Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-271916- -00000-0000

Fecha: 2013-11-19 16:30:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

SOLICITUD DE PATI

INVENCIÓN

TITULO: **COMPUESTOS DE DIHIDROISOXAZOL PARASITICIDA**

SOLICITANTE: **ELI LILLY AND COMPANY**

DIRECCIÓN: **Lilly Corporate Center, Indianápolis, Indiana 46285.**

APODERADO: **CARLOS R. OLARTE**

BOGOTÁ **19 de noviembre de 2013**

P2013/000168

OLARTEMOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-271916- -00000-0000

Fecha: 2013-11-19 16:30:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIY!I Eve: 378 FASENACIONAL!
Act. 411 PRESENTACION Folios: 5

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000168**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: ELI LILLY AND COMPANY

Dirección: Lilly Corporate Center, Indianapolis, Indiana 46285

Nacionalidad o Domicilio: Estados Unidos
Lugar de Constitución: Estados Unidos

Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Carrera 5 No. 34-03 Bogotá, Colombia
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.

Dirección: VER PAGINA ADJUNTA.

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2012/036883 Fecha Mayo 08, 2012

Publicación Internacional No. WO 2012/158396 A1 Fecha Noviembre 22, 2012

(6) **Título(54)** **COMPUESTOS DE DIHIDROISOXAZOL PARASITICIDA**

Clasificación Internacional (51) C07D 413/04, C07D 413/14, C07D 495/04, A01N 43/80

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
CN	Mayo19, 2011	PCT/CN2011/074294
CN	Marzo 23,2012	PCT/CN2012/072873

(9) **Comprobante de pago No.** 13- **Fecha** _____

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.
- [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. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2012/036883

Zengyun AN
P.O. Box 6288, Indianapolis,
Indiana 46206-6288
Estados Unidos de América
Nacionalidad: China

Liang CHEN
P.O. Box 6288, Indianapolis,
Indiana 46206-6288
Estados Unidos de América
Nacionalidad: China

Shuhui CHEN
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Estados Unidos de América
Nacionalidad: Estadounidense

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Estados Unidos de América
Nacionalidad: Estadounidense

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Nacionalidad: Estadounidense

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Nacionalidad: China

William Hunter WHITE
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Estados Unidos de América
Nacionalidad: Estadounidense

Wentao WU
P.O. Box 6288, Indianapolis,
Indiana 46206-6288
Estados Unidos de Améica
Nacionalidad: China

Yang ZHANG
P.O. Box 6288, Indianapolis,
Indiana 46206-6288
Estados Unidos de América
Nacionalidad: China

5

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 111447

Bogotá D.C., Noviembre 01 de 2013 - 13:42:13

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	558995802	31/10/2013	15.438.000.00

*** 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. 13-271916- -00000-0000

Fecha: 2013-11-19 16:30:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

Industria y Comercio SUPERINTENDENCIA	PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA *RELACIÓN DE ANEXOS*	
Dependencia: 2020	Fecha: 13 / 11 / 19 AAAA MM DD	Recorrido: 3
Tipo de Radicación: Entrada: X Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	13-271916-	0	7
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*
X	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:

EL CD ANEXO CONTIENE UN TOTAL DE 12 ARCHIVOS: 12 EN FORMATO P.D.F, LOS CUALES FUERON PROCESADOS.

CR

Industria y Comercio
SUPERINTENDENCIA

A

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-271916- -00000-0000

Fecha: 2013-11-19 16:30:06 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

PATENTE DE INVENCIÓN ☐ MODELO DE UTIL

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen).
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000168**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2 **SOLICITANTE (71)**	**Nombre:** ELI LILLY AND COMPANY **Dirección:** Lilly Corporate Center, Indianapolis, Indiana 46285 **Nacionalidad o Domicilio:** Estados Unidos **Lugar de Constitución:** Estados Unidos **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** Carrera 5 No. 34-03 Bogotá, Colombia **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olartemoure.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79.782.747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA. **Dirección:** VER PAGINA ADJUNTA. **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA.	

5 **PCT (86)**

Solicitud Internacional No. PCT/US2012/036883 Fecha Mayo 08, 2012

Publicación Internacional No. WO 2012/158396 A1 Fecha Noviembre 22, 2012

6 **Título(54)** **COMPUESTOS DE DIHIDROISOXAZOL PARASITICIDA**

Clasificación Internacional (51) C07D 413/04, C07D 413/14, C07D 495/04, A01N 43/80

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
CN	Mayo19, 2011	PCT/CN2011/074294
CN	Marzo 23,2012	PCT/CN2012/072873

9 **Comprobante de pago No.** 13- **Fecha** _____

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
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- [ ] 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. Búsqueda Internacional

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2012/036883

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P.O. Box 6288, Indianapolis,
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Nacionalidad: China

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Nacionalidad: China

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Estados Unidos de América
Nacionalidad: Estadounidense

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Estados Unidos de Améica
Nacionalidad: China

Yang ZHANG
P.O. Box 6288, Indianapolis,
Indiana 46206-6288
Estados Unidos de América
Nacionalidad: China

WK 9397304

ESCRITURA PUBLICA NUMERO: (1 2 2 7)

MIL DOSCIENTOS VEINTISIETE ---------

En la ciudad de Bogotá, Distrito Capital, República de Colombia, a los Veintiocho -- (28) días del mes de Octubre -- - del año dos mil ocho (2008), ante mi **MARIA EUGENIA ROJAS DE URUETA** NOTARIA(O) VEINTISIETE (27) DEL CIRCULO DE BOGOTA, se otorgó la escritura pública que se consigna en los siguientes términos:----------

---

CLASE DE ACTO: PROTOCOLIZACION DE PODER.----------

JAMES IAN RAISBECK LLÍNAS Y CARLOS REINALDO OLARTE GARCIA.- ----------

C.C. No. 79.376.996 Y 79.782.747.- ----------

Comparecieron **JAMES IAN RAISBECK LLÍNAS**, mayor de edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.376.996 de estado civil casado con sociedad conyugal vigente y **CARLOS REINALDO OLARTE GARCIA**, mayor de edad, vecino de Bogotá, identificado con la cédula de ciudadanía número 79.782.747, de estado civil casado con sociedad conyugal vigente, obrando en sus propios nombres y dijeron: ----------

PRIMERO.- Que presentan para su protocolización y custodia en los archivos de ésta notaría, bajo el número y lugar que a ésta escritura corresponda, en cinco (5) folios autenticados, un poder y sus traducciones los cuales son del siguiente tenor: ----------

PODER ----------

El suscrito ELI LILLY AND COMPANY, domiciliado en Lilly Corporate Center, Indianápolis, Indiana 46285 US por medio del

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

presente otorga a Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri, poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de patentes, modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial o extrajudicialmente, responder en juicio a todas las reclamaciones y demandas que por motivo de encomendado se presentaren, dándoles asimismo facultades para sustituir el presente y revocar dichas sustituciones.----------

Firma (ilegible) ----------

Fecha 17 July 2003----------

City, Country/ Ciudad, País: Indianápolis, Indiana, United Status of America.- ----------

Traduccion oficial del Inglés por Marlén Neira Castro resolución 2117 del Ministerio de Justicia de Colombia.- ----------

APOSTILLA EN PODER DE DE REPRESENTACION DE ELI LILLY AND COMPANY.

Bilingüe inglés- español otorgado en Indianapoles, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Meter G. Stringer, Director Ejecutivo y patentes Internacionales de Ely Lilly & Company.- ----------

Todd Rokita Secretario de Estado----------

Secretario de Estado de Indiana Estado de Indiana----------

APOSTILLA

(Convencion de la Haya del 5 octubre 1961)

WK 9397305

1. País: Estados Unidos de América- este documento público ----------

2. Ha sido firmado por: Catherine Michel

3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Jonson ----------

4 Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana ----------

Certificado

5. En: Indianapoles, Indiana ----------

6. El: 22 de julio de 2003.----------

7. Por el Secretario de Estado de Indiana 8 No. A2003-1279--------

9. Gran Sello del Estado de Indiana ----------

10. Firma ilegible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 de mayo de 2003, todas las apostillas del Secretario y de Estado de Indiana tienen el sello impreso electrónicamente. ----------

The Statehouse, Indianapoles, Indiana 46204, (307) 232-6531, fax (317) 233-3283- ----------

NOTARIA VEINTIUNO
Paula Eugenia Rojas de Urueta

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Meter G. Stringer, domiciliado en 7620 Castleton Faros, West Drive Indianápolis, Indiana- 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianápolis, Indiana, Estados Unidos..- ----------

MARLEN NEIRA CASTRO Traductor e Intérprete Oficial inglés-Español- Inglés----------

Resolución No. 2117 del 7 Oct 1987.- ----------

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

otorgado al Asesor General de la Compañía por el Comité Ejecutivo de la Junta Directiva de Eli Lilly and Company.----------
Firma del notario público Catherine Michel certifica sus funciones vencen el 21 de octubre de 2008- residente en el condado Johnson
Sello de notario público de Indiana.----------
Es traducción fiel de inglés, con copia archivo para confrontación, Bogotá 28 de julio-2003.----------
MARLEN NEIRA CASTRO Traductor e Intérprete Oficial Inglés-Español- Inglés ----------
Resolución No. 2117 del 7 Oct 1987.- ----------
SEGUNDO.- Que solicita a la señora Notaria la incorporación de dichos documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten ----------
---
Se advierte que la protocolización de documentos no da mayor fuerza o autenticidad de la que tienen dichos documentos.- ---
---
Esta escritura pública fue firmada fuera del Despacho Notarial, de conformidad con el artículo 12 del Decreto 2.148 de 1.983. -------
---
Se advirtió a los otorgantes de esta escritura de la obligación que tienen de leer la totalidad de su texto, a fin de verificar la exactitud de todos los datos en ella consignados, con el fin de aclarar, modificar o corregir lo pertinente antes de firmarla, la firma de la misma demuestra su aprobación total del texto, en consecuencia, la notaria no asume ninguna responsabilidad por errores o inexactitudes establecidas con posterioridad a la firma de (el, los) otorgante(s) y de la notaría, en tal caso, este (os) debe(n) ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por todos los que intervinieron en la inicial y sufragada por los mismos (articulo 35, decreto ley 960 de 1970).- ----------

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

ELI LILLY AND COMPANY

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita — Secretario de Estado

Secretario de Estado de Indiana — Estado de Indiana

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961

1. País: Estados Unidos de América- Este documento Público
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

CERTIFICADO

5. En Indianapolis, Indiana 6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana 8. No. A2003- 11279
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
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www.olarteraisbeck.com

Power of Attorney

The undersigned,

ELI LILLY AND COMPANY

domiciled in

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

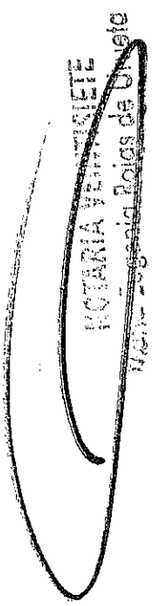
El suscrito,

ELI LILLY AND COMPANY

domiciliado en

Lilly Corporate Center, Indianapolis, Indiana 46285 US

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.



Signature/Firma

Date/Fecha: 17 July 2003

City,Country/Ciudad,País: Indianapolis, Indiana, United States of America

SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**

2. **This public document has been signed by** *Catherine Michel*

3. **acting in the capacity of circuit court clerk in & for** *Johnson* **County**

4. **and bears the seal/stamp of circuit court clerk in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**

6. **this** *Twenty-second* **day of** *July, 2003*

7. **by Secretary of State of Indiana**

8. **No. A2003-** *11279*

9. **Seal/Stamp:**

10. **Signature:**

Todd Rokita

Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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Fax: +57-1 638-6201

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Notarial Certification

On this date,
17 July 2003
The undersigned Notary Public certifies:

1. That
Peter G. Stringer
of legal age and domiciled in
7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
signed the foregoing document.

2. That the grantor has executed the foregoing document as Executive Director, International Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of America
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Delegation of Authority Concerning Certain Patent Matters, executed January 20, 2003; pursuant to the authority granted to the General Counsel of the Company by the executive Committee of the Board of Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):

NOTARY PUBLIC SEAL INDIANA

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
mayor de edad y domiciliado
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de

de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARIA TREINTA Y SIETE
María Eugenia Rojas de Urueta

Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

ESPACIO EN BLANCO

ESPACIO EN BLANCO

WK 9397306

ADVERTENCIA, OTORGAMIENTO Y AUTORIZACION.- Leído el presente instrumento por el (los) compareciente (s) y advertido (s) sobre las formalidades legales, lo aprueban y firman conmigo y ante mí la(el) Notaria(o) quién lo autoriza. ---Se utilizaron las hojas de papel Notarial Nos. WK 9397304, WK 9397305 Y WK 9397306 .

DERECHOS LEGALES: $ 39.630.00

RESOLUCION 8850 DE 2007

IVA $ 10.781.00

JAMES IAN RAISBECK LLÍNAS

C.C.No. 79.376.996 BOGOTA

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CARLOS REINALDO OLARTE GARCIA

C.C.No. 79.782.747 BOGOTA.

TEL: 601-7700

MARIA EUGENIA ROJAS DE URUETA

NOTARIA(O) VENTISIETE (27) DE BOGOTA

redb.

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Interesado

Dado en Santafé de Bogotá D.C., a 28 OCT 2008
El Notario Veintisiete de Santafé de Bogotá

REPUBLICA DE COLOMBIA
27
María Eugenia Rojas
de Urueta
NOTARIA
Notaría Veintisiete de Santafé de Bogotá

ESPACIO EN BLANCO

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application ELI LILLY AND COMPANY is entitled to claim priority of earlier application No. PCT/CN2011/074294 by virtue of the following:
VIII-3-1(iv)		an assignment from DEFAUW, Jean, Marie to ELI LILLY AND COMPANY, dated 20 May 2011 (20.05.2011)
VIII-3-1(iv)		an assignment from HOLMSTROM, Scott, Dale to ELI LILLY AND COMPANY, dated 20 May 2011 (20.05.2011)
VIII-3-1(iv)		an assignment from WHITE, William, Hunter to ELI LILLY AND COMPANY, dated 20 May 2011 (20.05.2011)
VIII-3-1(iv)		an assignment from AN, Zengyun to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from CHEN, Liang to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from CHEN, Shuhui to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from HU, Ping to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from TANG, Chongzhi to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from WU, Wentao to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from ZHANG, Yang to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-1(iv)		an assignment from WuXi AppTec., Co., Ltd. to ELI LILLY AND COMPANY, dated 24 April 2012 (24.04.2012)

VIII-3-2	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application ELI LILLY AND COMPANY is entitled to claim priority of earlier application No. PCT/CN2012/072878 by virtue of the following:
VIII-3-2(iv)		an assignment from DEFAUW, Jean, Marie to ELI LILLY AND COMPANY, dated 15 March 2012 (15.03.2012)
VIII-3-2(iv)		an assignment from HOLMSTROM, Scott, Dale to ELI LILLY AND COMPANY, dated 15 March 2012 (15.03.2012)
VIII-3-2(iv)		an assignment from WHITE, William, Hunter to ELI LILLY AND COMPANY, dated 15 March 2012 (15.03.2012)
VIII-3-2(iv)		an assignment from AN, Zengyun to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from CHEN, Liang to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from CHEN, Shuhui to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from HU, Ping to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from TANG, Chongzhi to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from WU, Wentao to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from ZHANG, Yang to WuXi AppTec., Co., Ltd., dated 06 April 2012 (06.04.2012)
VIII-3-2(iv)		an assignment from WuXi AppTec., Co., Ltd. to ELI LILLY AND COMPANY, dated 24 April 2012 (24.04.2012)

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application ELI LILLY AND COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, DEFAUW, Jean, Marie
VIII-2-1(ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, HOLMSTROM, Scott, Dale
VIII-2-1(ii)		ELI LILLY AND COMPANY is entitled as employer of the inventor, WHITE, William, Hunter
VIII-2-1(iv)		an assignment from AN, Zengyun to WuXi AppTec., Ltd., dated 06 April 2012 (06.04.2012)
VIII-2-1(iv)		an assignment from CHEN, Liang to WuXi AppTec., Ltd., dated 06 April 2012 (06.04.2012)
VIII-2-1(iv)		an assignment from CHEN, Shuhui to WuXi AppTec., Ltd., dated 06 April 2012 (06.04.2012)
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VIII-2-1(iv)		an assignment from WuXi AppTec., Co., Ltd. to ELI LILLY AND COMPANY, dated 24 April 2012 (24.04.2012)

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

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(21) International Application Number:
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8 May 2012 (08.05.2012)

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(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AN, Zengyun** [CN/CN]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **CHEN, Liang** [CN/CN]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **CHEN, Shuhui** [US/US]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **DEFAUW, Jean, Marie** [US/US]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **HOLMSTROM, Scott, Dale** [US/US]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **HU, Ping** [CN/CN]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **TANG, Chongzhi** [CN/CN]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Illinois 46206-6288 (US). **WHITE, William, Hunter** [US/US]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **WU, Wentao** [CN/CN]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **ZHANG, Yang** [CN/CN]; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

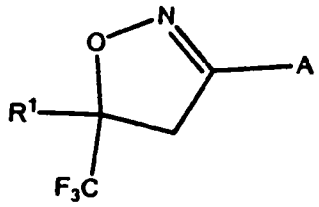
(74) Agents: **MCGRAW, Elizabeth A.** et al.; Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM,

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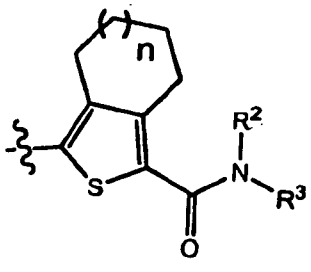
(54) Title: PARASITICIDAL DIHYDROISOXAZOLE COMPOUNDS

(57) Abstract: Provided are dihydroisoxazole compounds I useful for controlling parasites both in animals and agriculture. Further provided are methods for controlling parasite infestations of an animal by administering an effective amount of a compound as described above, or a pharmaceutically acceptable salt thereof, to an animal, as well as formulations for controlling parasite infestations using the compounds described above or an acceptable salt thereof, and an acceptable carrier. Also provided are compounds and processes useful for making the dihydroisoxazole compounds.

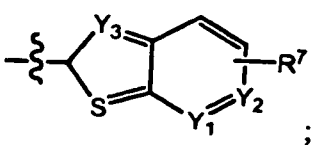


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WO 2012/158396 A1

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, RW, 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, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

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

Published:

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

PARASITICIDAL DIHYDROISOXAZOLE COMPOUNDS

Ectoparasites such as fleas, lice, flies, mosquitoes, ticks and mites, as well as endoparasites such as gastrointestinal tract nematodes, flukes, and filarids, are problematic for man and animal alike. Such parasites seriously impact productivity in the domesticated animal industry by reducing weight gain, causing poor quality hide, wool, and meat, and in some cases resulting in death. Ecto- and endoparasites are also responsible, in part, for the spread of disease and discomfort in food and companion animals. Ectoparasites in particular are known to harbor and transmit a variety of microbial pathogens, including bacteria, viruses and protozoan parasites, many of which are pathogenic to humans, other warm-blooded mammals and birds. Diseases in which ectoparasites have been implicated include, but are not limited to, malaria, lymphatic- and blood-born filariasis, trachoma, trypanosomiasis, Leishmaniasis, Rocky Mountain Spotted Fever, Lyme Disease, babesiosis, and food-borne illnesses due to *Salmonella, E. coli* and *Campylobacter*, for example.

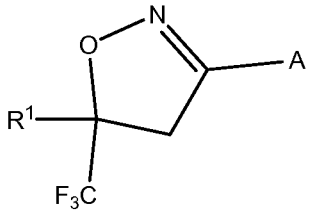
The medical importance of parasiticide infestations has prompted the development of reagents capable of controlling such. Commonly encountered methods to control parasiticide infestation, for example, have generally focused on use of insecticides, which are often unsuccessful or unsatisfactory for one or more of the following reasons: (1) failure of owner or applicator compliance (frequent administration is required); (2) behavioral or physiological intolerance of the animal to the pesticide product or means of administration; (3) the emergence of ectoparasites resistant to the reagent; and (4) negative impact on the environment and/or toxicity.

Specifically, ticks parasitize wild as well as domesticated animals and humans, and are known or suspected to be responsible for the transmission of pathogens including bacteria, viruses and protozoan parasites. Currently, ticks are considered to be second in the world to mosquitoes as vectors of human diseases, but they are considered to be the most important vector of pathogens in North America. Effective elimination of tick infestations is difficult and often impractical, due to the need for concomitant treatment of the immediate host as well as the environmental reservoir. Presently, tick control is effected by integrated pest management in which different control methods are adapted to one area or against one tick species with due consideration to their environmental effects.

While the use of insecticides and pesticides have been beneficial, alternative or improved compounds, formulations, and methods are needed. Desirable compounds, formulations, and methods would not only provide alternative therapies, but would also overcome one or more of the limitations of current approaches. Such limitations include toxicity and safety of both the animal and the user/owner, limited efficacy (*e.g.*, potency and duration), and resistance issues. Also impacting the beneficial use of insecticides and pesticides are administration obstacles, which include mode and recurrence of administration. For example, reducing the frequency of administration while maintaining efficacy is desirable, as excessive and repeated treatment of animals is often inconvenient and/or difficult.

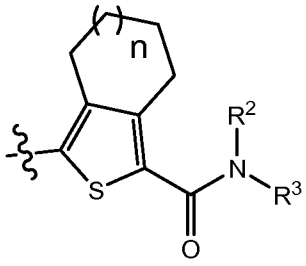
The present invention encompasses parasiticidal compounds, methods, and formulations for use in and on animals and plants, and which provide alternative options for combating parasiticidal infestations, particularly ectoparasiticidal infestations. Further, certain aspects of the invention overcome at least some limitations in the use of current insecticides and pesticides, particularly in providing effective long term, safe control of parasites.

Provided are compounds, and salts thereof, of formula I:

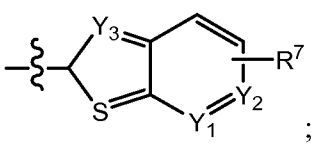


I

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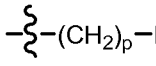


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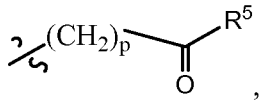
n is 0 or 1;

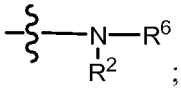
R^1 is thienyl or phenyl, said thienyl or phenyl substituted with 2 or 3 of the same or different halo atoms;

R^2 is at each occurrence independently hydrogen, C_1–C_5 alkyl, C_3–C_6 cycloalkyl, or C_1–C_5 haloalkyl;

R^3 is  ;

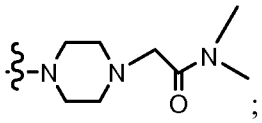
p is at each occurrence independently 0 or 1;

R^4 is C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, C_3–C_6 cycloalkyl optionally substituted with hydroxy, halo, or C_1–C_5 alkyl: C_3–C_5 cycloheteroalkyl optionally substituted with C_1–C_5 alkyl, C_3–C_6 cycloalkyl, or C_1–C_5 haloalkyl: phenyl, thienyl, pyridinyl, or  , wherein one of the carbons in said cycloalkyls, independently, or cycloheteroalkyl may form a carbonyl group, and wherein said phenyl, thienyl, or pyridinyl is optionally substituted with halo or a carbamoyl group;

R^5 is hydroxy, -O-(C_1–C_5 alkyl), or  ;

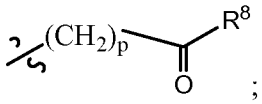
R^6 is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, or C_2–C_5 alkynyl;

or R^2 and R^3 combine to form, with the nitrogen to which they are attached,

 ;

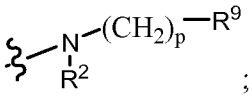
Y_1, Y_2, and Y_3 are carbon or nitrogen with at most only one of Y_1, Y_2, and Y_3 being nitrogen, and when Y_1, Y_2, or Y_3 is a carbon, each may be substituted by C_1–C_5 alkyl;

R^7 is hydrogen, halo, C_1–C_5 alkyl, or



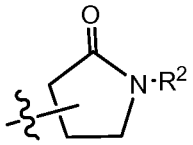
;

R^8 is hydroxy, -O-(C_1–C_5 alkyl), or

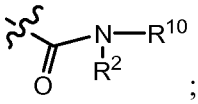


;

R^9 is C_1–C_5 alkyl,



or



; and

R^{10} is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, or C_2–C_5 alkynyl.

The invention provides a formulation, including a pharmaceutical formulation, comprising a compound or salt of formula I and one or more acceptable carriers. The formulation may further comprise at least one additional active ingredient. A pharmaceutical formulation of the invention may be a human pharmaceutical formulation or a veterinary pharmaceutical formulation.

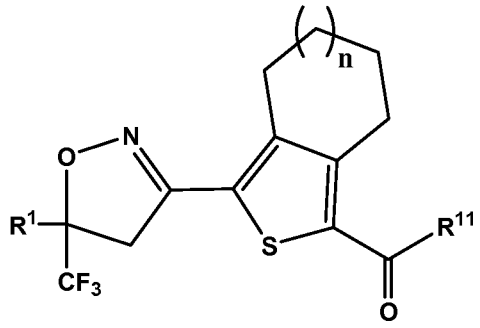
The invention provides a method of controlling ecto- and endoparasite infestations of an animal in need thereof comprising administering an effective amount of a compound or salt of formula I to said animal. The method may further provide administering at least one other active ingredient to said animal. The animal may be a mammal, and may be a human or a companion animal, for example, a dog or cat.

The present invention provides a method for preventing and treating diseases transmitted through parasites comprising administering at least one compound of the invention to an animal in need thereof.

The invention provides a method for controlling parasites, characterized in that a compound of formula I is allowed to act on the pests and/or their habitat. The invention provides the use of compounds or salts thereof of formula I for controlling pests.

The invention provides a compound or salt of formula I for use in therapy. The invention further provides a compound or salt of formula I for use in controlling ecto- and endoparasite infestations. The invention also provides use of a compound or salt of formula I for the manufacture of a formulation or medicament for controlling ecto- and endoparasite infestations.

The invention provides compounds of Formula II, or a salt thereof, of the formula



II

wherein n is 0 or 1;

R^1 is thienyl or phenyl, said thienyl or phenyl substituted with 2 or 3 of the same or different halo atoms; and

R^{11} is hydroxy, -O-(C_1-C_4 alkyl), or a halo atom.

These compounds have utility as intermediates in the processes for preparing certain compounds of Formula I. These Formula II compounds may be chemically modified to result in certain Formula I compounds.

The host animal may be a mammal or non-mammal, such as a bird (turkeys, chickens) or fish. Where the host animal is a mammal, it may be a human or non-human mammal. Non-human mammals include domestic animals, such as livestock animals and companion animals. Livestock animals include cattle, camellids, pigs, sheep, goats, and

horses. Companion animals include dogs, rabbits, cats, and other pets owned and maintained in close association with humans as part of the human-animal bond.

Parasites, sometimes also referred to as pests, include both ectoparasites and endoparasites. Ectoparasites include insect and acarine pests which commonly infest or infect animals, and include the egg, larval, pupal, nymphal, and adult stages thereof. Such pests include fleas, lice, mosquitoes, mites, ticks, beetles, and blood-sucking, biting, or nuisance fly species. Endoparasites include nematode pests which commonly infect animals, and include the egg, larval, and adult stages thereof. Such pests include helminths (hookworms, tapeworms, heartworms), and are commercially important because they cause serious diseases in animals, *e.g.* in sheep, pigs, goats, cattle, horses, donkeys, camels, dogs, cats, rabbits, guinea-pigs, hamsters, chicken, turkeys, guinea fowls and other farmed birds, as well as exotic birds. Typical nematodes are *Haemonchus, Trichostrcngyius, Qstertagia, Nematotiirus, Cooperia, Ascaris, Bunostonum, Gesophagostonum, Charbertia, Trichuris, Strongyius, Trïchonema, Dictyocaulus, Capsliarsa, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancyiostoma, Uncinaria, Toxascaris* and *Parascaris*. The trematodes include, in particular, the family of *Fasciolideae*, especially *Fasciola hepatica*.

Controlling refers to either ameliorating or eliminating a current infestation, or preventing an infestation, in or on an animal host or a plant.

Effective amount refers to the amount of a compound of formula I, or a salt thereof, sufficient to control an ecto- or endoparasite infestation, and includes causing a measurable reduction in the ecto- or endoparasite infestation population, and as such will depend upon several factors. For use on or in animals, ranges for a compound of formula I, or a salt thereof, in the methods include from 0.01 to 1000 mg/kg and more desirably, 0.1 to 100 mg/kg of the animal's body weight. The frequency of the administration will also be dependent upon several factors, and can be a single dose administered once a day, once a week, or once a month, for a duration determined by the attending doctor or veterinarian. Additional active ingredients may be administered with a compound of formula I.

Pharmaceutically acceptable as used in this application, for example with reference to salts and formulation components such as carriers, includes "veterinarily acceptable", and thus includes both human and animal applications independently.

Salts of the compounds of the invention, including pharmaceutically acceptable salts, and common methodology for preparing them, are known in the art. *See, e.g.,* P. Stahl, *et al.,* HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION AND USE, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.,* "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

The compounds of the invention and their salts may be formulated as pharmaceutical compositions for administration. Such pharmaceutical compositions and processes for making the same are known in the art for both humans and non-human mammals. *See, e.g.,* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, (A. Gennaro, *et al.,* eds., 19th ed., Mack Publishing Co., 1995). Formulations can be administered through various means, including oral administration, parenteral administration such as injection (intramuscular, subcutaneous, intravenous, intraperitoneal) or the like; topical application with or without transdermal penetration such as dipping, spray, bathing, washing, pouring-on and spotting-on, and dusting, or the like. Additional active ingredients may be included in the formulation containing a compound of the invention or a salt thereof.

Carrier is used herein to describe any ingredient other than the active component(s) in a formulation. The choice of carrier will to a large extent depend on factors such as the particular mode of administration or application, the effect of the carrier on solubility and stability, and the nature of the dosage form.

C_1–C_5 alkyl refers to straight chain and branched alkyls having one to five carbon atoms, and includes methyl, ethyl, propyl, n-butyl, iso-butyl, pentyl, isopentyl, and neopentyl.

C_2–C_5 alkynyl refers to straight chain and branched alkynyls having two to five carbon atoms, and includes ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 3-methyl-1-butynyl, pentynyl, isopentynyl, and neopentynyl.

Halogen or halo refers to fluorine, bromine, chlorine, and iodine.

Haloalkyl as used herein refers to an alkyl (as noted above) substituted with one or more halo atoms. Such groups include trifluoromethyl, difluoromethyl, fluoromethyl, methylchloride, dichloromethyl, pentylchloride, butyl chloride, and isopropyl chloride.

Cyanoalkyl as used herein refers to an alkyl (as noted above) substituted with a cyano group.

Alkylthio as used herein refers to an alkyl (as noted above) having a sulfur in the group.

C_3–C_6 cycloalkyl refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

C_3–C_5 cycloheteroalkyl refers to a saturated ring which has 3 to 5 carbons and a hetero atom. The hetero atom may be sulfur, oxygen, nitrogen, or a sulfonyl group.

Diseases transmitted through parasites, particularly ectoparasites, are, for example bacterial, viral, rickettsial and protozoal vector-borne diseases. Examples of viral diseases transmitted through arboviruses, *i.e.* arthropod borne viruses, are Crimean-Congo Hemorhagic Fever (CCHF), Febrile illness, Papataci fever, Encephalitis, Meningitis, which are caused by *Bunyaviridae* such as *Bunyavirus, Nairovirus or Phlebovirus*; Bluetongue, meningoencephalits, Febrile illness, hemorhagic fever, which are caused by *Reoviridae*, such as Orbivirus, Colitivirus; Febrile illness, rash, encephalitis, polyarthritis, lymphadenitis, which are caused by *Togaviridae*, such as Sindbisvirus, Chikungunya Virus; tick-borne meningoencephalitis, Dengue hemorhagic fever, encephalitis, Febrile illness, Yellow fever, which are caused by *Flaviviridae*, such as Flavivirus (including diverse sub-groups). Examples of bacterial diseases transmitted through parasites are Rickettsiosis, such as Rocky Mountain spotted fever, tick typhus caused by infection through *Rickettsia ssp*; Tularemia caused by infection through *Francisella tularensis*; *Borreliosis* or *Spirochaetosis*, such as Lyme disease, or relapsing fever, caused, by infection through *Borrelia ssp.*; Ehrllichiosis caused by infection through *Ehrlichia ssp.*; Plague, caused by infection through *Yersinia ssp*. Examples of protozoal or rickettsial borne diseases are Babesiosis, such as Texas fever, red water disease, Q-fever caused by infection through *Babesia ssp.*; Theileriosis, such as east coast fever, Mediterranean coast fever, caused by infection through *Theileria ssp.*; Nagana disease, Sleeping sickness caused by infection through *Trypanosoma ssp.*, Anaplasmosis caused by infection through *Anaplasma ssp.*; Malaria caused by infection through *Plasmodium ssp.*; Leishmaniasis caused by infection through *Leishmania ssp*.

Given their activity, certain of the compounds of the invention are suitable as soil insecticides against pests in the soil, as well as insecticides for plants, such as cereals, cotton, rice, maize, soya, potatoes, vegetables, fruit, tobacco, hops, citrus, and avocados. Certain compounds according to the invention are suitable for protecting plants and plant organs, for increasing the harvest yields, and for improving the quality of the harvested material which are encountered in agriculture, in horticulture, in forests, in gardens, and leisure facilities, and in the protection of stored products and of materials. They may be employed as plant protection agents.

All plants and plant parts can be treated in accordance with the invention. Plants are to be understood as meaning in the present context all plants and plant populations such as desired and undesired wild plants or crop plants (including naturally occurring crop plants). Crop plants can be plants which can be obtained by conventional plant breeding and optimization methods or by biotechnological and genetic engineering methods or by combinations of these methods, including the transgenic plants and including the plant cultivars protectable or not protectable by plant breeders' rights. Plant parts are to be understood as meaning all parts and organs of plants above and below the ground, such as shoot, leaf, flower and root, examples which may be mentioned being leaves, needles, stalks, stems, flowers, fruit bodies, fruits, seeds, roots, tubers and rhizomes. The plant parts also include harvested material, and vegetative and generative propagation material, for example cuttings, tubers, rhizomes, offshoots and seeds.

Treatment according to the invention of the plants and plant parts with the active compounds is carried out by conventional and known means, including directly acting on, or by allowing the compounds to act on, the surroundings, habitat or storage space by the customary treatment methods, for example by immersion, spraying, evaporation, fogging, scattering, painting on, injection and, in the case of propagation material, in particular in the case of seeds, also by applying one or more coats.

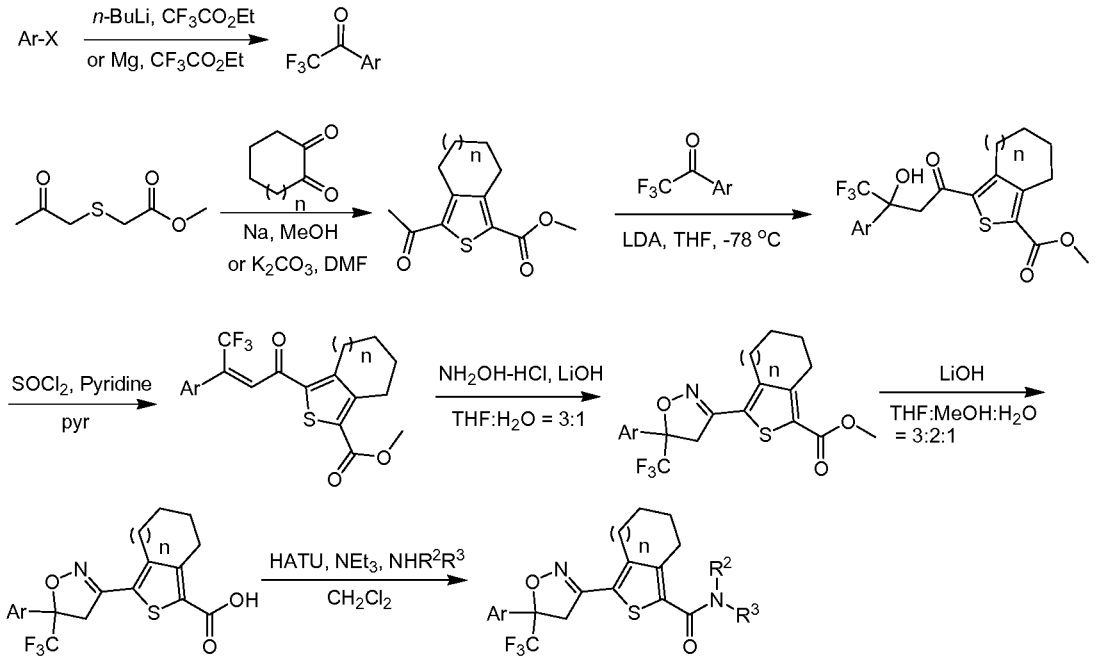
The compounds can be converted to the customary formulations, such as solutions, emulsions, wettable powders, water- and oil-based suspensions, powders, dusts, pastes, soluble powders, soluble granules, granules for broadcasting, suspension-emulsion concentrates, natural materials impregnated with active compound, synthetic materials impregnated with active compound, fertilizers and microencapsulations in polymeric substances.

These formulations are produced in a known manner, for example by mixing the active compounds with extenders, that is liquid solvents and/or solid carriers, optionally with the use of surfactants, that is emulsifiers and/or dispersants and/or foam-formers. The formulations are prepared either in suitable plants or else before or during the application.

Suitable for use as auxiliaries are substances which are suitable for imparting to the composition itself and/or to preparations derived therefrom (for example spray liquors, seed dressings) particular properties such as certain technical properties and/or also particular biological properties. Typical suitable auxiliaries are extenders, solvents, and carriers.

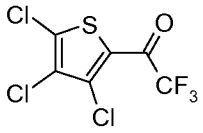
Following are Schemes A- J and examples for preparing the compounds of the invention. The Schemes, examples, and information contained therein are illustrative, and can be modified in ways known in the art to obtain the desired results.

Scheme A



Preparation 1

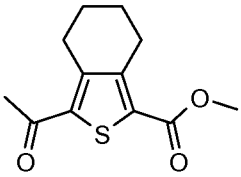
Methyl 2,2,2-trifluoro-1-(3,4,5-trichlorothiophen-2-yl)ethanone



Add a solution of n-BuLi (21.6 mL, 2.5 M in hexane, 54.0 mmol) to a solution of 2,3,4,5-tetrachloro-thiophene (10 g, 45.0 mmol) in dry THF (160 mL) at -78 ^{0}C and stir the mixture for 2 hours. Add a solution of trifluoro-acetic acid ethyl ester (9.59 g, 67.6 mmol) in THF (15 mL) and stir at -78 ^{0}C for additional 2.5 hours. Quench the reaction with saturated NH_4Cl solution (100 mL). Extract the aqueous mixture with EtOAc (100 mL X 3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, and evaporate under vacuum. Purify the residue by a flash column on silica gel eluting with PE:EtOAc (10:1 to 5:1) to afford 2,2,2-trifluoro-1-(3,4,5-trichloro-thiophen-2-yl)-ethanone as a brown oil (10.4 g, 81.9%). ^{13}F NMR (400 MHz, $CDCl_3$) δ -73.38 (s, 3F).

