta, p110delta, y p110gamma) como proteínas de fusión marcadas His N-terminal utilizando el sistema Gateway (Invitrogen, catálogo 11804-010 para pDEST8 yd 11806-015 para pDEST10). Las secuencias se verificaron antes de la expresión de la proteína recombinante utilizando el sistema de expresión del baculovirus con tecnología Gateway®. Los números de acceso para las subunidades son los siguientes:

p110 alfa (GB:U79143)

p110beta (GB:S67334)

p110delta (GB: U86453)

p110gamma (GB: X83368)

[00983] Las subunidades reguladoras de las P13Ks se clonan en pDEST8 como una proteína sin marcar utilizando el sistema Gateway (Catálogo # 11804-010). Las secuencias se verificaron antes de la expresión de la proteína recombinante utilizando el sistema de expresión del baculovirus con tecnología Gateway®. Los números de acceso para las subunidades son los siguientes:

p85 alfa (GB: BC030815)

p101(GB: AB028925)

[00984] La VPS34 (número de acceso GB:BC033004) se clona en pDEST20-Thombin como proteínas de fusión marcada GST N-terminal utilizando el sistema Gateway (Invitrogen, catálogo # 11804-013). Las secuencias se verificaron antes de la expresión de la proteína recombinante utilizando el sistema de expresión del baculovirus con tecnología Gateway®.

[00985] Para la expresión de los complejos p 100, el p85 (MOI de 4) se coinfecta con p110 alfa, beta, y delta respectivamente (1MOI) en células SF9 y se cosecho a 60 horas pos coinfección. El P110 gamma se infectó a 1 MOI y se cosechó a 60 horas pos infección.

[00986] Para la purificación, las P13Ks se purificaron por Ni-NTA Agarose (Qiagen #30250) seguido de Mono Q 10/100 GL (Ge Healthcare #17-5167-01). La VPS34 se purifica por Glutathione Sepharose 4 Fast Flow (GE Healthcare #17-5132-03) seguido de HiTrap Q (GE Healthcare #17-1153-01)

[00987] Para expresión la VPS34 se infectó a 1 MOI en células SF9 y se cosechó 72 horas pos infección.

[00988] Para purificación, la VPS34 se purifica por Glutathione Sepharose 4 Fast Flow (GE Healthcare #17-5132-03) seguido de HiTrap Q (GE Healthcare #17-1153-01)

[00989] **Condiciones de ensayo de la P13K y VPS34**

[00990] 1) método de ensayo enzimática P13K alfa humano

[00991] compuestos de 0,5 ul en DMSO se agregan a los pocillos de una placa microtítulo de 384 pocillos (Corning 3575). A temperatura ambiente: 10ul de buffer de reacción de PI3K (50 mM Hepes, 5mM DTT, 150mM NaCl, 10mM beta-glicerofosfato, 10mM MgCl2, 0,25mM colato de sodio y

0,001% de CHAPS, pH 7,00) que contiene ATP (25uM, Promega) se agrega seguido inmediatamente de 10ul de buffer de reacción de PI3K que contiene di-C8 PI(4,5)P2 (3,5uM, CellSignals) y PI3Kalfa (0,4875nM, Millennium Protein Sciences Group) y la mezcla se incuba con agitación a temperatura ambiente durante 30 minutos. A continuación 5ul de mezcla de detención de PI3K (50mM Hepes, 5mM DTT, 150 mM NaCl, 0,01% Tween-20, 15 mM EDTA y 25nM biotin-PI(3,4,5)P3 (Echelon) se agrega para templar la reacción seguido inmediatamente de la adición de 5ul de mezcla de detección HTRF (50mM Hepes, 5mM DTT, 150 mM NaCl, 0,01% Tween-20, 40mM KF, 10nM GST:GRP-1 PH dominio (Millennium Protein Sciences Group), 15nM estreptavidina-XL (CisBio) y 0,375nM de anticuerpo anti-GST Eu++ (CisBio) a pH 7,00). Las placas se incuban a continuación durante 1 hora a temperatura ambiente con agitación y luego se leen en un lector BMG PheraStar Plus.

[00992] 2) las isoformas de P13K beta, delta, y gamma humanas se ensayan utilizando el procedimiento que se describe para P13K alfa anterior pero con los siguientes cambios: PI3K beta (5,25nM), PI3K delta (0,75nM) and PI3K gamma (5nM). Todas las isoformas suministradas por Millennium Protein Science Group.

[00993] 3) la VPS34 se ensayó utilizando Adapta ™ Universal Kinase Assay Kit (Invitrogen).

[00994] 4) método de ensayo enzimático de VPS34 humana.

[00995] compuestos de 100 nl en DMSO se agregan a los pocillos de una placa microtítulo de 384 pocillos (Greiner 780076). A temperatura ambiente: 5ul de buffer de reacción de VPS34 (buffer de ensayo Invitrogen Q (se diluyó 1 en 5 con agua nanopura) más 2mM DTT y 2mM MnCl2) que contiene ATP (20uM, Promega) y 200uM de sustrato PI-PS

(Invitrogen PV5122) se agrega seguido inmediatamente por 5 ul de buffer de reacción de VPS34 (como el anterior) que contiene VPS34 (5nM, Millennium Protein Sciences Group) y la mezcla se incuba con agitación a temperatura ambiente durante 1 hora. Luego 5ul de mezcla de detección-detención de VPS34 (según instrucciones del kit de ensayo Invitrogen Adapta (PV5009) (contiene buffer de templado quinasa, buffer de TR-FRET, anticuerpo Adapta Eu anti-ADP y trazador Alexa Fluor 647 ADP)) se agrega para templar la reacción. Las placas se incuban a continuación durante 30 minutos a temperatura ambiente con agitación y luego se leen en un lector BMG PheraStar Plus.

[00996] Para los métodos de ensayo que se describieron anteriormente, la inhibición porcentual del compuesto de ensayo, en varias concentraciones, se calcula con relación a las muestras tratadas con control (DMSO y EDTA) La concentración del compuesto versus las curvas de inhibición porcentual se ajustan para generar los valores IC_{50}. Un experto en la técnica apreciará que los valores generados o bien como inhibición de porcentaje en una única concentración o los valores de IC_{50} están sujetos a variación experimental.

[00997] **Ensayos de célula P13K**

[00998] **1) Ensayo western en célula**

[00999] El ensayo pSer473 AKT LI-COR In-Cell Western es un ensayo inmunofluorescente cuantitativo que mide la fosforilación de serina 473 AKT (pSer473 AKT) en las líneas celulares tumorales WM266.4 y SKOV3 en cultivo celular.

[001000] Las células WM266.4 se propagan en medio esencial mínimo (MEM) (Invitrogen) que contiene L-glutamina, 10% de suero bovino fetal, 1 mM de MEM piruvato de sodio, y 0,1 mM de MEM aminoácidos no esenciales y las células

SKOV3 se propagan en medio McCoy's 5A (modificado) (Invitrogen) que contiene L-glutamina y 10% de suero bovino fetal. Ambas líneas celulares se mantienen en una cámara humidificada a 37°C con 5% de CO_2. Para el ensayo pSer473 AKT LI-COR In-Cell Western, las células 1.5 x 10^4 WM266.4 and 1.5 x 10^4 SKOV3 se cultivan en 100 µl de medio por pocillo en placas Optilux de 96 pocillos de base transparente, pared de color negro tratada con cultivo tisular (BD Biosciences) durante 16 a 20 horas. Antes de la adición de los compuestos, los medios celulares se eliminaron y se reemplazaron con 75 ul de medio fresco. Los compuestos de ensayo en DMSO se diluyeron 1:100 en medio. Los compuestos de ensayo diluidos se agregan a las células (25 ul por pocillo) en diluciones de 3 veces con un rango de concentración final de 0,0015 a 10 uM. Las células se incuban durante 2 horas en una cámara humidificada a 37°C con 5% de CO_2. Inmediatamente después de la incubación del compuesto, todo el líquido se elimina de los pocillos y las células se fijan con 4% de paraformaldehído en PBS (150 ul por pocillo) durante 20 minutos a temperatura ambiente. La solución de paraformaldehído se elimina de los pocillos y las células se permeabilizan con 200 ul de 0,1% de Triton X-100 en PBS por pocillo durante 10 min. x 3 a temperatura ambiente. Después de la eliminación de PBS 0,1% de Triton X-100, 150 µl de buffer bloqueador Odyssey (LI-COR Biosciences) se agrega a cada pocillo y las placas se incuban a temperatura ambiente durante 1.5 h. El buffer bloqueador se elimina de los pocillos y los anticuerpos primarios (Fosfo-AKT (Ser473) (D9E) XP™ Conejo mAb y AKT (pan) (40D4) Ratón mAb, Cell Signaling Technology) diluidos en buffer bloqueador Odyssey se agregan (50 µl por pocillo). Las placas se incuban a 4°C durante toda la noche. Las células se lavan durante 20 min. x 3 con PBS + 0,1% de Tween 20 (200 ul por pocillo). Los anticuerpos

secundarios (IRDye 680 IgG de cabra anti-conejo (H+L) e IRDye 800CW IgG de cabra anti-ratón (H+L), LI-COR Biosciences) se diluyen en buffer bloqueador Odyssey y se agregan a los pocillos (50 ul por pocillo) seguido de una incubación de 1 hora a temperatura ambiente, protegido de la luz. Las células se lavan durante 20 min. x 3 con PBS + 0,1% de Tween 20 (200 ul por pocillo). El buffer de lavado se elimina completamente de los pocillos después del último lavado, las placas se protegen de la luz hasta que se exploran y se analizan con el sistema de imágenes infrarrojo Odyssey (LI-COR Biosciences). Ambas pS473 AKT y AKT se visualizan simultáneamente con el fluoróforo de 680 nm que se indica mediante un color rojo y el fluoróforo de 800 nm que se indica mediante un color verde. Las unidades de fluorescencia relativas que derivan de las exploraciones permiten el análisis cuantitativo de ambas proteínas marcadas y la relación de pS473 AKT y AKT se calcula. Las curvas de respuesta a la concentración se generan diagramando las relaciones promedio de las muestras tratadas con el inhibidor de P13K con relación a los controles tratados con DMSO para determinar el cambio porcentual en la expresión de ps473 AKT, y los valores de inhibición porcentual en una única concentración o los valores de inhibición de desarrollo (IC_{50}) se determinan a partir de esas curvas. Un experto en la técnica apreciará que los valores generados o bien como inhibición de porcentaje en una única concentración o los valores de IC_{50} están sujetos a variación experimental.

[001001] 2) Ensayo de viabilidad de ATPlite

[001002] El ensayo ATPLite™ (perkin-Elmer) mide la adenosina-trifosfato celular (ATP) a través de la generación de una señal luminiscente formada a partir de la enzima luciérnaga luciferasa dependiente de ATP. La intensidad de la señal luminiscente se puede utilizar como

medida de la proliferación celular, y puede ser utilizada para evaluar los efectos antiproliferativos de los inhibidores de P13K.

[001003] Las células WM266.4 se propagaron en medio esencial mínimo (MEM) (Invitrogen) que contiene L-glutamina, 10% de suero bovino fetal, 1 mM de MEM piruvato de sodio, y 0,1 mM de MEM aminoácidos no esenciales se cultivan en placas transparentes/negras tratadas con cultivo tisular de 384 pocillos (Falcon) a 1 x 10^3 células por pocillo en un volumen de 75 ul en una cámara humidificada a 37°C con 5% de CO_2 durante 24 horas. Los compuestos de ensayo (2 ul en 100% de DMSO) se diluyen en 95 ul de medio de cultivo celular. Los compuestos de ensayo diluidos se agregan (8 ul por pocillo) a placas de 384 pocillos. El rango de concentración final de dilución en serie de 3 veces de los compuestos es 0,001 a 20 uM. Las placas se incuban durante 72 horas en una cámara humidificada a 37°C con 5% de CO_2. Una placa de control sin la adición del compuesto se procesa al inicio de la incubación de 72 horas como lectura en "tiempo cero" para la evaluación cuantitativa de viabilidad celular al inicio del ensayo. Después de 72 horas, todo excepto 25 µl de medio de cultivo celular se elimina de cada pocillo, seguido de la adición de 25 µl de reactivo ATPlite 1 paso (Perkin Elmer) a cada pocillo. La luminiscencia se mide sobre un contador de luminiscencia LEADSeeker (GE Healthcare Life Sciences). Las curves de respuesta de concentración se generan calculando la disminución de luminiscencia en muestras tratadas con el compuesto de ensayo con relación a los controles tratados con DMSO, y los valores de inhibición en porcentaje en una concentración única o los valores de inhibición de crecimiento (IC_{50}) se determinan a partir de las curvas. Un experto en la técnica apreciará que los valores generados o bien como

inhibición de porcentaje en una única concentración o los valores de IC_{50} están sujetos a variación experimental.

[001004] **Ensayos de células VPS34**

[001005] **1) ensayo de redistribución de dominio FYVE**

[001006] El ensayo de redistribución del dominio FYVE monitorea la translocación de EGFP-2XFYVE a partir de su ubicación inicial unida a (PtdIns(3)P) en endosomas tempranos al citoplasma en respuesta a los compuestos de ensayo. Las células U2OS recombinantes que expresan estables el dedo FYVE del homólogo humano del sustrato GenBank Acc. NM_004712) Hrs de tirosina quinasa regulado por el factor de crecimiento hepatocítico, se duplicó en tanden (GenBank Acc. NM_004712) y se fusionó al C-terminal de la proteína fluorescente verde mejorada (EGFP). Las células U2OS son células epiteliales adherentes que derivan del osteosarcoma humano. La expresión de EGFP-2X-FYVE es controlada mediante un promotor CMV estándar y la expresión continua se mantiene mediante la adición de geneticin al medio de cultivo. La localización de la proteína de fusión dentro de las células se refleja en el generador de imágenes Evotec Technologies OPERA y la señal de mancha integrada por señal celular se cuantifica utilizando Acapella software. Al utilizar esta información, los valores de inhibición en porcentaje a una concentración única o los valores IC_{50} para los inhibidores se pueden determinar.

[001007] Las células U2OS EGFP-2XFYVE se propagan en glucosa alta de medio Eagle modificado de Dulbecco (D-MEM) (Invitrogen cat. 11995) que contiene 10% de suero bovino fetal (HyClone cat. SH30071.02) y 0,5mg/ml de Geneticin (Invitrogen) y se mantiene en una cámara humidificada a 37°C con 5% de CO_2. 8 x 10^3 células se cultivan en 100 µl de medio

por pocillo en placas de 96 pocillos Optilux de base transparente de pared negra tratadas con tejido tisular (BDBiosciences) durante 16 a 24 horas.

[001008] Antes de la adición de los compuestos, los medios celulares se eliminaron y se reemplazaron con 75 ul de medio fresco. Los compuestos de ensayo en DMSO se diluyeron 1:100 en medio. Los compuestos de ensayo diluidos se agregan a las células (25 ul por pocillo) en diluciones de 3 veces con un rango de concentración final de 0,0015 a 10 uM. Las células se incuban durante 30 minutos en una cámara humidificada a 37°C con 5% de CO_2. Inmediatamente después de la incubación del compuesto, todo el líquido se elimina de los pocillos y las células se fijan con 4% de paraformaldehído en PBS (75 ul por pocillo) durante 15 minutos a temperatura ambiente. La solución de paraformaldehído se elimina de los pocillos y se lava una vez con PBS (100 µl por pocillo). El PBS se elimina y las células se incuban con tinte nuclear DRAQ5 (Alexis/Biostatus) (85 µl por pocillo). Las placas se cubren con lámina de metal adhesiva plástica Flash Plate y se reflejan sobre el generador de imágenes Evotec Technologies OPERA después de al menos 30 minutos de incubación. Las curvas de concentración se generan calculando la intensidad de mancha integrada por disminución de señal celular en muestras tratadas con el compuesto de ensayo con relación a los controles tratados con DMSO, y un inhibidor de control del 100%, y los valores de inhibición en porcentaje en una concentración única o los valores de inhibición de crecimiento (IC_{50}) se determinan a partir de las curvas. Un experto en la técnica apreciará que los valores generados o bien como inhibición de porcentaje en una única concentración o los valores de IC_{50} están sujetos a variación experimental.