Preparation 2

Methyl 3-acetyl-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate

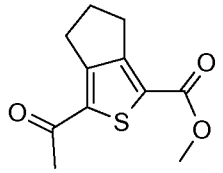


Add methyl 2-(2-oxopropylthio)acetate (35.4 g, 183.2 mmol) to a freshly prepared solution of solid sodium (8.78 g, 381.5 mmol) in dry MeOH (300 mL) at 0 ^{0}C, followed by addition of a solution of cyclohexane-1,2-dione (20 g, 152.6 mmol) in MeOH (30 mL). Stir the mixture at 0^0 C for 30 min and then at 50-60 ^{0}C for additional 1.5 hour. Remove the solvent under vacuum and dilute the residue with water (100 mL). Extract the aqueous mixture with ethyl acetate (100 mL X 3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, and evaporated under vacuum. Purify the residue by

a flash column on silica gel eluting with PE:EtOAc (50:1 to 30:1) to afford methyl 3-acetyl-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate as a white solid (10 g, 27.6%). MS (m/z): 239 (M+1).

Preparation 3

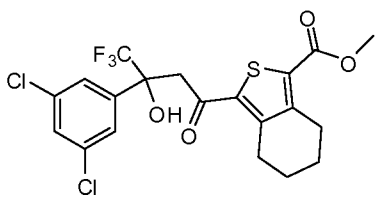
Methyl 3-acetyl-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate



Stir a mixture of Cyclopentane-1,2-dione (2.00 g, 20.4 mmol), methyl 2-(2-oxopropylthio)acetate (3.31 g, 20.4 mmol) and potassium carbonate (5.63 g, 40.8 mmol) in DMF (40 mL) at 80 ^{0}C for 4 hours. Filter off the mixture and remove the solvent under vacuum. Purify the residue by a flash column on silica gel eluting with PE:EtOAc (8:1 to 6:1) to afford 3-Acetyl-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester as a pale yellow solid (206mg, 4.5 %). MS (m/z): 225 (M+1).

Preparation 4

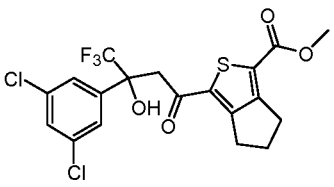
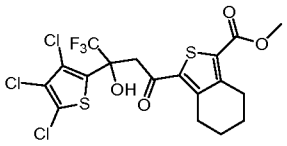
Methyl 3-(3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutanoyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate

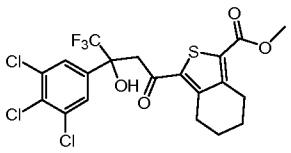
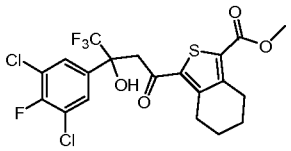
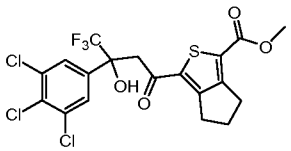


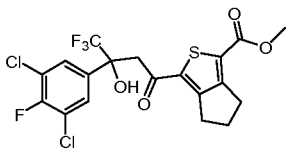
Add a solution of LDA (2M in THF, 19.5 mL, 3.89 mmol) to a suspension of 3-acetyl-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate (7.4 g, 3.11 mmol) in dry

THF (80 mL) at -78^{0}C under N_2. After stirring for 1.5 h, add 1-(3,5-Dichloro-phenyl)-2,2,2-trifluoro-ethanone (9.9 g, 3.73 mmol) to the reaction mixture and stir the resultant mixture at the same temperature for additional 2 hours. Quench the reaction with saturated NH_4Cl aqueous solution. Extract the aqueous mixture with EtOAc (100 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 50:1) to afford methyl 3-(3-(3,5-dichlorophenyl)- 4,4,4-trifluoro-3-hydroxybutanoyl) -4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate as an orange solid (9.1 g, 60.4 %). MS (m/z): 481 (M+1).

The following compounds are prepared essentially by the method of Preparation 4.

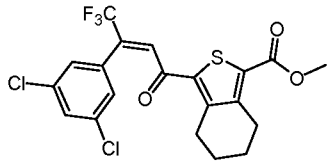
Prep. No.	Chemical name	Structure	Physical data
5	3-[3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 465 (M-1).
6	3-[4,4,4-Trifluoro-3-hydroxy-3-(3,4,5-trichloro-thiophen-2-yl)-butyryl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 519 (M-1).

Prep. No.	Chemical name	Structure	Physical data
7	3-[4,4,4-Trifluoro-3-hydroxy-3-(3,4,5-trichloro-phenyl)-butyryl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 515 (M+1)
8	3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 499 (M+1)
9	3-[4,4,4-Trifluoro-3-hydroxy-3-(3,4,5-trichloro-phenyl)-butyryl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 501 (M+1)

Prep. No.	Chemical name	Structure	Physical data
10	3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 485 (M+1)

Preparation 11

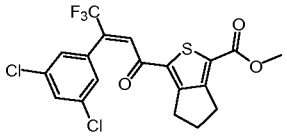
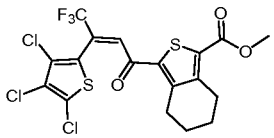
3-[3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester

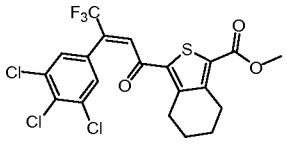
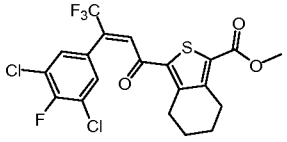
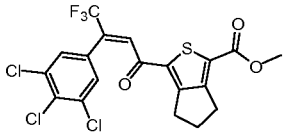


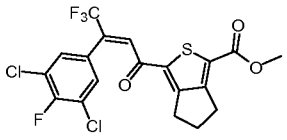
Stir a mixture of methyl 3-(3-(3,5-dichlorophenyl)-4,4,4-trifluoro -3- hydroxyl butanoyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate (9.1 g, 18.9 mmol), $SOCl_2$ (9.0 g, 5.5 mL, 75.6 mmol) and pyridine (2.99 g, 3.1 mL, 37.8 mmol) in anhydrous DCM (100 mL) at ambient temperature overnight. Dilute the resultant mixture with saturated NH_4Cl aqueous solution. Extract the aqueous mixture with DCM (100 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and

concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 50:1) to afford 3-[3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester as an orange solid (8.75 g, 100 %). (m/z): 463 (M+1).

The following compounds are prepared essentially by the method of Preparation 11.

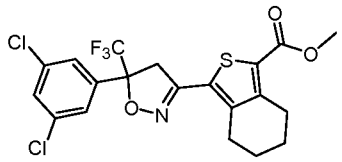
Prep. No.	Chemical name	Structure	Physical data
12	3-[3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 447 (M-1).
13	3-[4,4,4-Trifluoro-3-(3,4,5-trichloro-thiophen-2-yl)-but-2-enoyl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester]thiophene-1-carboxylic acid methyl ester		MS (m/z): 501 (M-1).

Prep. No.	Chemical name	Structure	Physical data
14	3-[4,4,4-Trifluoro-3-(3,4,5-trichloro-phenyl)-but-2-enoyl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 497 (M+1).
15	3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 481 (M+1).
16	3-[4,4,4-Trifluoro-3-(3,4,5-trichloro-phenyl)-but-2-enoyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 483 (M+1).

Prep. No.	Chemical name	Structure	Physical data
17	3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 467 (M+1).

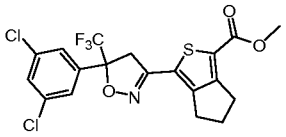
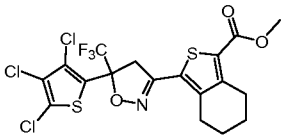
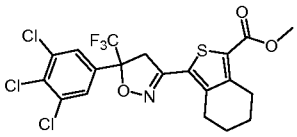
Preparation 18

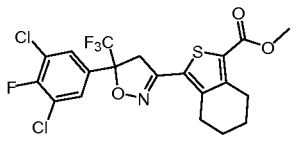
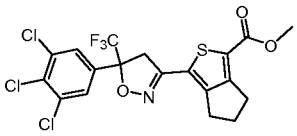
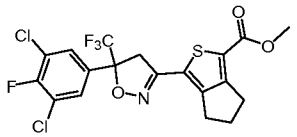
3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester



Stir a mixture of 3-[3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-but-2-enoyl]- 4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester (8.75 g, 18.9 mmol), NaOH (2.65 g, 66.1 mmol) and NH_2OH-HCl (2.6 g, 37.8 mmol) in MeOH (60 mL) and water (15 mL) at room temperature for 2.5 hour. After removal of solvent under vacuum, dilute the residue with ice water (50 mL). Acidify the aqueous mixture with conc. HCl to pH = 1 and extract the resultant mixture with EtOAc (50 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 50:1) to afford 3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester as an orange solid (8.1 g, 93.1%). MS (m/z): 478 (M+1).

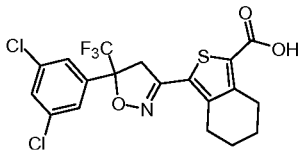
The following compounds are prepared essentially by the method of Preparation 18.

Prep. No.	Chemical name	Structure	Physical data
19	3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 464 (M+1).
20	3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 516 (M-1).
21	3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 512 (M+1).

Prep. No.	Chemical name	Structure	Physical data
22	3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 496 (M+1).
23	3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 498 (M+1).
24	3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester		MS (m/z): 482 (M+1).

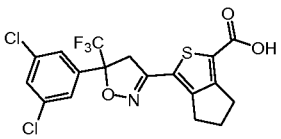
Preparation 25

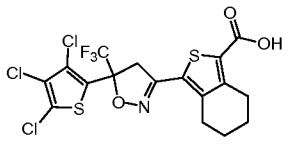
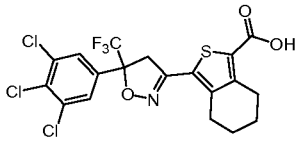
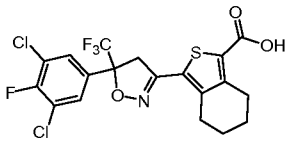
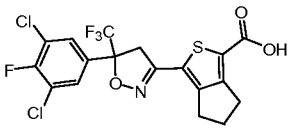
3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid

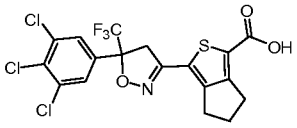


Stir a mixture of 3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester (8.1 g, 17.0 mmol) and LiOH-H_2O (3.57 g, 84.9 mmol) in MeOH (64 mL) and water (16 mL) at room temperature overnight. After removal of organic solvent under vacuum, dilute the residue with ice water (80 mL). Acidify the aqueous mixture with conc. HCl to pH = 1, and extract the resultant mixture with EtOAc (100 mL×3).The combined organic layers are washed brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 1:1) to afford 3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid as pale yellow solid (6.8 g, 86.4 %). MS (m/z): 464 (M+1).

The following compounds may be prepared essentially by the method of Preparation 25.

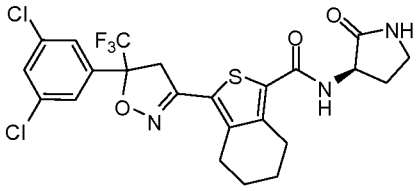
Prep. No.	Chemical name	Structure	Physical data
26	3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid		MS (m/z): 448 (M-1).

Prep. No.	Chemical name	Structure	Physical data
27	3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid		MS (m/z): 502 (M-1).
28	3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid		MS (m/z): 496 (M-1).
29	3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid		MS (m/z): 480 (M-1).
30	3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid		MS (m/z): 466 (M-1).

Prep. No.	Chemical name	Structure	Physical data
31	3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid		MS (m/z): 482 (M-1).

Example 32

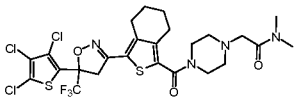
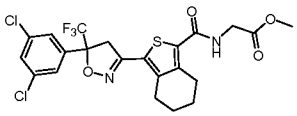
3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide

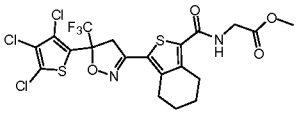
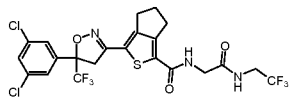
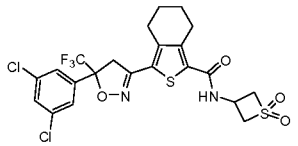


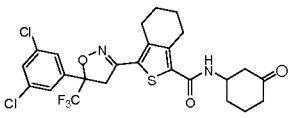
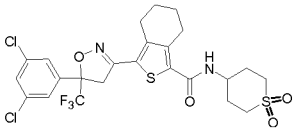
Stir a mixture of 3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (850 mg, 1.84 mmol), HATU (837 mg, 2.20 mmol) and DIEA (539 mg, 0.8 mL, 4.6 mmol) in DCM (8 mL) at room temperature for 15 min, followed by addition of (R)-3-aminopyrrolidin-2-one hydrochloride (315 mg, 2.76 mmol). Stir the reaction mixture at room temperature for additional 1.5 hour. Dilute the reaction mixture with water (20 mL) and extract with DCM (20 mL×3). The combined organic layers are washed brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by preparative HPLC to afford 3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide as a white solid (730 mg, 73.0 %). MS (m/z): 546 (M+1); ^{1}H NMR (400

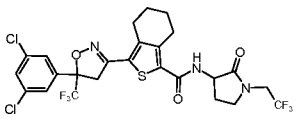
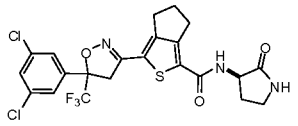
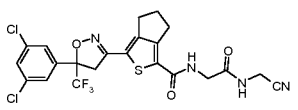
MHz, $CDCl_3$) δ 7.52-7.46 (m, 3H), 6.49 (s, 1H), 5.83 (s, 1H), 4.51-4.48 (m, 1H), 4.22 (d, *J*=17.2, 1H), 3.85 (d, *J*=17.2, 1H), 3.52-3.47 (m, 2H), 3.09-2.87 (m, 5H), 2.12-2.03 (m, 1H), 1.89-1.73 (m, 4H).

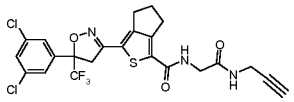
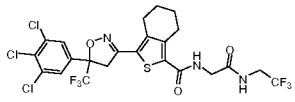
The following compounds may be prepared essentially by the method of Example 32.

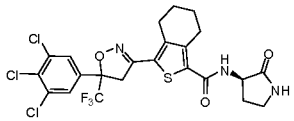
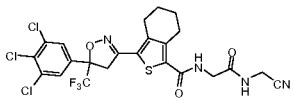
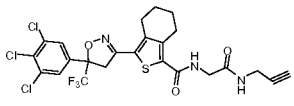
Ex. No.	Chemical name	Structure	Physical data
33	N,N-Dimethyl-2-(4-{3-[5-(3,4,5-trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-piperazin-1-yl)-acetamide		MS (m/z): 659 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07-4.02 (m, 2H), 3.68-3.80 (m, 4H), 3.49-3.41 (m, 2H), 3.09-3.01 (s, 3H), 3.01-2.95 (s, 3H), 2.91-2.85 (m, 2H), 2.84-2.78 (m, 4H), 2.69-2.63 (m, 2H), 1.87-1.72 (m, 4H).
Prep No. 34	({3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester		MS (m/z): 535 (M+1).

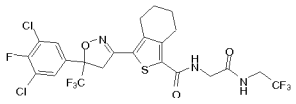
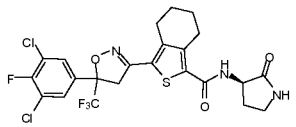
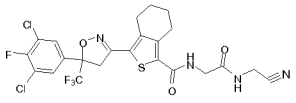
Ex. No.	Chemical name	Structure	Physical data
Prep No. 35	({3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester		MS (m/z): 575 (M+1).
36	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 588 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 7.01-6.95 (s, 1H), 6.79-6.71 (s, 1H), 4.21-4.18 (m, 2H), 4.06-3.91 (m, 3H), 3.65-3.59 (d, *J*=17.2, 1H), 2.98-2.87 (m, 4H), 2.59-2.49 (m, 2H).
37	3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-thietan-3-yl)-amide		MS (m/z): 567 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.44 (s, 1H), 6.59-6.58 (s, 1H), 4.91-4.89 (m, 1H), 4.64-4.59 (m, 2H), 4.07-4.03 (m, 3H), 3.70-3.65 (m, 1H), 2.97-2.91 (m, 4H), 1.80-1.86 (m, 4H).

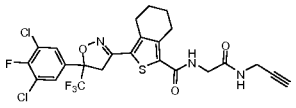
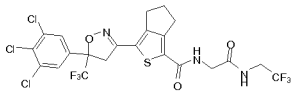
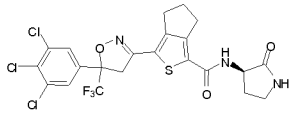
Ex. No.	Chemical name	Structure	Physical data
38	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3-oxocyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 559 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.48 (s, 2H), 7.43 (s, 1H), 5.73 (d, *J*=7.6 Hz, 1H), 4.46-4.42 (m, 1H), 4.06-4.02 (d, *J*=16 Hz, 1H), 3.68-3.64 (d, *J*=16 Hz, 1H), 2.93-2.89 (m, 4H), 2.82-2.77 (m, 1H), 2.47-2.30 (m, 3H), 2.17-2.15 (m, 1H), 2.02-1.95 (m, 1H), 1.88-1.78 (m, 6H).
39	3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-1l6-thiopyran-4-yl)-amide		MS (m/z): 559 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 3H), 5.77 (d, *J* = 7.6 Hz, 1H), 4.27-4.10 (m, 1H), 4.04 (d, *J* = 17.2 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.20 -3.05 (m, 4H), 2.94-2.86 (m, 4H), 2.42-2.40 (m, 2H), 2.26-2.16 (m, 2H), 1.79-1.74 (m, 4H).

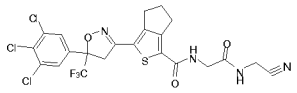
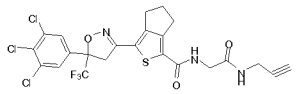
Ex. No.	Chemical name	Structure	Physical data
40	3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid [2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-yl]-amide		MS (m/z): 628 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.43 (m, 3H), 6.65-6.56 (m, 1H), 4.61-4.51 (m, 1H), 4.18-4.01 (m, 2H), 3.99-3.51 (m, 4H), 3.09-2.81 (m, 5H), 2.11-1.99 (m, 1H), 1.81-1.72 (m, 4H).
41	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 532 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 6.59-6.50 (s, 1H), 6.14-6.08 (s, 1H), 4.48-4.41 (m, 1H), 4.06-3.94 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 3.51-3.42 (m, 2H), 3.07-2.84 (m, 5H), 2.58-2.48 (m, 2H), 2.11-2.01 (m, 1H).
42	N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carb		MS (m/z): 545 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (s, 1H),7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 6.86-6.78 (s, 1H), 4.26-4.19 (m, 4H), 4.04-3.97 (d, *J*=17.2, 1H), 3.65-3.59 (d,

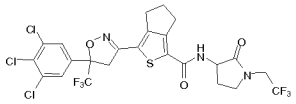
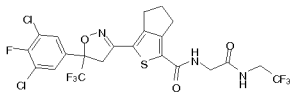
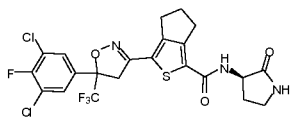
Ex. No.	Chemical name	Structure	Physical data
	oxamide		*J*=17.2, 1H), 3.09-2.84 (m, 4H), 2.58-2.48 (m, 2H).
43	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 544 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 6.86-6.68 (m, 2H), 4.19-4.05 (m, 4H), 4.04-3.97 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 3.03-2.87 (m, 4H), 2.58-2.48 (m, 2H), 2.29-2.26 (s, 1H).
44	N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 636(M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.32 (br, 1H), 6.95 (br, 1H), 4.26-4.25 (m, 2H), 4.06-3.83 (m, 3H), 3.66 (d, *J* = 16.8 Hz, 1H), 2.98-2.89 (m, 4H), 1.79 (br, 4H).

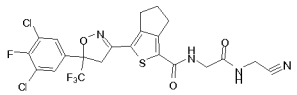
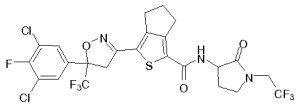
Ex. No.	Chemical name	Structure	Physical data
45	N-((R)-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 580(M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 6.62 (br, 1H), 6.17 (br, 1H), 4.47-4.46 (m, 1H), 4.07-4.02 (m, 1H), 3.75-3.64 (m, 1H), 3.49-3.43 (m, 2H), 3.02-2.88 (m, 2H), 2.09-2.01 (m, 1H), 1.77 (br, 4H).
46	N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 593(M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 2 H), 7.47 (m, 1 H), 6.81 (m, 1 H), 4.22 (m, 4 H), 4.06 (d, *J*=17.2, 1 H), 3.70 (d, *J*=17.2, 1 H), 2.90 (m, 4 H), 1.79 (m, 4 H).
47	N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 592(M+1). ^{1}H NMR (CDCl3, 400 MHz) δ 7. 63 (s, 2 H), 6.78 (m, 1 H), 6.50 (m, 1 H), 4.15 (m, 2 H), 4.10 (m, 2 H), 4.05 (d, *J*=16.8, 1 H), 3.67 (d, *J*=16.8, 1 H), 2.95 (m, 2 H), 2.90 (m, 2 H), 2.26 (m, 1 H), 1.79 (m, 4H).

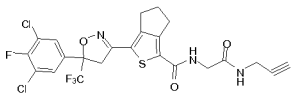
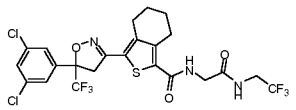
Ex. No.	Chemical name	Structure	Physical data
48	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 620(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.76 (d, *J*=6.4, 2H), 4.25 (d, *J*=17.6, 1H), 4.07 (s, 2H), 4.04-3.92 (m, 3H), 3.01-2.98 (m, 2H), 2.90-2.89 (m, 2H), 1.79 (m, 4H).
49	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 564(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.76 (d, *J*=6.4, 2H), 4.63 (t, *J*=9.6, 1H), 4.24 (d, *J*=17.6, 1H), 4.02 (d, *J*=17.6, 1H), 3.44-3.40 (m, 2H), 2.99-2.98 (m, 2H), 2.89 (m, 2H), 2.59-2.52 (m, 1H), 2.23-2.18 (m, 1H), 1.79-1.77 (m, 4H).
50	N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 577(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.77 (d, *J*=6.4, 2H), 4.28-4.21 (m, 3H), 4.05-4.00 (m, 3H), 3.00(t, *J*=6.0, 2H), 2.93-2.90 (m, 2H), 1.81-1.80 (m, 4H).

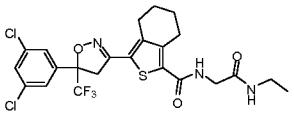
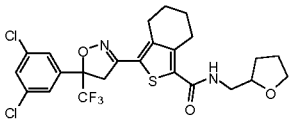
Ex. No.	Chemical name	Structure	Physical data
51	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 576(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.76 (d, *J*=6.4, 2H), 4.24 (d, *J*=17.6, 1H), 4.03-3.99 (m, 5H), 2.98 (t, *J*=6.0, 2H), 2.88-2.86 (m, 2H), 2.62 (t, *J*=2.4, 1H), 1.79-1.77 (m, 4H).
52	N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 622 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.64 (s, 2 H), 6.81 (brs, 1 H), 6.73 (brs, 1 H), 4.22 (d, *J*=4.8, 2 H), 3.99 (m, 3 H), 3.64 (d, *J*=17.2, 1 H), 2.99 (t, *J*=7.6, 2 H), 2.91 (t, *J*=7.6, 2 H), 2.55 (m, 2 H).
53	N-((R)-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 566 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7. 62 (s, 2 H), 6.46 (brs, 1 H), 6.16 (brs, 1 H), 4.47 (m, 1 H), 3.99 (d, *J*=17.2, 1 H), 3.61 (d, *J*=17.2, 1 H), 3.47 (m, 2 H), 2. 93 (m, 5 H), 2.53 (m, 2 H), 2.09 (m, 1 H).

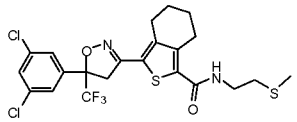
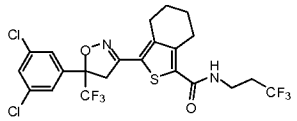
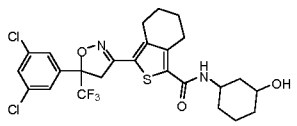
Ex. No.	Chemical name	Structure	Physical data
54	N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 579 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.62 (s, 2 H), 7.21 (brs, 1 H), 6.71 (brs, 1 H), 4.22 (d, *J*=6.0, 2 H), 4.18 (d, *J*=5.2, 2 H), 4.02 (d, *J*=17.2, 1 H), 3.63 (d, *J*=17.2, 1 H), 2.96 (t, *J*=7.2, 2 H), 2. 89 (t, *J*=7.2, 2 H), 2.56 (m, 2 H).
55	N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 578 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.62 (s, 2 H), 6.82 (brs, 1 H), 6.65 (brs, 1 H), 4.15 (d, *J*=4.8, 2 H), 4.10 (d, J_1=2.4, J_2=4.2, 2 H), 4.02 (d, *J*=16.8, 1 H), 3.62 (d, *J*=16.8, 1 H), 2.98 (t, *J*=7.2, 2 H), 2. 88 (t, *J*=7.2, 2 H), 2.55 (m, 2 H), 2. 27 (t, *J*=2.4, 2 H).

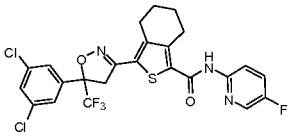
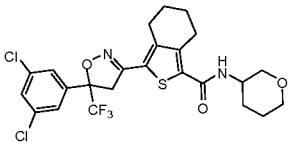
Ex. No.	Chemical name	Structure	Physical data
56	N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 648 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7. 62 (s, 2 H), 6.5 (brs, 1 H), 4.50 (m, 1 H), 4.09 (m, 1 H), 4.00 (d, *J*=17.2, 1 H), 3.84 (m, 1 H), 3.58 (m, 3 H), 2. 93 (m, 5 H), 2.52 (m, 2 H), 2.04 (m, 1 H).
57	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 606 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.0, 2 H), 6.92 (t, *J*=6.4, 1 H), 6.76 (t, *J*=4.8, 1 H), 4.21 (d, *J*=4.8, 1 H), 3.98 (m, 3 H), 3.61 (d, *J*=16.8, 1 H), 2.97 (t, *J*=7.6, 2 H), 2.89 (t, *J*=7.6, 2 H), 2.55 (m, 2H)
58	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 550 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.4, 2 H), 6.46 (brs, 1 H), 6.32 (brs, 1 H), 4.47 (m, 1 H), 3.99 (d, *J*=17.2, 1 H), 3.61 (d, *J*=17.2, 1 H), 3.48 (m, 2 H), 2. 93 (m, 5 H), 2.53 (m, 2 H), 2.06 (m, 1 H).

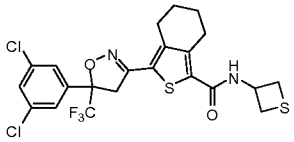
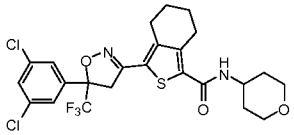
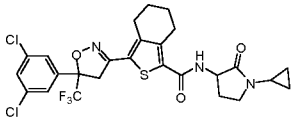
Ex. No.	Chemical name	Structure	Physical data
59	N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 563 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.0, 2 H), 7.41 (brs, 1 H), 6.84 (brs, 1 H), 4.20 (m, 4 H), 3.99 (d, *J*=16.8, 1 H), 3.63 (d, *J*=16.8, 1 H), 2.95 (t, *J*=7.2, 2 H), 2. 88 (t, *J*=7.2, 2 H), 2.53 (m, 2 H).
60	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 632 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.58 (d, *J*=6.0, 2H), 6.60-6.57 (m, 1H), 4.56-4.50 (m, 1H), 4.14-4.00 (m, 2H), 3.87-3.83 (m, 1H), 3.67-3.55 (m, 3H), 3.01-2.86 (m, 5H), 2.57-2.50 (m, 2H), 2.10-2.05 (m, 1H).

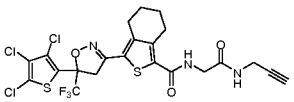
Ex. No.	Chemical name	Structure	Physical data
61	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 562 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.58 (d, *J*=6.0, 2H), 6.85 (brs, 1H), 6.70 (brs, 1H), 4.18 (d, *J*=4.8, 2H), 4.14-4.12 (m, 2H), 4.04 (d, *J*=17.2, 1H), 3.65 (d, *J*=17.2, 1H), 3.00(t, *J*=7.2, 2H), 2.90 (t, *J*=7.2, 2H), 2.60-2.55 (m, 2H), 2.29 (s, 1H).
62	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 602 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.52-7.46 (m, 3H), 7.12-7.01 (m, 1H), 6.85-6.78 (m, 1H), 4.28-4.20 (m, 2H), 4.08-3.91 (m, 3H), 3.68 (d, *J*=17.2, 1H), 3.07-2.87 (m, 4H), 1.89-1.73 (m, 4H).

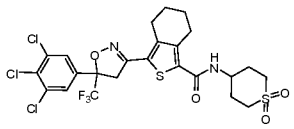
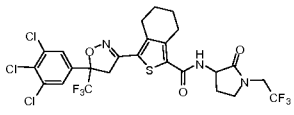
Ex. No.	Chemical name	Structure	Physical data
63	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-(ethylamino)-2-oxoethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 548 (M+1); 1H NMR (CDCl3, 400 MHz) δ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 2H), 7.42 (m, 1H), 6.80 (s, 1H), 5.96 (s, 1H), 4.09-4.02 (m, 3H), 3.69-3.65 (d, *J*=16 Hz, 1H), 3.40-3.33 (m, 2H), 3.00 (s, 2H), 2.92-2.90(m, 2H), 1.79 (s, 4H), 1.26-1.17 (m, 3H).
64	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 547 (M+1); 1H NMR (CDCl3, 400 MHz) δ7.48 (s, 2H), 7.42 (s, 1H), 6.23 (s, 1H), 4.08-4.02 (m, 2H), 3.91-3.86 (m, 1H), 3.81-3.76 (m, 2H), 3.69-3.65 (m, *J*=16 Hz, 1H), 3.34-3.28 (m, 1H), 3.00-2.85 (m, 4H), 2.06-1.98 (m, 1H), 1.96-1.89 (m, 2H), 1.79-1.77 (m, 4H), 1.64-1.59 (m, 1H).

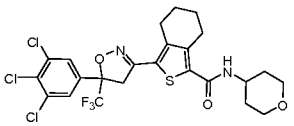
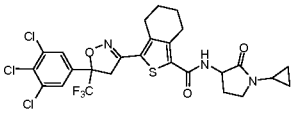
Ex. No.	Chemical name	Structure	Physical data
65	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-(methylthio)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 537 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.43 (s, 1H), 6.33 (s, 1H), 4.07-4.03 (d, *J*=16 Hz, 1H), 3.69-3.62 (m, 3H), 2.98 (s, 2H), 2.92-2.90 (m, 2H), 2.76-2.74 (m, 2H), 2.14 (s, 3H), 1.80-1.79 (m, 4H).
66	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3,3,3-trifluoropropyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 559 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.43 (s, 1H), 6.08-6.05 (m, 1H), 4.06-4.02 (d, *J*=16 Hz, 1H), 3.72-3.64 (m, 3H), 2.94-2.85 (m, 4H), 2.51-2.40 (m, 2H), 1.80-1.78 (m, 4H).
67	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3-hydroxycyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 561 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.43 (s, 1H), 6.85 (s, 1H), 4.21 (s, 1H), 4.09-4.02 (m, 2H), 3.69-3.64 (d, *J*=20 Hz, 1H), 2.96-2.89 (m, 5H), 2.05-1.78 (m, 9H), 1.49-1.38 (m, 2H).

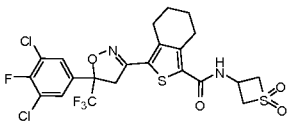
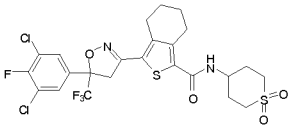
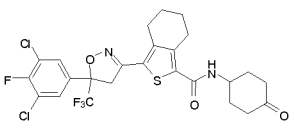
Ex. No.	Chemical name	Structure	Physical data
68	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(5-fluoropyridin-2-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 558 (M+1); 1H NMR (CDCl3, 400 MHz) δ 8.36 (s, 1H), 8.32-8.29 (m, 1H), 8.16 (d, *J*=2.4 Hz, 1H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 4.09-4.05 (d, *J*=16 Hz, 1H), 3.71-3.67 (d, *J*=16 Hz, 1H), 3.09 (s, 2H), 2.94-2.93 (m, 2H), 1.83 (s, 4H)
69	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 547 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.40 (s, 1H), 6.23 (d, *J*=9.6 Hz, 1H), 4.18-4.16 (s, 1H), 4.07-4.03 (d, *J*=16 Hz, 1H), 3.83-3.77 (m, 2H), 3.69-3.57 (m, 3H), 2.98-2.90 (m, 4H), 1.90-1.75 (m, 8H).

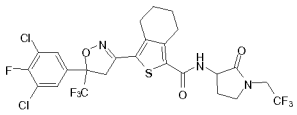
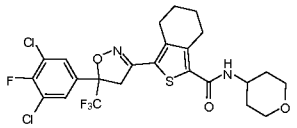
Ex. No.	Chemical name	Structure	Physical data
70	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(thietan-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 535 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.44 (s, 1H), 6.18 (d, *J* = 7.6 Hz, 1H), 5.40-5.34 (m, 1H), 4.06 (d, *J* = 17.2 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.46-3.36 (m, 4H), 2.97-2.90 (m, 4H), 1.81-1.78 (m, 4H).
71	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 547 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.47 (s, 2H), 7.41 (s, 1H), 5.74-5.72 (d, *J*=7.6 Hz, 1H), 4.19-4.11 (m, 1H), 4.10-4.06 (d, *J*=16 Hz, 1H), 4.04-3.96 (m, 2H), 3.69-3.65 (d, *J*=16 Hz, 1H), 3.53-3.43 (m, 2H), 2.94-2.88 (m, 4H), 2.00-1.97 (m, 2H), 1.77 (s, 4H), 1.60-1.50 (m, 2H).
72	N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carbo		MS (m/z): 586 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2 H), 7.43 (s, 1H), 6.50 (brs, 1 H), 4.43-4.40 (m, 1 H), 4.04 (d, *J* =16.8, 1 H), 3.65 (d, *J* =16.8, 1 H), 3.42-3.30 (m, 2 H), 2.99-2.82

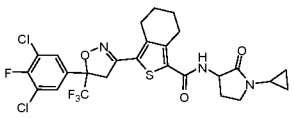
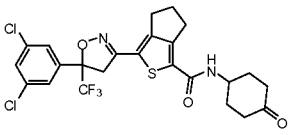
Ex. No.	Chemical name	Structure	Physical data
	xamide		(m, 5 H), 1.91-1.80 (m, 5 H), 0.83-0.763 (m, 4 H)
74	N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorothiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 600 (M+1); 1H NMR (CDCl3, 400 MHz) δ 6.92-6.77 (m, 2H), 4.21-4.09 (m, 4H), 4.08-4.04 (m, 2H), 3.09-2.88 (m, 4H), 1.87-1.71 (m, 4H).

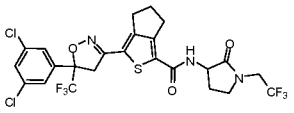
Ex. No.	Chemical name	Structure	Physical data
75	3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide		MS (m/z): 631 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.62 (s, 2H), 5.89-5.87 (m, 1H), 4.28-4.20 (m, 1H), 4.07-4.03 (d, *J*=16 Hz, 1H), 3.70-3.66 (d, *J*=16 Hz, 1H), 3.20-3.12 (m, 4H), 2.94-2.89 (m, 4H), 2.42-2.39 (m, 2H), 2.27-2.17 (m, 2H), 1.79 (s, 4H).
76	N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 664 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.63 (s, 2 H), 6.45 (brs, 1 H), 4.53 (brs, 1 H), 4.09 (m, 2 H), 3.85 (m, 1 H), 3.58 (m, 3 H), 2.95 (m, 4 H), 2.02 (m, 1 H), 1.79 (m, 4 H).

Ex. No.	Chemical name	Structure	Physical data
77	N-(tetrahydro-2H-pyran-4-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 583 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.61 (s, 2H), 5.70-5.68 (d, *J*=8.0 Hz, 1H), 4.19-4.11 (m, 1H), 3.70-3.66 (d, *J*=16 Hz, 1H), 4.00-3.97 (m, 2H), 3.68-3.64 (d, *J*=16 Hz, 1H), 3.54-3.48 (m, 2H), 2.94-2.88 (m, 4H), 2.00-1.98 (m, 2H), 1.79 (s, 4H), 1.64-1.50 (m, 2H).
78	N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 622 (M+1); 1H NMR (CDCl3, 400 MHz) δ 8.00 (s, 2 H), 6.53 (brs, 1 H), 4.43 (m, 1 H), 4.04 (d, *J*=17.2, 1 H), 3.65 (d, *J*=17.2, 1 H), 3.36 (m, 2 H), 2.83 (m, 5 H), 2.73 (m, 1 H), 1.84 (m, 5 H), 0.79 (m, 4 H).

Ex. No.	Chemical name	Structure	Physical data
79	3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-thietan-3-yl)-amide		MS (m/z): 585 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.76 (d, *J*=6.0, 2H), 4.65-4.56 (m, 1H), 4.53 (t, *J*=4.8, 2H), 4.28-4.23 (m, 3H), 4.02 (d, *J*=17.6, 1H), 2.97 (t, *J*=6.0, 2H), 2.90 (t, *J*=6.0, 2H), 1.80-1.76 (m, 4H).
80	3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide		MS (m/z): 613 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.0, 2 H), 5.75 (d, *J*=7.2, 1 H), 4.06 (d, *J*=16.8, 1 H), 3.65 (d, *J*=16.8, 1 H), 3.13 (m, 4 H), 2.91 (m, 4 H), 2.41 (m, 2 H), 2.23 (m, 2 H), 1.84 (m, 4 H).
81	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(4-oxocyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 577 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.48(d , *J*=6.0, 2H), 5.67 (d, *J*=6.8, 1H), 4.33 (m, 1H), 3.98(d, *J*=16.8, 1H), 3.58 (d, *J*=16.8, 1H), 2.82 (m, 4H), 2.40 (m, 6H), 1.65 (m, 6H)

Ex. No.	Chemical name	Structure	Physical data
82	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 646 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7. 50 (dd, J_1=2.4, J_2=6.0, 2 H), 6.44 (dd, J_1=4.8, J_2=12.0, 1 H), 4.46 (m, 1 H), 3.98 (m, 2 H), 3.78 (m, 1 H), 3.55 (m, 3 H), 2.83 (m, 5 H), 1.963 (m, 1 H), 1.71 (m, 4 H).
83	3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 565 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (d, J=5.6, 2 H), 5.59 (d, J=7.6, 1 H), 4.10 (m, 1 H), 3.98 (d, J=16.8, 1 H), 3.91 (m, 2 H), 3.58 (d, J=16.8, 1 H), 3.45 (m, 2 H), 2.84 (m, 4 H), 1.95 (m, 2 H), 1.72 (m, 4 H), 1.49 (m, 3 H).

Ex. No.	Chemical name	Structure	Physical data
84	N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 604 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.77 (d, *J*=6.0, 2H), 4.62 (t, *J*=9.6, 1H), 4.24 (d, *J*=17.6, 1H), 4.02 (d, *J*=17.6, 1H), 3.43-3.39 (m, 2H), 2.99-2.96 (m, 2H), 2.90-2.88 (m, 2H), 2.75-2.69 (m, 1H), 2.50-2.42 (m, 1H), 2.10-1.99 (m, 1H), 1.81-1.78 (m, 4H), 0.85-0.82 (m, 4H).
85	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(4-oxocyclohexyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 545 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.52-7.44 (m, 3H), 5.72-5.68 (m, 1H), 4.48-4.37 (m, 1H), 4.04-3.97 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 2.92-2.84 (m, 4H), 2.58-2.48 (m, 6H), 2.47-2.31 (m, 2H), 1.84-1.71 (m, 2H).

Ex. No.	Chemical name	Structure	Physical data
86	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide		MS (m/z): 614 (M+1); 1H NMR (CDCl3, 400 MHz) δ7.52-7.44 (m, 3H), 6.43-6.38 (s, 1H), 4.52-4.48 (m, 1H), 4.17-4.05 (m, 2H), 4.04-3.97 (d, *J*=17.2, 1H), 3.89-3.77 (m, 1H), 3.68-3.51 (m, 3H), 2.93-2.82 (m, 5H), 2.58-2.46 (m, 2H), 2.08-1.97 (m, 1H).

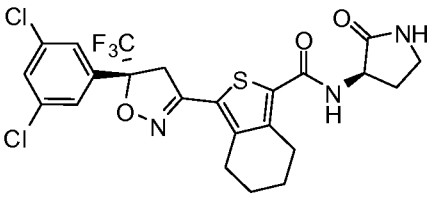
Example 87

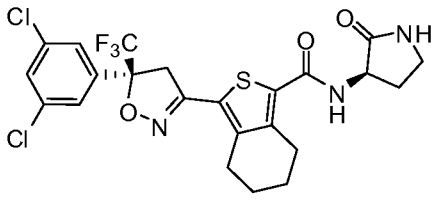
(A)

3-((R)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide and

(B)

3-((S)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide



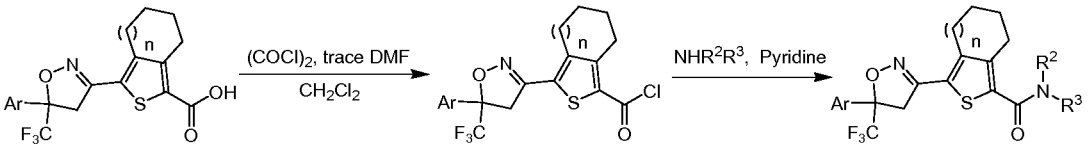


Separate 3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl) -N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide (6.2 g 11.29 mmol) by SFC (Column: Chiralcel OD 250×30mm I.D., 5um. Mobile phase: Supercritical CO_2/ MeOH=60/40, Flow rate:200 ml/min) to afford two diastereoisomers 3-((R)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-ox o pyrrolidin-3-yl)- 4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide (2.7 g, 4.92 mmol) and 3-((S)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-ox opyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide (2.6 g, 4.74 mmol) as a white solid.

(A) MS (m/z): 619.1 (M+73). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 2H), 7.42 (s, 1H), 6.56 (d, *J*=4.4 Hz 1H), 6.03 (s, 1H), 4.50-4.44 (m, 1H), 4.06-4.02 (d, *J*=16 Hz, 1H), 3.69-3.65 (d, *J*=16 Hz, 1H), 3.48-3.43 (m, 2H), 3.03-2.98 (m, 5H), 2.11-2.00 (m, 1H), 1.78 (s, 4H).

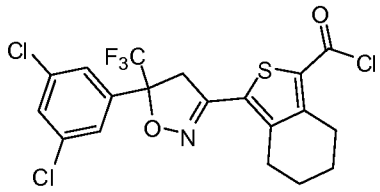
(B) MS (m/z): 619.1 (M+73). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (m, 2H), 7.41 (m, 1H), 6.77-6.73 (m, 1H), 6.38-6.31 (m, 1H), 4.51-4.45 (m, 1H), 4.05-4.01 (d, *J*=16 Hz, 1H), 3.71-3.67 (d, *J*=16 Hz, 1H), 3.49-3.39 (m, 2H), 3.00-2.85 (m, 5H), 2.04-2.03 (m, 1H), 1.74 (s, 4H).

Scheme B



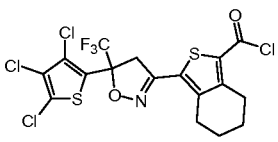
Preparation 88

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carbonyl chloride



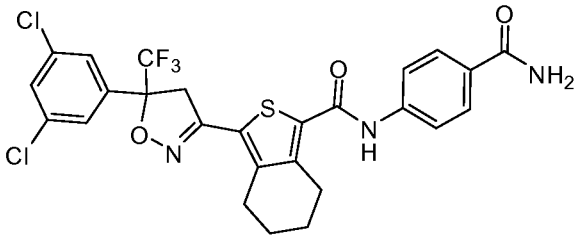
Stir a mixture of 3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (600 mg, 1.2 mmol), 2 drops DMF in oxalyl dichloride (5 mL) at ambient temperature for 3 hours. Remove the solvent under vacuum to afford 3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carbonyl chloride as a yellow solid (615 mg, 98%).

The following compound is prepared essentially by the method of Preparation 88.

Prep. No.	Chemical name	Structure	Physical data
89	3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl chloride		

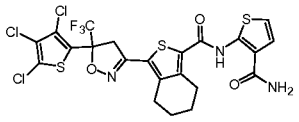
Example 90

N-(4-carbamoylphenyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide

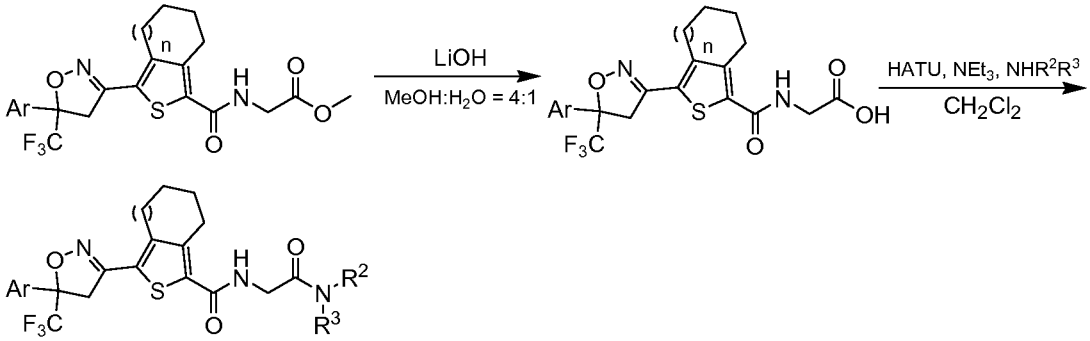


Stir a mixture of 3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carbonyl chloride (48 mg, 0.1 mmol) and 4-aminobenzamide (27 mg, 0.2 mmo) in pyridine (3 mL) at ambient temperature overnight. After removal solvent under vacuum, purify the residue by preparative HPLC to afford N-(4-carbamoylphenyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide as a white solid (36 mg, 62.0%). MS (m/z): 582.1 (M+1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J*=8.4 Hz, 2H), 7.65-7.63 (m, 3H), 7.49 (s, 2H), 7.44 (s, 1H), 6.03 (s, 1H), 5.61 (s, 1H), 4.09-4.05 (d, *J*=16 Hz, 1H), 3.72-3.68 (d, *J*=16 Hz, 1H), 3.07 (s, 2H), 2.94 (s, 2H), 1.76 (s, 4H).

The following compound is prepared essentially by the method of Example 90.

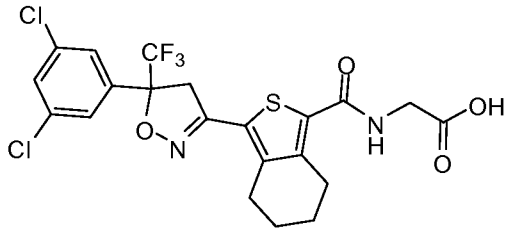
Ex. No.	Chemical name	Structure	Physical data
91	3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (3-carbamoyl-thiophen-2-yl)-amide		MS (m/z): 628 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6,) δ 8.08-8.02 (m, 1H), 7.81-7.78 (m, 1H), 4.58-4.43 (t, 2H), 3.13-2.84 (m, 4H), 1.79-1.64 (m, 4H).

Scheme C



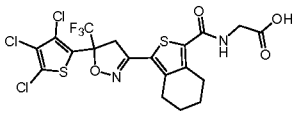
Preparation 92

2-(3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamido)acetic acid



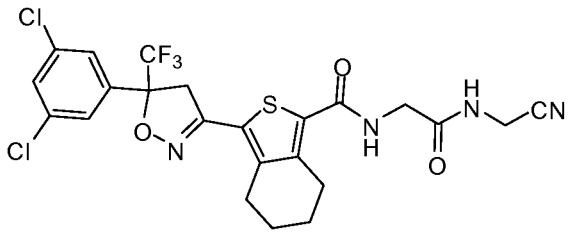
Stir a mixture of methyl 2-(3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamido)acetate (534 mg, 1.0 mmol) and LiOH-H_2O (168 mg, 4.0 mmol) in MeOH (20 mL) and water (5 mL) at room temperature for overnight. After removal of organic solvent under vacuum, dilute the residue with ice water (10 mL). Acidify the aqueous mixture with conc. HCl to pH = 1, and extract the resultant mixture with EtOAc (15 mL×3).The combined organic layers are washed brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 1:1) to afford 2-(3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamido)acetic acid as a pale yellow solid (427 mg, 82.0 %). MS (m/z): 521(M+1).

The following compound is prepared essentially by the method of Preparation 92.

Prep. No.	Chemical name	Structure	Physical data
93	({3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid		MS (m/z): 561 (M+1).

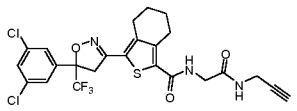
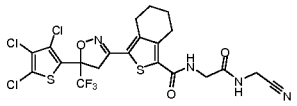
Example 94

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide

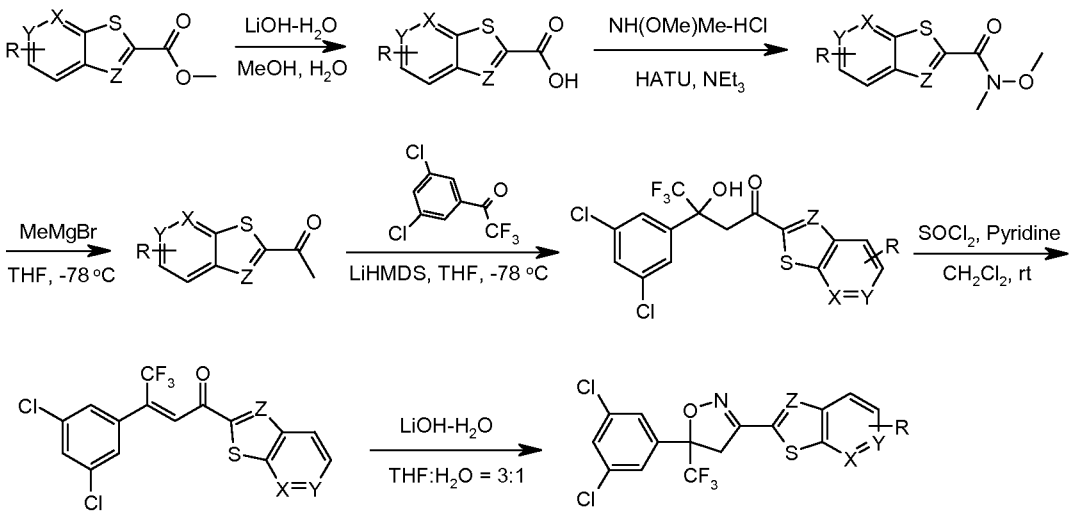


Stir a mixture of 2-(3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamido)acetic acid (230 mg, 0.44 mmol), HATU (251 mg, 0.66 mmol) and NEt_3 (133 mg, 1.32 mmol) in DCM (5 mL) at room temperature for 15 min, followed by addition of 2-aminoacetonitrile hydrochloride (61 mg, 0.65 mmol). Stir the reaction mixture at room temperature for additional 1.5 hour. Dilute the reaction mixture with water (20 mL) and extract with DCM (20 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by preparative HPLC to afford N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide as a white solid (110 mg, 44.7 %). MS (m/z): 559.1 (M+1). ^1H NMR (DMSO-d_6, 400 MHz) δ 8.64 (t, J=5.6 Hz, 1H), 8.22 (t, J=5.6 Hz, 1H), 7.81-7.80 (m 1H), 7.68 (s, 2H), 4.35-4.22 (m, 2H), 4.16-4.15 (m, 2H), 3.88-3.86 (m, 2H), 2.94-2.86 (m, 4H), 1.70-1.69 (m, 4H).

The following compounds are prepared essentially by the method of Example 94.

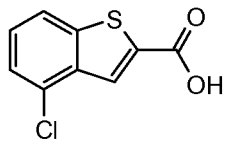
Ex. No.	Chemical name	Structure	Physical data
95	3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 558 (M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49-7.42 (m, 3H), 6.85 (br, 1H), 6.72 (br, 1H), 4.17-4.03 (m, 5H), 3.68 (d, J = 17.2 Hz, 1H), 3.00-2.90 (m, 4H), 2.25 (s, 1H), 1.79 (br, 4H).
96	N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorothiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide		MS (m/z): 599 (M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28-4.18 (m, 4H), 4.10-4.07 (m, 2H), 3.04-2.87 (m, 4H), 1.88-1.73 (m, 4H).

Scheme D



Preparation 201

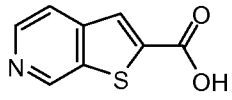
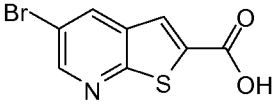
4-chlorobenzo[b]thiophene-2-carboxylic acid



Stir a mixture of methyl 4-chlorobenzo[b]thiophene-2-carboxylate (1.0 g, 4.44 mmol) and LiOH-H_2O (0.56 g, 13.3 mmol) in MeOH (30 mL) and water (10 mL) at room temperature overnight. Concentrate the reaction mixture under vacuum and then dilute the residue with ice water (20 mL). Acidify the aqueous mixture with conc. HCl solution to pH = 1. Extract the resultant mixture with EtOAc (15 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and evaporate under vacuum to afford 4-chlorobenzo[b]thiophene-2-carboxylic acid as a white solid (0.94 g, 100 %).

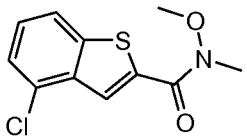
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.02 (m, 2H), 7.61-7.51 (m, 2H)

The following compounds are prepared essentially by the method of Preparation 201.

Prep No.	Chemical name	Structure	Physical data
202	Thieno[2,3-c]pyridine-2-carboxylic acid		MS (m/z): 180(M+1)
203	5-Bromo-thieno[2,3-b]pyridine-2-carboxylic acid		MS (m/z): 260 (M+1).

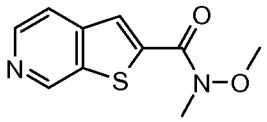
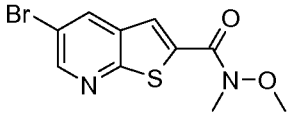
Preparation 204

4-chloro-N-methoxy-N-methylbenzo[b]thiophene-2-carboxamide



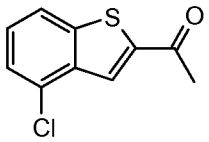
Stir a mixture of 4-chlorobenzo[b]thiophene-2-carboxylic acid (0.94 g, 4.44 mmol), N,O-dimethylhydroxylamine hydrochloride (0.86 g, 8.87 mmol), DCC (1.1 g, 5.32 mmol) and DIEA (1.43 g, 1.9 mL, 11.08 mmol) in DCM (8 mL) at ambient temperature for 2 hours. Filter the reaction mixture and the filtrate is washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by column chromatography on silica gel eluting with PE: EtOAc (5:1 to 3:1) to afford 4-chloro-N-methoxy-N-methylbenzo[b]thiophene-2-carboxamide as white solid (0.85 g, 75.2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.02 (m, 2H), 7.61-7.51 (m, 2H), 3.84-3.79 (s, 3H), 3.37-3.35 (s, 3H).

The following compound is prepared essentially by the method of Preparation 204.

Prep. No.	Chemical name	Structure	Physical data
205	N-methoxy-N-methylthieno[2,3-c]pyridine-2-carboxamide		MS (m/z): 223 (M+1).
206	5-bromo-N-methoxy-N-methylthieno[2,3-b]pyridine-2-carboxamide		MS (m/z): 301 (M+1).

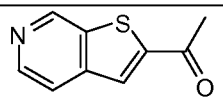
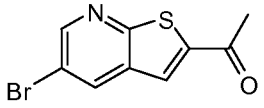
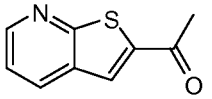
Preparation 207

1-(4-chlorobenzo[b]thiophen-2-yl)ethanone



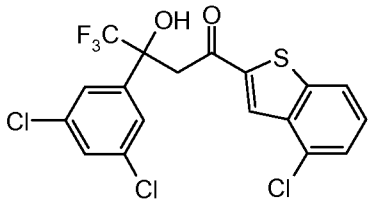
Add a solution of CH_3MgBr (3 M in THF, 1.7 ml, 4.99 mmol) to a suspension of 4-chloro-N-methoxy-N-methylbenzo[b]thiophene-2-carboxamide (0.85 g, 3.33 mmol) in dry THF (10 mL) at 0 ^{0}C. Then stir the mixture for overnight at ambient temperature. Quench the reaction with saturated NH_4Cl aqueous solution (15 mL) and extract the aqueous mixture with EtOAc (10 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc = 6:1) to afford 1-(4-chlorobenzo[b]thiophen-2-yl)ethanone as white solid (0.6 g, 86.9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (s, 1H), 7.75 (d, *J*=5.2, 1H), 7.47-7.36 (m, 2H), 2.72-2.68 (s, 3H).

The following compounds are prepared essentially by the method of Preparation 207.

Prep No.	Chemical name	Structure	Physical data
208	1-Thieno[2,3-c]pyridin-2-yl-ethanone		MS (m/z): 178 (M+1).
209	1-(5-Bromo-thieno[2,3-b]pyridin-2-yl)-ethanone		MS (m/z): 258 (M+1).
210	1-Thieno[2,3-b]pyridin-2-yl-ethanone		MS (m/z): 178 (M+1)

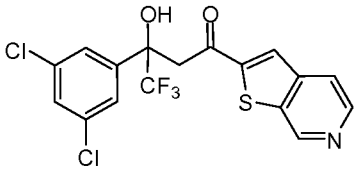
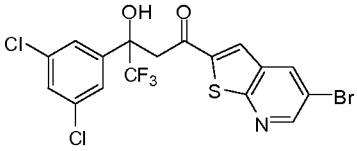
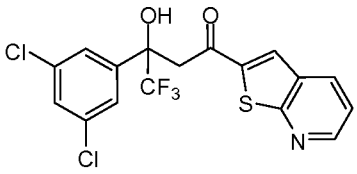
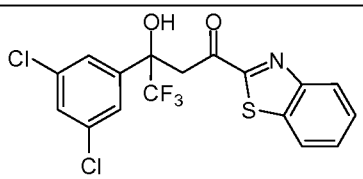
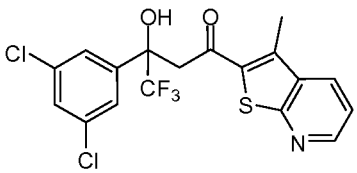
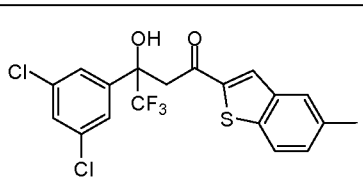
Preparation 211

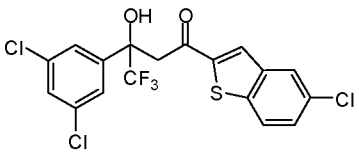
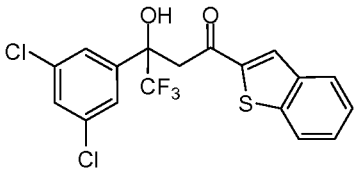
1-(4-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one



Add a solution of LiHMDS (1 M in THF, 4.3 ml, 4.31 mmol) to a mixture of 1-(4-chlorobenzo[b]thiophen-2-yl)ethanone (0.6 g, 2.87 mmol) in dry THF (10 mL) at -78 ^{0}C under N_2. After stirring 1.5 hour at -78 ^{0}C, add 1-(3,5-dichlorophenyl)-2,2,2-trifluoroethanone (836 mg, 3.44 mmol) to the reaction mixture and stir the resultant mixture for additional 2 hours. Quench the reaction with saturated NH_4Cl solution and extract the aqueous mixture with EtOAc (10 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum afford crude 1-(4-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one as brown solid (1.1 g, 84.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (s, 1H), 7.75 (d, *J*=5.2, 1H), 7.47-7.36 (m, 2H), 2.72-2.68 (s, 3H).

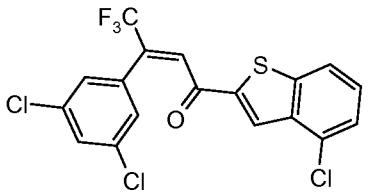
The following compounds are prepared essentially by the method of Preparation 211.

Prep. No.	Chemical name	Structure	Physical data
212	3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-1-thieno[2,3-c]pyridin-2-yl-butan-1-one		MS (m/z): 418 (M-1)
213	3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-1-(5-bromo-thieno[2,3-b]pyridin-2-yl)-butan-1-one		MS (m/z): 498 (M-1).
214	3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-1-thieno[2,3-b]pyridin-2-yl-butan-1-one		MS (m/z): 418 (M-1).
215	1-(benzo[d]thiazol-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one		MS (m/z): 418 (M-1).
216	3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxy-1-(3-methylbenzo[b]thiophen-2-yl)butan-1-one		MS (m/z): 431 (M-1).
217	3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxy-1-(5-methylbenzo[b]thiophen-2-yl)butan-1-one		MS (m/z): 431 (M-1).

Prep. No.	Chemical name	Structure	Physical data
218	1-(5-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one		MS (m/z): 451 (M-1).
219	1-(benzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one		MS (m/z): 417 (M-1).

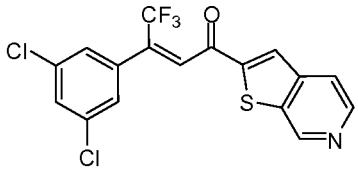
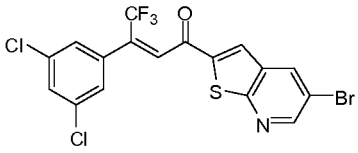
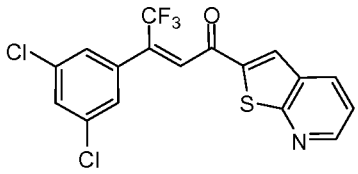
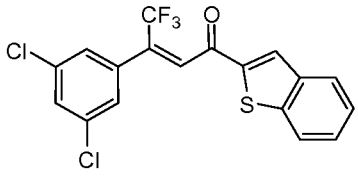
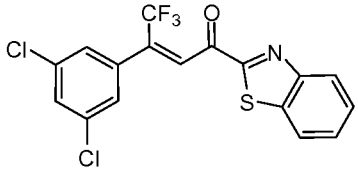
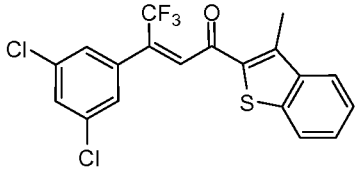
Preparation 220

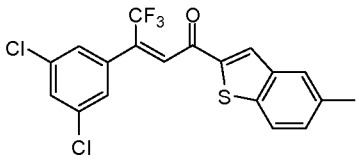
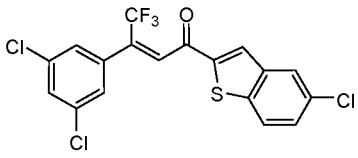
1-(4-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluorobut-2-en-1-one



Stir a mixture of 1-(4-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one (1.1 g, crude, 2.43 mmol), $SOCl_2$ (1.16 g, 0.7 mL, 9.43 mmol) and pyridine (384 mg, 0.4 mL, 4.86 mmol) in anhydrous DCM (10 mL) at ambient temperature for overnight. Dilute the mixture with saturated NH_4Cl solution and extract the aqueous mixture with DCM (10 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford crude 1-(4-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluorobut-2-en-1-one as brown solid (1.05 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ8.12-8.10 (s, 1H), 7.69-7.64 (m, 1H), 7.47-7.44 (m, 2H), 7.38-7.35 (m, 2H), 7.27-7.24 (m, 1H), 6.96 -6.92 (s, 1H).

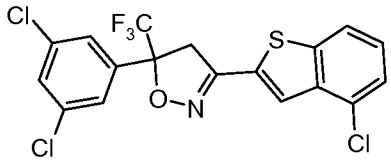
The following compounds are prepared essentially by the method of Preparation 220.

Prep. No.	Chemical name	Structure	Physical data
221	3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-1-thieno[2,3-c]pyridin-2-yl-but-2-en-1-one		MS (m/z): 400 (M-1).
222	3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-1-(5-bromo-thieno[2,3-b]pyridin-2-yl)-but-2-en-1-one		MS (m/z): 480 (M-1).
223	3-(3,5-Dichloro-phenyl)-4,4,4-trifluoro-1-thieno[2,3-b]pyridin-2-yl-but-2-en-1-one		MS (m/z): 400 (M-1).
224	1-(benzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluorobut-2-en-1-one		MS (m/z): 399
225	1-(benzo[d]thiazol-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluorobut-2-en-1-one		MS (m/z): 400
226	3-(3,5-dichlorophenyl)-4,4,4-trifluoro-1-(3-methylbenzo[b]thiophen-2-yl)but-2-en-1-one		MS (m/z): 413

Prep. No.	Chemical name	Structure	Physical data
227	3-(3,5-dichlorophenyl)-4,4,4-trifluoro-1-(5-methylbenzo[b]thiophen-2-yl)but-2-en-1-one		MS (m/z): 413
228	1-(5-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluorobut-2-en-1-one		MS (m/z): 433

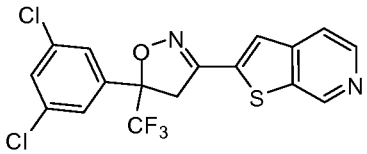
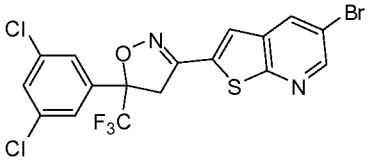
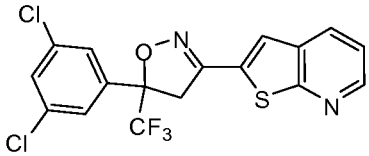
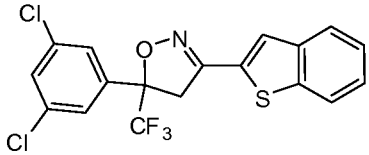
Example 229

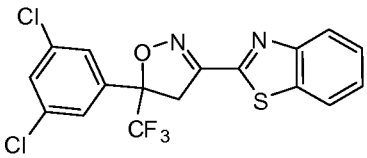
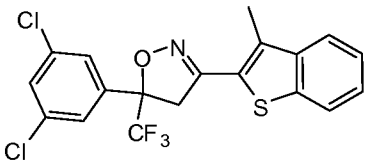
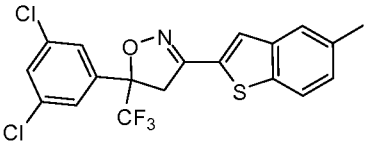
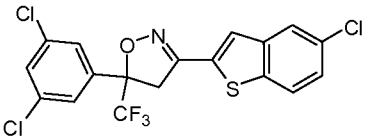
3-(4-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



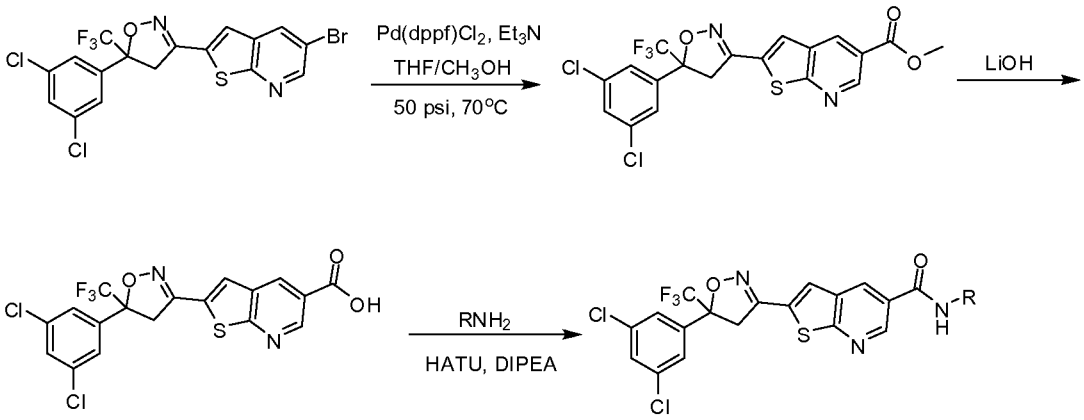
Stir a mixture of 1-(4-chlorobenzo[b]thiophen-2-yl)-3-(3,5-dichlorophenyl)-4,4,4-trifluorobut-2-en-1-one (1.05 g, crude, 2.43 mmol), NaOH (389 mg, 9.72 mmol) and NH_2OH-HCl (335 mg, 4.8 mmol) in MeOH (8 mL) and water (8 mL) at ambient temperature for 4 hours. After removal of solvent under vacuum, dilute the residue with ice water (20 mL). Extract the aqueous mixture with EtOAc (15 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by preparative HPLC to afford 3-(4-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole as white solid (305 mg, 28.1 %). MS (m/z): 450 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δδ 7.74 (d, *J*=8.0, 1H), 7.64-7.60 (s, 1H), 7.57-7.53 (m, 2H), 7.47-7.43 (m, 1H), 7.40-7.32.

The following compounds are prepared essentially by the method of Example 229.

Ex. No.	Chemical name	Structure	Physical data
230	2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-c]pyridine		MS (m/z): 417 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.55-8.57 (d, J = 5.6, 1H), 7.68-7.69 (d, J_1 = 5.6, J_2 = 1.2, 1H), 7.51-7.52 (d, J = 1.2, 2H), 7.49 (S, 1H), 7.45-7.46 (t, J = 3.6, 1H), 4.17-4.21 (d, J = 16.8, 1H), 3.79-3.83 (d, J = 16.8, 1H).
231	5-Bromo-2-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine		MS (m/z): 497 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 8.65-8.66 (d, J = 1.6, 1H), 8.18-8.19 (d, J = 2.0, 1H), 7.51 (S, 2H), 7.45-7.46 (d, J = 1.6, 1H), 7.32 (S, 1H), 4.13-4.17 (d, J = 16.8, 1H), 3.75-3.79 (d, J = 16.8, 1H).
232	2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine		MS (m/z): 417 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62-8.64 (d, J_1 = 4.4, J_2 = 1.6, 1H), 8.05-8.07 (d, J_1 = 8.0, J_2 = 1.6, 1H), 7.51-7.52 (d, J = 1.2, 2H), 7.44-7.45 (t, J = 3.6, 1H), 7.41 (s, 1H), 7.33-7.36 (m, 1H), 4.15-4.19 (d, J = 16.8, 1H), 3.77-3.81 (d, J = 16.8, 1H).
233	3-(benzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)		MS (m/z): 416 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J=8.0, 1H), 7.82 (d, J=8.0, 1H), 7.55-7.50 (m, 2H),

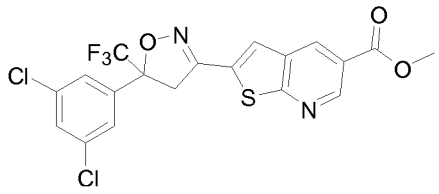
Ex. No.	Chemical name	Structure	Physical data
	-4,5-dihydroisoxazole		7.48-7.34 (m, 4H), 4.20 (d, *J*=16.8, 1H), 3.80 (d, *J*=17.6, 1H).
234	3-(benzo[d]thiazol-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole		MS (m/z): 417 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.2, 1H), 7.93 (d, *J*=7.2, 1H), 7.58-7.47 (m, 5H), 4.37 (d, *J*=18.0, 1H), 4.00 (d, *J*=18.0, 1H)
235	5-(3,5-dichlorophenyl)-3-(3-methylbenzo[b]thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole		MS (m/z): 430 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.78 (m, 2H), 7.53 (s, 2H), 7.53-7.43 (m, 3H), 4.17 (d, *J* = 16.8, 1H), 3.79 (d, *J* = 16.8, 1H), 2.67 (s, 3H).
236	5-(3,5-dichlorophenyl)-3-(5-methylbenzo[b]thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole		MS (m/z): 430 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0, 1H), 7.57 (s, 1H), 7.53 (s, 2H), 7.43 (t, *J* = 3.2, 1H), 7.36 (d, *J* = 7.0, 1H), 7.24 (d, *J* = 7.0, 1H), 4.17 (d, *J* = 16.8, 1H), 3.78 (d, *J* = 16.8, 1H), 2.47 (s, 3H).
237	3-(5-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole		MS (m/z): 450 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.75 (m, 2H), 7.51 (s, 2H), 7.45-7.44 (m, 1H), 7.40-7.38 (m, 2H), 4.18 (d, *J* = 16.8, 1H), 3.78 (d, *J* = 17.6, 1H).

Scheme E



Preparation 238

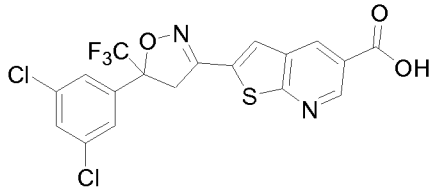
methyl 2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)thieno[2,3-b]pyridine-5-carboxylate



Stir a mixture of 5-bromo-2-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-*yl*]-thieno[2,3-b]pyridine (494 mg, 1 mmol), $Pd(dppf)Cl_2$ (100 mg) and triethyl amine (1 mL) in anhydrous THF (10 mL) and methanol (5 mL) under carbon monoxide (50 psi) at 70 °C for 10h. After removal of solvent under vacuum, purify the residue with silica gel chromatography (eluting with 10% ethyl acetate in petroleum ether) to afford methyl 2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)thieno[2,3-b]pyridine-5-carboxylate as a white solid (210 mg, 44.18%). MS (m/z): 475 (M+1).

Preparation 239

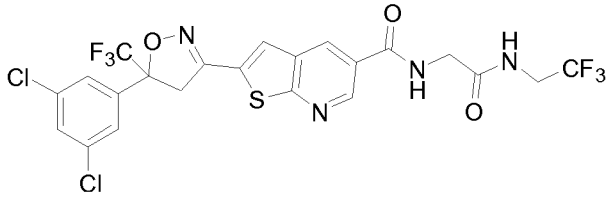
2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-*yl*]-thieno[2,3-b]pyridine-5-carboxylic acid



Add a solution of $LiOH\text{-}H_2O$ (76 mg, 2 mmol) in water (0.5 mL) to a solution of methyl 2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)thieno[2,3-b]pyridine-5-carboxylate (237 mg, 0.5 mmol) in THF(3 mL). Stir the mixture at temperature for 12 hours. After addition of 10 mL of water, acidify the mixture with concentrated HCl to PH = 6~7. Extract the resultant mixture with ethyl acetate (3 X 10 mL). The combined organic layers are washed brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-*yl*]-thieno[2,3-b]pyridine-5-carboxylic acid as pale yellow solid (170 mg, 73.9%), which is used in next step without further purification. MS (m/z): 461 (M+1).

Example 240

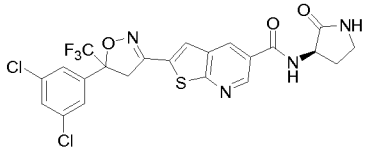
2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)thieno[2,3-b]pyridine-5-carboxamide



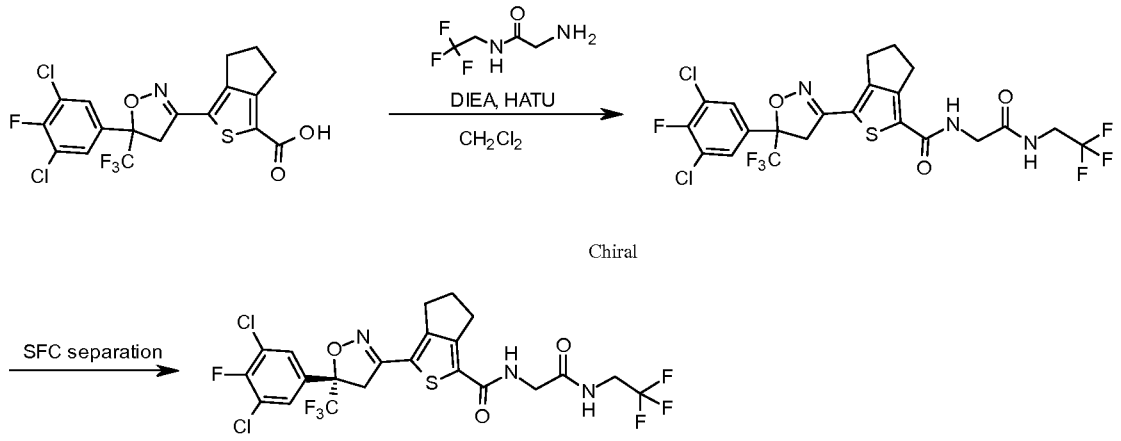
Stir a mixture of 2-Amino-N-(2,2,2-trifluoro-ethyl)-acetamide (156 mg, 1 mmol), 2-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine-5-carboxylic acid (160 mg, 0.24 mmol), HATU (150 mg, 0.39 mmol) and DIPEA (0.2 mL) at room temperature for for 10 hours. After removal of solvent, purify the mixture by

preparetive-HPLC to afford 2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)thieno[2,3-b]pyridine-5-carboxamide as a white solid (50 mg, 34.78%). MS (m/z): 599 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.51 (s, 1H), 7.52 (s, 2H), 7.44-7.41 (m, 2H), 7.22 (s, 1H), 6.64 (s, 1H), 4.27 (d, *J* = 5.2, 2H), 4.17 (d, *J* = 16.8, 1H), 4.04-3.95 (m, 2H), 3.80 (d, *J* = 16.08, 1H).