[001009] Como se detalla anteriormente, los compuestos de la invención inhiben la P13K y/o la VPS34. Ejemplos de isoformas de P13-quinasa clase I son PI3K α, β, γ y δ. En ciertas realizaciones, los compuestos de la invención inhiben una o más isoformas de P13K. En ciertas realizaciones, los compuestos de la invención inhiben en forma selectiva una isoforma particular de P13K. Por ejemplo, en algunas realizaciones los compuestos de la invención inhiben en forma selectiva la P13Kα. En algunas realizaciones los compuestos de la invención inhiben en forma selectiva la P13Kβ

[001010] Tal como se utiliza en la presente, el inhibidor selectivo se refiere a los compuestos que inhiben una o más de las isoformas P13K particulares con al menos aproximadamente >10 veces, o al menos aproximadamente >20 veces, o al menos aproximadamente >30 veces en forma selectiva para la única o más isoformas de P13K particulares con relación a las otras isoformas P13-quinasa Clase I en un ensayo bioquímico. A modo de ejemplo, los compuestos que inhiben la P13K β con al menos aproximadamente >10 veces, o al menos aproximadamente >20 veces, o al menos aproximadamente >30 veces de selectividad con relación a la P13K α, γ o δ son inhibidores selectivos de P13Kβ. En forma alternativa, los compuestos que inhiben la P13K β y δ con al menos aproximadamente >10 veces, o al menos aproximadamente >20 veces, o al menos aproximadamente >30 veces de selectividad con relación a la P13K α, o γ son inhibidores selectivos de P13K β y δ .

[001011] Como se detalla anteriormente, los compuestos de la invención inhiben la P13K. En ciertas realizaciones, los compuestos inhiben una o más isoformas de la P13K. En otras realizaciones, los compuestos de la

invención inhiben la PI3Kalfa y tienen una IC_{50} > 1.0 µM. Por ejemplo, estos compuestos incluyen 2, 3, 5, 6, 7, 8, 9, 11, 12, 15, 16, 17, 18, 19, 21, 22, 23, 25, 26, 27, 33, 34, 36, 37, 39, 43, 44, 45, 46, 47, 49, 51, 52, 55, 58, 59, 60, 62, 63, 65, 66, 68, 69, 70, 73, 75, 76, 77, 78, 79, 80, 81, 84, 85, 87, 88, 89, 91, 92. En otras realizaciones, los compuestos de la invención tienen una IC_{50} < 1.0 µM pero > 0.1 µM. Por ejemplo, estos compuestos incluyen los compuestos 1, 4, 10, 14, 20, 24, 28, 30, 31, 32, 35, 38, 40, 42, 48, 53, 54, 56, 57, 61, 64, 67, 71, 72, 74, 82, 83, 86, 90. Incluso en otras realizaciones, los compuestos de la invención tienen una IC_{50} < 0.1 µM. Por ejemplo, estos compuestos incluyen los compuestos 13, 29, 41, 50. Incluso en otras realizaciones, los compuestos de la invención inhiben la PI3Kbeta y tienen una IC_{50} > 1.0 µM. Por ejemplo, estos compuestos incluyen 2, 18, 22, 24, 29, 49, 55, 63, 67, 78. En otras realizaciones, los compuestos de la invención tienen una IC_{50} < 1.0 µM but > 0.1 µM. Por ejemplo, estos compuestos incluyen los compuestos 1, 4, 6, 8, 10, 12, 15, 17, 23, 25, 26, 27, 28, 32, 33, 34, 35, 37, 38, 39, 40, 42, 46, 47, 48, 53, 54, 56, 57, 58, 60, 61, 62, 64, 68, 69, 70, 71, 72, 73, 74, 76, 79, 82, 83, 84, 89. Incluso en otras realizaciones, los compuestos de la invención tienen una IC_{50} < 0.1 µM. Por ejemplo, estos compuestos incluyen los compuestos 3, 5, 7, 9, 11, 13, 14, 16, 19, 20, 21, 30, 31, 36, 41, 43, 44, 45, 50, 51, 52, 59, 65, 66, 75, 77, 80, 81, 85, 86, 87, 88, 90, 91, 92.

[001012] En algunas realizaciones, los compuestos de la invención inhiben PI3K α y β a una concentración de 1.1 µM con la inhibición porcentual como se muestra en la tabla a continuación.

compuesto	**Inhibición porcentual de PI3Kα**	**Inhibición porcentual de PI3Kβ**	**compuesto**	**Inhibición porcentual de PI3Kα**	**Inhibición porcentual de PI3Kβ**
91	27	105	**111**	7	77
93	9	80	**112**	95	110
94	58	97	**113**	25	100
95	68	101	**114**	40	106
96	58	109	**115**	45	97
97	53	101	**116**	46	98
98	58	111	**117**	48	94
99	12	72	**118**	28	104
100	20	98	**119**	9	88
101	30	105	**120**	18	97
102	30	78	**121**	11	59
103	2	71	**122**	49	106
104	26	109	**123**	64	105
105	21	98	**124**	79	109
106	58	103	**125**	46	99
107	49	103	**126**	42	103
108	44	100	**127**	40	110
109	6	76	**128**	46	106
110	5	41			

[001013] En algunas realizaciones, los compuestos de la invención inhiben PI3K δ y γ a una concentración de 1,0 μM con la inhibición porcentual como se muestra en la tabla a continuación.

compuesto	**Inhibición porcentual de PI3Kδ**	**Inhibición porcentual de PI3Kγ**	**compuesto**	**Inhibición porcentual de PI3Kδ**	**Inhibición porcentual de PI3Kγ**
91	84.8	15.4	**112**	114.5	69.0
93	46.0	9.5	**113**	78.8	32.5
94	102.4	52.6	**114**	112.8	56.9
95	86.1	23.9	**115**	63.0	12.0
96	96.0	36.2	**116**	83.0	36.7
97	89.8	17.8	**117**	78.5	14.7
98	108.5	67.6	**118**	89.3	27.5
99	55.4	6.4	**119**	62.6	7.6
100	65.5	13.2	**120**	77.0	11.0
102	38.1	6.8	**121**	77.3	7.3
103	38.6	6.4	**122**	96.2	49.6
104	93.0	28.8	**123**	96.8	36.6
105	51.2	9.8	**124**	112.0	74.2
106	88.8	51.8	**125**	85.1	25.9
107	87.3	20.2	**126**	100.4	37.6
108	99.6	38.1	**127**	100.4	55.0
109	35.4	3.9	**128**	114.2	63.4
111	60.5	6.9			

[001014] En algunas realizaciones, los compuestos de la invención inhiben la VPS34 a una concentración de 1,0 µM con la inhibición porcentual como se muestra en la tabla a continuación.

compuesto	**Inhibición porcentual de VPS34**	**compuesto**	**Inhibición porcentual de VPS34**	**compuesto**	**Inhibición porcentual de VPS34**
93	19.2	**106**	34.4	**119**	19.5
94	30.6	**107**	45.8	**120**	38.3
95	167.0	**108**	62.4	**121**	64.8
96	47.8	**109**	24.0	**122**	55.2
97	45.0	**111**	46.8	**123**	45.1
98	68.9	**112**	37.8	**124**	78.8
99	46.7	**113**	18.1	**125**	37.1
100	36.6	**114**	131.4	**126**	44.0
102	28.2	**115**	39.7	**127**	33.7
103	7.2	**116**	54.2	**128**	88.1
104	63.2	**117**	28.6		
105	22.6	**118**	68.2		

compuesto	**p110 alfa Inhibición porcentual**	**p110 beta Inhibición porcentual**	**p110 gamma Inhibición porcentual**	**p110 delta Inhibición porcentual**
129	83	106	32	109
130	21	73	22	62
131	75	78	5	80

132	45	103	53	77
133	84	101	26	74
134	21	72	8	44
135	78	87	8	99
136	80	110	67	109
137	12	54	12	30
138	43	86	13	69
139	77	100	24	105
140	76	47	62	74
141	17	89	15	66
142	15	67	7	47
143	58	115	62	85
144	63	94	19	111
145	64	98	9	97
146	67	103	23	110
147	83	96	18	107
148	41	98	34	69
149	54	109	75	117
150	2	54	6	35
151	72	105	17	108
152	61	97	16	106
153	75	84	11	87
154	79	108	39	108
155	29	64	28	53
156	13	47	2	33
157	55	68	7	101
158	18	94	20	69
159	18	61	5	31
160	74	101	20	107
161	14	60	7	40
162	38	93	33	83
163	97	110	25	106

164	100	107	44	112
165	64	77	14	87
166	92	82	3	85
167	105	103	26	110
168	23	107	58	110
169	65	89	7	65
170	84	106	26	105
171	59	106	60	99
172	28	101	6	60
173	69	67	3	83
174	15	70	8	59
175	19	85	7	36
176	76	109	35	109
177	79	100	34	106
178	20	109	38	88
179	29	60	5	89
180	60	102	21	102
181	85	91	35	108
182	83	100	45	107
183	-2	16	3	9
184	76	112	16	112
185	16	97	9	50
186	68	109	65	92
187	32	95	25	77
188	47	94	36	82
189	89	96	21	106
190	3	60	7	33
191	26	97	30	90
192	48	90	12	100
193	26	69	13	46
194	17	18		
195	52	74	8	88

196	69	91	12	105
197	15	23	4	19
198	18	108	35	70
199	21	64	16	42
200	101	118	60	111
201	74	105	37	110
202	12	80	8	54
203	10	88	16	67
204	70	101	25	90
205	42	114	64	83
206	90	96	11	106
207	27	83	9	51
208	42	108	47	107
209	92	107	34	108
210	52	110	68	92
211	111	111	13	106
212	87	109	38	112
213	57	80	35	109
214	46	84	14	46
215	29	85	8	51
216	64	91	11	99
217	30	74	24	60
218	61	102	14	97
219	32	101	31	107
220	92	91	9	99
221	62	94	8	100
222	68	98	9	102
223	67	94	21	102
224	70	92	15	103
225	51	52	51	84
226	46	98	14	93
227	-2	76	3	24

228	24	94	11	57
229	62	105	16	106
230	57	93	29	102
231	34	104	47	77
232	38	105	26	67
233	61	97	28	74
234	60	100	10	104
235	65	101	17	66
236	11	53	10	48
237	61	89		
238	72	88	11	96
239	30	68	27	41
240	52	79	8	98
241	59	107	27	104
242	81	104	36	112
243	12	66	4	45
244	77	101	14	101
245	73	109	15	104
246	15	81	8	43
247	83	105	21	104
248	89	106	35	109
249	51	98	9	56
250	53	92	5	88
251	14	96	12	44
252	58	85	12	60
253	20	64	2	27
254	49	96	8	91
255	0	55	5	39
256	25	87	8	57
257	31	97	30	68
258	18	86	13	47
259	69	100	25	101

260	37	74	6	37
261	79	113	33	105
262	0	69	4	12
263	48	105	43	84
264	32	99	28	100
265	64	109	64	111
266	36	90	8	52
267	100	113	43	111
268	82	95	16	102
269	72	100	15	101
270	81	114	24	111
271	35	82	8	63
272	70	96	10	70
273	88	73	7	98
274	98	109	38	107
275	17	47	14	44
276	4	15	6	12
277	95	97	55	116
278	23	98	35	83
279	19	106	42	78
280	35	106	34	92
281	52	96	56	97
282	14	99	21	64
283	96	98	18	99
284	39	114	66	110
285	16	83	18	77
286	36	92	50	104
287	84	109	69	112
288	14	85	19	76
289	11	32	10	32
290	23	104	49	104
291	36	107	57	105

292	4	82	6	56
293	98	108	78	110
294	47	94	35	101
295	101	111	76	112
296	37	79	14	107
297	26	104	33	77
298	11	95	38	103
299	39	109	42	108
300	44	105	46	97
301	55	107	49	89
302	21	100	15	97
303	99	110	69	115
304	6	25	7	32
305	37	106	37	74
306	81	109	51	108
307	15	84	9	62
308	41	106	39	92
309	56	101	66	108
310	34	106	64	105
311	55	104	64	105
312	64	105	47	92
313	73	117	30	86
314	42	109	42	104
315	97	110	75	114
316	78	106	62	111
317	20	77	29	70
318	18	96	14	76
319	59	105	50	113
320	16	94	35	97
321	67	73	59	86
322	64	104	28	67
323	66	61	46	97

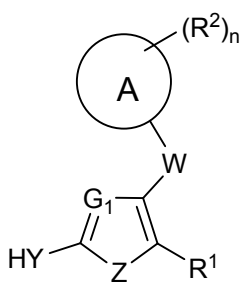
324	107	118	67	113
325	17	89	22	89
326	79	108	56	96
327	34	109	22	109
328	11	98	48	83
329	39	112	29	80
330	85	109	61	106
331	37	105	51	107
332	11	77	27	91
333	63	95	55	74
334	21	103	12	101
335	54	111	31	107
336	16	90	10	49
337	14	60	11	46
338	67	110	73	109
339	20	86	12	55
340	48	113	59	104
341	30	110	30	98
342	34	80	12	97
343	84	110	67	113
344	24	103	59	102
345	64	105	62	83
346	21	98	23	98
347	71	102	60	111
348	4	63	4	56
349	43	108	42	96
350	6	58	3	41
351	15	82	46	79
352	18	85	14	84
353	19	87	15	80
354	89	111	40	99
355	44	100	53	105

356	11	95	23	72
357	89	110	79	110
358	13	43	32	51
359	90	109	64	102
360	30	106	49	110
361	104	115	60	111
362	80	116	44	104
363	99	113	65	106
364	88	109	56	101
365	105	117	63	112
366	66	113	77	113
367	99	110	72	116
368	89	112	87	113
369	109	115	65	109
370	22	98	12	62

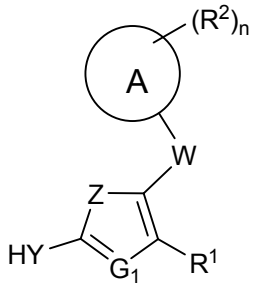
[001015] Mientras hemos descripto un número de realizaciones de esta invención, es evidente que nuestros ejemplos básicos pueden ser alterados para proporcionar otras realizaciones, las cuales utilizan los compuestos y los métodos de esta invención. Por lo tanto, se apreciará que el alcance de esta invención debe definirse por las reivindicaciones adjuntas más que por las realizaciones específicas, las cuales han sido representadas a modo de ejemplo.