The following compound is prepared essentially by the method of Example 240.

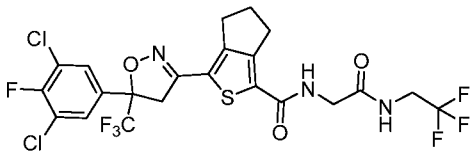
Ex. No.	Chemical name	Structure	Physical data
241	2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)thieno[2,3-b]pyridine-5-carboxamide		MS (m/z): 543 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.49 (s, 1H), 7.54 (s, 2H), 7.44-7.40 (m, 2H), 7.15 (S, 1H), 5.89 (s, 1H), 4.60 (s, 1H), 4.18 (d, *J* = 16.8, 1H), 3.80 (d, *J* = 16.8, 1H), 3.51-3.48 (m, 2H), 3.00-2.93 (m, 1H), 2.14-2.08 (m, 1H)

Scheme F



Example 242

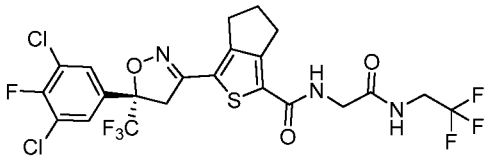
3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide



Stir a mixture of 3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid (1.0 g, 2.14 mmol), N,N-diisopropylethylamine (827 mg, 6.41 mmol), 2-amino-N-(2,2,2-trifluoroethyl) acetamide hydrochloride (658 mg, 2.56 mmol) and HATU (1.2 g, 3.2 mmol) in CH_2Cl_2 (10 mL) at room temperature for 2 hours. The reaction mixture is diluted with CH_2Cl_2 (50 mL) and is washed with water (10 mLx 3) and brine. Then the organic layer is dried over anhydrous Na_2SO_4 and is concentrated under vacuum. Purify the residue by preparative HPLC to afford 3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide as a white solid (1.1 g, 84.6 %). MS (m/z): 606.0 (M+1).

Example 243

(S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide

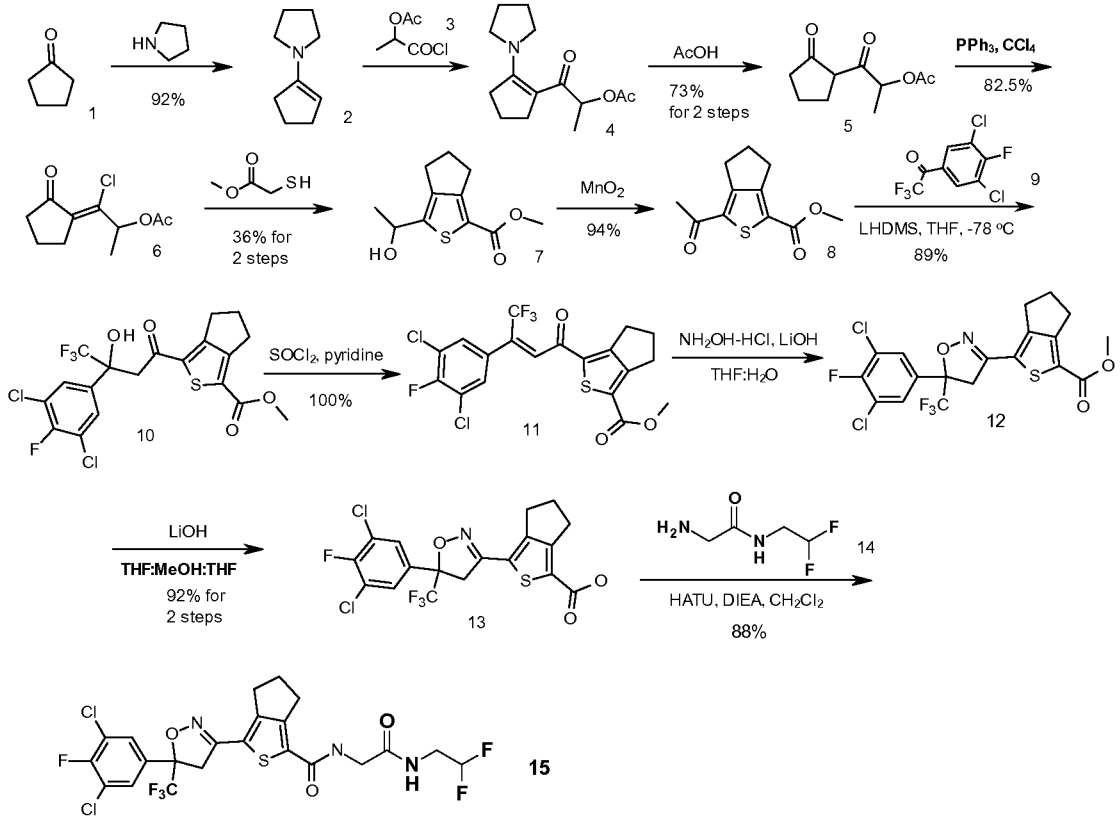


1 g of 3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide is separated by SFC to give (S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide (400 mg, 80 % yield, 100% ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J*=6.0, 2 H), 6.92 (t, *J*=6.4, 1 H), 6.76 (t, *J*=4.8, 1 H), 4.21 (d, *J*=4.8, 2 H), 3.98 (m, 3 H), 3.61 (d, *J*=16.8, 1 H), 2.97 (t, *J*=7.6, 2 H), 2.89 (t, *J*=7.6, 2 H), 2.55 (m, 2 H). MS (m/z): 606.0 (M+1).

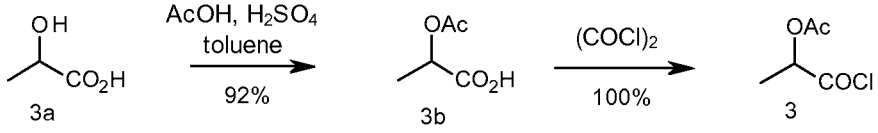
SFC analysis condition: Column: Chiralcel AD-H 250×4.6mm I.D., 5um. Mobile phase: ethanol in CO_2 from 5% to 40% over 3 minutes. Flow rate: 2.35 mL/min. Wavelength: 220 nm. The *S*-isomer elutes at 1.4 minutes. SFC separation condition: Instrument: Thar SFC 80; Column: AD 250mm*20mm, 20um; Mobile phase: A: Supercritical CO_2, B: MeOH (0.05% NH_3 H_2O), A:B =45:55 at 80ml/min; Column Temp: 38 ^{0}C; Nozzle Pressure: 100Bar; Nozzle Temp: 60 ^{0}C; Evaporator Temp: 20 ^{0}C; Trimmer Temp: 25 ^{0}C; Wavelength: 220nm

Scheme G



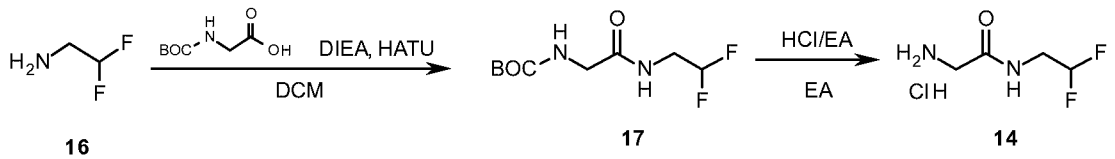
Scheme G(1)

Preparation of 1-chloro-1-oxopropan-2-yl acetate (3)



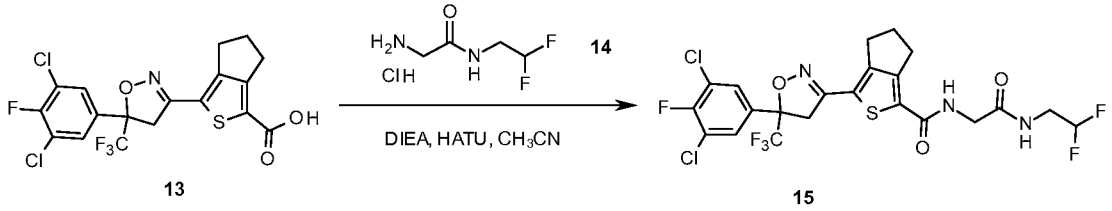
Scheme G(2)

Synthesis of 2-amino-N-(2,2-difluoro-ethyl) acetamide hydrochloride



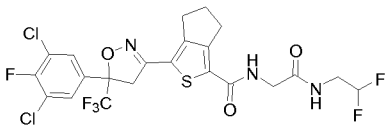
Scheme G(3)

Synthesis of 3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*] thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide

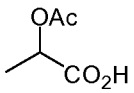


Example 244

3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide

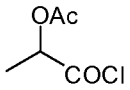


A) Synthesis of 2-acetoxy-propionic acid



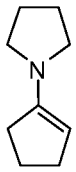
Reflux a mixture of 2-hydroxy-propionic acid (480 ml, 85% in water) and sulfuric acid (2 mL) in acetic acid (2500 mL) and toluene (300 mL) for overnight. After removal of solvent under vacuum, purify the residue by distillation to give 2-acetoxy-propionic acid (550 g, 92%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.27 (brs, 1H), 5.10 (m, 1H), 2.13 (s, 3H), 1.53 (d, *J*=7.2, 3H).

B) Synthesis of 1-chloro-1-oxopropan-2-yl acetate



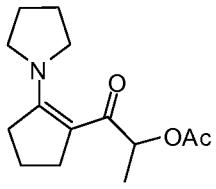
Stir a mixture of 2-acetoxy-propionic acid (550 g, 4.16 mol) in oxalyl chloride (500 mL) at room temperature for overnight. After removal of oxalyl chloride under vacuum, ~700g crude product is obtained (quantitative yield crude), which is used directly in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.16 (m, 1H), 2.13 (s, 3H), 1.58 (d, *J*=7.2, 3H).

C) Synthesis of 1-cyclopentenylpyrrolidine



Reflux a mixture of cyclopentanone (600 g, 7.14 mol), pyrrolidine (550 g, 4.68 mol) and toluene-4-sulfonic acid (5.0 g) in toluene (3 L) for 4 hours. After removal of solvent under vacuum, purify the residue by distillation carefully to give 1-cyclopent-1-enyl-pyrrolidineas colorless oil (898g, 6.55 mol, 91.8%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.04 (m, 1H), 3.06 (m, 4H), 2.39 (m, 4H), 1.85 (m, 6H).

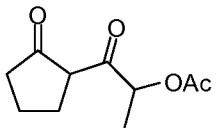
D) Synthesis of 1-oxo-1-(2-(pyrrolidin-1-yl)cyclopent-1-enyl)propan-2-yl acetate



Add dropwise a solution of 1-chloro-1-oxopropan-2-yl acetate (600 g, 3.98 mol) in toluene (1200 mL) to a solution of 1-cyclopent-1-enyl-pyrrolidine (546.7 g, 3.98 mol) and triethyl amine (483.9 g, 4.78 mol) in toluene (2400 mL). Reflux the mixture for overnight. Filter the mixture and concentrate the filtration to give crude 1-oxo-1-(2-(pyrrolidin-1-yl)cyclopent-1-enyl)propan-2-yl acetate (952 g), which is used in

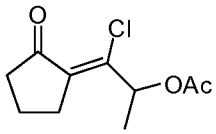
next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27 (m, 1H), 3.56 (m, 2H), 3.16 (m, 2H), 2.83 (m, 1H), 2.58 (m, 3H), 2.10 (s, 3H), 1.93 (m, 2H), 1.82 (m, 4H), 1.36 (d, *J*=7.2, 3H).

E) Synthesis of 1-oxo-1-(2-oxocyclopentyl)propan-2-yl acetate



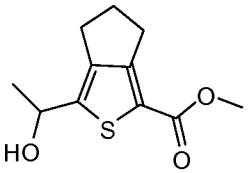
Stir a mixture of 1-oxo-1-(2-(pyrrolidin-1-yl) cyclopent-1-enyl)propan-2-yl acetate (952.0 g), acetic acid (1500 mL) and water (1500 mL) in tetrahydrofuran (3000 mL) at room temperature for 2 days. Dilute the mixture with water (1200 mL) and dichloromethane (1200 mL). The organic layer is washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (eluting with 3% to 10% ethyl acetate in petroleum ether) to give 1-oxo-1-(2-oxocyclopentyl)propan-2-yl acetate as oil (573.4g, 2.89 mol, 72.6% for 2 steps).

F) Synthesis of 1-chloro-1-(2-oxocyclopentylidene)propan-2-yl acetate



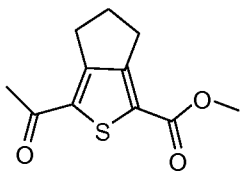
A mixture of 1-oxo-1-(2-oxocyclopentyl)propan-2-yl acetate (8.0 g, 0.04 mol) and tributylphosphane (13.9 g, 0.069 mol) in CCl_4 (100 mL) at 60℃ overnight. After removal of solvent, the residue is purified by silica gel column (eluting with 1% to 2.5% ethyl acetate in petroleum ether) to give a mixture of 1-chloro-1-(2-oxocyclopentylidene)propan-2-yl acetate and 1-(2-chlorocyclopent-1-enyl) -1-oxopropan-2-yl acetate (5.47 g, 6:1 based on HNMR) as yellow oil.

G) Synthesis of methyl 3-(1-hydroxyethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene- 1-carboxylate



Add sodium hydride (60% in mineral oil, 2.12 g, 0.053 mol) to a solution of mercapto-acetic acid methyl ester (2.8 g, 0.026 mol) in tetrahydrofuran (100 mL) at -10 °C~0 °C and stirred the mixture at -10 °C~0 °C for 1 hour. Then add a mixture of 1-chloro-1-(2-oxocyclopentylidene)propan-2-yl acetate and 1-(2-chlorocyclopent-1-enyl) -1-oxopropan-2-yl acetate (5.47 g, 0.025 mol, 6:1) in tetrahydrofuran (15 mL) at 0 °C. After stiring at 0 °C for overnight, dilute the reaction mixture with water and extract with ethyl acetate. The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue and K_2CO_3 (6.9 g, 0.05 mol) in MeOH (20 mL) is heated at 50 °C overnight. The solvent is removed. The residue is purified by silica gel chromatograph (eluting with 2.5% to 10% ethyl acetate in petroleum ether) to give 3-(1-hydroxy-ethyl)-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid methyl ester (3.2 g, 14.1 mmol, 35.6% for 2 steps) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.03 (m, 1H), 3.83 (m, 3H), 2.88 (m, 2H), 2.66 (m, 2H), 2.38 (m, 2H), 2.12 (s, 1H), 1.54 (d, *J*=7.2, 3H).

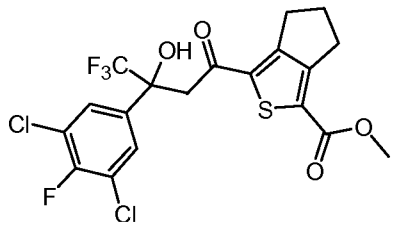
H) Synthesis of methyl
3-acetyl-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylate



Reflux a mixture of 3-(1-Hydroxy-ethyl)-5,6-dihydro-4H-cyclopenta[c] thiophene-1-carboxylic acid methyl ester (3.2 g, 0.0141 mol) and manganese dioxide (10.8 g, 0.124 mol) in dichloromethane for 2 hours. Filter the hot reaction mixture solution and concentrate the filtration under vacuum. Purify the residue by silica gel chromatograph (eluting with 2% to 10% ethyl acetate in petroleum ether) to give 3-acetyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid methyl ester as white

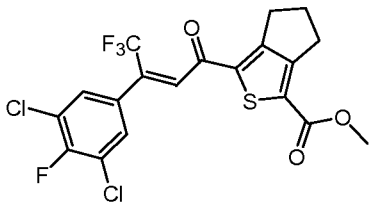
solid (3.0 g, 13.39 mmol, 94.5%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (s, 3H), 2.96 (m, 4H), 2.50 (s, 3H), 2.45 (m, 2H).

I) Synthesis of 3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester



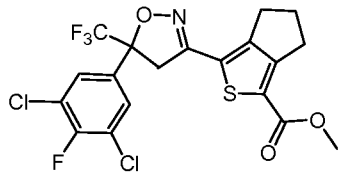
Add a solution of LiHDMS (1M in THF, 75 mL, 75 mmol) to a suspension of 3-acetyl-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester (14.0 g, 62.5 mmol) in dry THF (200 mL) at -78^{0}C under N_2. After stirring at room temperature for 1.5 h, add 1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone (17.9 g, 68.7 mmol) in dry THF (100 mL) to the reaction mixture and stir the resultant mixture at the same temperature for additional 2 hours. Quench the reaction with saturated NH_4Cl aqueous solution. Extract the aqueous mixture with EtOAc (100 mL×3). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 15:1) to afford 3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester as an orange solid (27 g, 89.3%). MS (m/z): 486 (M+1).

J) Synthesis of 3-[3-(3,5-Dichloro-4-fluorophenyl)-4,4,4-trifluorobut-2-enoyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester



Stir a mixture of 3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxyl-butyryl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester (26 g, 53.7 mmol), $SOCl_2$ (12.7 g, 7.8 mL, 0.107 mmol) and pyridine (42.3 g, 0.537 mmol) in anhydrous DCM (300 mL) at room temperature for 3 hours. Concentrate the mixture under vacuum. Purify the residue by silica gel chromatograph (PE:EtOAc 12:1) to afford 3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester as a pale yellow solid (25 g, 100 %). (m/z): 467 (M+1).

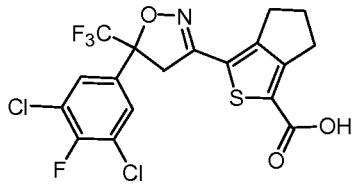
K) Synthesis of 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester



Stir a mixture of 3-[3-(3,5-Dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-but-2-enoyl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester (25 g, 53.6 mmol), NaOH (8.6 g, 0.214 mol) and NH_2OH-HCl (7.4 g, 0.107 mmol) in water (100 mL) and THF (200 mL) at room temperature for overnight. After removal of the solvent under vaccum, the solution is diluted with water and extracted with EtOAc (200 mL x 3). The combined organic layer is washed with brine, dried over anhydrous Na2SO4 and

concentrated by vacuum to afford 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl -4,5-dihydro-isoxazol-3-yl] -5,6- dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester as a white solid (26 g), which is used directly in the next step without purification. MS (m/z): 483(M+1).

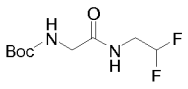
L) Synthesis of 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid



Stir a mixture of 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester (26 g, 54.1 mmol) and LiOH-H_2O (4.54 g, 0.108 mmol) in water (200 mL) and THF (400 mL) at 50 ^{0}C for 0.5 hour. After removal of organic solvent under vacuum, dilute the residue with ice water (100 mL). Acidify the aqueous mixture with conc. HCl to pH = 1, and extract the resultant mixture with EtOAc (200 mL×3). Purify the residue by silica gel chromatograph (EtOAc:MeOH 6:1) to afford 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H- cyclopenta[c]thiophene-1-carboxylic acid as a white solid (23 g, 91.7 % for 2 steps). MS (m/z): 468 (M+1).

M) Synthesis of [(2,2-difluoro-ethylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester

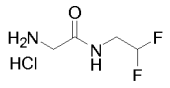
N)



To a solution of compound *tert*-butoxycarbonylamino acetic acid (19.6 g, 0.1 mol) in dichloromethane (200 mL) is added *N*,*N*-diisopropylethylamine (13.2 g, 0.1 mol), 2,2-difluoroethylamine (10 g, 0.1 mol) and HATU (23 g, 0.17 mol), after the addition the mixture is stirred at room temperature for 1 hour. After being detected by TLC and LCMS, the reaction mixture is diluted with dichloromethane, then the solution is washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated and the residue is dried in *vacuum* to give 30 g crude product, which is used directly in next step.

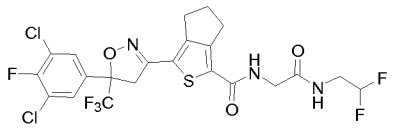
O) Synthesis of 2-amino-*N*-(2,2-difluoro-ethyl) acetamide hydrochloride

P)



To a solution of compound [(2,2-difluoro-ethylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester (30 g crude product, 0.13 mol) in acetic acid ethyl ester (100 mL) is added 4 M HCl (100 mL, 4 mol/L in acetic acid ethyl ester) dropwise under ice-water bath. After the additon the reaction mixture is warmed to room temperature and stirred for overnight. The precipitate is collected and dried in *vacuum* to give desired product (20 g, 93 % for two steps) as a white solid. 1H NMR (DMSO-d_6, 400 MHz): δ 8.91 (t, *J*=6.0, 1 H), 8.25 (brs, 3 H), 6.21-5.91 (m, 1 H), 3.64-3.53 (m, 4 H).

O) Synthesis of 3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide

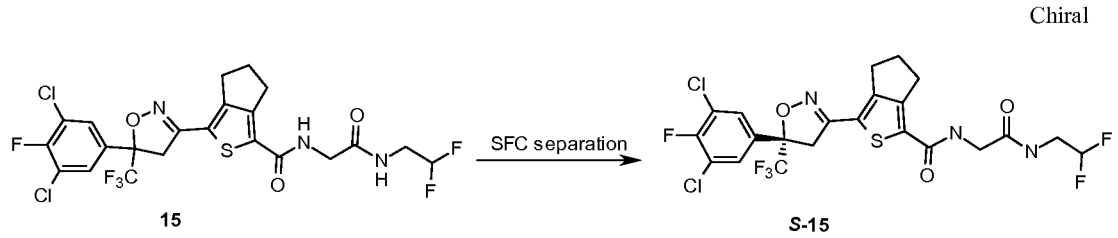


To a solution of compound 3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl -4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid (3

g, 6.4 mmol) in acetonitrile (30 mL) is added *N*,*N*-diisopropylethylamine (2.5 g, 19 mmol), 2-amino-*N*-(2,2-difluoro-ethyl)-acetamide hydrochloride (1.34 g, 7.7 mmol) and HATU (3.7 g, 9.6 mmol), after the addition the mixture is stirred at room temperature for 1 hour. After being detected by TLC and LCMS, the reaction mixture is concentrated and the residue is purified by column chromatography to afford desired product (3 g, 88 %). MS (m/z): 588.1 (M+1).

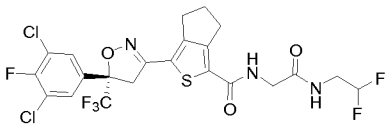
Scheme H

SFC Separation of Example 244 to provide *S* Form



Example 245

(*S*)-3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide



3 g of 3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide is separated by SFC separation to give desired product (1.4 g, 93 %).

1H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, *J*=6.0, 2 H), 6.64 (brs, 1 H), 6.40 (brs, 1 H), 6.03-5.73 (m, 1 H), 4.15 (d, *J*=5.2, 2 H), 4.01 (d, *J*=17.2, 1 H), 3.74-3.65 (m, 1 H), 3.62 (d, *J*=17.2, 1 H), 2.97 (t, *J*=7.6, 2 H), 2. 89 (t, *J*=7.6, 2 H), 2.56 (m, 2 H).

SFC conditions are as follows:

Instrument: Thar 350

Column: AD 250mm*50mm, 10um

Mobile phase: A: Supercritical CO2, B: EtOH, A:B =60:40 at 240ml/min

Column Temp: 38 ^{0}C

Nozzle Pressure: 100Bar

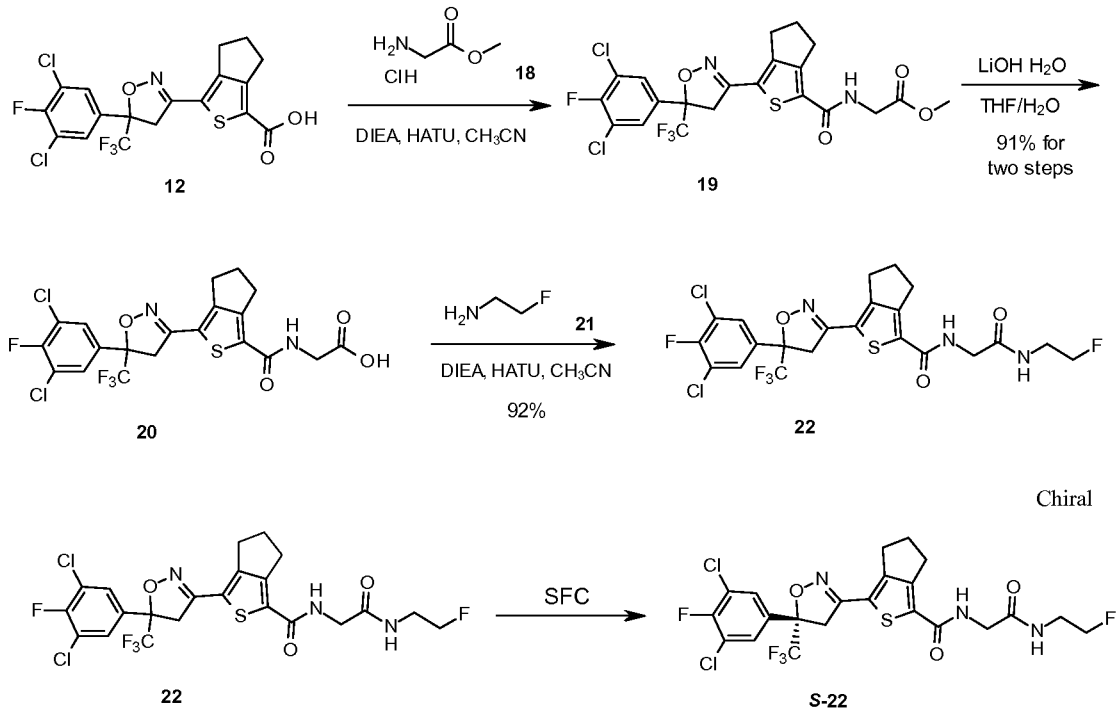
Nozzle Temp: 60 ^{0}C

Evaporator Temp: 20 ^{0}C

Trimmer Temp: 25 ^{0}C

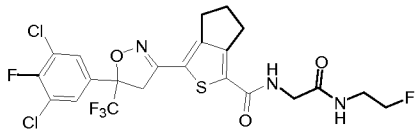
Wavelength: 220nm

Scheme I

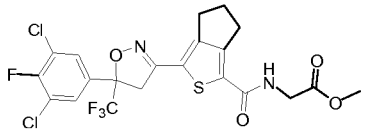


Example 246

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol -3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide

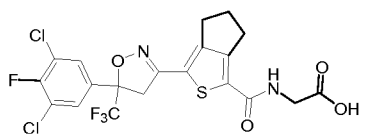


A) Synthesis of ({3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester



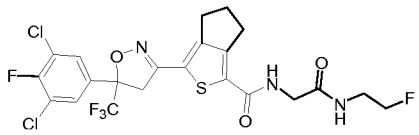
To a solution of compound 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro -isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid (10.0 g, 21.4 mmol) in dichloromethane (100 mL) is added triethylamine (6.49 g, 64.2 mmol), glycine methyl ester hydrochloride (3.2 g, 25.7 mmol) and HATU (12.2 g, 32.1 mmol), after the addition the mixture is stirred at room temperature for 1 hour. After being detected by TLC and LCMS, the reaction mixture is diluted with dichloromethane, then the solution is washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated and the residue is dried in *vacuum* to give 11 g crude product, which is used directly in next step.

B) Synthesis of ({3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol -3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carbonyl}-amino)-acetic acid



Stir a mixture of ({3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol -3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester (11 g, 18.6 mmol) and LiOH-H_2O (1.56 g, 37.2 mmol) in THF (100 mL) and water (50 mL) at room temperature for overnight. After being checked with TLC, the solvent is removed under vacuum, dilute the residue with water (50 mL). Acidify the aqueous mixture with 2M HCl to pH = 3, and extract the resultant mixture with EtOAc (100 mL×3), the combined organic layer is washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue is purified by silica gel chromatograph (PE : EtOAc 1:1) to afford ({3-[5-(3,5-Dichloro-4-fluoro-phenyl) -5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carbonyl}-amino)-acetic acid as a white solid (10.2 g, 90.7 % for two steps). MS (m/z): 525 (M+1).

C) Synthesis of 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol -3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide

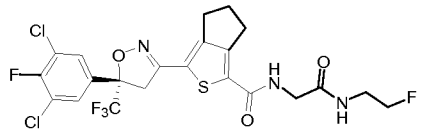


To a solution of compound ({3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl -4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carbonyl}-amino)-acetic acid (100 mg, 0.19 mmol) in acetonitrile (5 mL) is added *N*,*N*-diisopropylethylamine (49.3 mg, 0.38 mmol), 2-fluoro-ethylamine (14.4 mg, 0.23 mmol) and HATU (108.8 mg, 0.29 mmol), after finished the mixture is stirred at room temperature for 1 hour. After being detected by TLC and LCMS, the reaction mixture is concentrated and the residue is

purified by column chromatography to afford desired product (100 mg, 92 %). MS (m/z): 570.1 (M+1).

Example 247

(*S*)- 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro -isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl) -methyl]-amide



100 mg of 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide is separated by SFC separation to give desired product (40 mg, 80 %).

1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J*=6.0, 2 H), 6.64 (brs, 1 H), 6.34 (brs, 1 H), 4.52 (t, *J*=4.8, 1 H), 4.40 (t, *J*=4.8, 1 H), 4.06 (d, *J*=4.4, 2 H), 3.94 (d, *J*=17.2, 1 H), 3.63-3.52 (m, 3 H), 2.90 (t, *J*=7.6, 2 H), 2. 81 (t, *J*=7.6, 2 H), 2.47 (m, 2 H).

SFC conditions are as follows:

Instrument: Thar SFC 80

Column: AD 250mm*20mm, 20um

Mobile phase: A: Supercritical CO2 , B: EtOH （0.05%DEA） , A:B =45:55 at 80ml/min

Column Temp: 38℃

Nozzle Pressure: 100Bar

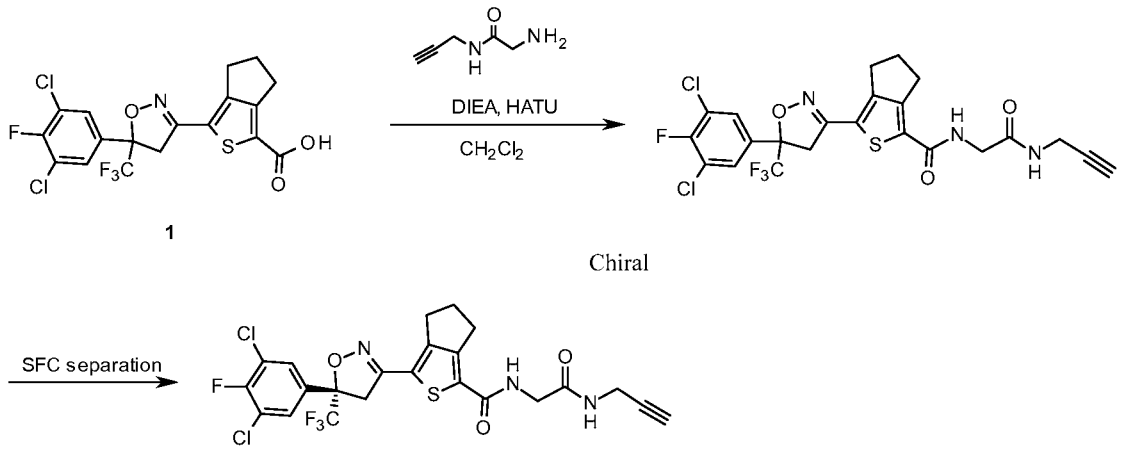
Nozzle Temp: 60℃

Evaporator Temp: 20℃

Trimmer Temp: 25℃

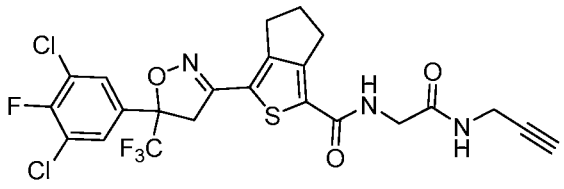
Wavelength: 220nm

Scheme J



Example 248

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide

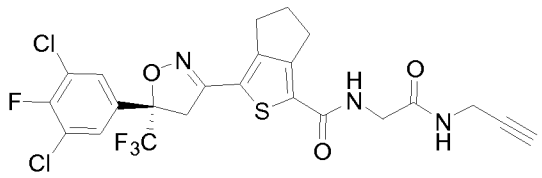


Stir a mixture of 3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid (0.8 g, 1.7 mmol), N,N-diisopropylethylamine (663 mg, 5.1 mmol), 2-amino-N-(prop-2-yn-1-yl) acetamide hydrochloride (305 mg, 2.0 mmol) and HATU (974 g, 2.6 mmol) in CH_2Cl_2 (10 mL) at room temperature for 2 hours. The reaction mixture is diluted with CH_2Cl_2 (40 mL) and is washed with water (10 mLx3) and brine. Then the organic layer is dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purify the residue by preparative

HPLC to afford 3-(5-(3,5-dichloro -4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide as a white solid (850 mg, 88.4 %). MS (m/z): 584.1 (M+Na).

Example 249

(S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide



850 mg of 3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide is separated by SFC to give (S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide (400 mg, 94 % yield, 99.7% ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J*=6.0, 2 H), 6.76 (t, *J*=4.8, 1 H), 6.46 (t, *J*=4.8, 1 H), 4.14 (m, 4 H), 4.03 (d, *J*=17.2, 1 H), 3.64 (d, *J*=17.2, 1 H), 2.99 (t, *J*=7.6, 2 H), 2.90 (t, *J*=7.6, 2 H), 2.56 (m, 2 H), 2.29 (t, *J*=2.8, 1 H). MS (m/z): 584.1 (M+Na).

SFC analysis condition: Column: Chiralcel AS-H 150×4.6mm I.D., 5um. Mobile phase: EtOH in CO_2 from 5% to 40% over 8 minutes. Flow rate: 3 mL/min. Wavelength: 220 nm. The *S*-isomer elutes at 4.00 minutes.

Instrument: Thar SFC 200; Column : AS 250mm*50mm,10um; Mobile phase: A: Supercritical CO_2 , B: EtOH, A:B =45:55 at 200ml/min; Column Temp: 38 ^{0}C; Nozzle Pressure: 100Bar; Nozzle Temp: 60 ^{0}C; Evaporator Temp: 20 ^{0}C; Trimmer Temp: 25 ^{0}C; Wavelength: 220nm.

***In Vitro* Helminth Assay**

Compounds may be evaluated against one or more life stages of helminth to measure anthelmintic activity. Compounds may be evaluated at a single concentration followed by serial dilution in order to determine minimal effective concentration. Typically, worms are exposed to compounds in a liquid solution for a predetermined period of time. Activity is measured through one or more variables, which may include an effect on worm motility (*e.g.*, moving versus non-moving) or viability (*e.g.*, live versus dead).

***In Vivo* Activity Against Nematodes**

Compounds may be evaluated against one or more life stages of helminth infestation in an animal to measure in vivo anthelmintic activity. Compounds may be evaluated a single dose, administered on a milligram per kilogram body weight basis, followed by dose titration in order to determine minimal effective point dose. In a rodent anthelmintic model, for example, adult Mongolian gerbils (*Meriones unguiculates*) infected with one or more species of Strongylid nematode (e.g., *Haemonchus contortus* and/or *Trichostrongylus colubriformis*) are dosed with compounds, administered via oral gavage. Gerbils are necropsied and gastrointestinal tract worm burden is measured and compared to untreated, infected control gerbils to determine the degree of anthelmintic activity. Similar testing may be conducted in higher species (*e.g.*, dogs, cats, sheep, cattle) whereby nematode burden in treated animals is compared to burden in untreated, infected animals to measure the potency and duration of anthelmintic activity.

***In Vitro* Larval Immersion Microassay (LIM)**

The larval immersion microassay may be conducted as described in White, *et al.*, J. Med. Entomol. 41: 1034-1042 (2004). Briefly, experimental test articles are formulated in dimethylsulfoxide (DMSO) to prepare a stock solution at a concentration of 10mM. Using 96-well microtiter plates, an aliquot of the 10mM sample is subsequently diluted in a water-based solution containing 1% ethanol and 0.2% Triton X-100, to obtain the desired concentration (typically 0.3mM or lower) of experimental test article in a

volume of 0.1ml (minimum n=3 replicates per compound or concentration). Approximately 30-50 Lone star tick larvae (*Amblyomma americanum*) are submerged into each well containing experimental test articles. After a 30 minute immersion period, larvae are removed with a wide-bore pipette tip in 0.05ml of fluid, dispensed into a commercial paper tissue biopsy bag which is sealed at the top with a plastic dialysis clip, inverted and allowed to air dry for 60 minutes. Bags containing larvae are then incubated at approximately 27 degrees Celsius and >90% relative humidity. After 24 hours, bags are opened, live and dead larvae are counted and percent larval mortality is calculated as follows: % Efficacy = (# dead larvae)/(# total larvae) X 100.

The following of the Examples exhibited efficacy, and at the level of ≥ 80% efficacy when tested in this assay at 300 micromolar: 32, 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, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87b, 94, 95, 96, 230, 231, 232, 233, 236, 237, 240, 241, 243, 244, 245, 246, 247, and 249.

<u>*In Vivo* Rodent Acaricide Test (RAT)</u>

Evaluation of experimental test articles may conducted using a modified version of the assay as described in Gutierrez *et al.*, J. Med. Entomol. 43(3): 526-532(2006). The assay may be modified by using a different tick species (the reference describes *Amblyomma americanum* ticks) such as *Dermacentor variabilis* ticks. Further, the reference describes using topical administration, but oral administration may be used. Briefly, experimental test articles are formulated in a solution of polyethylene glycol-300, propylene glycol and water to the desired concentration, typically 1 – 25 mg/ml, depending on solubility and desired point dose. Tick containment units (comprised of a baby nipple, ventilated screw cap top and reinforcing rubber washer) are attached to the dorsum of adult Sprague-Dawley rats. After attachment of containment units, approximately 10 unfed nymphal stage American dog ticks (*Dermacentor variabilis*) are placed inside of each containment unit. Approximately 24 hours after infestation, test article formulations are administered to rats via oral gavage. Negative control rats receive polyethylene glycol-300, propylene glycol and water alone.