REIVINDICACIONES

1. Un compuesto de formula **IA-a** o **IB-a:**



IA-a

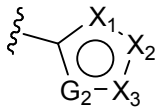


IB-a

o una sal aceptable para uso farmacéutico del mismo, donde:

Z es S o Se;

R^1 es CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$, donde:

CY es  ; donde:

G_2 es –N= , =N–, o $-N(R^{3'})$ –, donde:

cada aparición de R^3 y $R^{3'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido, donde:

X_1, X_2, y X_3, son cada uno de ellos independientemente N, $NR^{3'}$, O, S, o CR^4, siempre que sólo uno de X_1, X_2, o X_3 pueda ser O, S, o $NR^{3'}$;

cada aparición de R^4 es independientemente hidrógeno, -CN, halógeno, $-Z_3-R^6$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, o cicloalifático de 3 a 10 miembros, donde:

Z_3 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido, –O–, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$,

$-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, o $-OC(O)-$;

R^{4a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^6 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6},

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

o donde dos apariciones adyacentes de $R^{3'}$ o R^4, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de R^{12b}, tomadas juntas con un átomo de nitrógeno al cual están

unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_3 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o $-CN$;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5

heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

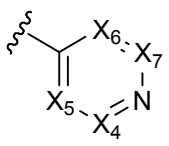
donde:

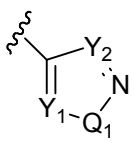
Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, $-S(O)-$, $S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o $-OC(O)-$;

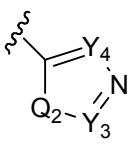
R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

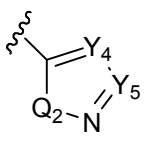
R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es un grupo opcionalmente sustituido seleccionado de:

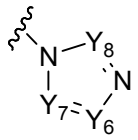


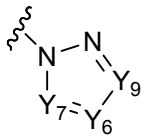






A , **B** , **C** , **D**





E o **F** ;

donde cada aparición de X_4, X_5, X_6, y X_7 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o $-NR^5$;

cada aparición de Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, e Y_9 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de Y_6, Y_7, Y_8, e Y_9 sean N;

o donde dos apariciones adyacentes de X_4 y X_5, X_6 y X_7, Y_1 y Q_1, Y_3 y Q_2, o Y_4 y Y_5 tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

donde R^{10} es $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, o $-V_1-T_1-R^{10b}$ donde:

V_1 es $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$,
$-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$,
$-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$,
$-SO_2-$, o $-SO_2NR^{11}-$;

cada aparición de R^{10a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo

de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}$ $C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, o $-C(O)N(R^{11})-O-$ o donde T_1 forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

cada aparición de R^{10b} es independientemente hidrógeno, halógeno, CN, $-NO2$, $-N(R^{11})2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})2$, $-S(O)2N(R^{11})2$, $-OC(O)N(R^{11})2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})2$, o $-N(R^{11})SO2N(R^{11})2$, o un grupo opcionalmente sustituido seleccionado de alifático C1-6, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{10c} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

R^{10a} y R^{10c} tomados juntos con un átomo de nitrógeno al cual están unidos forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional independientemente seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{11} es independientemente hidrógeno o , -$C(O)R^{11a}$, -CO_2R^{11a} , -$C(O)N(R^{11a})_2$, -$C(O)N(R^{11a})$-OR^{11a}, -SO_2R^{11a}, -$SO_2N(R^{11a})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{11a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^5 es independientemente hidrógeno o , -$C(O)R^{5a}$, -CO_2R^{5a}, -$C(O)N(R^{5b})_2$, -SO_2R^{5a}, -$SO_2N(R^{5b})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

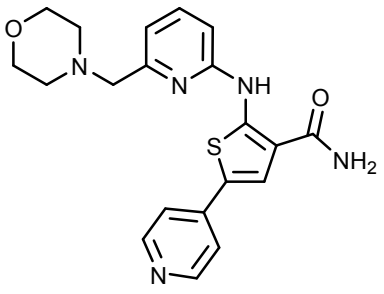
donde cada aparición de R^{5a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros,

heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

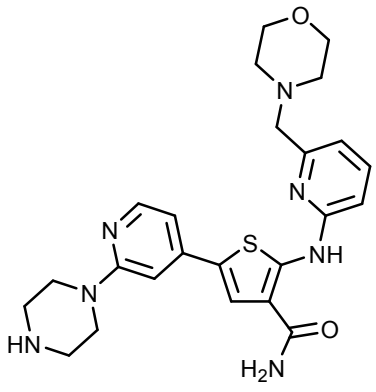
donde cada aparición de R^{5b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{5b} tomados juntos con el átomo de nitrógeno al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

siempre que:

a) para los compuestos de fórmula IB-a los compuestos sean diferentes de:

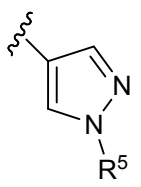
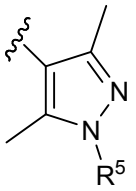
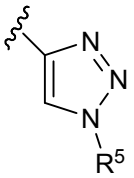


,

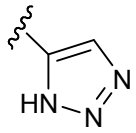
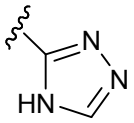
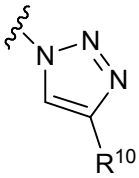


; y

cuando G^1 es CR^8, R^1 es $CONH_2$, y W es NH, entonces HY es diferente de

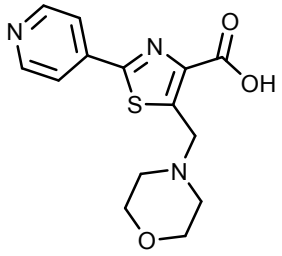
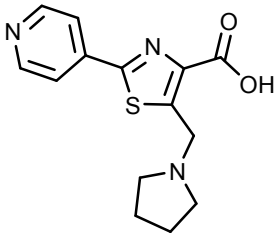
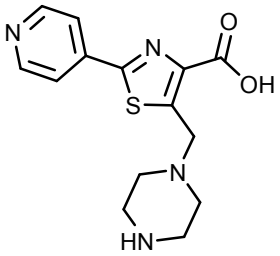




, , ,

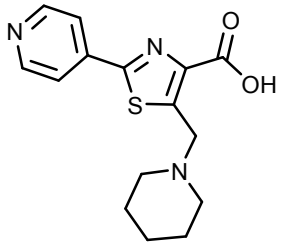
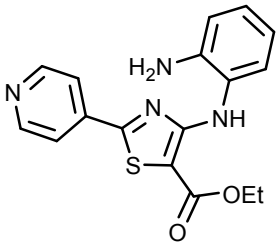




, , o ; y

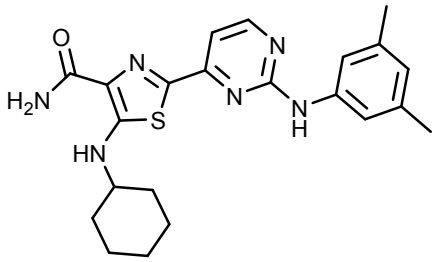
b) el compuesto es diferente de:

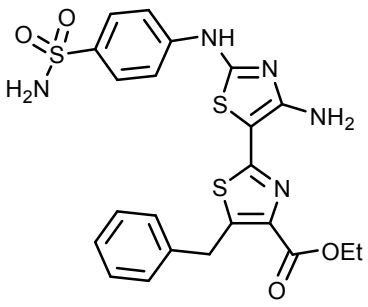
, , ,

, ,

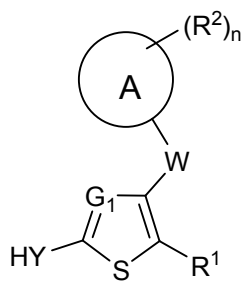


,

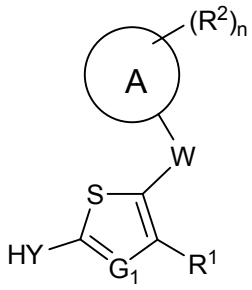


.

2. Un compuesto de formula **IA** o **IB:**



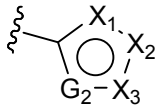
IA



IB

o una sal aceptable para uso farmacéutico del mismo, donde:

R^1 es CY, $-C(O)N(R^3)_2$, $-C(O)OR^3$, $-C(O)(NH)OH$, $-C(=NH)NHOH$, $-C(O)NR^3N(R^3)_2$, $-C(=N-NH_2)NH_2$, $-C(=N)N(R^3)_2$, donde:

CY es  ; donde:

G_2 es $-N=$, $=N-$, o $-N(R^{3'})-$, donde:

cada aparición de R^3 y $R^{3'}$ es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido, donde:

X_1, X_2, y X_3, son cada uno de ellos independientemente N, $NR^{3'}$, O, S, o CR^4, siempre que sólo uno de X_1, X_2, o X_3 pueda ser O, S, o $NR^{3'}$;

cada aparición de R^4 es independientemente hidrógeno, -CN, halógeno, $-Z_3-R^6$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, o cicloalifático de 3 a 10 miembros, donde:

Z_3 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido, –O-, $-N(R^{4a})-$, -S-, -S(O)-, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{4a}-$, $-N(R^{4a})C(O)-$, $-N(R^{4a})CO_2-$, $-S(O)_2NR^{4a}-$, $-N(R^{4a})S(O)_2-$, $-OC(O)N(R^{4a})-$, $-N(R^{4a})C(O)NR^{4a}-$, $-N(R^{4a})S(O)_2N(R^{4a})-$, o -OC(O)-;

R^{4a} es hidrógeno o un alifático C_{1-6} opcionalmente sustituido, y

R^6 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-4}`,

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

o donde dos apariciones adyacentes de $R^{3'}$ o R^4, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, y:

cada aparición de R^{12a} es independientemente halógeno, -CN, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$, o dos apariciones de

R^{12b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$,

$-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

n es 0 a 4;

W se selecciona de $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$,$-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o $-CN$;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

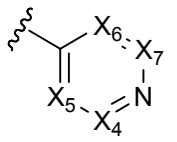
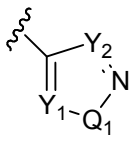
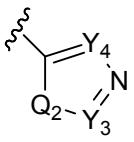
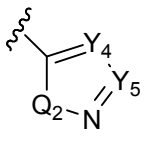
donde:

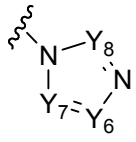
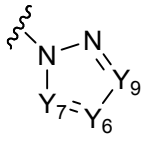
Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, $-S(O)-$, $S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o $-OC(O)-$;

R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es un grupo opcionalmente sustituido seleccionado de:


A ,

B ,

C ,

D


E ,

o **F** ;

donde cada aparición de X_4, X_5, X_6, y X_7 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o $-NR^5$;

cada aparición de Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, e Y_9 es independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de Y_6, Y_7, Y_8, e Y_9 sean N;

o donde dos apariciones adyacentes de X_4 y X_5, X_6 y X_7, Y_1 y Q_1, Y_3 y Q_2, o Y_4 y Y_5 tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre;

donde R^{10} es $-R^{10b}$, $-V_1-R^{10c}$, $-T_1-R^{10b}$, o $-V_1-T_1-R^{10b}$ donde:

V_1 es $-NR^{11}-$, $-NR^{11}-C(O)-$, $-NR^{11}-C(S)-$, $-NR^{11}-C(NR^{11})-$, $-NR^{11}C(O)OR^{10a}-$, $-NR^{11}C(O)NR^{11}-$, $-NR^{11}C(O)SR^{10a}-$, $-NR^{11}C(S)OR^{10a}-$, $-NR^{11}C(S)NR^{11}-$, $-NR^{11}C(S)SR^{10a}-$, $-NR^{11}C(NR^{11})OR^{10a}-$, $-NR^{11}C(NR^{11})NR^{11}-$, $-NR^{11}S(O)_2-$, $-NR^{11}S(O)_2NR^{11}-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{11}-$, $-C(O)NR^{11}O-$, $-SO_2-$, o $-SO_2NR^{11}-$;

cada aparición de R^{10a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

T_1 es una cadena de alquileno C_1-C_6 opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{11})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{11})-$, $-S(O)_2N(R^{11})-$, $-OC(O)N(R^{11})-$, $-N(R^{11})C(O)-$, $-N(R^{11})SO_2-$, $-N(R^{11a})C(O)O-$, $-NR^{10a}$ $C(O)N(R^{10a})-$, $-N(R^{10a})S(O)_2N(R^{10a})-$, $-OC(O)-$, or $-C(O)N(R^{11})-O-$ o donde T_1 forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

cada aparición de R^{10b} es independientemente hidrógeno, halógeno, CN, $-NO_2$, $-N(R^{11})_2$, $-OR^{10a}$, $-SR^{10a}$, $-S(O)_2R^{10a}$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-C(O)N(R^{11})_2$, $-S(O)_2N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-N(R^{11})C(O)R^{10a}$, $-N(R^{11})SO_2R^{10a}$, $-N(R^{11})C(O)OR^{10a}$, $-N(R^{11})C(O)N(R^{11})_2$, o $-N(R^{11})SO_2N(R^{11})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{10c} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

R^{10a} y R^{10c} tomados juntos con un átomo de nitrógeno al cual están unidos forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional independientemente seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{11} es independientemente hidrógeno o , $-C(O)R^{11a}$, $-CO_2R^{11a}$, $-C(O)N(R^{11a})_2$, $-C(O)N(R^{11a})-OR^{11a}$, $-SO_2R^{11a}$, $-SO_2N(R^{11a})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

donde cada aparición de R^{11a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático $C1_{-6}$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^5 es independientemente hidrógeno o , $-C(O)R^{5a}$, $-CO_2R^{5a}$, $-C(O)N(R^{5b})_2$, $-SO_2R^{5a}$, $-SO_2N(R^{5b})_2$, o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

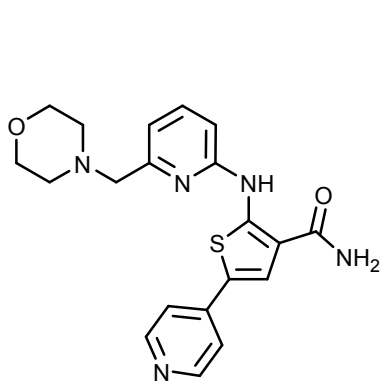
donde cada aparición de R^{5a} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros,

heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

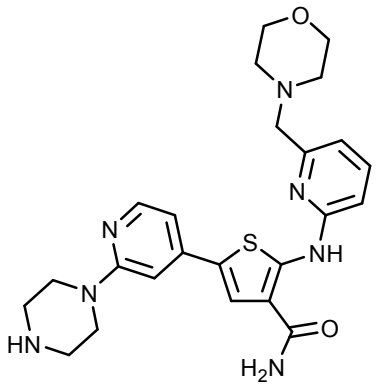
donde cada aparición de R^{5b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{5b} tomados juntos con el átomo de nitrógeno al cual están unidos, forman un grupo opcionalmente sustituido seleccionado de heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

siempre que:

a) para los compuestos de fórmula IB los compuestos sean diferentes de:

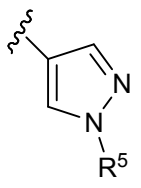
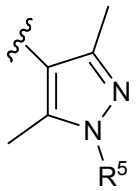
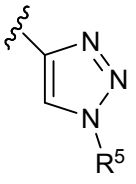


,

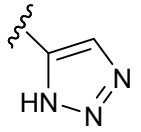
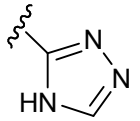
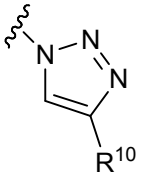


; y

cuando G^1 es CR^8, R^1 es $CONH_2$, y W es NH, entonces HY es diferente de

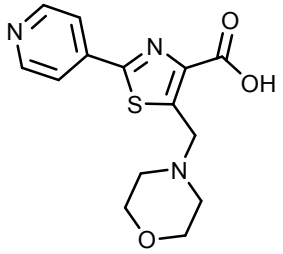
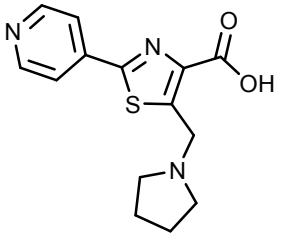
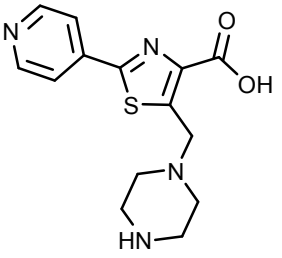




, , ,

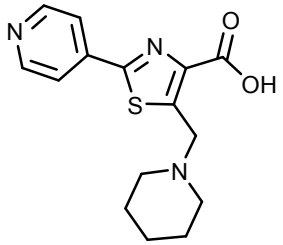
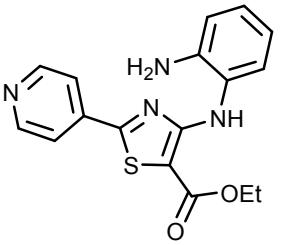




, , o ; y

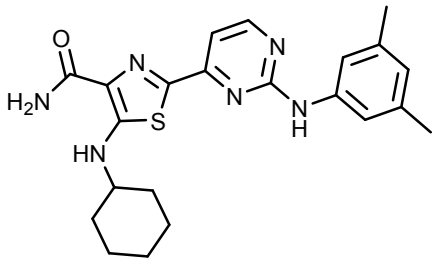
b) el compuesto es diferente de:

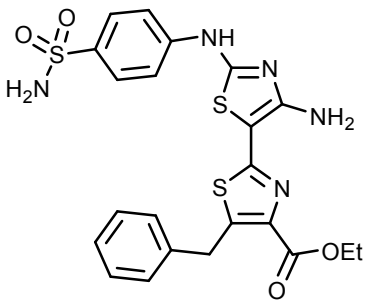
, , ,

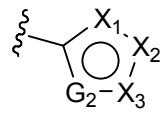
, ,



,



.