Depending on compound availability, a minimum of three (3) and a maximum of five (5) rats are utilized per treatment group. Forty-eight (48) hours post-treatment, containment units are removed and live and dead ticks were counted. Live tick counts are transformed using the natural logarithm transformation plus one (Ln count + 1); addition of one to each count serve to adjust for counts that were zero. Geometric mean (GM) group tick counts are obtained via back-transformation of group mean transformed counts and subtracting one. The non-treated control group is used for comparison to the groups receiving experimental test articles for the calculation of percent efficacy (% reduction in live tick counts). The efficacy of treatments is calculated by comparing the geometric mean (GM) number of live ticks observed on treated rats with the GM number of live ticks counted on the negative control rats, using the following formula:

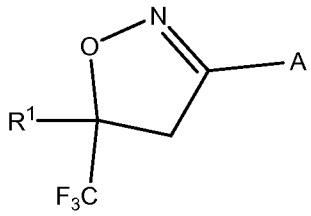
$$\% \text{ Efficacy} = \frac{(\text{GM \# live ticks control} - \text{GM \# live ticks treated})}{\text{GM \# live ticks control}} \times 100$$

The following Examples exhibited ≥ 50% efficacy when tested in this assay at a dose of not more than 25 mpk: 32, 36, 38, 39, 41, 42, 43, 45, 46, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 87b, 95, 96, 234, 235, 240, 241, 243, 244, 245, 246, 247, and 249.

Activity in the above assays demonstrates the compounds of the invention are useful for controlling ecto- or endoparasite infestations.

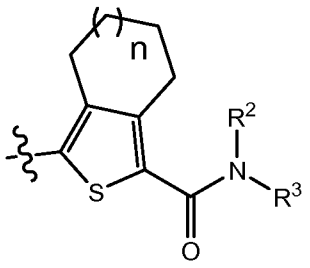
The following are embodiments of the invention and are non-limiting.

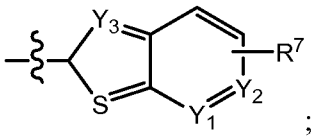
1. A compound, or a salt thereof, of formula I



I

wherein A is



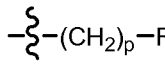
or 

;

n is 0 or 1;

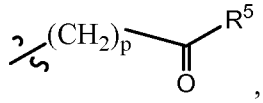
R^1 is thienyl or phenyl, said thienyl or phenyl substituted with 2 or 3 of the same or different halo atoms;

R^2 is at each occurrence independently hydrogen, C_1–C_5 alkyl, C_3–C_6 cycloalkyl, or C_1–C_5 haloalkyl;

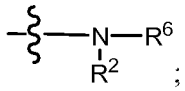
R^3 is 

;

p is at each occurrence independently 0 or 1;

R^4 is C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, C_3–C_6 cycloalkyl optionally substituted with hydroxy, halo, or C_1–C_5 alkyl: C_3–C_5 cycloheteroalkyl optionally substituted with C_1–C_5 alkyl, C_3–C_6 cycloalkyl, or C_1–C_5 haloalkyl: phenyl, thienyl, pyridinyl, or 

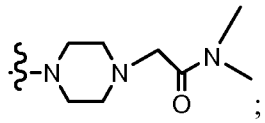
, wherein one of the carbons in said cycloalkyls, independently, or cycloheteroalkyl may form a carbonyl group, and wherein said phenyl, thienyl, or pyridinyl is optionally substituted with halo or a carbamoyl group;

R^5 is hydroxy, -O-(C_1–C_5 alkyl), or 

;

R^6 is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, or C_2–C_5 alkynyl;

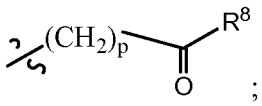
or R^2 and R^3 combine to form, with the nitrogen to which they are attached,



;

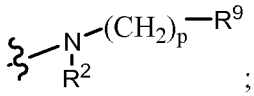
Y_1, Y_2, and Y_3 are carbon or nitrogen with at most only one of Y_1, Y_2, and Y_3 being nitrogen, and when Y_1, Y_2, or Y_3 is a carbon, each may be substituted by C_1–C_5 alkyl;

R^7 is hydrogen, halo, C_1–C_5 alkyl, or



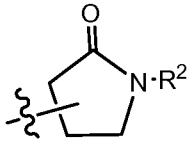
;

R^8 is hydroxy, -O-(C_1–C_5 alkyl), or

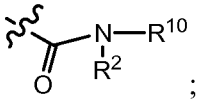


;

R^9 is C_1–C_5 alkyl,



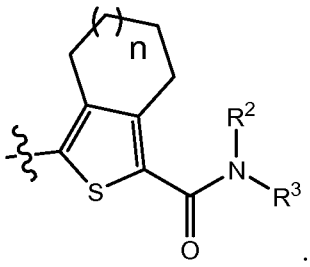
or



; and

R^{10} is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, or C_2–C_5 alkynyl.

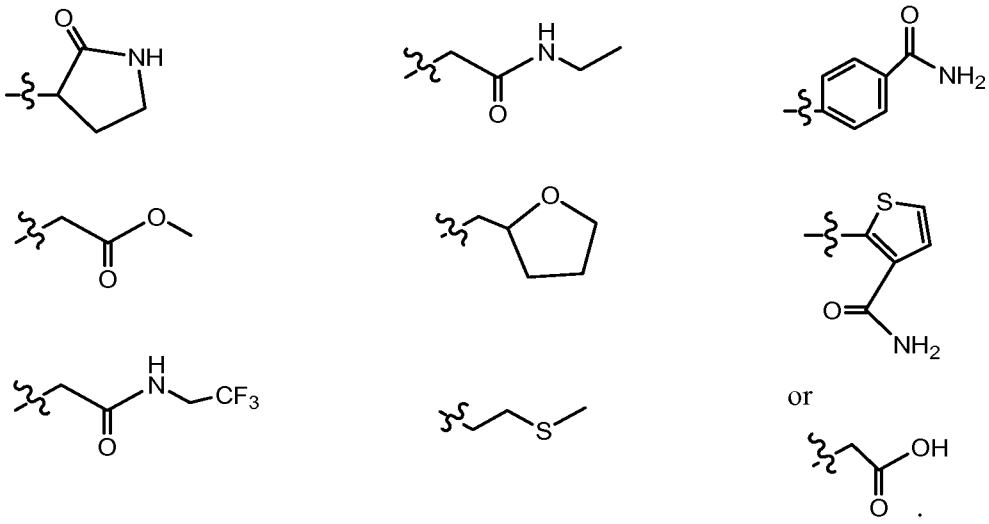
2. A compound of clause 1 wherein A is



.

3. A compound according to any of clauses 1-2 wherein R^2 is hydrogen and n is 1.

4. A compound of according to any of clauses 1-3 wherein R^3 is



5 .

5. A compound according to any of clauses 1 to 4, or salt thereof, being

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N,N-Dimethyl-2-(4-{3-[5-(3,4,5-trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-piperazin-1-yl)-acetamide;

({3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester;

({3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-thietan-3-yl)-amide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3-oxocyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-1l6-thiopyran-4-yl)-amide;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid [2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin- 3-yl]-amide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-((R)-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-((R)-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-(ethylamino)-2-oxoethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-(methylthio)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3,3,3-trifluoropropyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3-hydroxycyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(5-fluoropyridin-2-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(thietan-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorothiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide;

N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(tetrahydro-2H-pyran-4-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-thietan-3-yl)-amide;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(4-oxocyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(4-oxocyclohexyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-((R)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-((S)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(4-carbamoylphenyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (3-carbamoyl-thiophen-2-yl)-amide;

2-(3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl) - 4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamido)acetic acid;

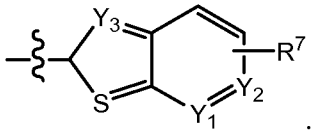
({3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide; or

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorothiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide.

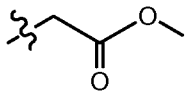
6. A compound of clause 1 wherein A is

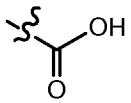


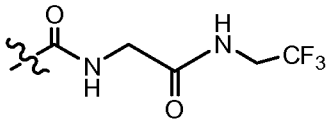
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7. A compound of clause 1 or 6 wherein Y_1 is nitrogen.

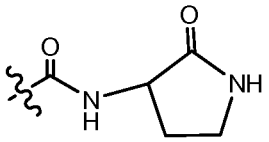
8. A compound according to any of clauses 1, 6, or 7, wherein R^7 is







or



.

9. A compound according to any of clauses 6-8, or salt therof, being

3-(4-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-c]pyridine;

5-Bromo-2-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine;

2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine;

3-(benzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-(benzo[d]thiazol-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-(3,5-dichlorophenyl)-3-(3-methylbenzo[b]thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-(3,5-dichlorophenyl)-3-(5-methylbenzo[b]thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-(5-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

methyl 2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)thieno[2,3-b]pyridine-5-carboxylate;

2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-*yl*]-thieno[2,3-b]pyridine-5-carboxylic acid;

2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)thieno[2,3-b]pyridine-5-carboxamide; or

2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)thieno[2,3-b]pyridine-5-carboxamide.

10. A compound, or salt thereof, being

(S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide;

(*S*)-3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amid;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide;

(*S*)- 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl) -methyl]-amide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide; or

(S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide.

11. A formulation comprising a compound or salt of any of clauses 1-10 and one or more acceptable carriers.

12. The formulation of clause 11 wherein it further comprises at least one additional active ingredient.

13. The formulation of clause 11 or clause 12 wherein it is a human pharmaceutical formulation.

14. The formulation of clause 11 or clause 12 wherein it is a veterinary pharmaceutical formulation.

15. A method of controlling a parasite infestation in or on an animal in need thereof comprising administering an effective amount of a compound or salt of any of clauses 1-10 to said animal.

16. The method of clause 15 wherein at least one other active ingredient is administered to said animal.

17. The method of clause 15 or clause 16 wherein said animal is a human.

18. The method of clause 15 or clause 16 wherein said animal is a companion animal.

19. The method of clause 17 or clause 18 wherein said companion animal is a dog or cat.

20. The method oaccording to any of clauses 15-19 wherein said parasite is a tick.

21. The method of clause 15 wherein said animal is a livestock animal.

22. A method for preventing or treating diseases transmitted through parasites comprising administering an effective amount of a compound of any of clauses 1-10 to an animal in need thereof.

23. The method of clause 22 wherein at least one other active ingredient is administered to said animal.

24. The method of clause 22 or clause 23 wherein said animal is a human.

25. The method of clause 22 wherein said animal is a companion animal.

26. The method of clause 25 wherein said companion animal is a dog or cat.

27. The method according to any of clauses 22-26 wherein said parasite is a tick.

28. The method of clause 22 or clause 23 wherein said animal is a livestock animal.

29. A method for controlling parasites, characterized in that a compound of any of clauses 1-10 is allowed to act on the pests or their habitat, or both.

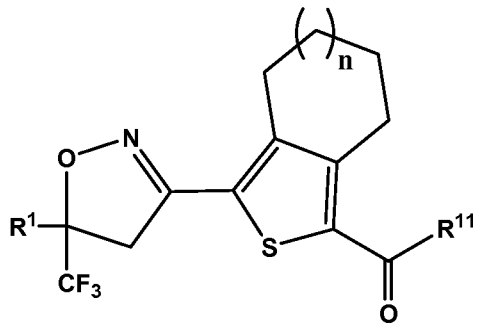
30. The method of clause 29 wherein the compound is placed on a plant or an animal.

31. Use of compounds or salts thereof of any of clauses 1-10 for controlling parasites.

32. A compound or salt according to any of clauses 1-10 for use in therapy.

33. A compound or salt according to any of clauses 1-10 for use in controlling an ectoparasite infestation.

34. A compound, or salt thereof, of Formula II



II

wherein n is 0 or 1;

R^1 is thienyl or phenyl, said thienyl or phenyl substituted with 2 or 3 of the same or different halo atoms; and

R^{11} is hydroxy, -O-(C_1-C_4 alkyl), or a halo atom.

35. The compound of 34 wherein R^1 is phenyl substituted with 2 or 3 of the same or different halo atoms.

36. The compound according to clauses 34 or 35 wherein R^{11} is hydroxy.

37. The compound according to any of clauses 34-36 wherein it is

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5 ,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5 ,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid;

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)- 4,5,6,7-tetrahydrobenzo[c]thiophene-1-carbonyl chloride; or

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl chloride.

38. A compound according to clause 34 wherein it is 3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dih ydro-4H-cyclopenta[c]thiophene-1-carboxylic acid.

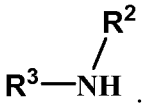
39. A compound according to clause 34 wherein it is 3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4 H-cyclopenta[c]thiophene-1-carboxylic acid.

40. A compound according to clause 34 wherein it is 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid.

41. A compound according to clause 34 wherein it is 3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid.

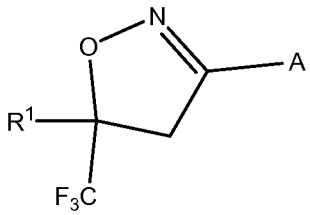
42. A process for preparing a compound according to clauses 1-5 or 10, comprising synthetically modifying a compound according to any of clauses 34-41.

43. The process of clause 42 wherein a compound according to any of clauses 34-41 is reacted with a compound of the formula



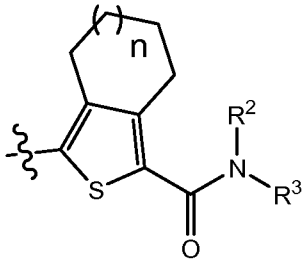
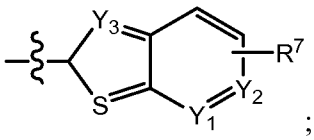
We claim:

1. A compound, or a salt thereof, of formula I



I

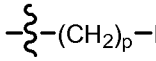
wherein A is

 or  ;

n is 0 or 1;

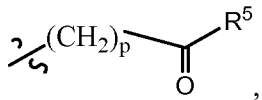
R^1 is thienyl or phenyl, said thienyl or phenyl substituted with 2 or 3 of the same or different halo atoms;

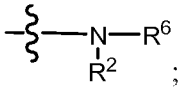
R^2 is at each occurrence independently hydrogen, C_1–C_5 alkyl, C_3–C_6 cycloalkyl, or C_1–C_5 haloalkyl;

R^3 is  ;

p is at each occurrence independently 0 or 1;

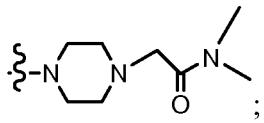
R^4 is C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, C_3–C_6 cycloalkyl optionally substituted with hydroxy, halo, or C_1–C_5 alkyl: C_3–C_5 cycloheteroalkyl optionally substituted with C_1–C_5 alkyl, C_3–C_6 cycloalkyl, or C_1–C_5

haloalkyl: phenyl, thienyl, pyridinyl, or  , wherein one of the carbons in said cycloalkyls, independently, or cycloheteroalkyl may form a carbonyl group, and wherein said phenyl, thienyl, or pyridinyl is optionally substituted with halo or a carbamoyl group;

R^5 is hydroxy, -O-(C_1–C_5 alkyl), or  ;

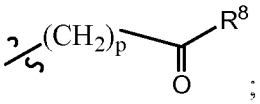
R^6 is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, or C_2–C_5 alkynyl;

or R^2 and R^3 combine to form, with the nitrogen to which they are attached,

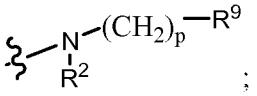
 ;

Y_1, Y_2, and Y_3 are carbon or nitrogen with at most only one of Y_1, Y_2, and Y_3 being nitrogen, and when Y_1, Y_2, or Y_3 is a carbon, each may be substituted by C_1–C_5 alkyl;

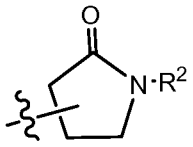
R^7 is hydrogen, halo, C_1–C_5 alkyl, or

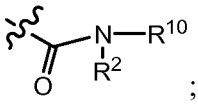
 ;

R^8 is hydroxy, -O-(C_1–C_5 alkyl), or

 ;

R^9 is C_1–C_5 alkyl,

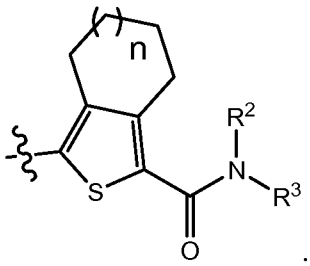


or 

; and

R^{10} is hydrogen, C_1–C_5 alkyl, C_1–C_5 haloalkyl, C_1–C_5 cyanoalkyl, C_1–C_5 alkylthio, or C_2–C_5 alkynyl.

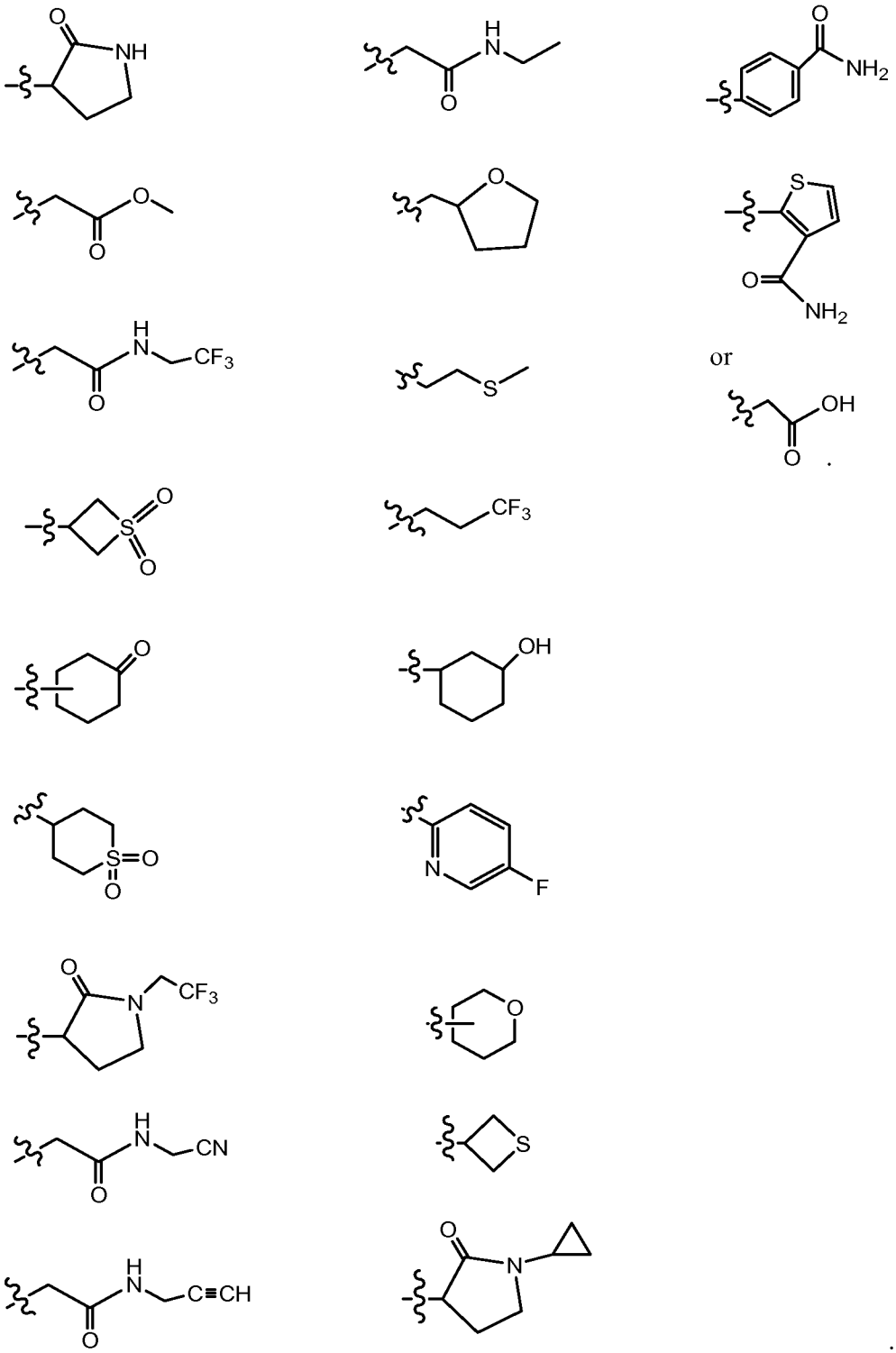
2. A compound of claim 1 wherein A is



.

3. A compound of claim 1 wherein R^2 is hydrogen and n is 1.

4. A compound of claim 1 wherein R^3 is



5 .

5. A compound of claim 1, or salt thereof, being

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N,N-Dimethyl-2-(4-{3-[5-(3,4,5-trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-piperazin-1-yl)-acetamide;

({3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester;

({3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid methyl ester;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-thietan-3-yl)-amide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3-oxocyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-1l6-thiopyran-4-yl)-amide;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid [2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin- 3-yl]-amide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-((R)-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-((R)-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-(ethylamino)-2-oxoethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-(methylthio)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3,3,3-trifluoropropyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(3-hydroxycyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(5-fluoropyridin-2-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(thietan-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(2-oxo-2-(prop-2-ynylamino)ethyl)-3-(5-(3,4,5-trichlorothiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide;

N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(tetrahydro-2H-pyran-4-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-thietan-3-yl)-amide;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(4-oxocyclohexyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(1-cyclopropyl-2-oxopyrrolidin-3-yl)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(4-oxocyclohexyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-((R)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-((S)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

N-(4-carbamoylphenyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid (3-carbamoyl-thiophen-2-yl)-amide;

2-(3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl) - 4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamido)acetic acid;

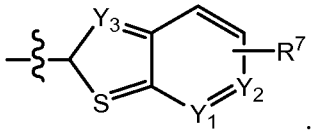
({3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl}-amino)-acetic acid;

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide; or

N-(2-(cyanomethylamino)-2-oxoethyl)-3-(5-(3,4,5-trichlorothiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxamide.

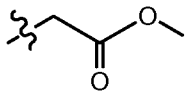
6. A compound of claim 1 wherein A is

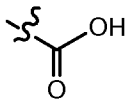


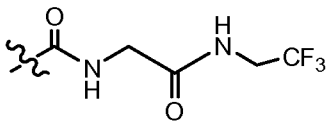
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7. A compound of claim 6 wherein Y_1 is nitrogen.

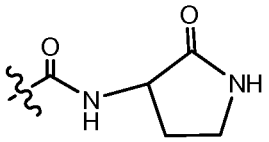
8. A compound of claim 6 wherein R^7 is







or



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9. A compound of claim 6, or salt therof, being

3-(4-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-c]pyridine;

5-Bromo-2-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine;

2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-thieno[2,3-b]pyridine;

3-(benzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-(benzo[d]thiazol-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-(3,5-dichlorophenyl)-3-(3-methylbenzo[b]thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-(3,5-dichlorophenyl)-3-(5-methylbenzo[b]thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-(5-chlorobenzo[b]thiophen-2-yl)-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

methyl 2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)thieno[2,3-b]pyridine-5-carboxylate;

2-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-*yl*]-thieno[2,3-b]pyridine-5-carboxylic acid;

2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)thieno[2,3-b]pyridine-5-carboxamide; or

2-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-((R)-2-oxopyrrolidin-3-yl)thieno[2,3-b]pyridine-5-carboxamide.

11. A compound, or salt thereof, being

(S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(2,2,2-trifluoroethylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide;

3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amide;

(*S*)-3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-1-carboxylic acid [(2,2-difluoro-ethylcarbamoyl)-methyl]-amid;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide;

(*S*)- 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro -isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid [(2-fluoro-ethylcarbamoyl) -methyl]-amide;

3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide; or

(S)-3-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-N-(2-oxo-2-(prop-2-ynylamino)ethyl)-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxamide.

11. A formulation comprising a compound or salt of claim 1 and one or more acceptable carriers.

12. The formulation of claim 11 wherein it further comprises at least one additional active ingredient.

13. The formulation of claim 11 wherein it is a human pharmaceutical formulation.

14. The formulation of claim 11 wherein it is a veterinary pharmaceutical formulation.

15. A method of controlling a parasite infestation in or on an animal in need thereof comprising administering an effective amount of a compound or salt of claim 1 to said animal.

16. The method of claim 15 wherein at least one other active ingredient is administered to said animal.

17. The method of claim 15 wherein said animal is a human.

18. The method of claim 15 wherein said animal is a companion animal.

19. The method of claim 18 wherein said companion animal is a dog or cat.

20. The method of claim 15 wherein said parasite is a tick.

21. The method of claim 15 wherein said animal is a livestock animal.

22. A method for preventing or treating diseases transmitted through parasites comprising administering an effective amount of a compound of claim 1 to an animal in need thereof.

23. The method of claim 22 wherein at least one other active ingredient is administered to said animal.

24. The method of claim 22 wherein said animal is a human.

25. The method of claim 22 wherein said animal is a companion animal.

26. The method of claim 25 wherein said companion animal is a dog or cat.

27. The method of claim 22 wherein said parasite is a tick.

28. The method of claim 22 wherein said animal is a livestock animal.

29. A method for controlling parasites, characterized in that a compound of claim 1 is allowed to act on the pests or their habitat, or both.

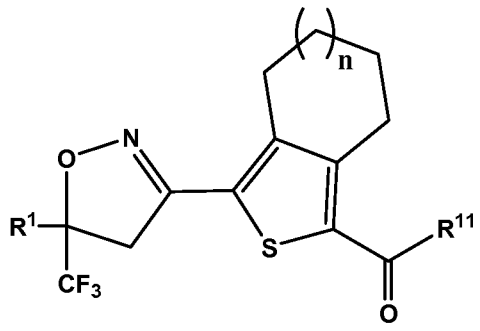
30. The method of claim 29 wherein the compound is placed on a plant or an animal.

31. Use of compounds, or salts thereof, of claim 1 for controlling parasites.

32. A compound, or salt thereof, of claim 1 for use in therapy.

33. A compound, or salt thereof ,of claim 1 for use in controlling an ectoparasite infestation.

34. A compound, or salt thereof, of Formula II



II

wherein n is 0 or 1;

R^1 is thienyl or phenyl, said thienyl or phenyl substituted with 2 or 3 of the same or different halo atoms; and

R^{11} is hydroxy, -O-(C_1-C_4 alkyl), or a halo atom.

35. The compound of 34 wherein R^1 is phenyl substituted with 2 or 3 of the same or different halo atoms.

36. The compound according to claim 34 wherein R^{11} is hydroxy.

37. The compound of claim 34 wherein it is

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5 ,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxaz ol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid methyl ester;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl] -4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5 ,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid;

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid;

3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid;

3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid;

3-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carbonyl chloride; or

3-[5-(3,4,5-Trichloro-thiophen-2-yl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carbonyl chloride.

38. A compound according to claim 34 wherein it is 3-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid.

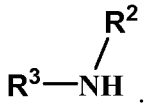
39. A compound according to claim 34 wherein it is 3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-5,6-dihydro-4H-cyclopenta[c]thiophene-1-carboxylic acid.

40. A compound according to claim 34 wherein it is 3-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid.

41. A compound according to claim 34 wherein it is 3-[5-(3,4,5-Trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-4,5,6,7-tetrahydro-benzo[c]thiophene-1-carboxylic acid.

42. A process for preparing a compound of claim 1, comprising synthetically modifying a compound of claim 34.

43. The process of claim 42 wherein a compound of claim 34 is reacted with a compound of the formula



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/036883

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 C07D495/04 A01N43/80
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/154528 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; WAGERLE TY [US]; XU MING [US]) 18 December 2008 (2008-12-18) claims 1,8; table 17	1-43
A,P	WO 2012/038851 A1 (PFIZER [US]; CURTIS MICHAEL PAUL [US]; ELLSWORTH EDMUND LEE [US]) 29 March 2012 (2012-03-29) claims 1,13	1-43
A	WO 2010/079077 A1 (NOVARTIS AG [CH]; NANCHEN STEVE [CH]; GAUVRY NOELLE [FR]; PAUTRAT FRAN) 15 July 2010 (2010-07-15) claims 1,15	1-43
A	WO 2007/079162 A1 (DU PONT [US]; LAHM GEORGE PHILIP [US]; SHOOP WESLEY LAWRENCE [US]; XU) 12 July 2007 (2007-07-12) claims 1,18	1-43

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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
13 June 2012	20/06/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gettins, Marc

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/036883

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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C07D 413/04 (2006.01) C07D 495/04 (2006.01)
C07D 413/14 (2006.01) A01N 43/80 (2006.01)

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(71) Solicitante *(para todos los Estados designados excepto US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

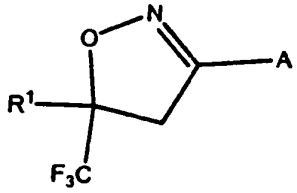
(72) Inventores; y

(75) Inventores/Solicitantes (para US únicamente): AN, Zengyun [CN/CN]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). CHEN, Liang [CN/CN]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). CHEN, Shuhui [US/US]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). DEFAUW, Jean, Marie [US/US]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). HOLMSTROM, Scott, Dale [US/US]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206- 6288 (US). HU, Ping [CN/CN]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). TANG, Chongzhi [CN/CN]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Illinois 46206-6288 (US). WHITE, William, Hunter [US/US]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). WU, Wentao [CN/CN]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US). ZHANG, Yang [CN/CN]; c/o Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(74): Agente: MCGRAW, Elizabeth A. et al.; Eli Lilly and Company, PO. Box 6288, Indianapolis, Indiana 46206- 6288 (US).

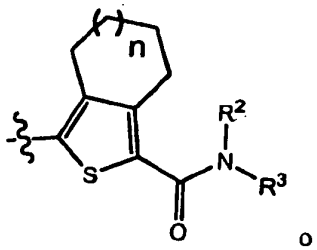
(81) Estados Designados *(a menos que se indique de otra forma, para cada tipo de protección nacional disponible)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU,

(54) Título: COMPUESTOS DE DIHIDROISOXAZOL PARASITICIDA

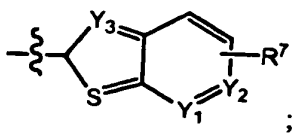


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(57) Resumen: Se proporcionan compuestos de dihidroisoxazol I útiles para el control de parásitos tanto en animales como en agricultura. Además se proporcionan métodos para controlar infestaciones de parásitos de un animal administrando una cantidad efectiva de un compuesto como se describe anteriormente, o una sal del mismo farmacéuticamente aceptable, a un animal, así como a formulaciones para controlar infestaciones de parásitos usando los compuestos descritos anteriormente o una sal del mismo farmacéuticamente aceptable, y un portador. También se proporcionan compuestos y procesos útiles para elaborar los compuestos de dihidroisoxazol.

LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, RS, SC, SD, SE, SG, SK, SL, SM, ST, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados designados *(a menos que se indique de otra forma, para cada tipo de protección nacional disponible)*: Patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW); Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR). Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaración bajo la Regla 4.17

- el derecho del solicitante a solicitar y ser otorgada una patente (Regla 4.17(ii))

- el derecho del solicitante a reivindicar la prioridad de la primera solicitud (Regla 4.17(iii))

Publicada:
- con el reporte de búsqueda internacional (Artículo 21(3))

COMPUESTOS, MÉTODOS Y FORMULACIONES PARASITICIDAS

ANTECEDENTES DE LA INVENCIÓN

Los ectoparásitos tales como pulgas, piojos, moscas, mosquitos, garrapatas y ácaros, así como también endoparásitos tales como nemátodos del tracto gastrointestinal, tremátodos, y filáridos, son problemáticos para el hombre y animales por igual. Tales parásitos impactan seriamente la productividad en la industria de animales domésticos reduciendo la ganancia de peso, causando que la piel, lana y carne sea de mala calidad, y en algunos casos resulte en la muerte. Los ecto y endo-parásitos también son responsables, en parte, de la propagación de enfermedades y malestares en animales destinados al consumo y de compañía. Los ectoparásitos en particular son bien conocidos por albergar y transmitir una variedad de patógenos microbianos, incluyendo bacterias, virus y parásitos protozoarios, muchos de los cuales son patógenos para humanos, otros mamíferos y aves de sangre caliente. Las enfermedades en las cuales los ectoparásitos han estado implicados incluyen, pero no se limitan a, malaria, filariasis linfática y transmitida por la sangre, tracoma, tripanosomiasis, Leishmaniasis, Fiebre Maculosa de las Montañas Rocosas, la enfermedad de Lyme, babesiosis y enfermedades transmitidas por los alimentos *debido a Salmonella, E. coli y Campilobacter, por ejemplo.*

La importancia médica de infestaciones ectoparasiticidas ha impulsado el desarrollo de reactivos capaces de controlar tales infestaciones. Los métodos comúnmente encontrados para controlar infestaciones ectoparasiticidas, por ejemplo, generalmente se han enfocado en el uso de insecticidas, que a menudo son infructuosos o insatisfactorios por una o más de las siguientes razones: (1) falta de cumplimiento de propietario o aplicador (se requiere administración frecuente); (2) intolerancia conductual o fisiológica del animal al producto pesticida o medios de administración; (3) el surgimiento de ectoparásitos resistentes al reactivo; y (4) impacto negativo sobre el medio ambiente y/o toxicidad.

Específicamente, las garrapatas parasitan animales silvestres así como domesticados y humanos, y se sabe o sospecha que son responsables de la transmisión de patógenos incluyendo bacterias, virus y parásitos protozoarios. Actualmente, se considera que las garrapatas están en segundo lugar a nivel mundial con respecto a los mosquitos como vectores de enfermedades humanas, pero se consideran que son el vector más importante de patógenos en América del Norte. La eliminación efectiva de las infestaciones de garrapatas es difícil y a menudo impráctica, debido a la necesidad de tratamiento concomitante del huésped inmediato, así como el depósito ambiental. Actualmente, el control de garrapatas es

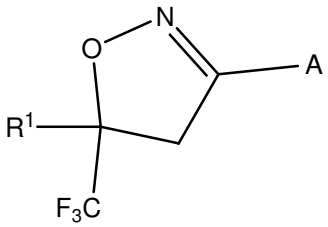
efectuado por el manejo integrado de plagas en el cual métodos de control diferentes están adaptados a un área o contra una especie de garrapatas con la debida consideración para sus efectos ambientales.

Mientras que el uso de insecticidas y pesticidas han sido benéfico, son necesarios métodos, formulaciones y compuestos alternativos o mejorados. Los métodos, formulaciones y compuestos deseables no sólo proporcionarían terapias alternativas, sino también podrían superar por lo menos algunas limitaciones de los enfoques actuales. Tales limitaciones incluyen toxicidad y seguridad tanto del animal como del usuario/propietario, eficacia limitada (potencia y duración) y problemas de resistencia. También el impacto al uso benéfico de insecticidas y pesticidas son obstáculos de la administración, los cuales incluyen el modo y la recurrencia de la administración. Por ejemplo, reducir la frecuencia de administración, mientras se mantiene la eficacia es deseable, ya que el tratamiento excesivo y repetido de animales suele ser inconveniente y/o difícil.

La presente invención abarca compuestos, métodos y formulaciones parasiticidas para uso en y sobre animales y plantas, y los cuales proporcionan opciones alternativas para combatir infestaciones parasiticidas, particularmente infestaciones ectoparasiticidas. Además, ciertos aspectos de la invención superan al menos algunas limitaciones en el uso

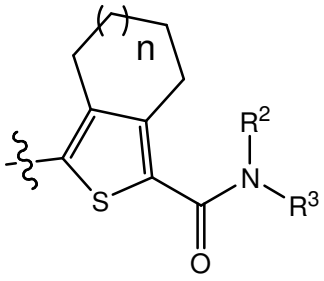
de insecticidas y pesticidas actuales, particularmente proporcionando control seguro, a largo plazo efectivo, de parásitos.

Se proporcionan compuestos, y sales de los mismos, de fórmula I:

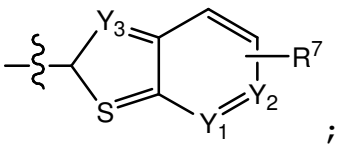


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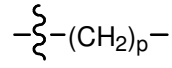


;

n es 0 o 1;

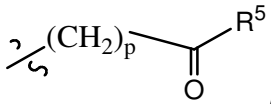
R^1 es tienilo o fenilo, tal tienilo o fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo;

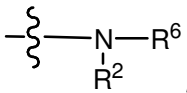
R^2 es en cada caso independientemente hidrógeno, alquilo C_1–C_5, cicloalquilo C_3–C_6, o haloalquilo C_1–C_5;

R^3 es  ;

p es en cada caso independientemente 0 o 1;

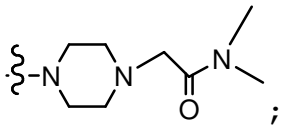
R^4 es alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo

C_1–C_5, alquiltio C_1–C_5, cicloalquilo C_3–C_6 opcionalmente sustituido con hidroxi, halo, o alquilo C_1–C_5: Cicloheteroalquilo C_3–C_5 opcionalmente sustituido con alquilo C_1–C_5, cicloalquilo C_3–C_6, o haloalquilo C_1–C_5: fenilo, tienilo, piridinilo, o  , en donde uno de los carbonos en tales cicloalquilos, independientemente, o cicloheteroalquilo puede formar un grupo carbonilo, y en donde tal fenilo, tienilo, o piridinilo es opcionalmente sustituido con un grupo halo o carbamoilo;

R^5 es hidroxi, –O–(alquilo C_1–C_5), o  ;

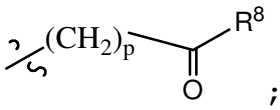
R^6 es hidrógeno, alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, o alquinilo C_2–C_5;

o R^2 y R^3 se combinan para formar, con el nitrógeno al cual están unidos,

 ;

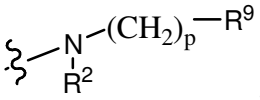
Y_1, Y_2, y Y_3 son carbono o nitrógeno con a lo sumo solamente uno de Y_1, Y_2, y Y_3 siendo nitrógeno, y cuando Y_1, Y_2, o Y_3 es un carbono, cada uno puede ser sustituido por alquilo C_1–C_5;

R^7 es hidrógeno, halo, alquilo C_1–C_5, o



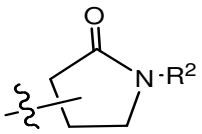
;

R^8 es hidroxi, –O–(alquilo C_1–C_5), o

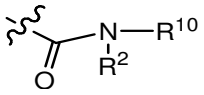


;

R^9 es alquilo C_1–C_5,



o



; y

R^{10} es hidrógeno, alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, o alquinilo C_2–C_5.

La invención proporciona una formulación, que incluye una formulación farmacéutica, que comprende un compuesto o sal de fórmula I y uno o más portadores aceptables. La formulación puede además comprender al menos un ingrediente activo adicional. Una formulación farmacéutica de la invención puede ser una formulación farmacéutica humana o una formulación farmacéutica veterinaria.