3. El compuesto de la reivindicación 1 o 2, donde R^1 es CY, y CY es  .

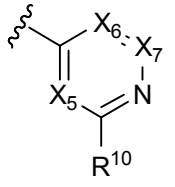
4. El compuesto de la reivindicación 1 o 2, donde X_1 es N, G_2 es $-N(R^{3'})-$, y X_2 y X_3 son CH.

5. El compuesto de la reivindicación 1 o 2, donde X_1 y X_2 son N, G_2 es $-N(R^{3'})-$, y X_3 es CH.

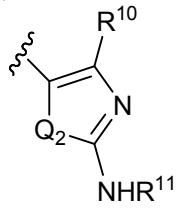
6. El compuesto de la reivindicación 1 o 2, donde X_3 es N, G_2 es $-N(R^{3'})-$, y X_1 y X_2 son CH.

7. El compuesto de la reivindicación 1 o 2, donde X_1 es N, X_2 es CH, X_3 es $-N(R^{3'})-$, y G_2 es =N-.

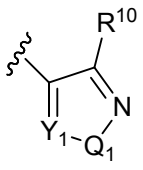
8. El compuesto de la reivindicación 1 o 2, donde HY se selecciona de:



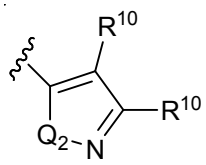
H ,

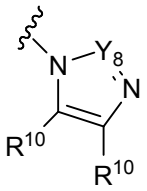


J ,



K ,



L , o  **M;**

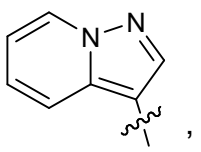
donde cada aparición de X_5, X_6, y X_7 es independientemente –CR^{10} o N, siempre que no más de dos apariciones de X_5, X_6, y X_7 sean N;

cada aparición de Q_1 y Q_2 es independientemente S, O o –NR^5;

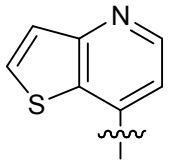
cada aparición de Y_1 e Y_7 es independientemente –CR^{10} o N;

o donde dos apariciones adyacentes de X_6 y X_7, o Y_1 y Q_1, tomados juntos con el átomo al cual están unidos, forman un grupo fusionado opcionalmente sustituido seleccionado de arilo de 5 a 6 miembros, o heteroarilo de 5 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre.

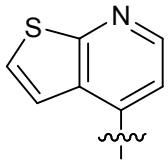
9. El compuesto de la reivindicación 8, donde HY se selecciona de:

 ,

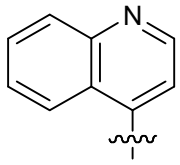
i

 ,

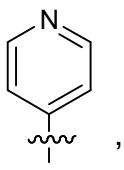
ii

 ,

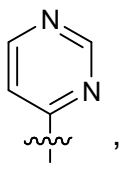
iii

 ,

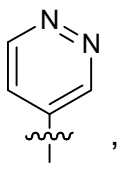
iv

 ,

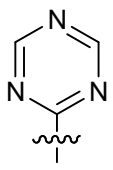
v

 ,

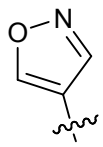
vi

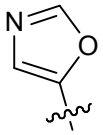
 ,

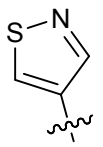
vii

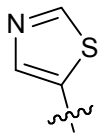
 ,

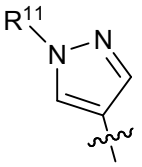
viii

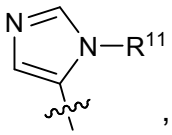

,
ix

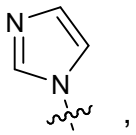

,
x

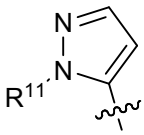

,
xi

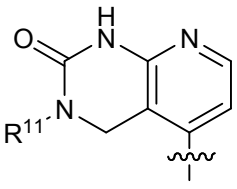

,
xii

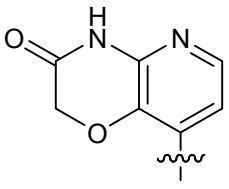

,
xiii

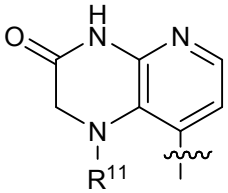

,
xiv

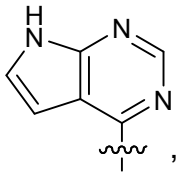

,
xv

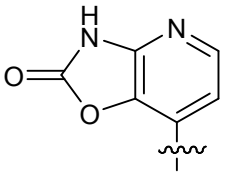

,
xvi

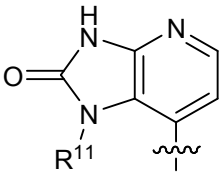

,
xvii

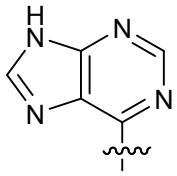

,
xviii

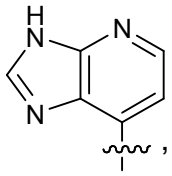

,
xix

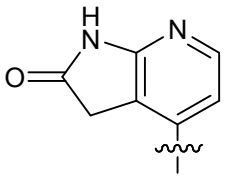

,
xx

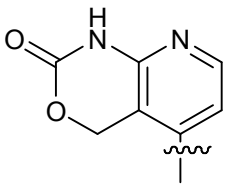

,
xxi

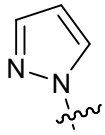

,
xxii

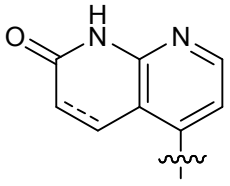

,
xxiii

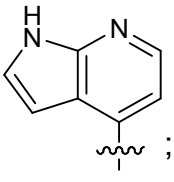

,
xxiv


,
xxv


,
xxvi

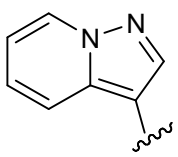

,
xxvii

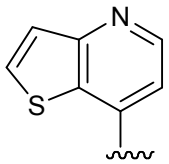

, or
xxviii

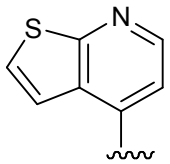

;
xxix

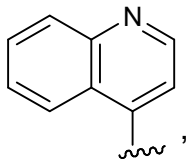
donde cada grupo HY está además opcionalmente sustituido con una o más apariciones de R^{10}, y ------ en **xviii** representa un enlace simple o un enlace doble.

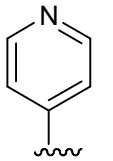
10. El compuesto de la reivindicación 9, donde HY se selecciona de:

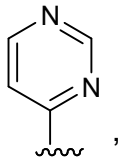

i

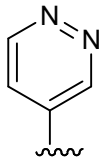

ii

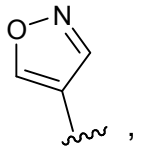

iii

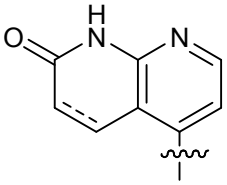

iv

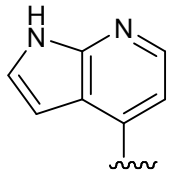

V

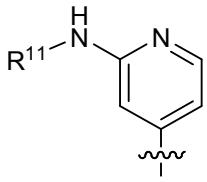

vi

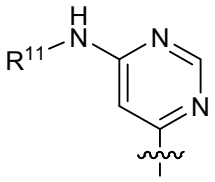

vii

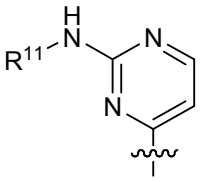

ix

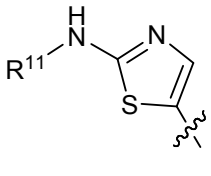

xxviii


xxix


xxx


xxxi


xxxii


xxxiii

donde cada grupo HY está además opcionalmente sustituido con una o más apariciones de R^{10}, y ------ en **xviii** representa un enlace simple o un enlace doble.

11. El compuesto de la reivindicación 1 o 2, donde G_1 es $C(R^8)$.

12. El compuesto de la reivindicación 1 o 2, donde G_1 es CH.

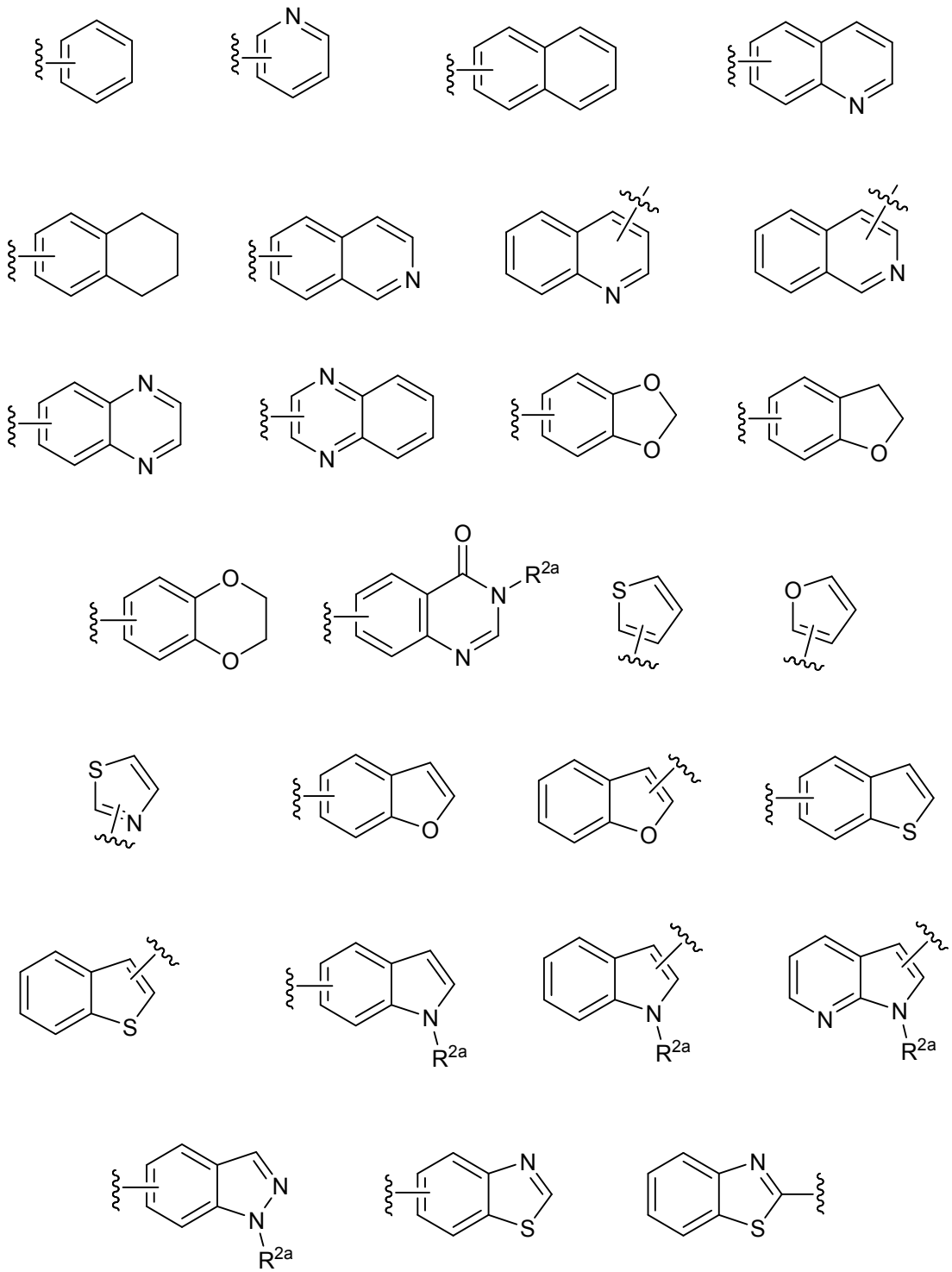
13. El compuesto de la reivindicación 1 o 2, donde G_1 es N.

14. El compuesto de la reivindicación 1 o 2, donde W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN; y donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido, y cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 3 a 6 miembros opcionalmente sustituido.

15. El compuesto de la reivindicación 14, donde W es $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, o $-N(R^{7a})C(O)-$, donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido; y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

16. El compuesto de la reivindicación 1 o 2, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

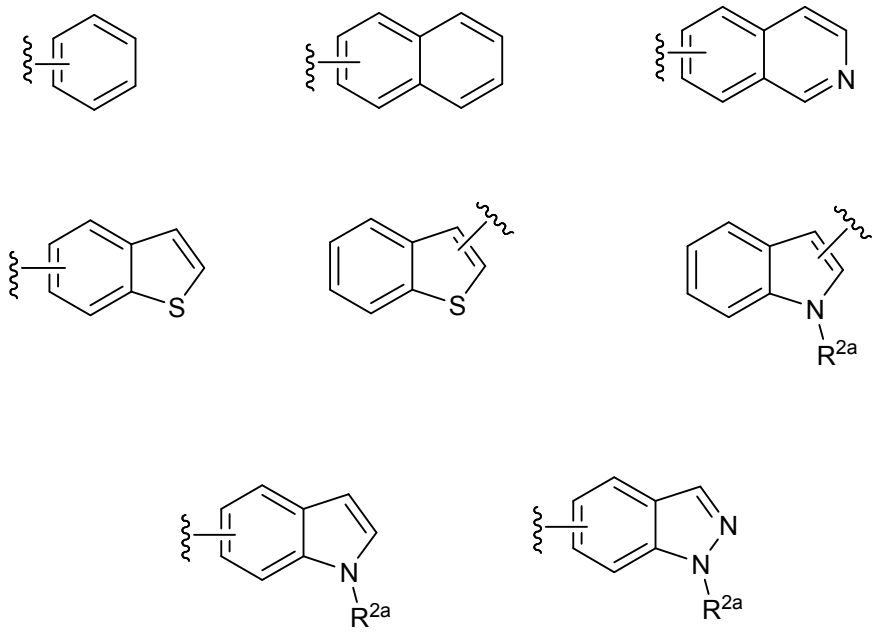
17. El compuesto de la reivindicación 16, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

18. El compuesto de la reivindicación 16, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

19. El compuesto de la reivindicación 16, donde:

el anillo A es un grupo naftilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

20. El compuesto de la reivindicación 16, donde:

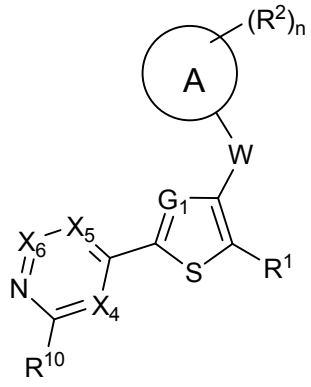
el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

21. El compuesto de la reivindicación 19, donde el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2.

22. El compuesto de la reivindicación 19, donde el anillo A es un grupo naftilo, y n es 0.

23. El compuesto de la reivindicación 20, donde el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

24. Un compuesto que tiene la siguiente fórmula **II**:



II

donde:

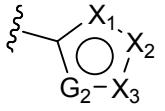
X_4, X_5 y X_6 son cada uno de ellos independientemente $-CR^{10}$ o N, siempre que no más de dos apariciones de X_4, X_5 y X_6 sean N;

o dos grupos adyacentes seleccionados de R^{10}, X_4, X_5, y X_6, tomados juntos, forman un grupo opcionalmente sustituido seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,; arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

25. El compuesto de la reivindicación 24, donde uno de X^4, X^5, o X^6 es N.

26. El compuesto de la reivindicación 24, donde todos de X^4, X^5, o X^6 son CR^{10}.

27. El compuesto de la reivindicación 24, donde cada aparición de R^{10} se selecciona independientemente de –CN, $-OR^{10a}$, $-N(R^{11})_2$, alquilo C_{1-4}, $-N(R^{11})COR^{10a}$, o donde dos apariciones de R^{10} tomadas juntas con los átomos a los cuales están unidos forman un grupo opcionalmente sustituido seleccionado de un anillo cicloalifático de 5 o 6 miembros fusionado, heterociclilo de 4 a 10 miembros, arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros, donde los anillos heterociclilo y heteroarilo tienen 1 a 3 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre.

28. El compuesto de la reivindicación 24, donde R^1 es CY, y CY es 

.

29. El compuesto de la reivindicación 28, donde X_1 es N, G_2 es $-N(R^{3'})-$, y X_2 y X_3 son CH.

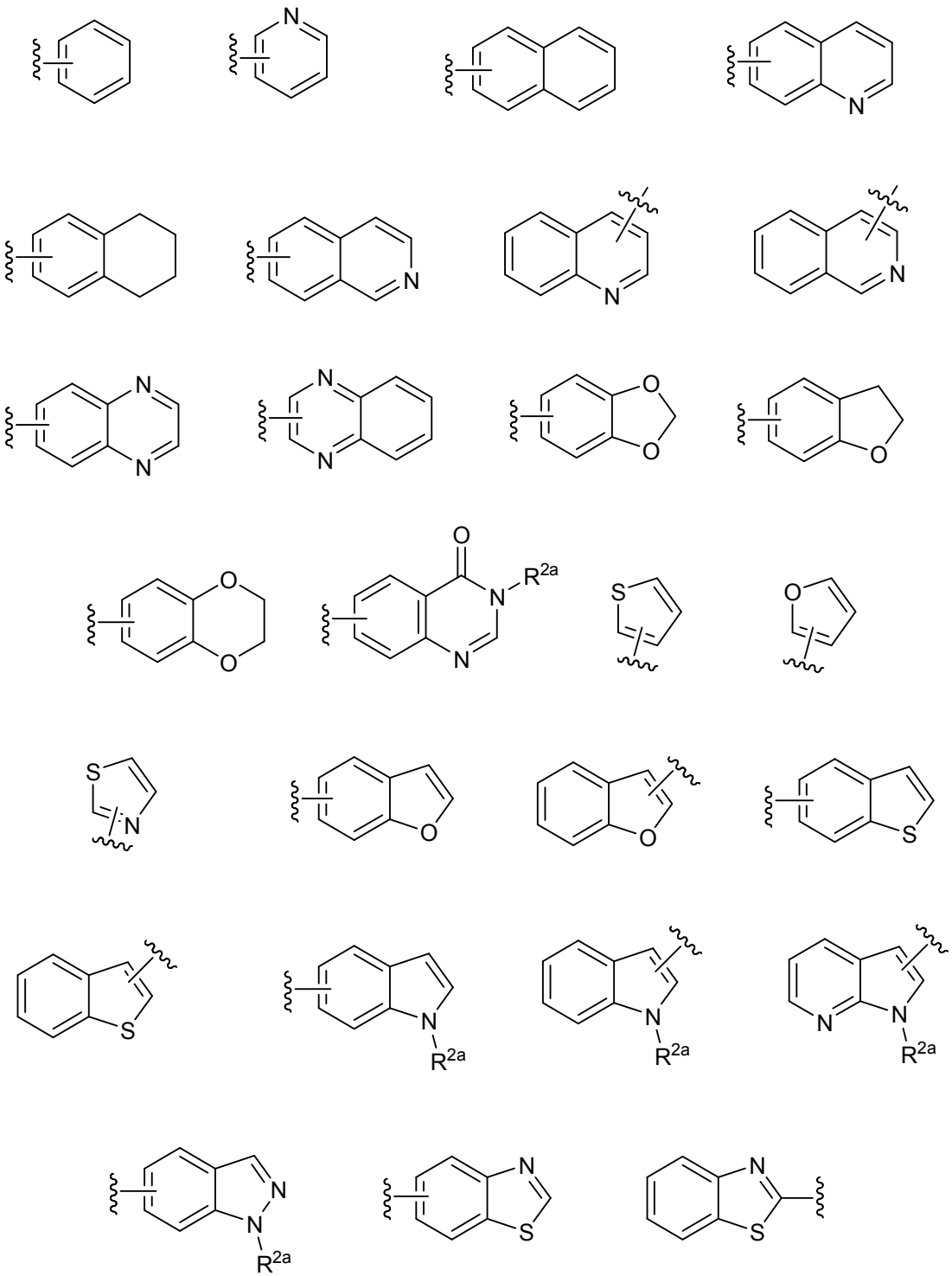
30. El compuesto de la reivindicación 28, donde X_1 y X_2 son N, G_2 es $-N(R^{3'})-$, y X_3 es CH.

31. El compuesto de la reivindicación 28, donde X_3 es N, G_2 es -$N(R^{3'})$-, y X_1 y X_2 son CH.

32. El compuesto de la reivindicación 28, donde X_1 es N, X_2 es CH, X_3 es -$N(R^{3'})$-, y G_2 es =N-.

33. El compuesto de la reivindicación 24, donde el anillo A es arilo de 6 a 10 miembros opcionalmente sustituido o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

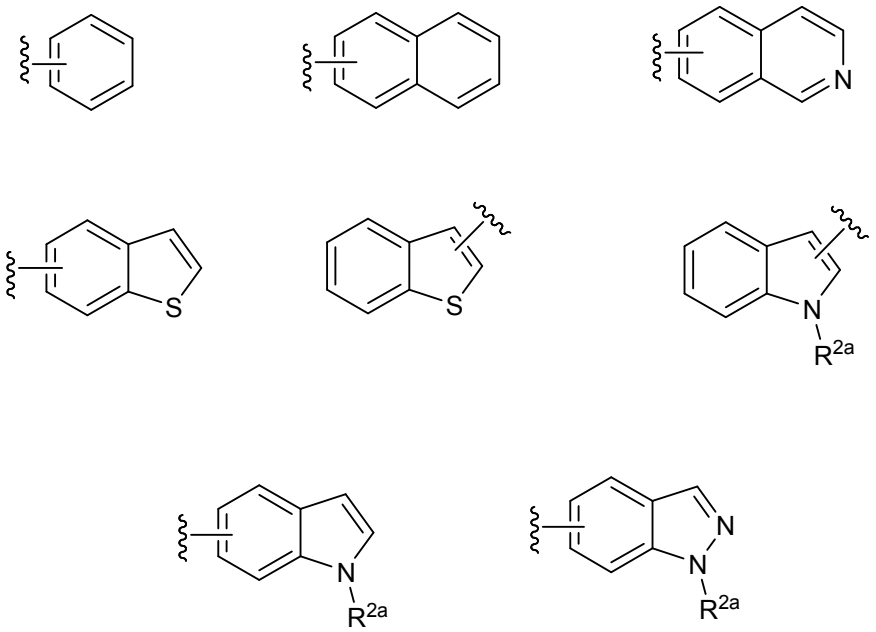
34. El compuesto de la reivindicación 33, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

35. El compuesto de la reivindicación 33, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

36. El compuesto de la reivindicación 33, donde:

el anillo A es un grupo naftilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

37. El compuesto de la reivindicación 33, donde el anillo A es un grupo fenilo opcionalmente sustituido con 1 a 3 apariciones independientes de halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

38. El compuesto de la reivindicación 36, donde el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2.

39. El compuesto de la reivindicación 38, donde el anillo A es un grupo naftilo, y n es 0.

40. El compuesto de la reivindicación 37, donde el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

41. El compuesto de la reivindicación 24, donde W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 se selecciona de hidrógeno, alifático C_{1-4} opcionalmente sustituido, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN; y

donde cada aparición de R^{7e} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

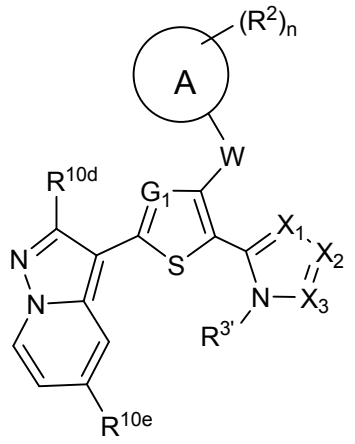
donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno,

oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

42. El compuesto de la reivindicación 41, donde W es $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, o $-N(R^{7a})C(O)-$, donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido; y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

43. Un compuesto que tiene la fórmula **III:**



III

donde R^{10d} es hidrógeno, o alquilo C_{1-4} opcionalmente sustituido, y R^{10e} es R^{10}.

44. El compuesto de la reivindicación 43, donde R^{10e} es $-T_1-R^{10b}$, o hidrógeno.

45. El compuesto de la reivindicación 43, donde R^{10e} es hidrógeno, $-CH_2N(R^{11})_2$, o $-CH_2N(R^{11})C(=NR^{11})N(R^{11})_2$, donde R^{11} es $-C(O)R^{11a}$, un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

46. El compuesto de la reivindicación 45, donde cuando R^{11} es un grupo alifático C_{1-6} opcionalmente sustituido, el grupo alifático C_{1-6} además se define como $-(CH_2)_xR^{11b}$ o $-(CH_2)_xN(R^{11b})_2$, $-(CH_2)_xN(R^{11b})C(O)R^{11b}$, o $-(CH_2)_xN(R^{11b})C(O)OR^{11b}$, donde R^{11b} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, y x es 1 a 3.

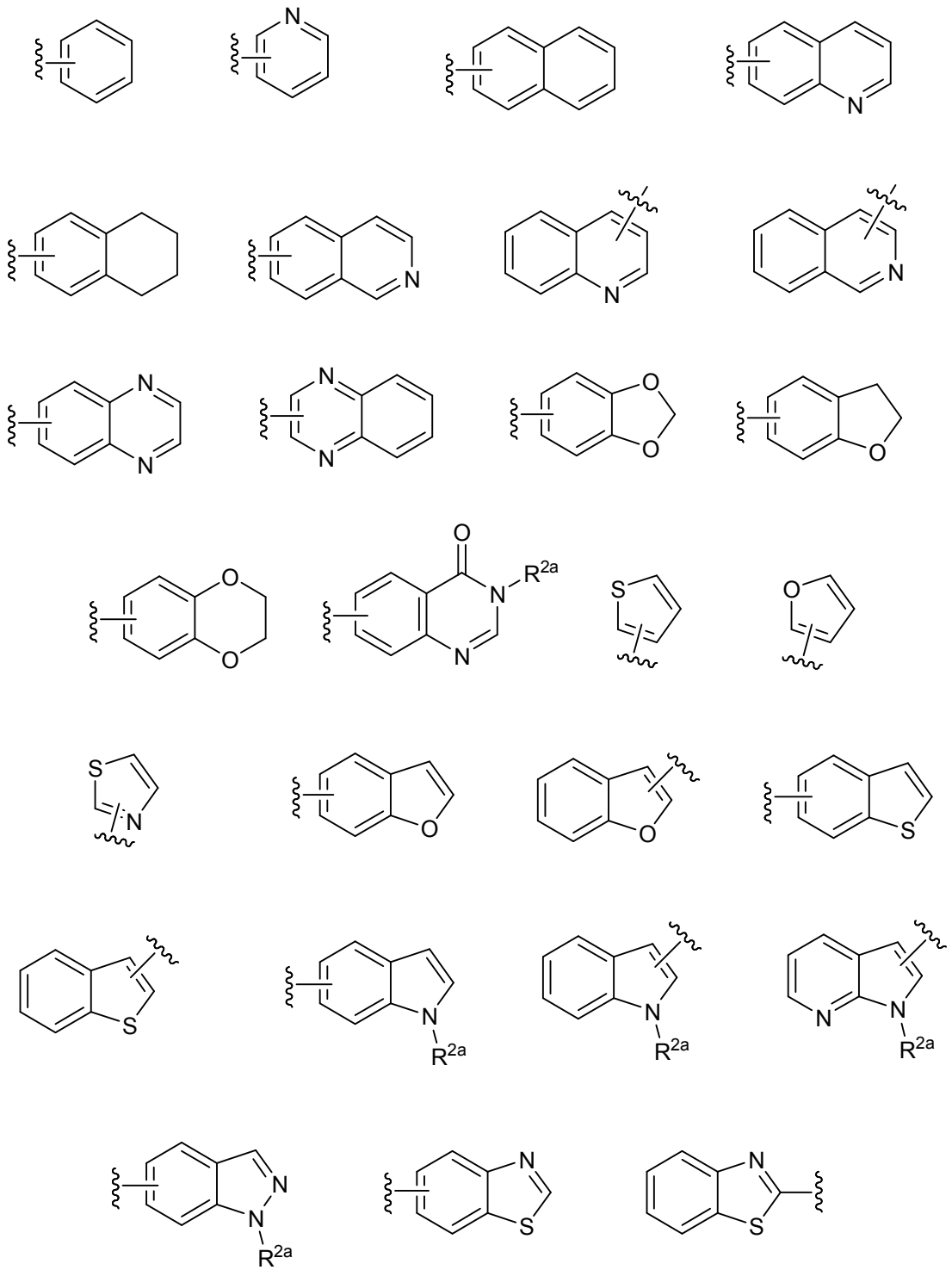
47. El compuesto de la reivindicación 43, donde X_1 es N, y X_2 y X_3 son CH.