La invención proporciona un método para controlar infestaciones de ecto– y endoparásitos de un animal en necesidad del mismo que comprende administrar una cantidad efectiva de un compuesto o sal de fórmula I a tal animal. El método puede además proporcionar administrar al menos otro ingrediente activo a tal animal. El animal puede ser un mamífero, y puede ser un humano o un animal de compañía, por

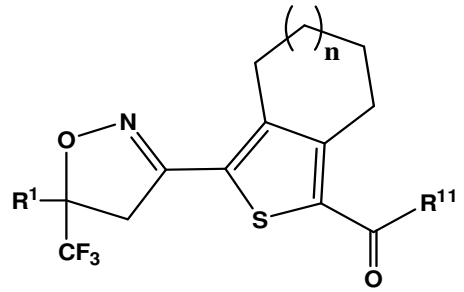
ejemplo, un perro o gato.

La presente invención proporciona un método para prevenir y tratar enfermedades transmitidas a través de parásitos que comprende administrar al menos un compuesto de la invención a un animal en necesidad del mismo.

La invención proporciona un método para controlar parásitos, caracterizado porque un compuesto de fórmula I se deja actuar en las plagas y/o su hábitat. La invención proporciona el uso de compuestos o sales de los mismos de fórmula I para controlar plagas.

La invención proporciona un compuesto o sal de fórmula I para uso en terapia. La invención además proporciona un compuesto o sal de fórmula I para uso en el control de infestaciones de ecto- y endoparásitos. La invención también proporciona el uso de un compuesto o sal de fórmula I para la manufactura de una formulación o medicamento para controlar infestaciones de ecto- y endoparásitos.

La invención proporciona compuestos de fórmula II, o una sal del mismo, de la fórmula



II

en donde n es 0 o 1;

R^1 es tienilo o fenilo, tal tienilo o fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo; y

R^{11} es hidroxi, –O–(alquilo C_1–C_4), o un átomo de halo.

Estos compuestos tienen utilidad como intermediarios en los procesos para preparar ciertos compuestos de fórmula I. Estos compuestos de Fórmula II pueden ser químicamente modificados para resultar en ciertos compuestos de Fórmula I.

El animal hospedero puede ser un mamífero o no mamífero, tal como un ave (pavos, pollos) o pez. En donde el animal hospedero es un mamífero, puede ser un mamífero humano o no humano. Los mamíferos no humanos incluyen animales domésticos, tales como animales de ganado y animales de compañía. Los animales de ganado incluyen vacas, camélidos, cerdos, ovejas, cabras y caballos. Los animales de compañía incluyen perros, conejos, gatos, y otras mascotas de propiedad y mantenidas en asociación cercana con humanos como parte de la unión humano-animal.

Los parásitos, algunas veces también referidos como mascotas, incluyen tanto ectoparásitos como endoparásitos. Los ectoparásitos incluyen plagas de insectos y ácaros las cuales comúnmente infestan o animales infectados, e incluyen

las etapas de huevos, larvas, pupas, ninfas, y adultos de los mismos. Tales plagas incluyen moscas, piojos, mosquitos, ácaros, pulgas, escarabajos, y especies de moscas que succionan, pican o molestas. Los endoparásitos incluyen plagas de nemátodos las cuales comúnmente infectan animales, e incluyen las etapas de huevo, larvas y adultas del mismo. Tales plagas incluyen helmintos (lombrices, tenias, gusanos del corazón), y son comercialmente importantes debido a que causan enfermedades serias en animales, *por ejemplo* en ovejas, cerdos, cabras, vacas, caballos, monos, camellos, perros, gatos, conejos, cobayos, hámsteres, pollos, pavos, gallinas de guinea y otras aves de granja, así como también aves exóticas. Los nemátodos típicos son *Haemonchus, Trichostrcngyius, Qstertagia, Nematotiirus, Cooperia, Ascaris, Bunostonum, Gesophagostonum, Charbertia, Trichuris, Strongyius, Trïchonema, Dictyocaulus, Capsliarsa, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancyiostoma, Uncinaria, Toxascaris* y *Parascaris*. Los tremátodos incluyen, en particular, la familia de *Fasciolideae*, especialmente *Fasciola hepatica*.

El control se refiere a ya sea aliviar o eliminar una infestación actual, o prevenir una infestación, en o sobre un hospedero animal o una planta.

Cantidad efectiva se refiere a la cantidad de un compuesto de fórmula I, o una sal del mismo, suficiente para

controlar una infestación de ecto- o endoparásito, e incluye causar una reducción medible en la población de infestación de ecto- o endoparásito, y como tal dependerá de varios factores. Para uso en o dentro de animales, varía para un compuesto de fórmula I, o una sal del mismo, en los métodos incluyen desde 0.01 hasta 1000 mg/kg y más deseablemente, 0.1 hasta 100 mg/kg del peso corporal del animal. La frecuencia de la administración también dependerá de varios factores, y puede ser una dosis única administrada una vez al día, una vez a la semana, o una vez al mes, por una duración determinada por el doctor o veterinario que atiende. Los ingredientes activos adicionales pueden ser administrados con un compuesto de fórmula I.

Farmacéuticamente aceptable como se usa en esta publicación, por ejemplo con referencia a sales y componentes de formulación tales como portadores, incluye “veterinariamente aceptable”, y de este modo incluye aplicaciones tanto humanas como animales independientemente.

Las sales de los compuestos de la invención, que incluyen sales farmacéuticamente aceptables, y metodología común para prepararlos, se conocen en la técnica. *Véase, por ejemplo,* P. Stahl, *et al.,* Handbook of Pharmaceutical Salts: Properties, Selection and Use, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.,* “Pharmaceutical Salts,” *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, Enero 1977.

Los compuestos de la invención y sus sales pueden ser formulados como composiciones farmacéuticas para administración. Tales composiciones farmacéuticas y procesos para elaborar las mismas se conocen en la técnica para mamíferos tanto humanos como no humanos. *Véase, por ejemplo,* remington: The Science and practice of pharmacy, (A. Gennaro, *et al.*, eds., 19th ed., Mack Publishing Co., 1995). Las formulaciones pueden ser administradas a través de varios medios, que incluyen administración oral, administración parenteral tal como inyección (intramuscular, subcutánea, intravenosa, intraperitoneal) o similares; la aplicación tópica con o sin penetración transdermal tal como inmersión, atomización, bañarse, lavarse, vertido en y moteado en, y pulverización, o similares. Los ingredientes activos adicionales pueden ser incluidos en la formulación que contiene un compuesto de la invención o una sal del mismo.

El portador se usa en la presente para describir cualquier ingrediente distinto del(los) componente(s) activo(s) en una formulación. La elección del portador será en gran medida dependiendo de factores tales como el modo particular de administración o aplicación, el efecto del portador en solubilidad y estabilidad, y la naturaleza de la forma dosificada.

Alquilo C_1–C_5 se refiere a alquilos de cadena recta y ramificada que tienen uno a cinco átomos de carbono, e

incluyen metilo, etilo, propilo, n-butilo, iso-butilo, pentilo, isopentilo, y neopentilo.

Alquinilo C_2-C_5 se refiere a alquinilos de cadena recta y ramificada que tienen dos a cinco átomos de carbono, e incluyen etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 3-metil-1-butinilo, pentinilo, isopentinilo, y neopentinilo.

Halógeno o halo se refiere a flúor, bromo, cloro, y yodo.

Haloalquilo como se usa en la presente se refiere a un alquilo (como se indicó anteriormente) sustituido con uno o más átomos de halo. Tales grupos incluyen trifluorometilo, difluorometilo, fluorometilo, cloruro de metilo, diclorometilo, cloruro de pentilo, cloruro de butilo, y cloruro de isopropilo.

Cianoalquilo como se usa en la presente se refiere a un alquilo (como se indicó anteriormente) sustituido con un grupo ciano.

Alquiltio como se usa en la presente se refiere a un alquilo (como se indicó anteriormente) que tiene un azufre en el grupo.

Cicloalquilo C_3-C_6 se refiere a ciclopropilo, ciclobutilo, ciclopentilo, y ciclohexilo.

Cicloheteroalquilo C_3-C_5 se refiere a un anillo saturado el cual tiene 3 a 5 carbonos y un heteroátomo. El heteroátomo puede ser un grupo azufre, oxígeno, nitrógeno o

sulfonilo.

Enfermedades transmitidas a través de parásitos, particularmente ectoparásitos, son, por ejemplo enfermedades bacterianas, virales, rickettsiales y de transmisión vectorial por protozoarios. Ejemplos de enfermedades virales transmitidas a través de arbovirus, *es decir,* virus transmitidos por artrópodos, con Fiebre Hemorrágica de Crimea-Congo (CCHF), enfermedades Febriles, fiebre Papataci, Encefalitis, Meningitis, las cuales son causadas por *Bunyaviridae* tales como *Bunyavirus, Nairovirus o Phlebovirus*; Fiebre catarral ovina, meningoencefalits, enfermedades Febriles, fiebre hemorrágica, las cuales son causadas por *Reoviridae*, tales como Orbivirus, Colitivirus; enfermedad Febril, sarpullido, encefalitis, poliartritis, linfadenitis, las cuales son causadas por *Togaviridae*, tales como Sindbisvirus, Virus de Chikungunya; meningoencefalitis transmitida por garrapatas, fiebre hemorrágica del Dengue, encefalitis, enfermedades Febriles, fiebre Amarilla, las cuales son causadas por *Flaviviridae*, tales como Flavivirus (que incluyen diversos sub-grupos). Ejemplos de enfermedades bacterianas transmitidas a través de parásitos son Rickettsiosis, tales como fiebre Maculosa de las Montañas Rocosas, tifo por garrapata causada por infección a través de *Rickettsia ssp*; Tularemia causada por infección a través de *Francisella tularensis*; *Borreliosis* o *Spirochaetosis*, tales

como enfermedad de Lyme, o fiebre recurrente, causada, por infección a través de *Borrelia ssp.*; Erliquiosis causada por infección a través de *Ehrlichia ssp.*; Plaga, causada por infección a través de *Yersinia ssp*. Ejemplos de enfermedades transmitidas rickettsiales o protozoarias son Babesiosis, tales como fiebre de Texas, enfermedad de agua roja, fiebre-Q causada por infección a través de *Babesia ssp.*; Teileriosis, tales como fiebre de la costa del este, fiebre de la costa Mediterránea, causada por infección a través de *Theileria ssp.*; enfermedad de Nagana, enfermedad del sueño causada por infección a través de *Trypanosoma ssp.*, Anaplasmosis causada por infección a través de *Anaplasma ssp.*; Malaria causada por infección a través de *Plasmodium ssp.*; Leishmaniasis causada por infección a través de *Leishmania ssp*.

Dada su actividad, ciertos compuestos de la invención son adecuados como insecticidas del suelo contra plagas en el suelo, así como también insecticidas para plantas, tales como cereales, algodón, arroz, maíz, soya, papa, verduras, frutas, tabaco, lúpulo, cítricos, y aguacates. Ciertos compuestos de acuerdo con la invención son adecuados para la protección de las plantas y órganos de la planta, para aumentar los rendimientos de la cosecha, y para mejorar la calidad del material cosechado que se encuentran en la agricultura, en horticultura, en bosques, en jardines, e instalaciones de ocio, y en la protección de productos

almacenados y de materiales. Se pueden emplear como agentes de protección de plantas.

Todas las plantas y partes de la planta se pueden tratar de acuerdo con la invención. Las plantas se debe entender que significan, en el presente contexto, todas las plantas y las poblaciones de plantas tales como plantas de cultivo (incluyendo las plantas de cultivo que se presentan naturalmente) o plantas silvestres deseadas y no deseadas. Las plantas de cultivo pueden ser plantas que se pueden obtener por métodos de optimización y reproducción de plantas convencionales o por métodos biotecnológicos y de ingeniería genética o por combinaciones de estos métodos, incluyendo las plantas transgénicas e incluyendo las variedades de plantas susceptibles de protección o no susceptibles de protección por los derechos de los cultivadores de plantas. Las partes de planta se debe entender que significan todas las partes y órganos de las plantas por encima y por debajo de la tierra, tales como brote, hoja, flor y raíz, ejemplos que pueden mencionarse son hojas, agujas, tallos, pedúnculos, flores, cuerpos de frutos, frutos, semillas, raíces, tubérculos y rizomas. Las partes de la planta también incluyen material cosechado, y material de propagación vegetativa y generativa, por ejemplo esquejes, tubérculos, rizomas, ramas y semillas.

El tratamiento de acuerdo con la invención de las plantas y partes de la planta con los compuestos activos se

realiza por medios convencionales y conocidos, incluyendo directamente actuando en, o permitiendo que los compuestos actúen en, los espacios circundantes, de almacenamiento o hábitat por los métodos de tratamiento habituales, por ejemplo por inmersión, pulverización, evaporación, nebulización, dispersión, pintado, inyección y, en el caso del material de propagación, en particular en el caso de semillas, también por aplicación de una o más capas.

Los compuestos se pueden convertir a las formulaciones tradicionales, tales como soluciones, emulsiones, polvos humectables, suspensiones basadas en agua y aceite, polvos, polvillos, pastas, polvos solubles, gránulos solubles, gránulos para difusión, concentrados de suspensión-emulsión, materiales naturales impregnados con compuesto activo, materiales sintéticos impregnados con el compuesto activo, fertilizantes y microencapsulaciones en sustancias poliméricas.

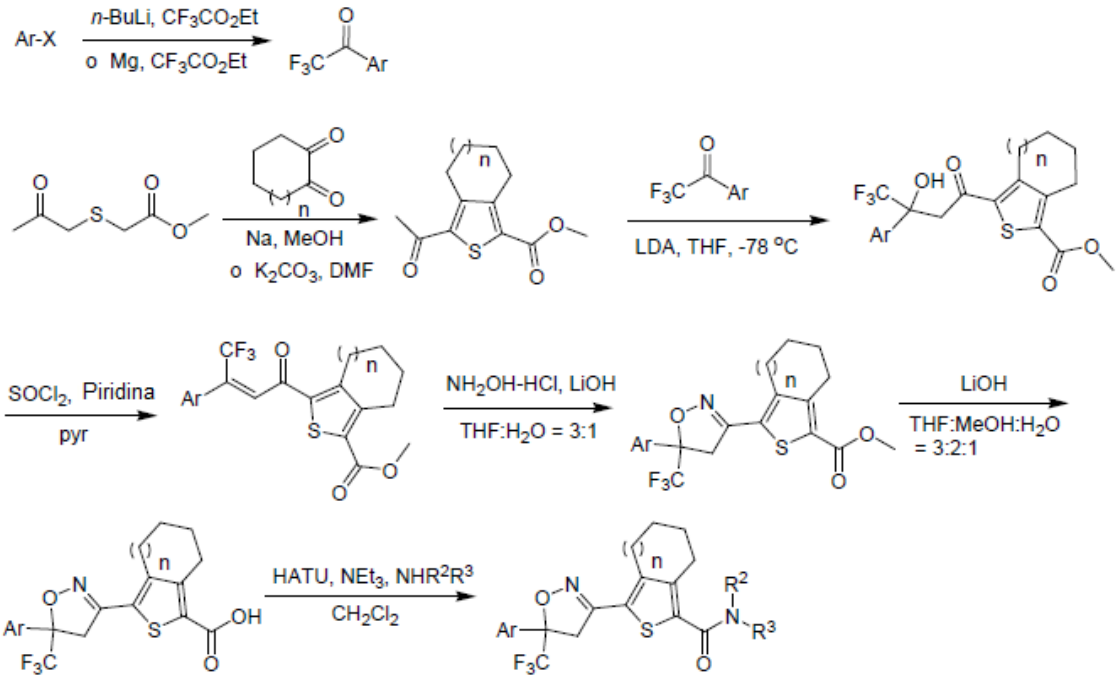
Estas formulaciones son producidas en una manera conocida, por ejemplo mezclando los compuestos activos con extendedores, es decir solventes líquidos y/o portadores sólidos, opcionalmente con el uso de tensoactivos, es decir emulsificadores y/o dispersantes y/o formadores de espuma. Las formulaciones son preparadas ya sea en plantas adecuadas o más antes o durante la aplicación.

Adecuado para uso como auxiliares son sustancias

las cuales son adecuadas para impartir a la composición misma y/o a las preparaciones derivadas de las mismas (por ejemplo, licores atomizados, tratamiento de semillas) propiedades particulares tales como ciertas propiedades técnicas y/o también propiedades biológicas particulares. Los auxiliares adecuados típicos son extendedores, solventes, y portadores.

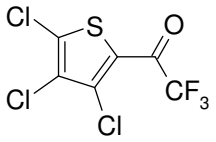
Los siguientes son Esquemas de reacción A–J y ejemplos para preparar los compuestos de la invención. Los Esquemas de reacción, ejemplos, e información contenida aquí son ilustrativos, y pueden ser modificados en formas conocidas en la técnica para obtener los resultados deseados.

Esquema de reacción A



Preparación 1

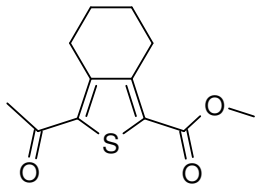
2,2,2-trifluoro-1-(3,4,5-triclorotiofen-2-il)etanona de metilo



Se agregó una solución de n-BuLi (21.6 mL, 2.5 M en hexano, 54.0 mmol) a una solución de 2,3,4,5-tetracloro-tiofeno (10 g, 45.0 mmol) en THF seco (160 mL) a -78 ^{0}C y la mezcla se agitó por 2 horas. Se agregó una solución de éster etílico del ácido trifluoro-acético (9.59 g, 67.6 mmol) en THF (15 mL) y se agitó a -78 ^{0}C por 2.5 horas adicionales. La reacción se apagó con solución saturada de NH_4Cl (100 mL). La mezcla acuosa se extrajo con EtOAc (100 mL X 3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro, y evaporaron bajo vacío. El residuo se purificó por una columna instantánea sobre gel de sílice eluyendo con PE:EtOAc (10:1 a 5:1) para proporcionar 2,2,2-trifluoro-1-(3,4,5-tricloro-tiofen-2-il)-etanona como un aceite marrón (10.4 g, 81.9%). ^{13}F NMR (400 MHz, $CDCl_3$) δ -73.38 (s, 3F).

Preparación 2

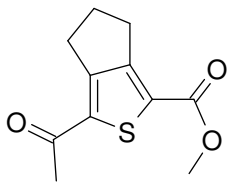
3-acetil-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato de metilo



Se agregó 2-(2-oxopropilthio)acetato de metilo (35.4 g, 183.2 mmol) a una solución recientemente preparada de sodio sólido (8.78 g, 381.5 mmol) en MeOH seco (300 mL) a 0 ^{0}C, seguido por adición de una solución de ciclohexan-1,2-diona (20 g, 152.6 mmol) en MeOH (30 mL). La mezcla se agitó a 0^0 C por 30 min y después a 50-60 ^{0}C por 1.5 horas adicionales. El solvente se removió bajo vacío y el residuo se diluyó con agua (100 mL). La mezcla acuosa se extrajo con acetato de etilo (100 mL X 3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro, y evaporaron bajo vacío. El residuo se purificó por una columna instantánea sobre gel de sílice eluyendo con PE:EtOAc (50:1 a 30:1) para proporcionar 3-acetil-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato de metilo como un sólido blanco (10 g, 27.6%). MS (m/z): 239 (M+1).

Preparación 3

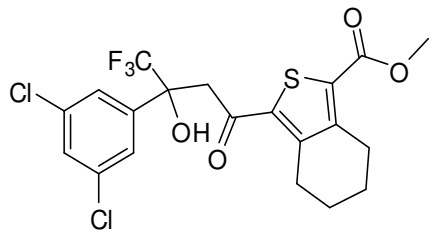
Metilo 3-acetil-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato de



Una mezcla de Ciclopentan-1,2-diona (2.00 g, 20.4 mmol), 2-(2-oxopropiltio)acetato de metilo (3.31 g, 20.4 mmol) y carbonato de potasio (5.63 g, 40.8 mmol) en DMF (40 mL) a 80 ^{0}C por 4 horas. La mezcla se filtró y el solvente se removió bajo vacío. El residuo se purificó por una columna instantánea sobre gel de sílice eluyendo con PE:EtOAc (8:1 a 6:1) para proporcionar éster metílico del ácido 3-Acetil-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico como un sólido amarillo pálido (206mg, 4.5 %). MS (m/z): 225 (M+1).

Preparación 4

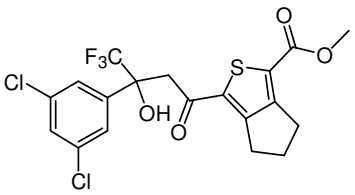
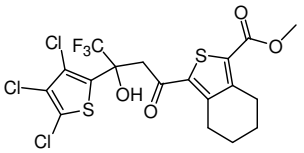
3-(3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutanoil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato de metilo

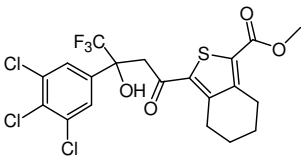
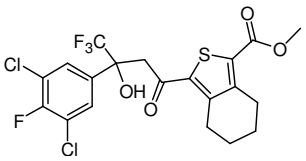


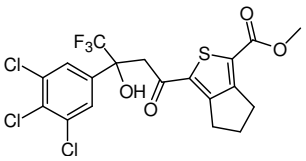
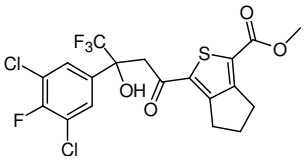
Se agregó una solución de LDA (2M en THF, 19.5 mL, 3.89 mmol) a una suspensión de 3-acetil-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato (7.4 g, 3.11 mmol) en THF seco (80 mL) a -78^{0}C bajo N_2. Después de la agitación por 1.5 h, se agregó 1-(3,5-Dicloro-fenil)-2,2,2-trifluoro-etanona (9.9 g, 3.73 mmol) a la mezcla de reacción y la mezcla resultante se agitó a la misma temperatura por 2 horas adicionales. La reacción se apagó con solución acuosa

saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc (100 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 50:1) para proporcionar 3-(3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutanoil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato de metilo como un sólido anaranjado (9.1 g, 60.4 %). MS (m/z): 481 (M+1).

Los siguientes compuestos son preparados esencialmente por el método de la Preparación 4.

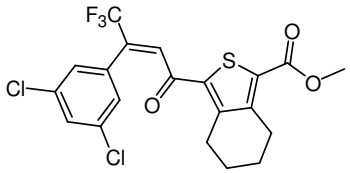
Prep. No.	Nombre químico	Estructura	Datos físicos
5	éster metílico del ácido 3-[3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-3-hidroxi-butiril]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 465 (M-1).
6	éster metílico del ácido 3-[4,4,4-Trifluoro-3-hidroxi-3-		MS (m/z): 519 (M-1).

Prep. No.	Nombre químico	Estructura	Datos físicos
	(3,4,5-tricloro-tiofen-2-il)-butiril]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		
7	éster metílico del ácido 3-[4,4,4-Trifluoro-3-hidroxi-3-(3,4,5-tricloro-fenil)-butiril]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 515 (M+1)
8	éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-3-hidroxi-butiril]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 499 (M+1)

Prep. No.	Nombre químico	Estructura	Datos físicos
9	éster metílico del ácido 3-[4,4,4-Trifluoro-3-hidroxi-3-(3,4,5-tricloro-fenil)-butiril]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 501 (M+1)
10	éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-3-hidroxi-butiril]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 485 (M+1)

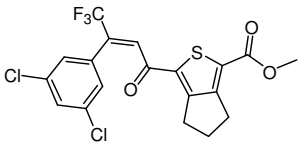
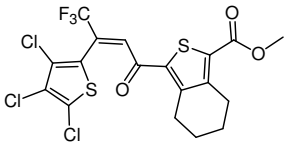
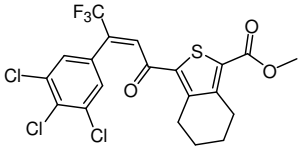
Preparación 11

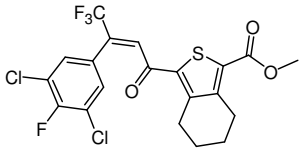
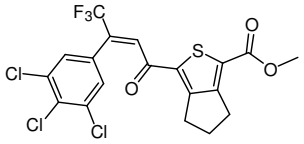
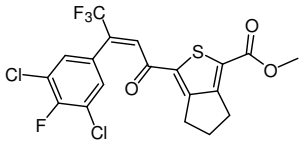
éster metílico del ácido 3-[3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-but-2-enoil]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico



Una mezcla de 3-(3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxilbutanoil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxilato de metilo (9.1 g, 18.9 mmol), $SOCl_2$ (9.0 g, 5.5 mL, 75.6 mmol) y piridina (2.99 g, 3.1 mL, 37.8 mmol) en DCM anhidro (100 mL) a temperatura ambiente durante la noche. La mezcla resultante se diluyó con solución acuosa saturada de NH_4Cl. La mezcla acuosa se extrajo con DCM (100 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 50:1) para proporcionar éster metílico del ácido 3-[3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-but-2-enoil]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico como un sólido anaranjado (8.75 g, 100 %). (m/z): 463 (M+1).

Los siguientes compuestos son preparados esencialmente por el método de la Preparación 11.

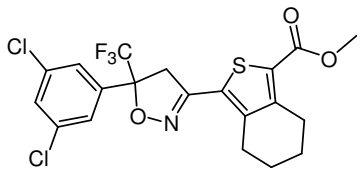
Prep. No.	Nombre químico	Estructura	Datos físicos
12	éster metílico del ácido 3-[3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-but-2-enoil]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 447 (M-1).
13	éster metílico del ácido 3-[4,4,4-Trifluoro-3-(3,4,5-tricloro-tiofen-2-il)-but-2-enoil]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-éster metílico del ácido carboxílico] tiofen-1-carboxílico		MS (m/z): 501 (M-1).
14	éster metílico del ácido 3-[4,4,4-Trifluoro-3-(3,4,5-tricloro-fenil)-but-2-enoil]-		MS (m/z): 497 (M+1).

Prep. No.	Nombre químico	Estructura	Datos físicos
	4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		
15	éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-but-2-enoil]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 481 (M+1).
16	éster metílico del ácido 3-[4,4,4-Trifluoro-3-(3,4,5-tricloro-fenil)-but-2-enoil]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 483 (M+1).
17	éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-but-2-enoil]-5,6-dihidro-4H-		MS (m/z): 467 (M+1).

Prep. No.	Nombre químico	Estructura	Datos físicos
	ciclopenta[c] tiofen-1-carboxílico		

Preparación 18

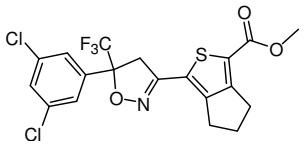
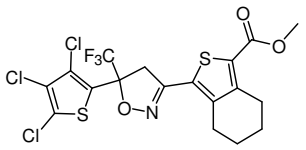
éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico

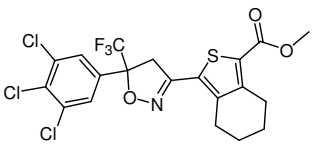
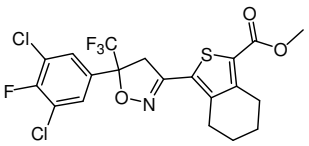
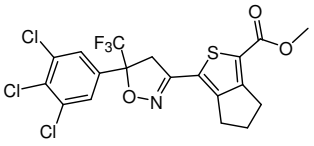


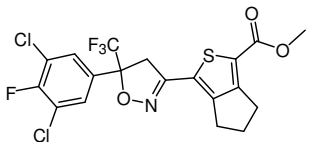
Se agitó una mezcla de éster metílico del ácido 3-[3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-but-2-enoil]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico (8.75 g, 18.9 mmol), NaOH (2.65 g, 66.1 mmol) y NH_2OH-HCl (2.6 g, 37.8 mmol) en MeOH (60 mL) y agua (15 mL) a temperatura ambiente por 2.5 horas. Después de la eliminación del solvente bajo vacío, el residuo se diluyó con agua helada (50 mL). La mezcla acuosa se acidificó con HCl conc. a pH = 1 y la mezcla resultante se extrajo con EtOAc (50 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 50:1) para proporcionar éster metílico del ácido 3-[5-(3,5-Dicloro-

fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico como un sólido anaranjado (8.1 g, 93.1%). MS (m/z): 478 (M+1).

Los siguientes compuestos son preparados esencialmente por el método de la Preparación 18.

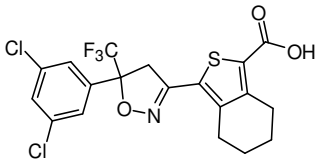
Prep. No.	Nombre químico	Estructura	Datos físicos
19	éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 464 (M+1).
20	éster metílico del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 516 (M-1).

Prep. No.	Nombre químico	Estructura	Datos físicos
21	éster metílico del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 512 (M+1).
22	éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 496 (M+1).
23	éster metílico del ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]		MS (m/z): 498 (M+1).

Prep. No.	Nombre químico	Estructura	Datos físicos
	tiofen-1-carboxílico		
24	éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 482 (M+1).

Preparación 25

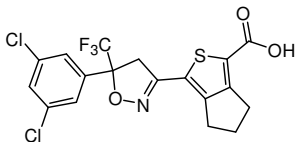
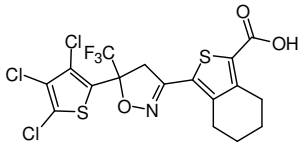
ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico

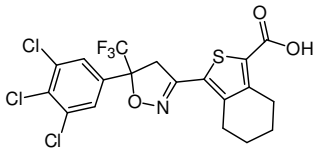
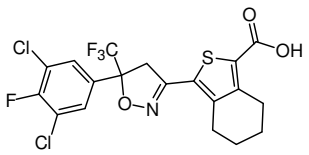
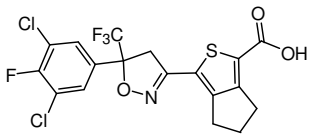


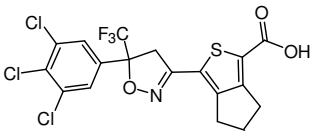
Se agitó una mezcla de éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico (8.1 g, 17.0 mmol) y $LiOH-H_2O$ (3.57 g, 84.9 mmol) en MeOH (64 mL) y agua (16 mL) a temperatura ambiente durante la noche. Después de la eliminación del solvente orgánico bajo vacío, el

residuo se diluyó con agua helada (80 mL). La mezcla acuosa se acidificó con HCl conc. a pH = 1, y la mezcla resultante se extrajo con EtOAc (100 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 1:1) para proporcionar ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico como un sólido amarillo pálido (6.8 g, 86.4 %). MS (m/z): 464 (M+1).

Los siguientes compuestos pueden ser preparados esencialmente por el método de la Preparación 25.

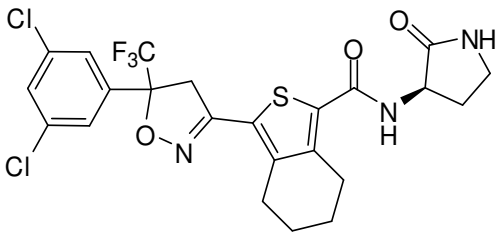
Prep. No.	Nombre químico	Estructura	Datos físicos
26	ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 448 (M-1).
27	ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-		MS (m/z): 502 (M-1).

Prep. No.	Nombre químico	Estructura	Datos físicos
	4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		
28	ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 496 (M-1).
29	ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 480 (M-1).
30	ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-		MS (m/z): 466 (M-1).

Prep. No.	Nombre químico	Estructura	Datos físicos
	ciclopenta[c] tiofen-1-carboxílico		
31	ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico		MS (m/z): 482 (M-1).

Ejemplo 32

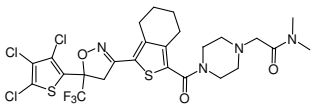
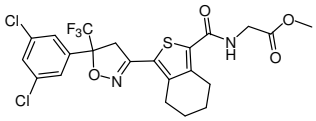
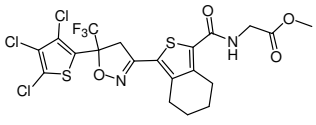
3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida

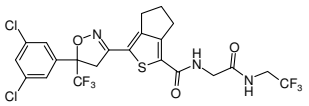
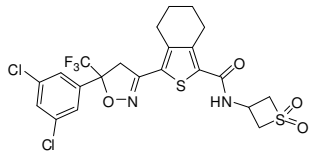
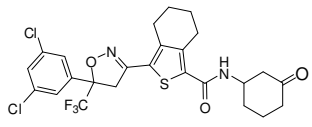


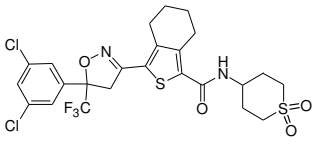
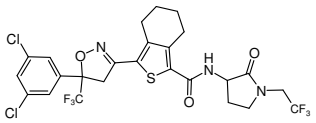
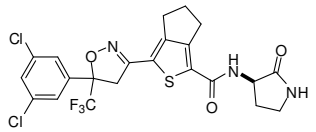
Se agitó una mezcla de ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico (850 mg, 1.84 mmol), HATU (837 mg, 2.20 mmol) y DIEA (539 mg, 0.8 mL, 4.6 mmol) en DCM (8 mL) a temperatura ambiente por 15 min, seguido por

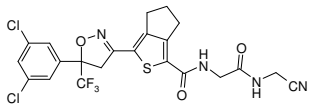
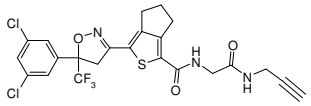
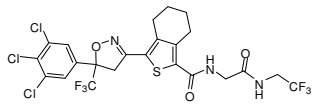
adición de clorhidrato de (R)-3-aminopirrolidin-2-ona (315 mg, 2.76 mmol). La mezcla de reacción se agitó a temperatura ambiente por 1.5 horas adicionales. La mezcla de reacción se diluyó con agua (20 mL) y extrajo con DCM (20 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por HPLC preparativa para proporcionar 3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida como un sólido blanco (730 mg, 73.0 %). MS (m/z): 546 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.46 (m, 3H), 6.49 (s, 1H), 5.83 (s, 1H), 4.51-4.48 (m, 1H), 4.22 (d, *J*=17.2, 1H), 3.85 (d, *J*=17.2, 1H), 3.52-3.47 (m, 2H), 3.09-2.87 (m, 5H), 2.12-2.03 (m, 1H), 1.89-1.73 (m, 4H).

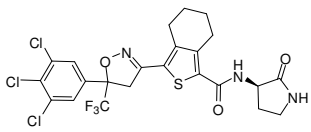
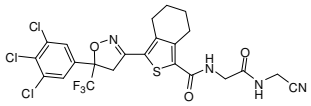
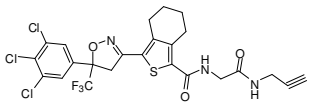
Los siguientes compuestos pueden ser preparados esencialmente por el método del Ejemplo 32.

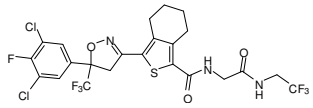
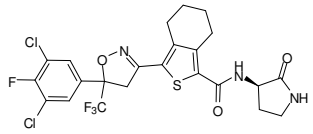
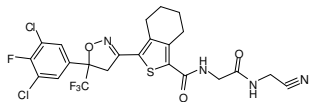
Ej. No.	Nombre químico	Estructura	Datos físicos
33	N,N-Dimetil-2-(4-{3-[5-(3,4,5-tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-piperazin-1-il)-acetamida		MS (m/z): 659 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07-4.02 (m, 2H), 3.68-3.80 (m, 4H), 3.49-3.41 (m, 2H), 3.09-3.01 (s, 3H), 3.01-2.95 (s, 3H), 2.91-2.85 (m, 2H), 2.84-2.78 (m, 4H), 2.69-2.63 (m, 2H), 1.87-1.72 (m, 4H).
Prep No. 34	éster metílico del ácido ({3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético		MS (m/z): 535 (M+1).
Prep No. 35	éster metílico del ácido ({3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético		MS (m/z): 575 (M+1).

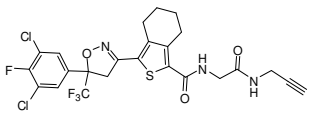
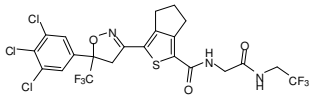
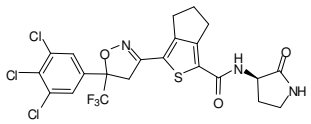
Ej. No.	Nombre químico	Estructura	Datos físicos
36	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetil amino)etil)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 588 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 7.01-6.95 (s, 1H), 6.79-6.71 (s, 1H), 4.21-4.18 (m, 2H), 4.06-3.91 (m, 3H), 3.65-3.59 (d, *J*=17.2, 1H), 2.98-2.87 (m, 4H), 2.59-2.49 (m, 2H).
37	(1,1-dioxo-tietan-3-il)-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 567 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.44 (s, 1H), 6.59-6.58 (s, 1H), 4.91-4.89 (m, 1H), 4.64-4.59 (m, 2H), 4.07-4.03 (m, 3H), 3.70-3.65 (m, 1H), 2.97-2.91 (m, 4H), 1.80-1.86 (m, 4H).
38	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3-oxociclohexil)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 559 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.48 (s, 2H), 7.43 (s, 1H), 5.73 (d, *J*=7.6 Hz, 1H), 4.46-4.42 (m, 1H), 4.06-4.02 (d, *J*=16 Hz, 1H), 3.68-3.64 (d, *J*=16 Hz, 1H), 2.93-2.89 (m, 4H), 2.82-2.77 (m, 1H), 2.47-2.30 (m, 3H), 2.17-2.15 (m, 1H), 2.02-1.95 (m, 1H), 1.88-1.78 (m, 6H).

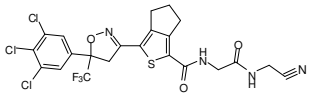
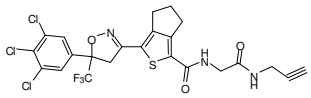
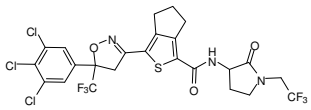
Ej. No.	Nombre químico	Estructura	Datos físicos
39	(1,1-dioxo-hexahidro-1l6-tiopiran-4-il)-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 559 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 3H), 5.77 (d, *J* = 7.6 Hz, 1H), 4.27-4.10 (m, 1H), 4.04 (d, *J* = 17.2 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.20-3.05 (m, 4H), 2.94-2.86 (m, 4H), 2.42-2.40 (m, 2H), 2.26-2.16 (m, 2H), 1.79-1.74 (m, 4H).
40	[2-oxo-1-(2,2,2-trifluoro-etil)-pirrolidin-3-il]-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 628 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.43 (m, 3H), 6.65-6.56 (m, 1H), 4.61-4.51 (m, 1H), 4.18-4.01 (m, 2H), 3.99-3.51 (m, 4H), 3.09-2.81 (m, 5H), 2.11-1.99 (m, 1H), 1.81-1.72 (m, 4H).
41	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 532 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 6.59-6.50 (s, 1H), 6.14-6.08 (s, 1H), 4.48-4.41 (m, 1H), 4.06-3.94 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 3.51-3.42 (m, 2H), 3.07-2.84 (m, 5H), 2.58-2.48 (m, 2H), 2.11-2.01 (m, 1H).