48. El compuesto de la reivindicación 43, donde X_1 y X_2 son N, y X_3 es CH.

49. El compuesto de la reivindicación 43, donde X_3 es N, y X_1 y X_2 son CH.

50. El compuesto de la reivindicación 43, donde el anillo A es arilo de 6 a 10 miembros opcionalmente sustituido o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

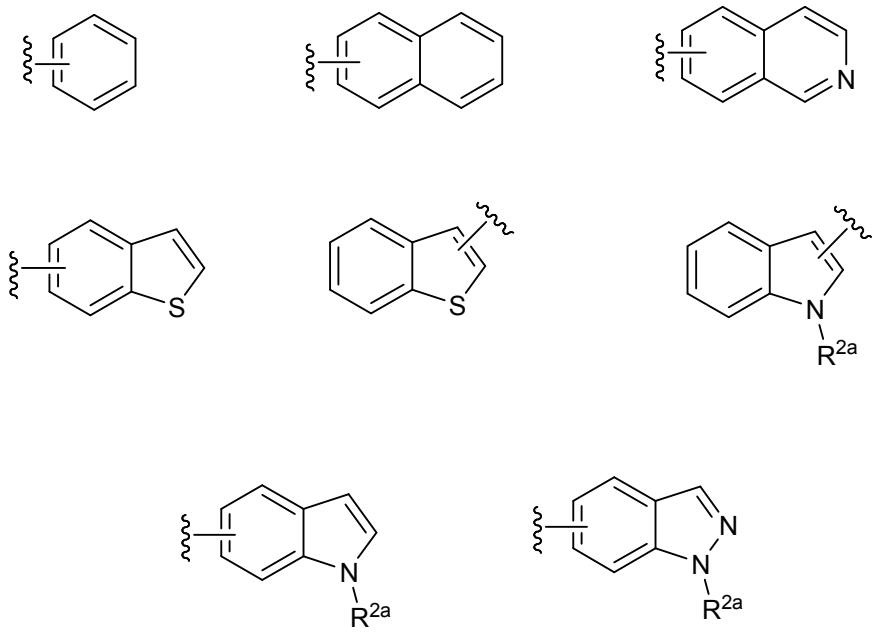
51. El compuesto de la reivindicación 50, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

52. El compuesto de la reivindicación 50, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

53. El compuesto de la reivindicación 50, donde:

el anillo A es un grupo naftilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H;

54. El compuesto de la reivindicación 50, donde el anillo A es un grupo fenilo opcionalmente sustituido con 1 a 3 apariciones independientes de halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

55. El compuesto de la reivindicación 54, donde el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

56. El compuesto de la reivindicación 53, donde el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2.

57. El compuesto de la reivindicación 56, donde el anillo A es un grupo naftilo, y n es 0.

58. El compuesto de la reivindicación 43, donde W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 se selecciona de hidrógeno, alifático C_{1-4} opcionalmente sustituido, $-N(R^{7b})_2$, $-OR^{7a}$, $-SR^{7a}$, halo, o –CN; y

donde cada aparición de R^{7e} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

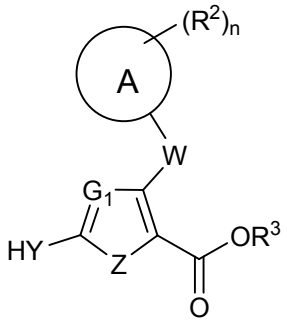
donde cualquiera de dos apariciones de R^7, R^{7a}, o R^{7b} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno,

oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o

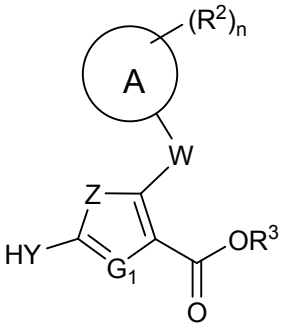
cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

59. El compuesto de la reivindicación 58, donde W es $-C(H)(N(R^{7b})_2)-$, $-CH_2-$, $-C(H)(OR^{7a})-$, $-NR^{7b}-$, o $-N(R^{7a})C(O)-$, donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido; y cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

60. Un compuesto de formula **IA-i-a** o **IB-i-a:**



IA-i-a



IB-i-a

o una sal aceptable para uso farmacéutico del mismo, donde:

Z es S o Se;

R^3 es hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, o:

dos grupos R^2 adyacentes se toman juntos con sus átomos intervinientes para formar un anillo parcialmente insaturado, saturado de 4 a 7 miembros opcionalmente sustituido, o arilo que tiene de 0 a 4 heteroátomos seleccionados de nitrógeno, oxígeno o azufre;

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$,

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{12b} tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10

miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno, $-N(R^{7b})_2$, o un grupo opcionalmente sustituido seleccionado de cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

W se selecciona de un enlace covalente, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7c}$, $-SR^{7a}$, o F;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, , $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

cada aparición de R^{7c} es independientemente un alifático C_{1-6} opcionalmente sustituido o un cicloalifático de 3 a 7 miembros opcionalmente sustituido; o

donde cualquiera de dos apariciones de R^7, R^{7a}, R^{7b} o R^{7c} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente

sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

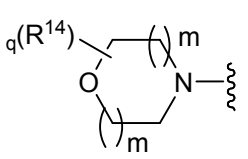
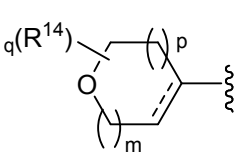
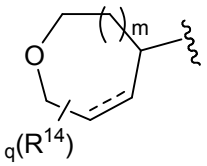
G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

donde:

Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, -S(O)-, $S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o -OC(O)-;

R^{8a} es hidrógeno o un alifático C_{1-4} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es  ,  o  ;

------ representa un enlace simple o un enlace doble;

donde cada aparición de R^{14} es independientemente $-R^{14a}$ o $-T_1-R^{14d}$, donde:

cada aparición de R^{14a} como permiso de valencia y estabilidad, es independientemente flúor, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$,

$-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, o $-N(R^{14e})SO_2N(R^{14b})_2$, o dos apariciones de R^{14b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14e} es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido; y

T_1 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, o $-C(O)N(R^{14a})-O-$ o donde T_1 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

n es 0 a 6;

q es 0 a 4;

m es 1 o 2; y

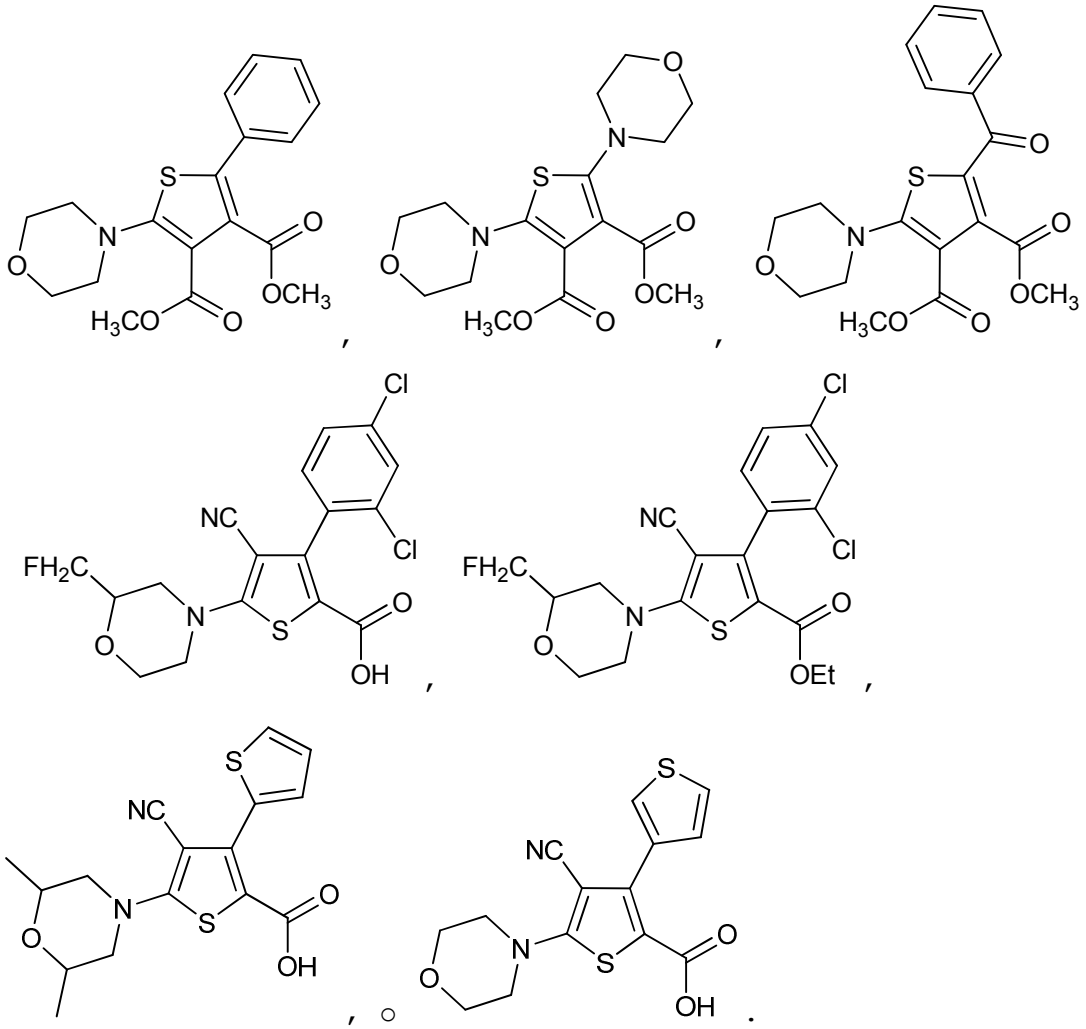
P es 0, 1, o 2;

siempre que para los compuestos en donde Z es S:

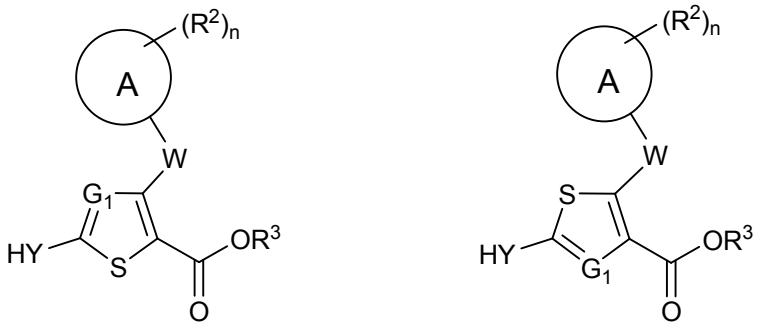
a) Cuando G_1 es C-CN, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido, 2-clorofenilo, 4-clorofenilo, 2-fluorofenilo, 4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 4-metilfenilo, 3-metoxifenilo, 4-metoxifenilo, 3,4-dimetoxifenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, o 3-(acetilamino)fenilo;

b) cuando G_1 es N, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido o 2-clorofenilo; y

c) el compuesto es diferente de:



61. Un compuesto de formula **IA** o **IB:**



IA-i **IB-i**

o una sal aceptable para uso farmacéutico del mismo, donde:

R^3 es hidrógeno o un alifático C_{1-6} opcionalmente sustituido;

El anillo A es un grupo seleccionado de cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^2 es independientemente $-R^{12a}$, $-T_2-R^{12d}$, o $-V_2-T_2-R^{12d}$, o:

dos grupos R^2 adyacentes se toman juntos con sus átomos intervinientes para formar un anillo parcialmente insaturado, saturado de 4 a 7 miembros opcionalmente sustituido, o arilo que tiene de 0 a 4 heteroátomos seleccionados de nitrógeno, oxígeno o azufre;

cada aparición de R^{12a} es independientemente halógeno, $-CN$, $-NO_2$, $-R^{12c}$, $-N(R^{12b})_2$, $-OR^{12b}$, $-SR^{12c}$, $-S(O)_2R^{12c}$, $-C(O)R^{12b}$, $-C(O)OR^{12b}$, $-C(O)N(R^{12b})_2$, $-S(O)_2N(R^{12b})_2$, $-OC(O)N(R^{12b})_2$, $-N(R^{12e})C(O)R^{12b}$, $-N(R^{12e})SO_2R^{12c}$, $-N(R^{12e})C(O)OR^{12b}$, $-N(R^{12e})C(O)N(R^{12b})_2$, o $-N(R^{12e})SO_2N(R^{12b})_2$,

cada aparición de R^{12b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; o dos apariciones de R^{12b} tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un anillo heterociclilo de 4 a 7 miembros que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10

miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12d} es independientemente hidrógeno, $-N(R^{7b})_2$, o un grupo opcionalmente sustituido seleccionado de cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{12e} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido;

cada aparición de V_2 es independientemente $-N(R^{12e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{12e})-$, $-S(O)_2N(R^{12e})-$, $-OC(O)N(R^{12e})-$, $-N(R^{12e})C(O)-$, $-N(R^{12e})SO_2-$, $-N(R^{12e})C(O)O-$, $-N(R^{12e})C(O)N(R^{12e})-$, $-N(R^{12e})SO_2N(R^{12e})-$, $-OC(O)-$, o $-C(O)N(R^{12e})-O-$; y

T_2 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente está interrumpida por $-N(R^{13})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{13})-$, $-S(O)_2N(R^{13})-$, $-OC(O)N(R^{13})-$, $-N(R^{13})C(O)-$, $-N(R^{13})SO_2-$, $-N(R^{13})C(O)O-$, $-N(R^{13})C(O)N(R^{13})-$, $-N(R^{13})S(O)_2N(R^{13})-$, $-OC(O)-$, o $-C(O)N(R^{13})-O-$ o donde T_2 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo donde R^{13} es hidrogeno o un grupo alifático C_{1-4} opcionalmente sustituido;

W se selecciona de un enlace covalente, $-C(R^7)_2-$, $-C(=C(R^7)_2)-$, $-C(R^7)_2O-$, $-C(R^7)_2NR^{7a}-$, $-O-$, $-N(R^{7b})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)NR^{7a}-$, o $-N(R^{7a})C(O)-$, donde:

cada aparición de R^7 es independientemente hidrógeno o un grupo opcionalmente sustituido

seleccionado de alifático C_{1-6}, arilo de 6 a 10 miembros, heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, $-N(R^{7b})_2$, $-OR^{7c}$, $-OR^{7a}$, $-SR^{7a}$, o F;

cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido o cicloalifático C_{3-6} opcionalmente sustituido;

cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, cicloalifático C_{3-6} opcionalmente sustituido, $-C(O)R^{7a}$, , $-C(O)OR^{7a}$, $S(O)R^{7a}$, o $-S(O)_2R^{7a}$; o

cada aparición de R^{7c} es independientemente un alifático C_{1-6} opcionalmente sustituido o un cicloalifático de 3 a 7 miembros opcionalmente sustituido; o

donde cualquiera de dos apariciones de R^7, R^{7a}, R^{7b} o R^{7c} tomadas juntas con el átomo al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

o donde cualquiera de dos apariciones de R^{7a} y R^2, o R^{7b} y R^2 tomadas juntas con el átomo de nitrógeno al cual están unidas, forman un grupo opcionalmente sustituido seleccionado del anillo cicloalifático de 3 a 6 miembros, arilo de 6 a 10 miembros, heterociclilo de 3 a 6 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, o heteroarilo de 5 a 10 miembros

que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre,

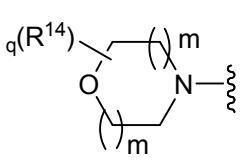
G_1 es N o $-CR^8$, donde R^8 es H, –CN, halógeno, $-Z_2-R^9$, alifático C_{1-6}, o cicloalifático de 3 a 10-miembros

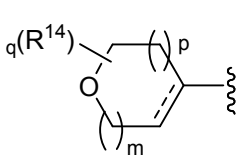
donde:

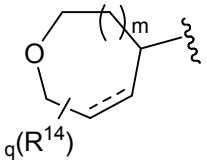
Z_2 se selecciona de una cadena de alquileno C_{1-3} opcionalmente sustituido –O-, $-N(R^{8a})-$, -S-, $-S(O)-$, $S(O)_2-$, $-C(O)-$, $-CO_2-$, $-C(O)NR^{8a}-$, $-N(R^{8a})C(O)-$, $-N(R^{8a})CO_2-$, $-S(O)_2NR^{8a}-$, $-N(R^{8a})S(O)_2-$, $-OC(O)N(R^{8a})-$, $-N(R^{8a})C(O)NR^{8a}-$, $-N(R^{8a})S(O)_2N(R^{8a})-$, o $-OC(O)-$;

R^{8a} es hidrógeno o un alifático C_{1-6} opcionalmente sustituido, y

R^9 es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático $C1_{-6}$, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y

HY es 

, 

o 

;

------ representa un enlace simple o un enlace doble;

donde cada aparición de R^{14} es independientemente $-R^{14a}$ o $-T_1-R^{14d}$, donde:

cada aparición de R^{14a} como permiso de valencia y estabilidad, es independientemente flúor, =O, =S, -CN, $-NO_2$, $-R^{14c}$, $-N(R^{14b})_2$, $-OR^{14b}$, $-SR^{14c}$, $-S(O)_2R^{14c}$, $-C(O)R^{14b}$, $-C(O)OR^{14b}$, $-C(O)N(R^{14b})_2$, $-S(O)_2N(R^{14b})_2$, $-OC(O)N(R^{14b})_2$, $-N(R^{14e})C(O)R^{14b}$, $-N(R^{14e})SO_2R^{14c}$, $-N(R^{14e})C(O)OR^{14b}$, $-N(R^{14e})C(O)N(R^{14b})_2$, o $-N(R^{14e})SO_2N(R^{14b})_2$, o dos apariciones de R^{14b}, tomadas juntas con un átomo de nitrógeno al cual están unidas, forman un anillo

heterociclilo de 4 a 7 miembros opcionalmente sustituido que tiene 0 a 1 heteroátomo adicional seleccionado de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14b} es independientemente hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14c} es independientemente un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14d} es independientemente hidrógeno o un cicloalifático de 3 a 10 miembros opcionalmente sustituido, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

cada aparición de R^{14e} es independientemente hidrógeno o un alifático C_{1-6} opcionalmente sustituido; y

T_1 es una cadena de alquileno C_{1-6} opcionalmente sustituido donde la cadena alquileno opcionalmente

está interrumpida por $-N(R^{14a})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{14a})-$, $-S(O)_2N(R^{14a})-$, $-OC(O)N(R^{14a})-$, $-N(R^{14a})C(O)-$, $-N(R^{14a})SO_2-$, $-N(R^{14a})C(O)O-$, $-NR^{14a}C(O)N(R^{14a})-$, $-N(R^{14a})S(O)_2N(R^{14a})-$, $-OC(O)-$, o $-C(O)N(R^{14a})-O-$ o donde T_1 o una porción del mismo opcionalmente forma parte de un cicloalifático de 3 a 7 miembros opcionalmente sustituido o un anillo heterociclilo;

n es 0 a 6;

q es 0 a 4;

m es 1 o 2; y

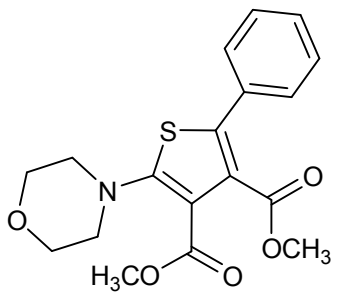
P es 0, 1, o 2;

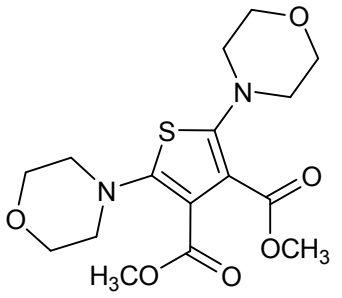
siempre que:

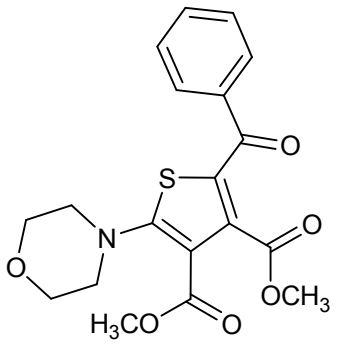
a) Cuando G_1 es C-CN, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido, 2-clorofenilo, 4-clorofenilo, 2-fluorofenilo, 4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 4-metilfenilo, 3-metoxifenilo, 4-metoxifenilo, 3,4-dimetoxifenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, o 3-(acetilamino)fenilo;

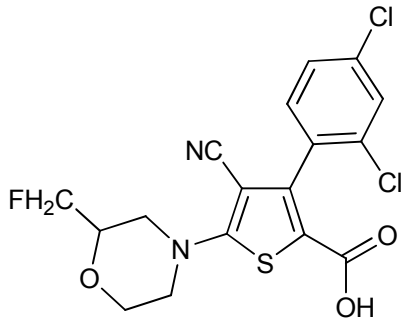
b) cuando G_1 es N, HY es morfolina no sustituida, R^1 es -C(O)OH, -C(O)OMe, o -C(O)OEt, y W es un enlace covalente, entonces el anillo A es diferente de fenilo no sustituido o 2-clorofenilo; y

c) el compuesto es diferente de:

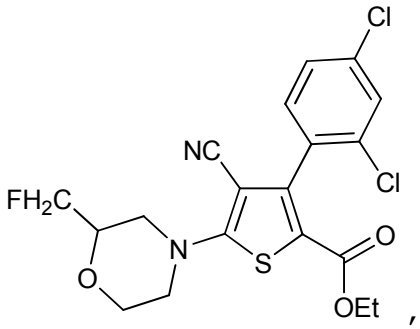


,


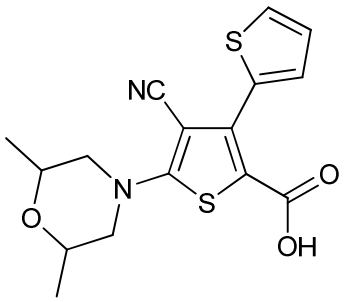
,




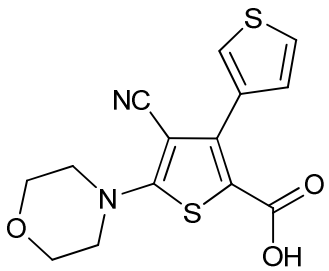
,



,



, o



.

62. El compuesto de la reivindicación 60 o 61, donde G_1 es N.

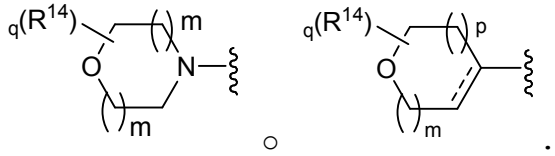
63. El compuesto de la reivindicación 60 o 61, donde G_1 es $C(R^8)$.

64. El compuesto de la reivindicación 63, donde R^8 es –CN, halógeno, o alifático C_{1-6}.

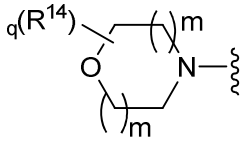
65. El compuesto de la reivindicación 63, donde R^8 es alquilo C_{1-4}, alquenilo C_{2-4}, o alquinilo C_{2-4}

66. El compuesto de la reivindicación 63, donde R^8 es –CN, o alquinilo C_{2-4}.

67. El compuesto de la reivindicación 60 o 61, donde HY se selecciona de:



68. El compuesto de la reivindicación 67, donde HY es



69. El compuesto de la reivindicación 88, donde ambas apariciones de m son 1.

70. El compuesto de la reivindicación 88, donde q es 0.

71. El compuesto de la reivindicación 60 o 61, donde R^3 es H.

72. El compuesto de la reivindicación 60 o 61, donde R^3 es alifático C_{1-6}.

73. El compuesto de la reivindicación 62, donde R^3 es alquilo C_{1-4}.

74. El compuesto de la reivindicación 63, donde R^3 es metilo o etilo.

75. El compuesto de la reivindicación 60 o 61, donde W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-N(R^{7b})_2$, o F; y cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 3 a 6 miembros opcionalmente

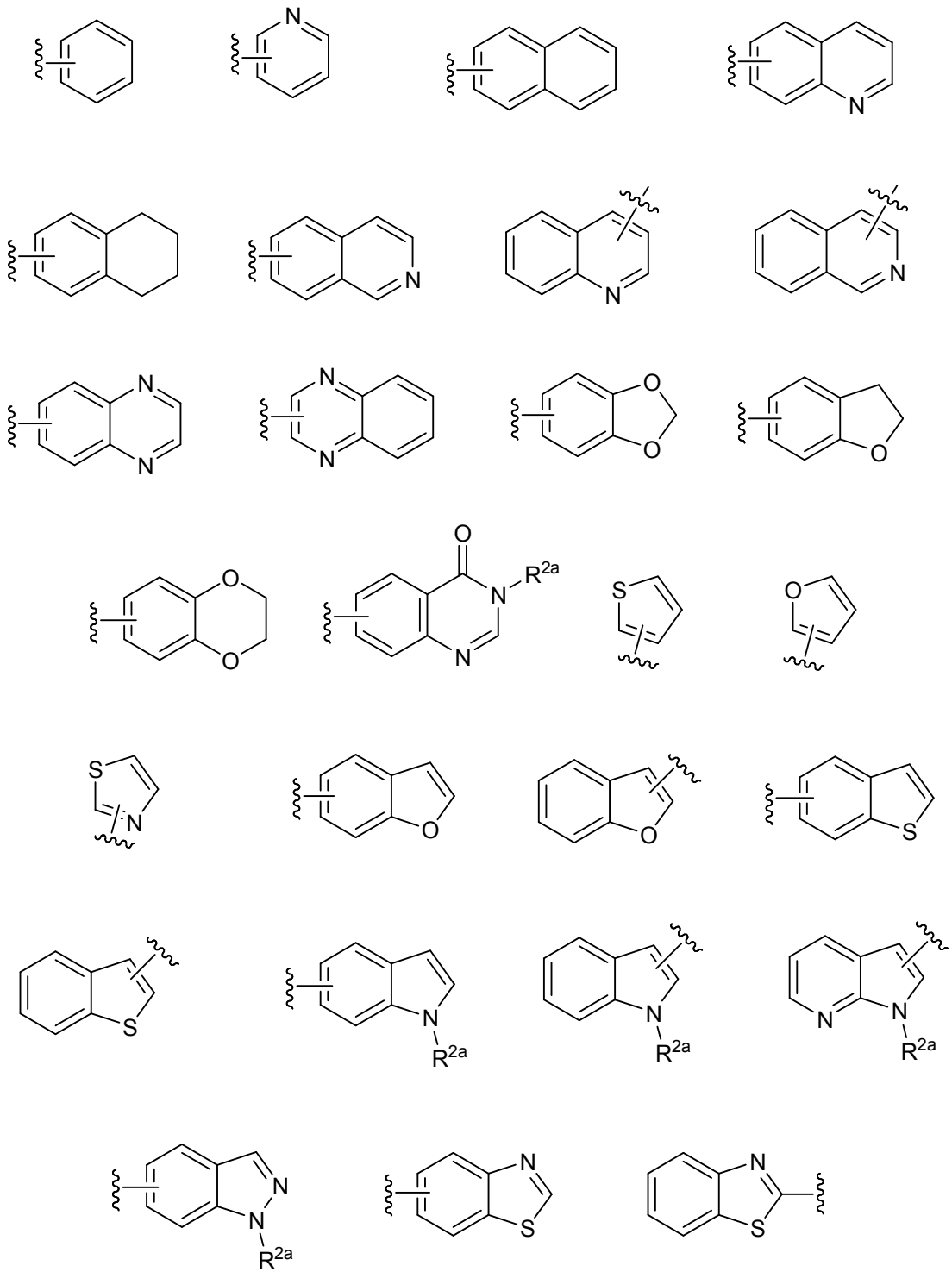
sustituido; y donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

76. El compuesto de cualquiera de las reivindicaciones 60 o 61, donde W es $-C(H)(N(R^{7b})_2)-$ o $-CH_2-$, donde cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

77. El compuesto de cualquiera de las reivindicaciones 60 o 61, donde W es un enlace covalente.

78. El compuesto de la reivindicación 60 o 61, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

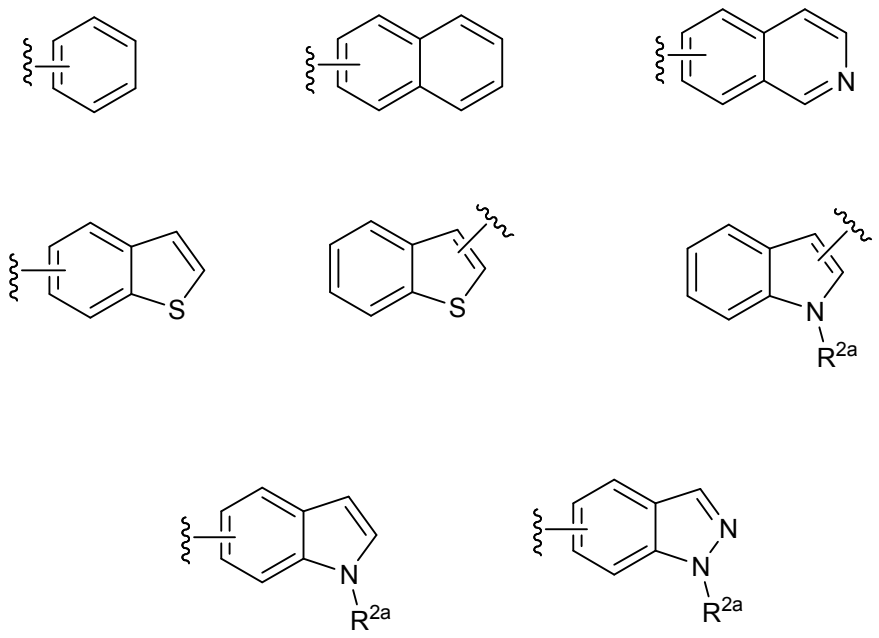
79. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente

seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

80. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

81. El compuesto de la reivindicación 80, donde:

el anillo A es un grupo naftilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3},

$-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o $-C(O)H$;

82. El compuesto de la reivindicación 60 o 61, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $-C(H)(N(R^{7b})_2)-$ o $-CH_2-$, donde cada aparición de R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

83. El compuesto de la reivindicación 82, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $-CH_2-$.

84. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o $-C(O)H$;

85. El compuesto de la reivindicación 84, donde el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN , $-OC_{1-3}$ alquilo, o $-OC_{1-3}$ haloalquilo; y n es 0 a 3.