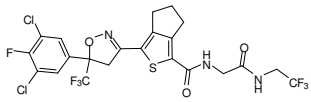
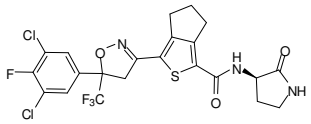
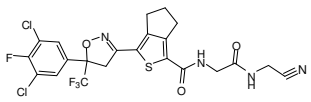
Ej. No.	Nombre químico	Estructura	Datos físicos
42	N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 545 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (s, 1H),7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 6.86-6.78 (s, 1H), 4.26-4.19 (m, 4H), 4.04-3.97 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 3.09-2.84 (m, 4H), 2.58-2.48 (m, 2H).
43	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 544 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.48-7.44 (m, 1H), 6.86-6.68 (m, 2H), 4.19-4.05 (m, 4H), 4.04-3.97 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 3.03-2.87 (m, 4H), 2.58-2.48 (m, 2H), 2.29-2.26 (s, 1H).
44	N-(2-oxo-2-(2,2,2-trifluoro etilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 636(M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.32 (br, 1H), 6.95 (br, 1H), 4.26-4.25 (m, 2H), 4.06-3.83 (m, 3H), 3.66 (d, *J* = 16.8 Hz, 1H), 2.98-2.89 (m, 4H), 1.79 (br, 4H).

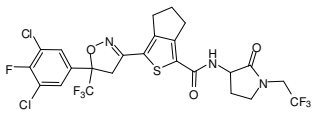
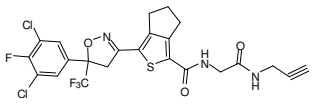
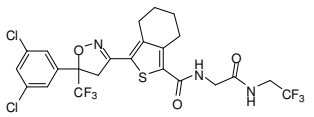
Ej. No.	Nombre químico	Estructura	Datos físicos
45	N-((R)-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 580(M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 6.62 (br, 1H), 6.17 (br, 1H), 4.47-4.46 (m, 1H), 4.07-4.02 (m, 1H), 3.75-3.64 (m, 1H), 3.49-3.43 (m, 2H), 3.02-2.88 (m, 2H), 2.09-2.01 (m, 1H), 1.77 (br, 4H).
46	N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 593(M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 2 H), 7.47 (m, 1 H), 6.81 (m, 1 H), 4.22 (m, 4 H), 4.06 (d, *J*=17.2, 1 H), 3.70 (d, *J*=17.2, 1 H), 2.90 (m, 4 H), 1.79 (m, 4 H).
47	N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 592(M+1). ^{1}H NMR (CDCl3, 400 MHz) δ 7. 63 (s, 2 H), 6.78 (m, 1 H), 6.50 (m, 1 H), 4.15 (m, 2 H), 4.10 (m, 2 H), 4.05 (d, *J*=16.8, 1 H), 3.67 (d, *J*=16.8, 1 H), 2.95 (m, 2 H), 2.90 (m, 2 H), 2.26 (m, 1 H), 1.79 (m, 4H).

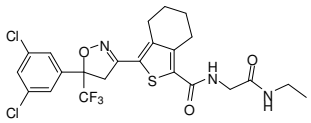
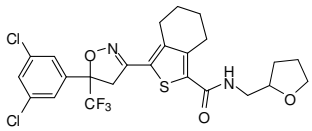
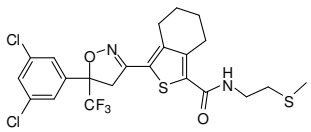
Ej. No.	Nombre químico	Estructura	Datos físicos
48	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoro etilamino)etil)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 620(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.76 (d, *J*=6.4, 2H), 4.25 (d, *J*=17.6, 1H), 4.07 (s, 2H), 4.04-3.92 (m, 3H), 3.01-2.98 (m, 2H), 2.90-2.89 (m, 2H), 1.79 (m, 4H).
49	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 564(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.76 (d, *J*=6.4, 2H), 4.63 (t, *J*=9.6, 1H), 4.24 (d, *J*=17.6, 1H), 4.02 (d, *J*=17.6, 1H), 3.44-3.40 (m, 2H), 2.99-2.98 (m, 2H), 2.89 (m, 2H), 2.59-2.52 (m, 1H), 2.23-2.18 (m, 1H), 1.79-1.77 (m, 4H).
50	N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 577(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.77 (d, *J*=6.4, 2H), 4.28-4.21 (m, 3H), 4.05-4.00 (m, 3H), 3.00(t, *J*=6.0, 2H), 2.93-2.90 (m, 2H), 1.81-1.80 (m, 4H).

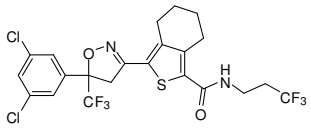
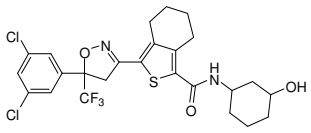
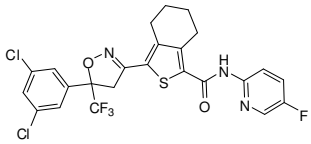
Ej. No.	Nombre químico	Estructura	Datos físicos
51	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 576(M+1); ^{1}H NMR ($CDOD_3$, 400 MHz) δ 7.76 (d, *J*=6.4, 2H), 4.24 (d, *J*=17.6, 1H), 4.03-3.99 (m, 5H), 2.98 (t, *J*=6.0, 2H), 2.88-2.86 (m, 2H), 2.62 (t, *J*=2.4, 1H), 1.79-1.77 (m, 4H).
52	N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 622 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.64 (s, 2 H), 6.81 (brs, 1 H), 6.73 (brs, 1 H), 4.22 (d, *J*=4.8, 2 H), 3.99 (m, 3 H), 3.64 (d, *J*=17.2, 1 H), 2.99 (t, *J*=7.6, 2 H), 2.91 (t, *J*=7.6, 2 H), 2.55 (m, 2 H).
53	N-((R)-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 566 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7. 62 (s, 2 H), 6.46 (brs, 1 H), 6.16 (brs, 1 H), 4.47 (m, 1 H), 3.99 (d, *J*=17.2, 1 H), 3.61 (d, *J*=17.2, 1 H), 3.47 (m, 2 H), 2. 93 (m, 5 H), 2.53 (m, 2 H), 2.09 (m, 1 H).

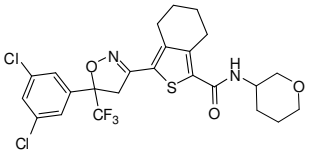
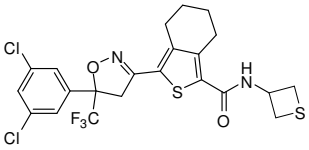
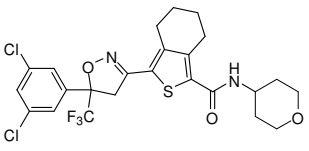
Ej. No.	Nombre químico	Estructura	Datos físicos
54	N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 579 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.62 (s, 2 H), 7.21 (brs, 1 H), 6.71 (brs, 1 H), 4.22 (d, *J*=6.0, 2 H), 4.18 (d, *J*=5.2, 2 H), 4.02 (d, *J*=17.2, 1 H), 3.63 (d, *J*=17.2, 1 H), 2.96 (t, *J*=7.2, 2 H), 2. 89 (t, *J*=7.2, 2 H), 2.56 (m, 2 H).
55	N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 578 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.62 (s, 2 H), 6.82 (brs, 1 H), 6.65 (brs, 1 H), 4.15 (d, *J*=4.8, 2 H), 4.10 (d, J_1=2.4, J_2=4.2, 2 H), 4.02 (d, *J*=16.8, 1 H), 3.62 (d, *J*=16.8, 1 H), 2.98 (t, *J*=7.2, 2 H), 2. 88 (t, *J*=7.2, 2 H), 2.55 (m, 2 H), 2. 27 (t, *J*=2.4, 2 H).
56	N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 648 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7. 62 (s, 2 H), 6.5 (brs, 1 H), 4.50 (m, 1 H), 4.09 (m, 1 H), 4.00 (d, *J*=17.2, 1 H), 3.84 (m, 1 H), 3.58 (m, 3 H), 2. 93 (m, 5 H), 2.52 (m, 2 H), 2.04 (m, 1 H).

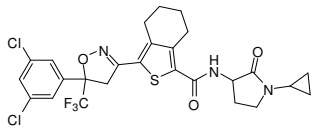
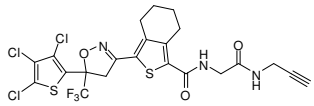
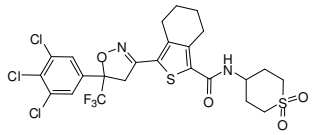
Ej. No.	Nombre químico	Estructura	Datos físicos
57	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoro etilamino)etil)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 606 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.0, 2 H), 6.92 (t, *J*=6.4, 1 H), 6.76 (t, *J*=4.8, 1 H), 4.21 (d, *J*=4.8, 1 H), 3.98 (m, 3 H), 3.61 (d, *J*=16.8, 1 H), 2.97 (t, *J*=7.6, 2 H), 2.89 (t, *J*=7.6, 2 H), 2.55 (m, 2H)
58	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 550 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.4, 2 H), 6.46 (brs, 1 H), 6.32 (brs, 1 H), 4.47 (m, 1 H), 3.99 (d, *J*=17.2, 1 H), 3.61 (d, *J*=17.2, 1 H), 3.48 (m, 2 H), 2. 93 (m, 5 H), 2.53 (m, 2 H), 2.06 (m, 1 H).
59	N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 563 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.0, 2 H), 7.41 (brs, 1 H), 6.84 (brs, 1 H), 4.20 (m, 4 H), 3.99 (d, *J*=16.8, 1 H), 3.63 (d, *J*=16.8, 1 H), 2.95 (t, *J*=7.2, 2 H), 2. 88 (t, *J*=7.2, 2 H), 2.53 (m, 2 H).

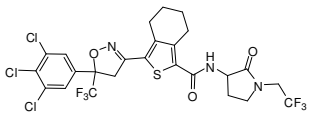
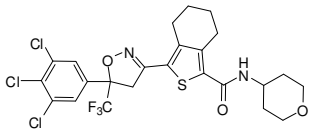
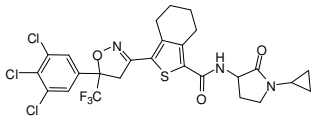
Ej. No.	Nombre químico	Estructura	Datos físicos
60	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil) pirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 632 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.58 (d, *J*=6.0, 2H), 6.60-6.57 (m, 1H), 4.56-4.50 (m, 1H), 4.14-4.00 (m, 2H), 3.87-3.83 (m, 1H), 3.67-3.55 (m, 3H), 3.01-2.86 (m, 5H), 2.57-2.50 (m, 2H), 2.10-2.05 (m, 1H).
61	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxamida		MS (m/z): 562 (M+1); ^{1}H NMR (CDCl3, 400 MHz) δ 7.58 (d, *J*=6.0, 2H), 6.85 (brs, 1H), 6.70 (brs, 1H), 4.18 (d, *J*=4.8, 2H), 4.14-4.12 (m, 2H), 4.04 (d, *J*=17.2, 1H), 3.65 (d, *J*=17.2, 1H), 3.00(t, *J*=7.2, 2H), 2.90 (t, *J*=7.2, 2H), 2.60-2.55 (m, 2H), 2.29 (s, 1H).
62	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoro etilamino)etil)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 602 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.52-7.46 (m, 3H), 7.12-7.01 (m, 1H), 6.85-6.78 (m, 1H), 4.28-4.20 (m, 2H), 4.08-3.91 (m, 3H), 3.68 (d, *J*=17.2, 1H), 3.07-2.87 (m, 4H), 1.89-1.73 (m, 4H).

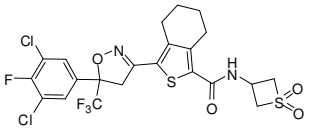
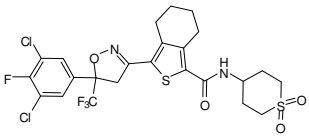
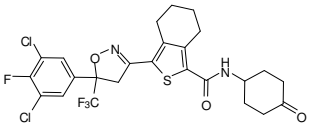
Ej. No.	Nombre químico	Estructura	Datos físicos
63	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-(etilamino)-2-oxoetil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 548 (M+1); 1H NMR ($CDCl_3$, 400 MHz) δ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 2H), 7.42 (m, 1H), 6.80 (s, 1H), 5.96 (s, 1H), 4.09-4.02 (m, 3H), 3.69-3.65 (d, *J*=16 Hz, 1H), 3.40-3.33 (m, 2H), 3.00 (s, 2H), 2.92-2.90(m, 2H), 1.79 (s, 4H), 1.26-1.17 (m, 3H).
64	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((tetrahidrofuran-2-il)metil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 547 (M+1); 1H NMR ($CDCl_3$, 400 MHz) δ7.48 (s, 2H), 7.42 (s, 1H), 6.23 (s, 1H), 4.08-4.02 (m, 2H), 3.91-3.86 (m, 1H), 3.81-3.76 (m, 2H), 3.69-3.65 (m, *J*=16 Hz, 1H), 3.34-3.28 (m, 1H), 3.00-2.85 (m, 4H), 2.06-1.98 (m, 1H), 1.96-1.89 (m, 2H), 1.79-1.77 (m, 4H), 1.64-1.59 (m, 1H).
65	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-(metiltio)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 537 (M+1); 1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 2H), 7.43 (s, 1H), 6.33 (s, 1H), 4.07-4.03 (d, *J*=16 Hz, 1H), 3.69-3.62 (m, 3H), 2.98 (s, 2H), 2.92-2.90 (m, 2H), 2.76-2.74 (m, 2H), 2.14 (s, 3H), 1.80-1.79 (m, 4H).

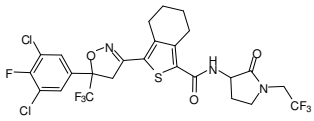
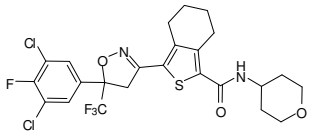
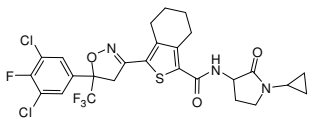
Ej. No.	Nombre químico	Estructura	Datos físicos
66	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3,3,3-trifluoropropil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 559 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.43 (s, 1H), 6.08-6.05 (m, 1H), 4.06-4.02 (d, *J*=16 Hz, 1H), 3.72-3.64 (m, 3H), 2.94-2.85 (m, 4H), 2.51-2.40 (m, 2H), 1.80-1.78 (m, 4H).
67	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3-hidroxiciclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 561 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.43 (s, 1H), 6.85 (s, 1H), 4.21 (s, 1H), 4.09-4.02 (m, 2H), 3.69-3.64 (d, *J*=20 Hz, 1H), 2.96-2.89 (m, 5H), 2.05-1.78 (m, 9H), 1.49-1.38 (m, 2H).
68	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(5-fluoropiridin-2-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 558 (M+1); 1H NMR (CDCl3, 400 MHz) δ 8.36 (s, 1H), 8.32-8.29 (m, 1H), 8.16 (d, *J*=2.4 Hz, 1H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 4.09-4.05 (d, *J*=16 Hz, 1H), 3.71-3.67 (d, *J*=16 Hz, 1H), 3.09 (s, 2H), 2.94-2.93 (m, 2H), 1.83 (s, 4H)

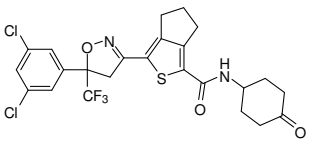
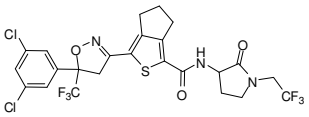
Ej. No.	Nombre químico	Estructura	Datos físicos
69	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 547 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.40 (s, 1H), 6.23 (d, *J*=9.6 Hz, 1H), 4.18-4.16 (s, 1H), 4.07-4.03 (d, *J*=16 Hz, 1H), 3.83-3.77 (m, 2H), 3.69-3.57 (m, 3H), 2.98-2.90 (m, 4H), 1.90-1.75 (m, 8H).
70	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tietan-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 535 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2H), 7.44 (s, 1H), 6.18 (d, *J* = 7.6 Hz, 1H), 5.40-5.34 (m, 1H), 4.06 (d, *J* = 17.2 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.46-3.36 (m, 4H), 2.97-2.90 (m, 4H), 1.81-1.78 (m, 4H).
71	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-4-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 547 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.47 (s, 2H), 7.41 (s, 1H), 5.74-5.72 (d, *J*=7.6 Hz, 1H), 4.19-4.11 (m, 1H), 4.10-4.06 (d, *J*=16 Hz, 1H), 4.04-3.96 (m, 2H), 3.69-3.65 (d, *J*=16 Hz, 1H), 3.53-3.43 (m, 2H), 2.94-2.88 (m, 4H), 2.00-1.97 (m, 2H), 1.77 (s, 4H), 1.60-1.50 (m, 2H).

Ej. No.	Nombre químico	Estructura	Datos físicos
72	N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 586 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (s, 2 H), 7.43 (s, 1H), 6.50 (brs, 1 H), 4.43-4.40 (m, 1 H), 4.04 (d, *J* =16.8, 1 H), 3.65 (d, *J* =16.8, 1 H), 3.42-3.30 (m, 2 H), 2.99-2.82 (m, 5 H), 1.91-1.80 (m, 5 H), 0.83-0.763 (m, 4 H)
74	N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorotiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 600 (M+1); 1H NMR (CDCl3, 400 MHz) δ 6.92-6.77 (m, 2H), 4.21-4.09 (m, 4H), 4.08-4.04 (m, 2H), 3.09-2.88 (m, 4H), 1.87-1.71 (m, 4H).
75	(1,1-dioxo-hexahidro-tiopiran-4-il)-amida del ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 631 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.62 (s, 2H), 5.89-5.87 (m, 1H), 4.28-4.20 (m, 1H), 4.07-4.03 (d, *J*=16 Hz, 1H), 3.70-3.66 (d, *J*=16 Hz, 1H), 3.20-3.12 (m, 4H), 2.94-2.89 (m, 4H), 2.42-2.39 (m, 2H), 2.27-2.17 (m, 2H), 1.79 (s, 4H).

Ej. No.	Nombre químico	Estructura	Datos físicos
76	N-(2-oxo-1-(2,2,2-trifluoroetil) pirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 664 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.63 (s, 2 H), 6.45 (brs, 1 H), 4.53 (brs, 1 H), 4.09 (m, 2 H), 3.85 (m, 1 H), 3.58 (m, 3 H), 2.95 (m, 4 H), 2.02 (m, 1 H), 1.79 (m, 4 H).
77	N-(tetrahidro-2H-piran-4-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 583 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.61 (s, 2H), 5.70-5.68 (d, *J*=8.0 Hz, 1H), 4.19-4.11 (m, 1H), 3.70-3.66 (d, *J*=16 Hz, 1H), 4.00-3.97 (m, 2H), 3.68-3.64 (d, *J*=16 Hz, 1H), 3.54-3.48 (m, 2H), 2.94-2.88 (m, 4H), 2.00-1.98 (m, 2H), 1.79 (s, 4H), 1.64-1.50 (m, 2H).
78	N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 622 (M+1); 1H NMR (CDCl3, 400 MHz) δ 8.00 (s, 2 H), 6.53 (brs, 1 H), 4.43 (m, 1 H), 4.04 (d, *J*=17.2, 1 H), 3.65 (d, *J*=17.2, 1 H), 3.36 (m, 2 H), 2.83 (m, 5 H), 2.73 (m, 1 H), 1.84 (m, 5 H), 0.79 (m, 4 H).

Ej. No.	Nombre químico	Estructura	Datos físicos
79	(1,1-dioxo-tietan-3-il)-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 585 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.76 (d, *J*=6.0, 2H), 4.65-4.56 (m, 1H), 4.53 (t, *J*=4.8, 2H), 4.28-4.23 (m, 3H), 4.02 (d, *J*=17.6, 1H), 2.97 (t, *J*=6.0, 2H), 2.90 (t, *J*=6.0, 2H), 1.80-1.76 (m, 4H).
80	(1,1-dioxo-hexahidro-tiopiran-4-il)-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 613 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.56 (d, *J*=6.0, 2 H), 5.75 (d, *J*=7.2, 1 H), 4.06 (d, *J*=16.8, 1 H), 3.65 (d, *J*=16.8, 1 H), 3.13 (m, 4 H), 2.91 (m, 4 H), 2.41 (m, 2 H), 2.23 (m, 2 H), 1.84 (m, 4 H).
81	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(4-oxociclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 577 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.48(d, *J*=6.0, 2H), 5.67 (d, *J*=6.8, 1H), 4.33 (m, 1H), 3.98(d, *J*=16.8, 1H), 3.58 (d, *J*=16.8, 1H), 2.82 (m, 4H), 2.40 (m, 6H), 1.65 (m, 6H)

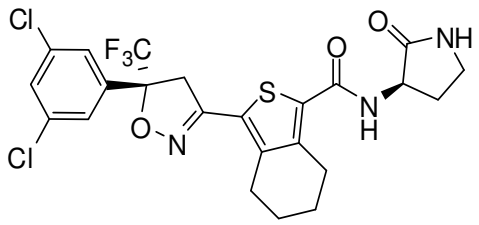
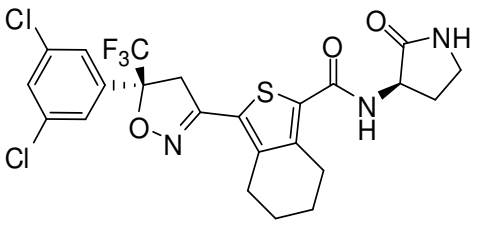
Ej. No.	Nombre químico	Estructura	Datos físicos
82	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil) pirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 646 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7. 50 (dd, J_1=2.4, J_2=6.0, 2 H), 6.44 (dd, J_1=4.8, J_2=12.0, 1 H), 4.46 (m, 1 H), 3.98 (m, 2 H), 3.78 (m, 1 H), 3.55 (m, 3 H), 2.83 (m, 5 H), 1.963 (m, 1 H), 1.71 (m, 4 H).
83	3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-4-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 565 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.49 (d, J=5.6, 2 H), 5.59 (d, J=7.6, 1 H), 4.10 (m, 1 H), 3.98 (d, J=16.8, 1 H), 3.91 (m, 2 H), 3.58 (d, J=16.8, 1 H), 3.45 (m, 2 H), 2.84 (m, 4 H), 1.95 (m, 2 H), 1.72 (m, 4 H), 1.49 (m, 3 H).
84	N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c] tiofen-1-carboxamida		MS (m/z): 604 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.77 (d, J=6.0, 2H), 4.62 (t, J=9.6, 1H), 4.24 (d, J=17.6, 1H), 4.02 (d, J=17.6, 1H), 3.43-3.39 (m, 2H), 2.99-2.96 (m, 2H), 2.90-2.88 (m, 2H), 2.75-2.69 (m, 1H), 2.50-2.42 (m, 1H), 2.10-1.99 (m, 1H), 1.81-1.78 (m, 4H), 0.85-0.82 (m, 4H).

Ej. No.	Nombre químico	Estructura	Datos físicos
85	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(4-oxociclohexil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 545 (M+1); 1H NMR (CDCl3, 400 MHz) δ 7.52-7.44 (m, 3H), 5.72-5.68 (m, 1H), 4.48-4.37 (m, 1H), 4.04-3.97 (d, *J*=17.2, 1H), 3.65-3.59 (d, *J*=17.2, 1H), 2.92-2.84 (m, 4H), 2.58-2.48 (m, 6H), 2.47-2.31 (m, 2H), 1.84-1.71 (m, 2H).
86	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida		MS (m/z): 614 (M+1); 1H NMR (CDCl3, 400 MHz) δ7.52-7.44 (m, 3H), 6.43-6.38 (s, 1H), 4.52-4.48 (m, 1H), 4.17-4.05 (m, 2H), 4.04-3.97 (d, *J*=17.2, 1H), 3.89-3.77 (m, 1H), 3.68-3.51 (m, 3H), 2.93-2.82 (m, 5H), 2.58-2.46 (m, 2H), 2.08-1.97 (m, 1H).

Ejemplo 87

(A) 3-((R)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida y

(B) 3-((S)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida

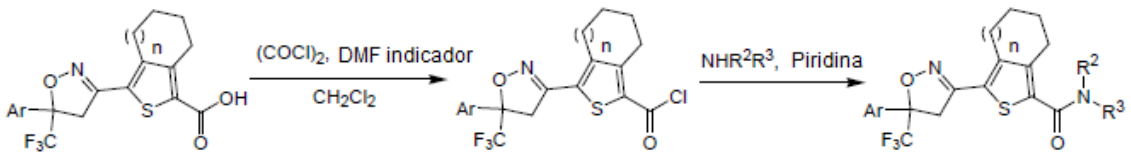
Se separó 3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida (6.2 g 11.29 mmol) por SFC (Columna: Chiralcel OD 250×30mm I.D., 5um. Fase móvil: CO_2 Supercrítico/ MeOH=60/40, Velocidad de flujo:200 ml/min) para proporcionar dos diastereoisómeros 3-((R)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxo pirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida (2.7 g, 4.92 mmol) y 3-((S)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida (2.6 g, 4.74 mmol) como un sólido blanco.

(A) MS (m/z): 619.1 (M+73). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (s, 2H), 7.42 (s, 1H), 6.56 (d, *J*=4.4 Hz 1H), 6.03 (s, 1H), 4.50-4.44 (m, 1H), 4.06-4.02 (d, *J*=16 Hz, 1H), 3.69-3.65 (d, *J*=16 Hz, 1H), 3.48-3.43 (m, 2H), 3.03-2.98 (m, 5H), 2.11-2.00 (m, 1H), 1.78 (s, 4H).

(B) MS (m/z): 619.1 (M+73). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (m, 2H), 7.41 (m, 1H), 6.77-6.73 (m, 1H), 6.38-6.31 (m, 1H), 4.51-4.45 (m, 1H), 4.05-4.01 (d, *J*=16 Hz, 1H), 3.71-

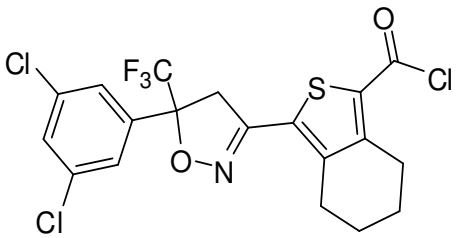
3.67 (d, *J*=16 Hz, 1H), 3.49-3.39 (m, 2H), 3.00-2.85 (m, 5H), 2.04-2.03 (m, 1H), 1.74 (s, 4H).

Esquema de reacción B



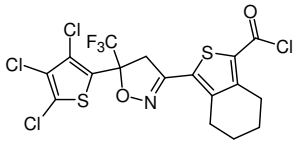
Preparación 88

cloruro de 3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carbonilo



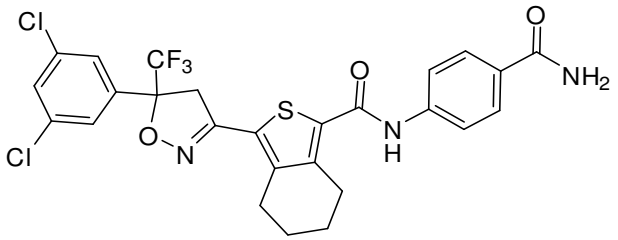
Se agitó una mezcla de ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico (600 mg, 1.2 mmol), 2 gotas de DMF en dicloruro de oxalilo (5 mL) a temperatura ambiente por 3 horas. El solvente se removió bajo vacío para proporcionar cloruro de 3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carbonilo como un sólido amarillo (615 mg, 98%).

El siguiente compuesto se preparó esencialmente por el método de la Preparación 88.

Prep. No.	Nombre químico	Estructura	Datos físicos
89	cloruro de 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonilo		

Ejemplo 90

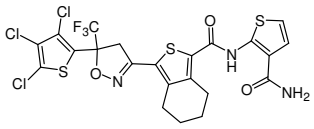
N-(4-carbamoilfenil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida



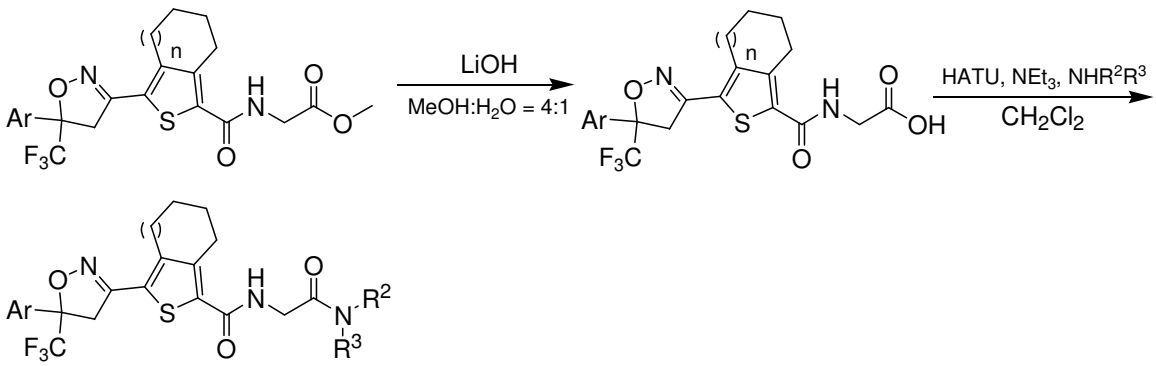
Se agitó una mezcla de cloruro de 3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carbonilo (48 mg, 0.1 mmol) y 4-aminobenzamida (27 mg, 0.2 mmol) en piridina (3 mL) a temperatura ambiente durante la noche. Después de la

eliminación del solvente bajo vacío, el residuo se purificó por HPLC preparativa para proporcionar N-(4-carbamoilfenil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida como un sólido blanco (36 mg, 62.0%). MS (m/z): 582.1 (M+1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J*=8.4 Hz, 2H), 7.65-7.63 (m, 3H), 7.49 (s, 2H), 7.44 (s, 1H), 6.03 (s, 1H), 5.61 (s, 1H), 4.09-4.05 (d, *J*=16 Hz, 1H), 3.72-3.68 (d, *J*=16 Hz, 1H), 3.07 (s, 2H), 2.94 (s, 2H), 1.76 (s, 4H).

El siguiente compuesto se preparó esencialmente por el método del Ejemplo 90.

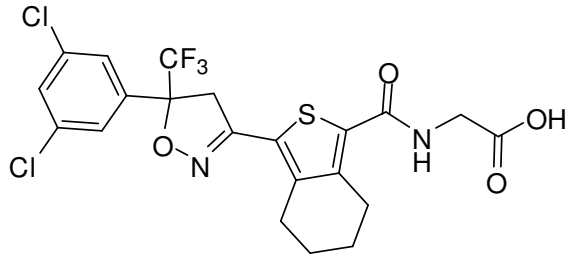
Ej. No.	Nombre químico	Estructura	Datos físicos
91	(3-carbamoil-tiofen-2-il)-amida del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico		MS (m/z): 628 (M+1); ^{1}H NMR (400 MHz, DMSO-d_6,) δ 8.08-8.02 (m, 1H), 7.81-7.78 (m, 1H), 4.58-4.43 (t, 2H), 3.13-2.84 (m, 4H), 1.79-1.64 (m, 4H).

Esquema de reacción C



Preparación 92

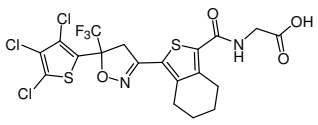
ácido 2-(3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamido)acético



Se agitó una mezcla de 2-(3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamido)acetato de metilo (534 mg, 1.0 mmol) y LiOH-H_2O (168 mg, 4.0 mmol) en MeOH (20 mL) y agua (5 mL) a temperatura ambiente durante la noche. Después de la eliminación del solvente orgánico bajo vacío, el residuo se diluyó con agua helada (10 mL). La mezcla acuosa se acidificó con HCl conc. a pH = 1, y la mezcla resultante se extrajo con EtOAc (15 mL×3).Las capas orgánicas combinadas se lavaron con salmuera, secaron sobre Na_2SO_4 anhidro y

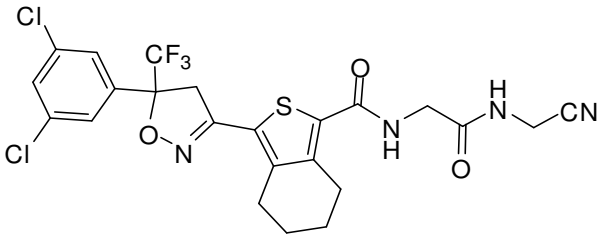
concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 1:1) para proporcionar ácido 2-(3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamido)acético como un sólido amarillo pálido (427 mg, 82.0 %). MS (m/z): 521(M+1).

El siguiente compuesto se preparó esencialmente por el método de la Preparación 92.

Prep. No.	Nombre químico	Estructura	Datos físicos
93	ácido ({3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético		MS (m/z): 561 (M+1).

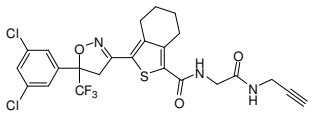
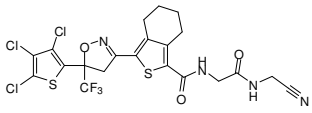
Ejemplo 94

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida

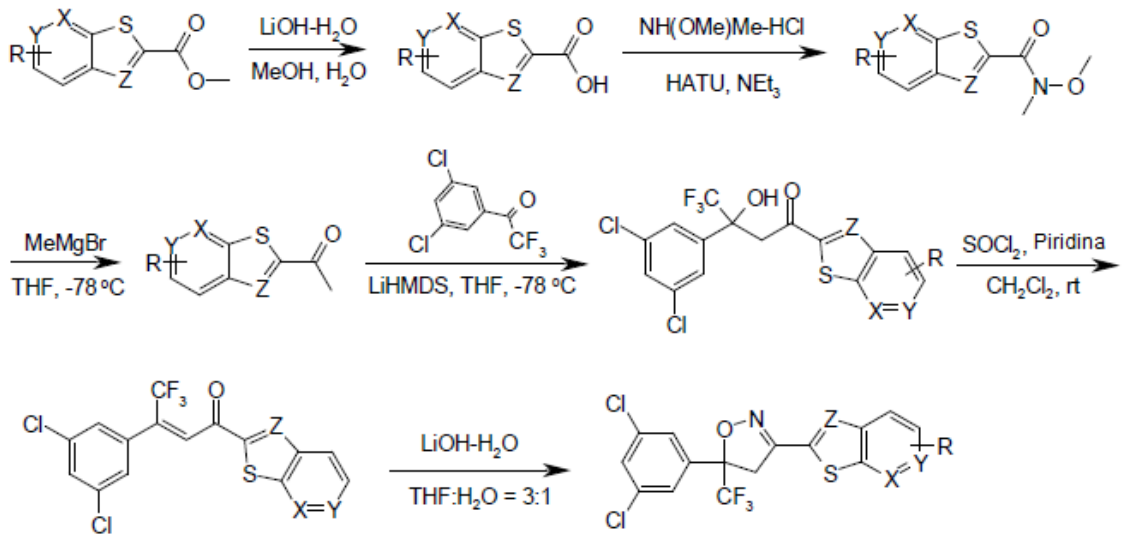


Se agitó una mezcla de ácido 2-(3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamido)acético (230 mg, 0.44 mmol), HATU (251 mg, 0.66 mmol) y NEt_3 (133 mg, 1.32 mmol) en DCM (5 mL) a temperatura ambiente por 15 min, seguido por adición de clorhidrato de 2-aminoacetonitrilo (61 mg, 0.65 mmol). La mezcla de reacción se agitó a temperatura ambiente por 1.5 horas adicionales. La mezcla de reacción se diluyó con agua (20 mL) y extrajo con DCM (20 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por HPLC preparativa para proporcionar N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida como un sólido blanco (110 mg, 44.7 %). MS (m/z): 559.1 (M+1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.64 (t, J=5.6 Hz, 1H), 8.22 (t, J=5.6 Hz, 1H), 7.81-7.80 (m 1H), 7.68 (s, 2H), 4.35-4.22 (m, 2H), 4.16-4.15 (m, 2H), 3.88-3.86 (m, 2H), 2.94-2.86 (m, 4H), 1.70-1.69 (m, 4H).

Los siguientes compuestos son preparados esencialmente por el método del Ejemplo 94.

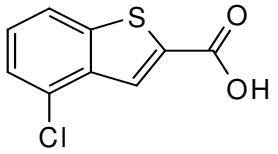
Ej. No.	Nombre químico	Estructura	Datos físicos
95	3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 558 (M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49-7.42 (m, 3H), 6.85 (br, 1H), 6.72 (br, 1H), 4.17-4.03 (m, 5H), 3.68 (d, *J* = 17.2 Hz, 1H), 3.00-2.90 (m, 4H), 2.25 (s, 1H), 1.79 (br, 4H).
96	N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorotiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida		MS (m/z): 599 (M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28-4.18 (m, 4H), 4.10-4.07 (m, 2H), 3.04-2.87 (m, 4H), 1.88-1.73 (m, 4H).

Esquema de reacción D



Preparación 201

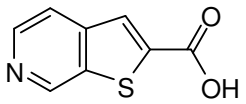
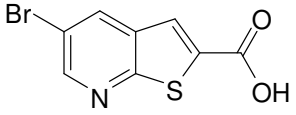
ácido 4-clorobenzo[b]tiofen-2-carboxílico



Se agitó una mezcla de 4-clorobenzo[b]tiofen-2-carboxilato de metilo (1.0 g, 4.44 mmol) y LiOH-H_2O (0.56 g, 13.3 mmol) en MeOH (30 mL) y agua (10 mL) a temperatura ambiente durante la noche. La mezcla de reacción se concentró bajo vacío y después el residuo se diluyó con agua helada (20 mL). La mezcla acuosa se acidificó con solución conc. de HCl a pH = 1. La mezcla resultante se extrajo con EtOAc (15 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y evaporaron bajo vacío para proporcionar ácido 4-clorobenzo[b]tiofen-2-

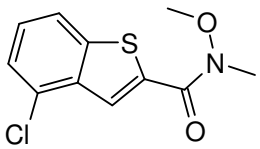
carboxílico como un sólido blanco (0.94 g, 100 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.02 (m, 2H), 7.61–7.51 (m, 2H)

Los siguientes compuestos son preparados esencialmente por el método de la Preparación 201.

Prep No.	Nombre químico	Estructura	Datos físicos
202	ácido Tieno[2,3-c]piridina-2-carboxílico		MS (m/z): 180(M+1)
203	ácido 5-Bromo-tieno[2,3-b]piridina-2-carboxílico		MS (m/z): 260 (M+1).