86. El compuesto de la reivindicación 85, donde el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN , OCH_3, o $-OCF_3$; y n es 0 a 3.

87. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

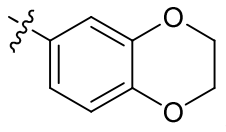
88. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo fenilo, n es 1, y R^2 está en la posición para.

89. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones para y meta.

90. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo naftilo, R^2 es halógeno y n es 0, 1 o 2.

91. El compuesto de la reivindicación 60 o 61, donde el anillo A es un grupo naftilo, y n es 0.

92. El compuesto de la reivindicación 90, donde el anillo A es un grupo 2-naftilo.

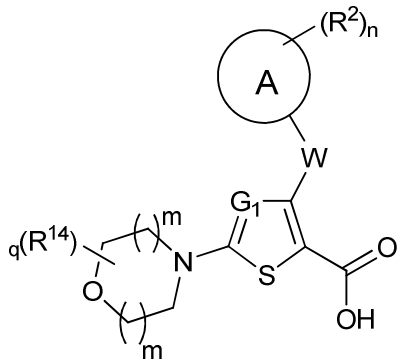
93. El compuesto de la reivindicación 60 o 61, donde el anillo A es  .

94. El compuesto de la reivindicación 60 o 61, donde el anillo A es un cicloalifático de 3 a 10 miembros o heterociclilo de 4 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

95. El compuesto de la reivindicación 94, donde el anillo A es un anillo heterociclilo de 3, 4, 5, 6, o 7 miembros N-enlazados.

96. El compuesto de la reivindicación 95, donde el anillo A está sustituido con uno o más grupos alquilo C_{1-3}.

97. Un compuesto que tiene la siguiente fórmula **II-A**:



II-A.

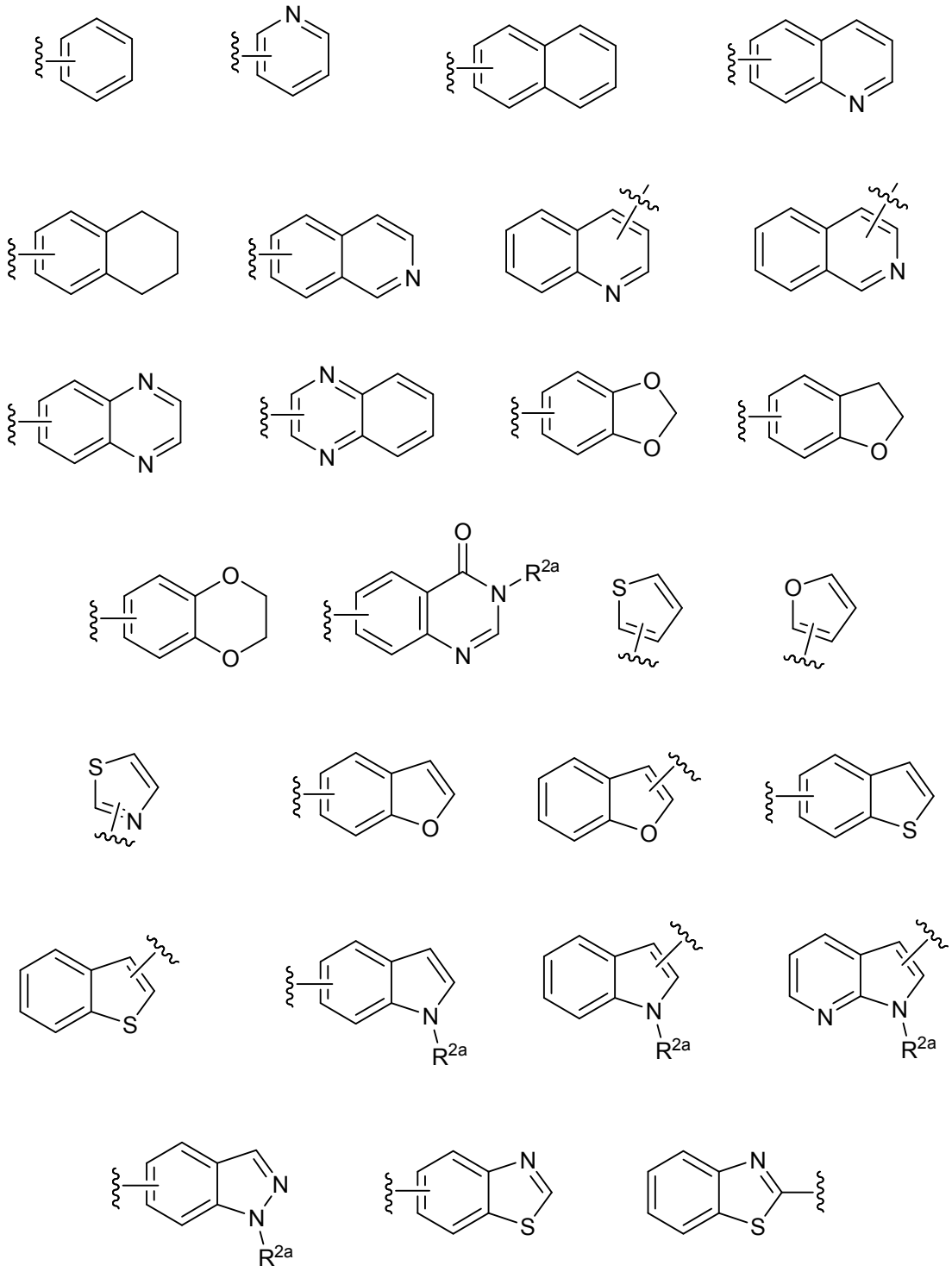
98. El compuesto de la reivindicación 97, donde W es $-C(R^7)_2-$, donde una aparición de R^7 es hidrógeno y la otra aparición de R^7 es hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-N(R^{7b})_2$, o F; y cada aparición de R^{7b} es independientemente hidrógeno, alifático C_{1-6} opcionalmente sustituido, $-C(O)R^{7a}$, o $-S(O)_2R^{7a}$; o donde dos apariciones de R^{7b}, tomados juntos con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 3 a 6 miembros opcionalmente sustituido; y donde cada aparición de R^{7a} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

99. El compuesto de la reivindicación 97, donde W es $-C(H)(N(R^{7b})_2)-$, o $-CHR^7$, donde cada aparición de R^7 o R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

100. El compuesto de la reivindicación 97, donde W es un enlace covalente y G_1 es N.

101. El compuesto de la reivindicación 97, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; y n es 0 a 3.

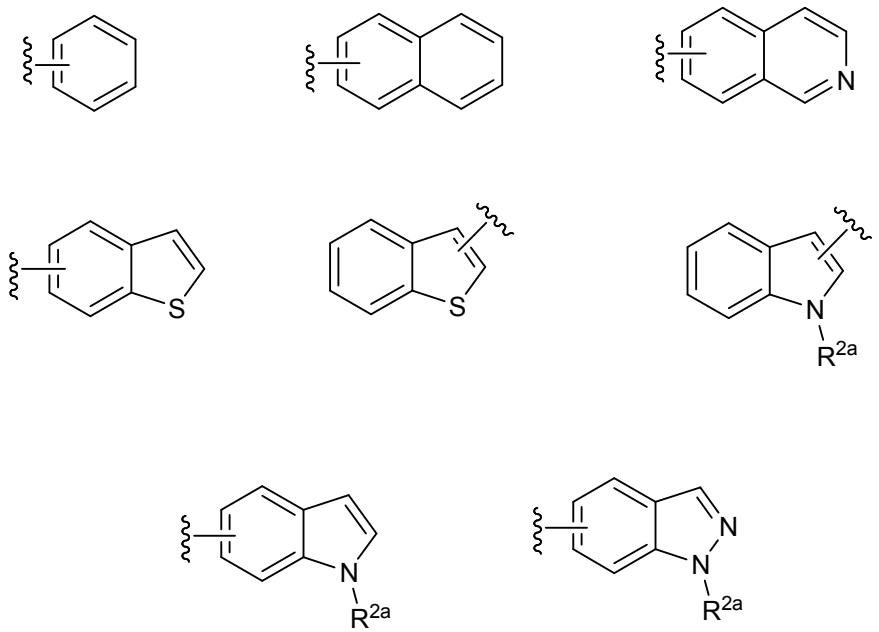
102. El compuesto de la reivindicación 97, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6},

cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

103. El compuesto de la reivindicación 102, donde A es un grupo seleccionado de:



donde el anillo A está además opcionalmente sustituido con n apariciones de R^2, y donde R^{2a} es hidrógeno o un grupo opcionalmente sustituido seleccionado de alifático C_{1-6}, cicloalifático de 3 a 10 miembros, heterociclilo de 4 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre, arilo de 6 a 10 miembros, o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre;

104. El compuesto de la reivindicación 97, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $-C(H)(N(R^{7b})_2)-$ o $-CHR^7-$, donde cada aparición de R^7 o R^{7b} es independientemente hidrógeno o alifático C_{1-6} opcionalmente sustituido.

105. El compuesto de la reivindicación 104, donde el anillo A es arilo de 6 a 10 miembros o heteroarilo de 5 a 10 miembros que tiene 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre; n es 0 a 3, y W es $-CH_2-$.

106. El compuesto de la reivindicación 97, donde el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o $-C(O)H$;

107. El compuesto de la reivindicación 106, donde el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN , $-OC_{1-3}$ alquilo, o $-OC_{1-3}$ haloalquilo; y n es 0 a 3.

108. El compuesto de la reivindicación 107, donde el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, -CN , OCH_3, o $-OCF_3$; y n es 0 a 3.

109. El compuesto de la reivindicación 108, donde el anillo A es un grupo fenilo, R^2 es halógeno y n es 1 a 2.

110. El compuesto de la reivindicación 109, donde el anillo A es un grupo fenilo, n es 1, y R^2 está en la posición para.

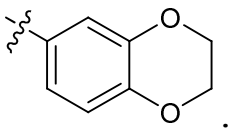
111. El compuesto de la reivindicación 109, donde el anillo A es un grupo fenilo, n es 2, y los dos grupos R^2 están en las posiciones para y meta.

112. El compuesto de la reivindicación 101, donde el anillo A es un grupo naftilo, R^2 es halógeno y n es 1 a 2.

113. El compuesto de la reivindicación 101, donde el anillo A es un grupo naftilo, y n es 0.

114. El compuesto de la reivindicación 101, donde el anillo A es un grupo 2-naftilo.

115. El compuesto de la reivindicación 101, donde el anillo A es



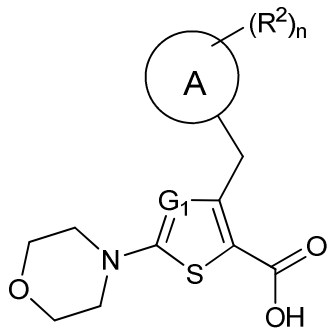
.

116. El compuesto de la reivindicación 101, donde el anillo A es un cicloalifático de 3 a 10 miembros o heterociclilo de 4 a 10 miembros que tiene de 1 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno, o azufre.

117. El compuesto de la reivindicación 101, donde el anillo A es un anillo heterociclilo de 3, 4, 5, 6, o 7 miembros N-enlazados.

118. El compuesto de la reivindicación 117, donde el anillo A está sustituido con uno o más grupos alquilo C_{1-3}.

119. Un compuesto que tiene la fórmula **III-A**:



III-A

donde G_1 es N o $-CR^8$, y R^8 es –CN

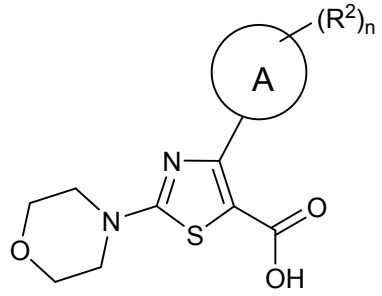
120. El compuesto de la reivindicación 119, donde:

el anillo A es un grupo naftilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0.

121. El compuesto de la reivindicación 119, donde:

el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

122. El compuesto de la reivindicación 61, en donde el compuesto tiene la fórmula **IV-A**:



IV-A.

123. El compuesto de la reivindicación 122, donde:

el anillo A es un grupo naftilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 o 3.

124. El compuesto de la reivindicación 122, donde:

el anillo A es un grupo fenilo; cada aparición de R^2 es independientemente halógeno, alquilo C_{1-3}, -CN, haloalquilo C_{1-3}, $-OC_{1-3}$ alquilo, $-OC_{1-3}$ haloalquilo, $-NHC(O)C_{1-3}$ alquilo, $-NHC(O)NHC_{1-3}$ alquilo, $-NHS(O)_2C_{1-3}$ alquilo, o –C(O)H; y n es 0 a 3.

125. Una composición que comprende un compuesto de cualquiera de las reivindicaciones 1, 2, 24, 43, 60, 61, 97, 119 o 122, y un vehículo aceptable para uso farmacéutico.

126. Un método para tratar un trastorno proliferativa en un paciente que comprende administrar a dicho paciente una cantidad eficaz para uso terapeútico de un compuesto de la reivindicación 1, 2, 24, 43, 60, 61, 97, 119 o 122.

127. El método de la reivindicación 126, que además comprende administrar un agente terapéutico adicional.

128. El método de la reivindicación 126, que además comprende administrar un agente quimioterapéutico adicional.

129. El método de la reivindicación 126, donde el trastorno proliferativo es cáncer de pecho, cáncer de vejiga, cáncer de colon, glioma, glioblastoma, cáncer de pulmón, cáncer hepatocelular, cáncer gástrico, melanoma, cáncer de tiroides, cáncer del endometrio, cáncer renal, cáncer del cuello uterino, cáncer pancreático, cáncer esofágico, cáncer de próstata, cáncer de cerebro, o cáncer de ovarios.

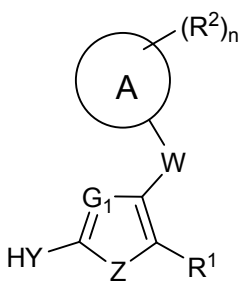
130. Un método para tratar un trastorno inflamatorio o cardiovascular en un paciente que comprende administrar a dicho paciente una cantidad eficaz para uso terapeútico de un compuesto de cualquiera de las reivindicaciones 1, 2, 24, 43, 60, 61, 97, 119 o 122.

131. El método de la reivindicación 130, donde el trastorno inflamatorio o cardiovascular se selecciona de alergias/anafilaxis, inflamación aguda o crónica, artritis reumatoide, trastornos autoinmunes, trombosis, hipertensión, hipertrofia cardiaca, e insuficiencia cardiaca.

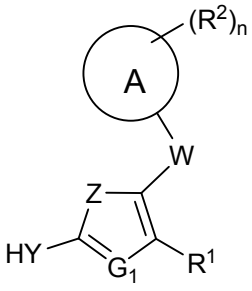
132. Un método para inhibir la actividad de P13K o VPS34 en un paciente que comprende administrar una composición que comprende una cantidad eficaz para uso terapeútico de un compuesto de cualquiera de las reivindicaciones 1, 2, 24, 43, 60, 61, 97, 119 o 122.

RESUMEN

La invención provee compuestos de formula **IA-a** o **IB-a** y sus correspondientes subconjuntos:



IA-a



IB-a

donde Z, HY, R^1, R^2, G_1, W, n, y A y sus correspondientes subconjuntos son como se describen en la memoria descriptiva. Los compuestos son inhibidores de P13K y de este modo son útiles para tratar trastornos proliferativos, inflamatorios, o cardiovasculares.