Preparación 204

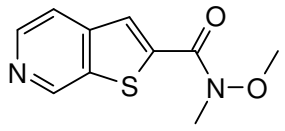
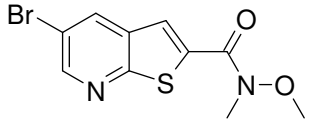
4-cloro-N-metoxi-N-metilbenzo[b]tiofen-2-carboxamida



Se agitó una mezcla de ácido 4-clorobenzo[b]tiofen-2-carboxílico (0.94 g, 4.44 mmol), Clorhidrato de N,O-dimetilhidroxilamina (0.86 g, 8.87 mmol), DCC (1.1 g, 5.32 mmol) y DIEA (1.43 g, 1.9 mL, 11.08 mmol) en DCM (8 mL) a temperatura ambiente por 2 horas. La mezcla de reacción se filtró y lo filtrado se lavó con salmuera, se secó sobre Na_2SO_4 anhidro y concentró bajo vacío. El residuo se purificó

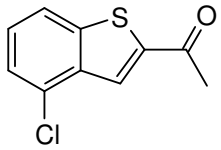
por cromatografía en columna sobre gel de sílice eluyendo con PE: EtOAc (5:1 a 3:1) para proporcionar 4-cloro-N-metoxi-N-metilbenzo[b]tiofen-2-carboxamida como un sólido blanco (0.85 g, 75.2 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.02 (m, 2H), 7.61-7.51 (m, 2H), 3.84-3.79 (s, 3H), 3.37-3.35 (s, 3H).

El siguiente compuesto se preparó esencialmente por el método de la Preparación 204.

Prep. No.	Nombre químico	Estructura	Datos físicos
205	N-metoxi-N-metiltieno[2,3-c]piridina-2-carboxamida		MS (m/z): 223 (M+1).
206	5-bromo-N-metoxi-N-metiltieno[2,3-b]piridina-2-carboxamida		MS (m/z): 301 (M+1).

Preparación 207

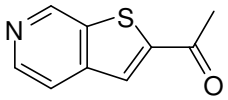
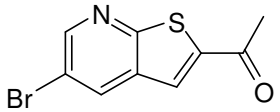
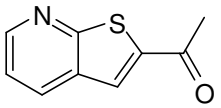
1-(4-clorobenzo[b]tiofen-2-il)etanona



Se agregó una solución de CH_3MgBr (3 M en THF, 1.7 ml, 4.99 mmol) a una suspensión de 4-cloro-N-metoxi-N-metilbenzo[b]tiofen-2-carboxamida (0.85 g, 3.33 mmol) en THF seco (10 mL) a 0 ^{0}C. Después la mezcla se agitó durante la

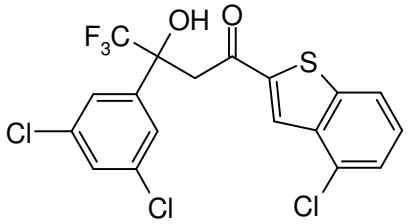
noche a temperatura ambiente. La reacción se apagó con solución acuosa saturada de NH_4Cl (15 mL) y la mezcla acuosa se extrajo con EtOAc (10 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc = 6:1) para proporcionar 1-(4-clorobenzo[b]tiofen-2-il)etanona como un sólido blanco (0.6 g, 86.9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (s, 1H), 7.75 (d, *J*=5.2, 1H), 7.47-7.36 (m, 2H), 2.72-2.68 (s, 3H).

Los siguientes compuestos son preparados esencialmente por el método de la Preparación 207.

Prep No.	Nombre químico	Estructura	Datos físicos
208	1-Tieno[2,3-c]piridin-2-il-etanona		MS (m/z): 178 (M+1).
209	1-(5-Bromo-tieno[2,3-b]piridin-2-il)-etanona		MS (m/z): 258 (M+1).
210	1-Tieno[2,3-b]piridin-2-il-etanona		MS (m/z): 178 (M+1)

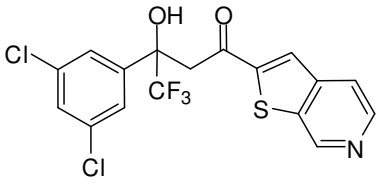
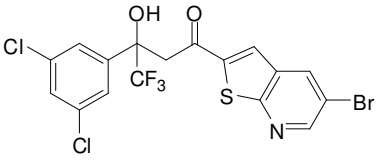
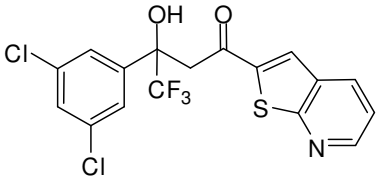
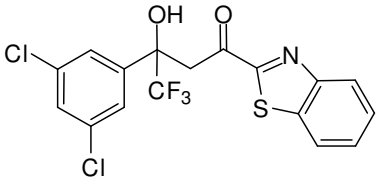
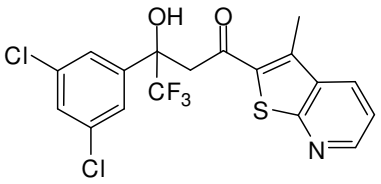
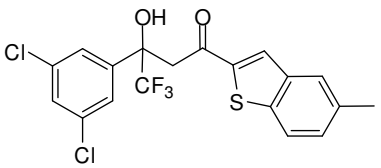
Preparación 211

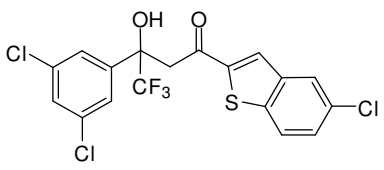
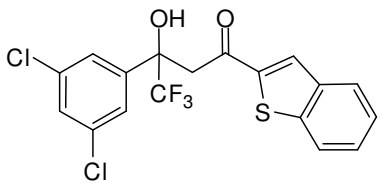
1-(4-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutan-1-ona



Se agregó una solución de LiHMDS (1 M en THF, 4.3 ml, 4.31 mmol) a una mezcla de 1-(4-clorobenzo[b]tiofen-2-il)etanona (0.6 g, 2.87 mmol) en THF seco (10 mL) a -78 ^{0}C bajo N_2. Después de agitar 1.5 horas a -78 ^{0}C, se agregó 1-(3,5-diclorofenil)-2,2,2-trifluoroetanona (836 mg, 3.44 mmol) a la mezcla de reacción y la mezcla resultante se agitó por 2 horas adicionales. La reacción se apagó con solución saturada de NH_4Cl y la mezcla acuosa se extrajo con EtOAc (10 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío para proporcionar 1-(4-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutan-1-ona cruda como un sólido marrón (1.1 g, 84.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (s, 1H), 7.75 (d, *J*=5.2, 1H), 7.47-7.36 (m, 2H), 2.72-2.68 (s, 3H).

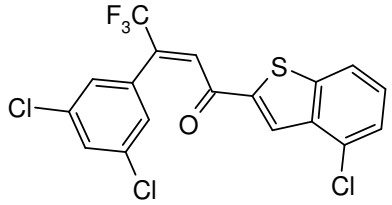
Los siguientes compuestos son preparados esencialmente por el método de la Preparación 211.

Prep. No.	Nombre químico	Estructura	Datos físicos
212	3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-3-hidroxi-1-tieno[2,3-c]piridin-2-il-butan-1-ona		MS (m/z): 418 (M-1)
213	3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-3-hidroxi-1-(5-bromo-tieno[2,3-b]piridin-2-il)-butan-1-ona		MS (m/z): 498 (M-1).
214	3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-3-hidroxi-1-tieno[2,3-b]piridin-2-il-butan-1-ona		MS (m/z): 418 (M-1).
215	1-(benzo[d]tiazol-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutan-1-ona		MS (m/z): 418 (M-1).
216	3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxi-1-(3-metilbenzo[b]tiofen-2-il)butan-1-ona		MS (m/z): 431 (M-1).
217	3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxi-1-(5-metilbenzo[b]tiofen-2-il)butan-1-ona		MS (m/z): 431 (M-1).

Prep. No.	Nombre químico	Estructura	Datos físicos
218	1-(5-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutan-1-ona		MS (m/z): 451 (M-1).
219	1-(benzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutan-1-ona		MS (m/z): 417 (M-1).

Preparación 220

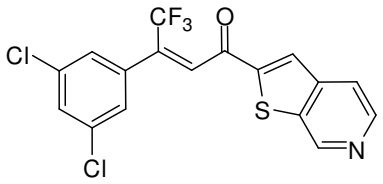
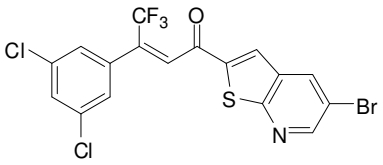
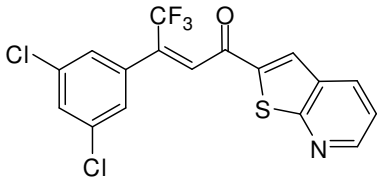
1-(4-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluorobut-2-en-1-ona

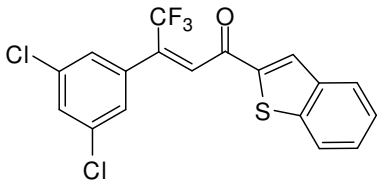
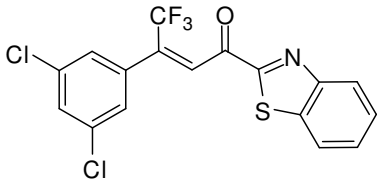
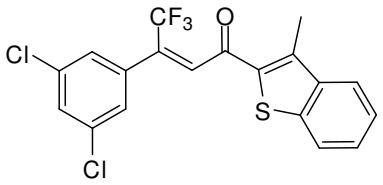
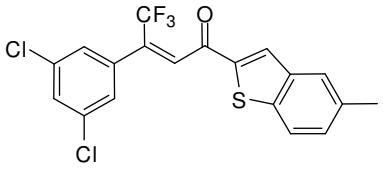


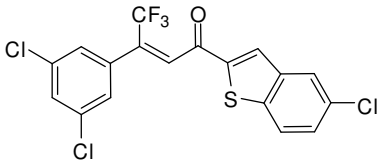
Se agitó una mezcla de 1-(4-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluoro-3-hidroxibutan-1-ona (1.1 g, cruda, 2.43 mmol), $SOCl_2$ (1.16 g, 0.7 mL, 9.43 mmol) y piridina (384 mg, 0.4 mL, 4.86 mmol) en DCM anhidro (10 mL) a temperatura ambiente durante la noche. La mezcla se diluyó con solución saturada de NH_4Cl y la mezcla acuosa se extrajo con DCM (10 mL×3). Las capas orgánicas combinadas se lavaron

con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío para proporcionar 1-(4-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluorobut-2-en-1-ona cruda como un sólido marrón (1.05 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.12-8.10 (s, 1H), 7.69-7.64 (m, 1H), 7.47-7.44 (m, 2H), 7.38-7.35 (m, 2H), 7.27-7.24 (m, 1H), 6.96-6.92 (s, 1H).

Los siguientes compuestos son preparados esencialmente por el método de la Preparación 220.

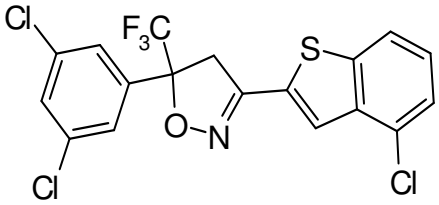
Prep. No.	Nombre químico	Estructura	Datos físicos
221	3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-1-tieno[2,3-c]piridin-2-il-but-2-en-1-ona		MS (m/z): 400 (M-1).
222	3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-1-(5-bromo-tieno[2,3-b]piridin-2-il)-but-2-en-1-ona		MS (m/z): 480 (M-1).
223	3-(3,5-Dicloro-fenil)-4,4,4-trifluoro-1-tieno[2,3-b]piridin-2-il-but-2-en-1-ona		MS (m/z): 400 (M-1).

Prep. No.	Nombre químico	Estructura	Datos físicos
224	1-(benzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluorobut-2-en-1-ona		MS (m/z): 399
225	1-(benzo[d]tiazol-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluorobut-2-en-1-ona		MS (m/z): 400
226	3-(3,5-diclorofenil)-4,4,4-trifluoro-1-(3-metilbenzo[b]tiofen-2-il)but-2-en-1-ona		MS (m/z): 413
227	3-(3,5-diclorofenil)-4,4,4-trifluoro-1-(5-metilbenzo[b]tiofen-2-il)but-2-en-1-ona		MS (m/z): 413

Prep. No.	Nombre químico	Estructura	Datos físicos
228	1-(5-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluorobut-2-en-1-ona		MS (m/z): 433

Ejemplo 229

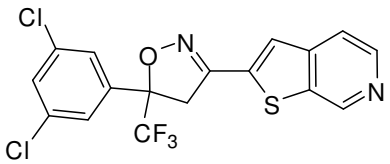
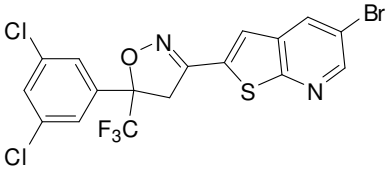
3-(4-clorobenzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol

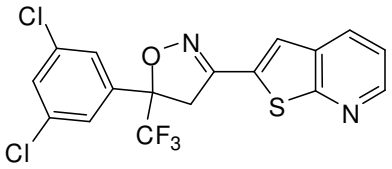
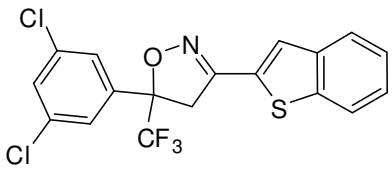


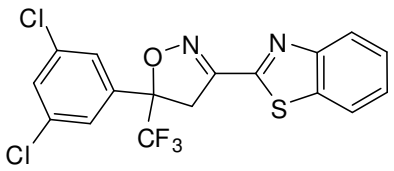
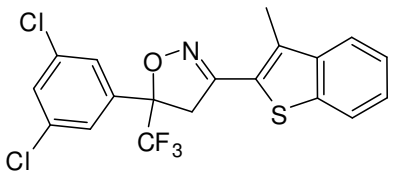
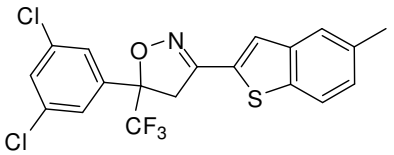
Se agitó una mezcla de 1-(4-clorobenzo[b]tiofen-2-il)-3-(3,5-diclorofenil)-4,4,4-trifluorobut-2-en-1-ona (1.05 g, cruda, 2.43 mmol), NaOH (389 mg, 9.72 mmol) y NH_2OH-HCl (335 mg, 4.8 mmol) en MeOH (8 mL) y agua (8 mL) a temperatura ambiente por 4 horas. Después de la eliminación del solvente bajo vacío, el residuo se diluyó con agua helada (20 mL). La mezcla acuosa se extrajo con EtOAc (15 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se

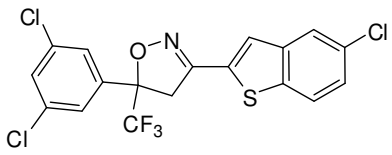
purificó por HPLC preparativa para proporcionar 3-(4-clorobenzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol como un sólido blanco (305 mg, 28.1 %). MS (m/z): 450 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δδ 7.74 (d, *J*=8.0, 1H), 7.64-7.60 (s, 1H), 7.57-7.53 (m, 2H), 7.47-7.43 (m, 1H), 7.40-7.32.

Los siguientes compuestos son preparados esencialmente por el método del Ejemplo 229.

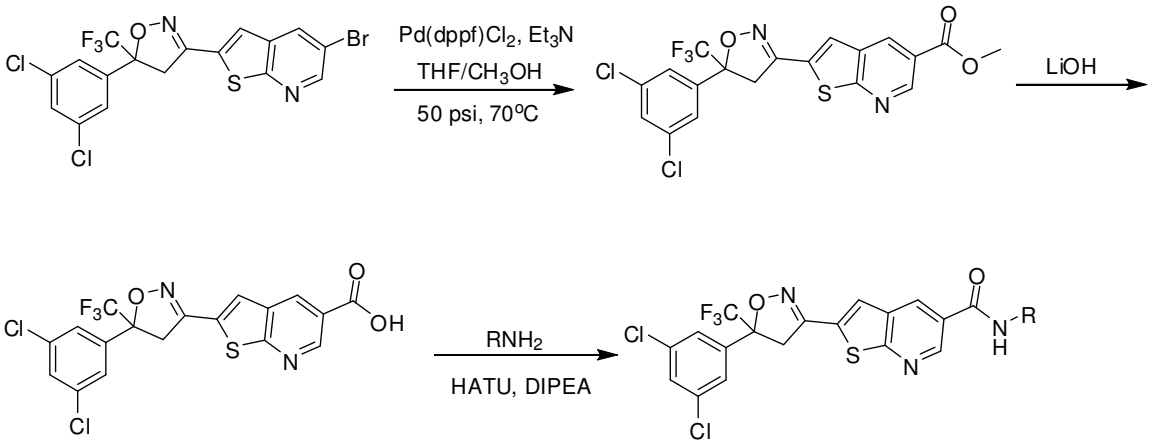
Ej. No.	Nombre químico	Estructura	Datos físicos
230	2-[5-(3,5-Dicloro-fenil)-5-trifluoro metil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-c]piridina		MS (m/z): 417 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.55-8.57 (d, *J* = 5.6, 1H), 7.68-7.69 (d, J_1 = 5.6, J_2 = 1.2, 1H), 7.51-7.52 (d, *J* = 1.2, 2H), 7.49 (S, 1H), 7.45-7.46 (t, *J* = 3.6, 1H), 4.17-4.21 (d, *J* = 16.8, 1H), 3.79-3.83 (d, *J* = 16.8, 1H).
231	5-Bromo-2-[5-(3,5-dicloro-fenil)-5-trifluoro metil-4,5-		MS (m/z): 497 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 8.65-8.66 (d, J = 1.6, 1H), 8.18-8.19 (d, J = 2.0, 1H), 7.51 (S,

Ej. No.	Nombre químico	Estructura	Datos físicos
	dihidro-isoxazol-3-il]-tieno[2,3-b]piridina		2H), 7.45-7.46 (d, J = 1.6, 1H), 7.32 (S, 1H), 4.13-4.17 (d, J = 16.8, 1H), 3.75-3.79 (d, J = 16.8, 1H).
232	2-[5-(3,5-Dicloro-fenil)-5-trifluoro metil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-b]piridina		MS (m/z): 417 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62-8.64 (d, J_1 = 4.4, J_2 = 1.6, 1H), 8.05-8.07 (d, J_1 = 8.0, J_2 = 1.6, 1H), 7.51-7.52 (d, J = 1.2, 2H), 7.44-7.45 (t, J = 3.6, 1H), 7.41 (s, 1H), 7.33-7.36 (m, 1H), 4.15-4.19 (d, J = 16.8, 1H), 3.77-3.81 (d, J = 16.8, 1H).
233	3-(benzo[b] tiofen-2-il)-5-(3,5-dicloro fenil)-5-(trifluoro metil)-4,5-dihidroisoxazol		MS (m/z): 416 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J=8.0, 1H), 7.82 (d, J=8.0, 1H), 7.55-7.50 (m, 2H), 7.48-7.34 (m, 4H), 4.20 (d, J=16.8, 1H), 3.80 (d, J=17.6, 1H).

Ej. No.	Nombre químico	Estructura	Datos físicos
234	3-(benzo[d]tiazol-2-il)-5-(3,5-dicloro fenil)-5-(trifluoro metil)-4,5-dihidroisoxazol		MS (m/z): 417 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.2, 1H), 7.93 (d, *J*=7.2, 1H), 7.58-7.47 (m, 5H), 4.37 (d, *J*=18.0, 1H), 4.00 (d, *J*=18.0, 1H)
235	5-(3,5-dicloro fenil)-3-(3-metilbenzo [b]tiofen-2-il)-5-(trifluoro metil)-4,5-dihidroisoxazol		MS (m/z): 430 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.78 (m, 2H), 7.53 (s, 2H), 7.53-7.43 (m, 3H), 4.17 (d, *J* = 16.8, 1H), 3.79 (d, *J* = 16.8, 1H), 2.67 (s, 3H).
236	5-(3,5-dicloro fenil)-3-(5-metilbenzo [b]tiofen-2-il)-5-(trifluoro metil)-4,5-dihidroisoxazol		MS (m/z): 430 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0, 1H), 7.57 (s, 1H), 7.53 (s, 2H), 7.43 (t, *J* = 3.2, 1H), 7.36 (d, *J* = 7.0, 1H), 7.24 (d, *J* = 7.0, 1H), 4.17 (d, *J* = 16.8, 1H), 3.78 (d, *J* = 16.8, 1H), 2.47 (s, 3H).

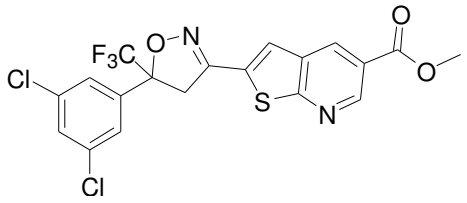
Ej. No.	Nombre químico	Estructura	Datos físicos
237	3-(5-clorobenzo[b]tiofen-2-il)-5-(3,5-dicloro fenil)-5-(trifluoro metil)-4,5-dihidroisoxazol		MS (m/z): 450 (M+1). 1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.75 (m, 2H), 7.51 (s, 2H), 7.45-7.44 (m, 1H), 7.40-7.38 (m, 2H), 4.18 (d, *J* = 16.8, 1H), 3.78 (d, *J* = 17.6, 1H).

Esquema de reacción E



Preparación 238

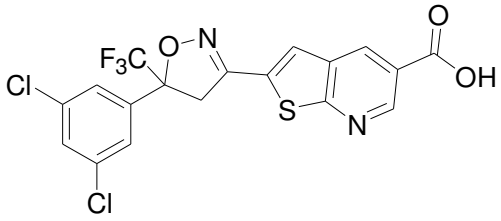
2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)tieno[2,3-b]piridina-5-carboxilato de metilo



Se agitó una mezcla de 5-bromo-2-[5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-*il*]-tieno[2,3-b]piridina (494 mg, 1 mmol), $Pd(dppf)Cl_2$ (100 mg) y trietil amina (1 mL) en THF anhidro (10 mL) y metanol (5 mL) bajo monóxido de carbono (50 psi) a 70 °C por 10h. Después de la eliminación del solvente bajo vacío, el residuo se purificó con cromatografía en gel de sílice (eluyendo con 10% de acetato de etilo en éter de petróleo) para proporcionar 2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)tieno[2,3-b]piridina-5-carboxilato de metilo como un sólido blanco (210 mg, 44.18%). MS (m/z): 475 (M+1).

Preparación 239

ácido 2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-*il*]-tieno[2,3-b]piridina-5-carboxílico

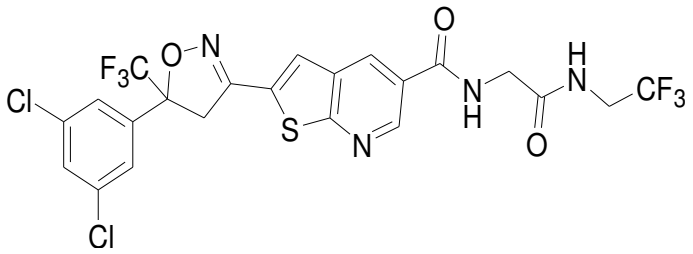


Se agregó una solución de $LiOH-H_2O$ (76 mg, 2 mmol) en agua (0.5 mL) a una solución de 2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)tieno[2,3-

b]piridina-5-carboxilato de metilo (237 mg, 0.5 mmol) en THF(3 mL). La mezcla se agitó a temperatura por 12 horas. Después de la adición de 10 mL de agua, la mezcla se acidificó con HCl concentrado a PH = 6~7. La mezcla resultante se extrajo con acetato de etilo (3 X 10 mL). Las capas orgánicas combinadas se lavaron con salmuera, secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío para proporcionar ácido 2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-*il*]-tieno[2,3-b]piridina-5-carboxílico como un sólido amarillo pálido (170 mg, 73.9%), el cual se usó en la siguiente etapa sin purificación adicional. MS (m/z): 461 (M+1).

Ejemplo 240

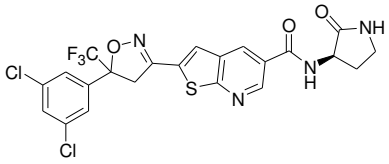
2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)tieno[2,3-b]piridina-5-carboxamida



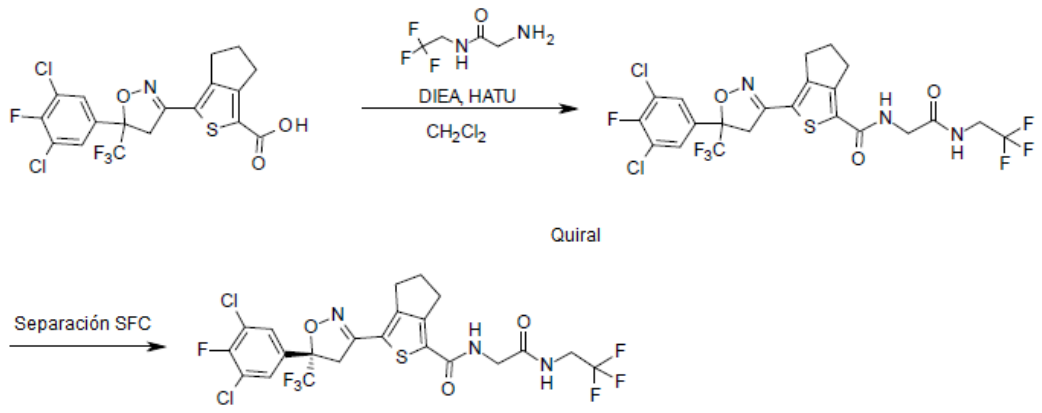
Se agitó una mezcla de 2-Amino-N-(2,2,2-trifluoro-etil)-acetamida (156 mg, 1 mmol), ácido 2-[5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-b]piridina-5-carboxílico (160 mg, 0.24 mmol), HATU (150 mg,

0.39 mmol) y DIPEA (0.2 mL) a temperatura ambiente por 10 horas. Después de la eliminación del solvente, la mezcla se purificó por HPLC preparativa para proporcionar 2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)tieno[2,3-b]piridina-5-carboxamida como un sólido blanco (50 mg, 34.78%). MS (m/z): 599 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.51 (s, 1H), 7.52 (s, 2H), 7.44-7.41 (m, 2H), 7.22 (s, 1H), 6.64 (s, 1H), 4.27 (d, *J* = 5.2, 2H), 4.17 (d, *J* = 16.8, 1H), 4.04-3.95 (m, 2H), 3.80 (d, *J* = 16.08, 1H).

El siguiente compuesto se preparó esencialmente por el método del Ejemplo 240.

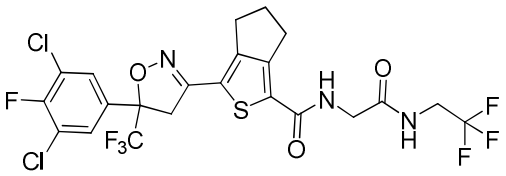
Ej. No.	Nombre químico	Estructura	Datos físicos
241	2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)tieno[2,3-b]piridina-5-carboxamida		MS (m/z): 543 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.49 (s, 1H), 7.54 (s, 2H), 7.44-7.40 (m, 2H), 7.15 (S, 1H), 5.89 (s, 1H), 4.60 (s, 1H), 4.18 (d, *J* = 16.8, 1H), 3.80 (d, *J* = 16.8, 1H), 3.51-3.48 (m, 2H), 3.00-2.93 (m, 1H), 2.14-2.08 (m, 1H)

Esquema de reacción F



Ejemplo 242

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida

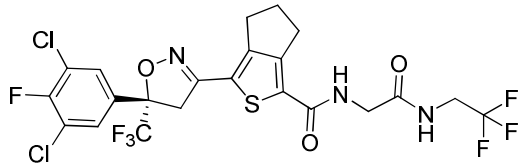


Se agitó una mezcla de ácido 3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (1.0 g, 2.14 mmol), N,N-diisopropiletilamina (827 mg, 6.41 mmol), clorhidrato de 2-amino-N-(2,2,2-trifluoroetil)acetamida (658 mg, 2.56 mmol) y HATU (1.2 g, 3.2 mmol) en CH_2Cl_2 (10 mL) a temperatura ambiente por 2 horas. La mezcla de reacción se diluyó con CH_2Cl_2 (50 mL) y se lavó con agua (10 mLx 3) y salmuera. Después la capa orgánica se secó sobre Na_2SO_4

anhidro y se concentró bajo vacío. El residuo se purificó por HPLC preparativa para proporcionar 3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida como un sólido blanco (1.1 g, 84.6 %). MS (m/z): 606.0 (M+1).

Ejemplo 243

(S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida



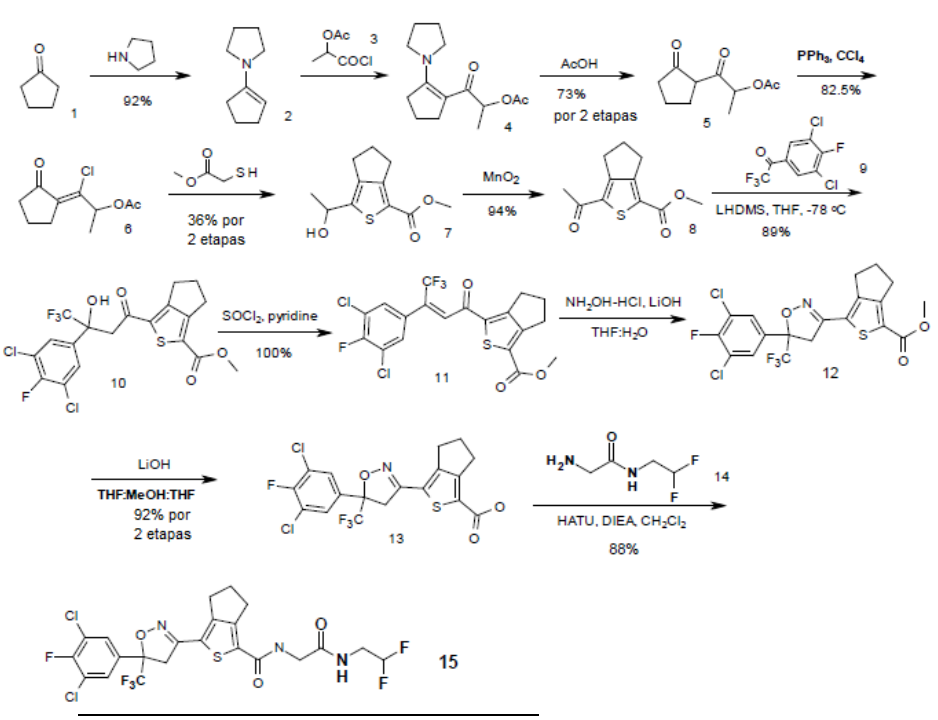
1 g de 3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida se separó por SFC para dar (S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida (400 mg, 80 % de rendimiento, 100% de ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J*=6.0, 2 H), 6.92 (t, *J*=6.4, 1 H), 6.76 (t, *J*=4.8, 1 H), 4.21 (d, *J*=4.8, 2 H),

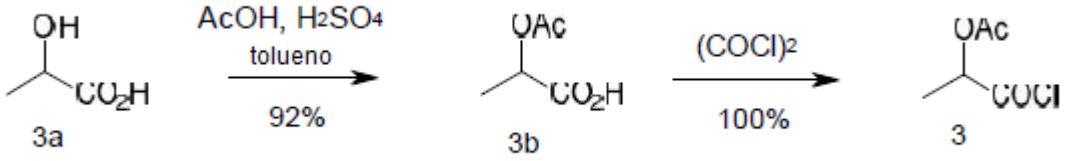
3.98 (m, 3 H), 3.61 (d, *J*=16.8, 1 H), 2.97 (t, *J*=7.6, 2 H), 2.89 (t, *J*=7.6, 2 H), 2.55 (m, 2 H). MS (m/z): 606.0 (M+1).

Condición de análisis SFC: Columna: Chiralcel AD-H 250×4.6mm I.D., 5um. Fase móvil: etanol en CO_2 de 5% a 40% durante 3 minutos. Velocidad de flujo: 2.35 mL/min. Longitud de onda: 220 nm. El isómero-S eluye a 1.4 minutos. Condición de separación SFC: Instrumento: Thar SFC 80; Columna: AD 250mm*20mm, 20um; Fase móvil: A: CO_2 Supercrítico, B: MeOH (0.05% NH_3 H_2O), A:B =45:55 a 80ml/min; Temp. de Columna: 38 ^{0}C; Presión de Boquilla: 100Bar; Temp. de Boquilla: 60 ^{0}C; Temp. de Evaporador: 20 ^{0}C; Compensador de Temp.: 25 ^{0}C; Longitud de onda: 220nm

Esquema de reacción G

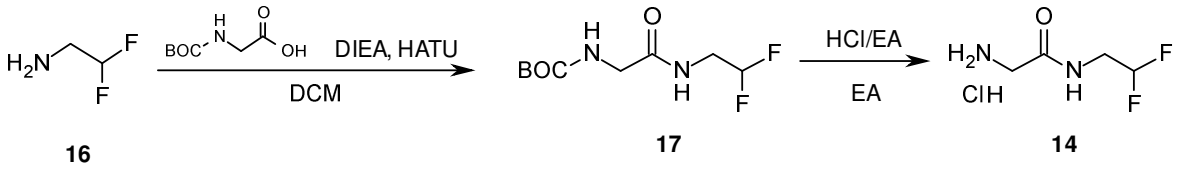


Preparación de acetato de 1-cloro-1-oxopropan-2-ilo (3)



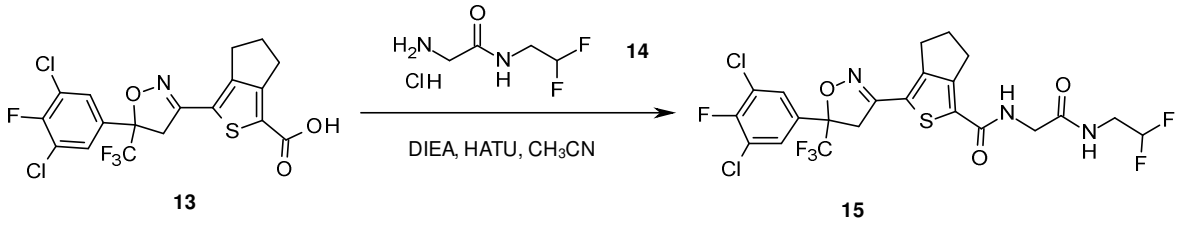
Esquema de reacción G(2)

Síntesis de clorhidrato de 2-amino-N-(2,2-difluoro-etil)acetamida



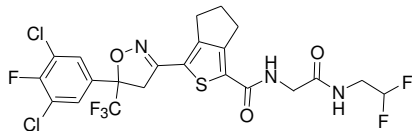
Esquema de reacción G(3)

Síntesis de [(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico

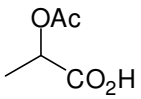


Ejemplo 244

[(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico

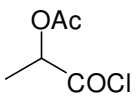


A) Síntesis de ácido 2-acetoxi-propiónico



Se sometió a reflujo una mezcla de ácido 2-hidroxi-propiónico (480 ml, 85% en agua) y ácido sulfúrico (2 mL) en acético ácido (2500 mL) y tolueno (300 mL) durante la noche. Después de la eliminación del solvente bajo vacío, el residuo se purificó por destilación para dar ácido 2-acetoxi-propiónico (550 g, 92%) como un aceite incoloro. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.27 (brs, 1H), 5.10 (m, 1H), 2.13 (s, 3H), 1.53 (d, *J*=7.2, 3H).

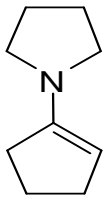
B) Síntesis de acetato de 1-cloro-1-oxopropan-2-il



Se agitó una mezcla de ácido 2-acetoxi-propiónico (550 g, 4.16 mol) en cloruro de oxalilo (500 mL) a temperatura ambiente durante la noche. Después de la

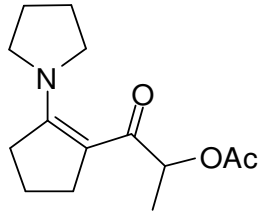
eliminación de cloruro de oxalilo bajo vacío, se obtuvo ~700g del producto crudo (rendimiento cuantitativo crudo), el cual se usó directamente en la siguiente etapa. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.16 (m, 1H), 2.13 (s, 3H), 1.58 (d, *J*=7.2, 3H).

C) Síntesis de 1-ciclopentenilpirrolidina



Se sometió a reflujo una mezcla de ciclopentanona (600 g, 7.14 mol), pirrolidina (550 g, 4.68 mol) y ácido toluen-4-sulfónico (5.0 g) en tolueno (3 L) por 4 horas. Después de la eliminación del solvente bajo vacío, el residuo se purificó por destilación cuidadosamente para dar 1-ciclopent-1-enil-pirrolidina como un aceite incoloro (898g, 6.55 mol, 91.8%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.04 (m, 1H), 3.06 (m, 4H), 2.39 (m, 4H), 1.85 (m, 6H).

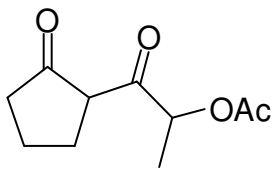
D) Síntesis de acetato de 1-oxo-1-(2-(pirrolidin-1-il)ciclopent-1-enil)propan-2-ilo



Se agregó por goteo una solución de acetato de 1-

cloro-1-oxopropan-2-ilo (600 g, 3.98 mol) en tolueno (1200 mL) a una solución de 1-ciclopent-1-enil-pirrolidina (546.7 g, 3.98 mol) y trietil amina (483.9 g, 4.78 mol) en tolueno (2400 mL). La mezcla se sometió a reflujo durante la noche. La mezcla se filtró y la filtración se concentró para dar acetato de 1-oxo-1-(2-(pirrolidin-1-il)ciclopent-1-enil)propan-2-ilo crudo (952 g), el cual se usó en la siguiente etapa sin purificación adicional. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27 (m, 1H), 3.56 (m, 2H), 3.16 (m, 2H), 2.83 (m, 1H), 2.58 (m, 3H), 2.10 (s, 3H), 1.93 (m, 2H), 1.82 (m, 4H), 1.36 (d, *J*=7.2, 3H).

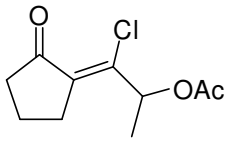
E) Síntesis de acetato de 1-oxo-1-(2-oxociclopentil)propan-2-ilo



Se agitó una mezcla de acetato de 1-oxo-1-(2-(pirrolidin-1-il)ciclopent-1-enil)propan-2-ilo (952.0 g), ácido acético (1500 mL) y agua (1500 mL) en tetrahidrofurano (3000 mL) a temperatura ambiente por 2 días. La mezcla se diluyó con agua (1200 mL) y diclorometano (1200 mL). La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 anhidro y concentró bajo vacío. El residuo se purificó por cromatografía en gel de sílice (eluyendo con 3% a 10% de

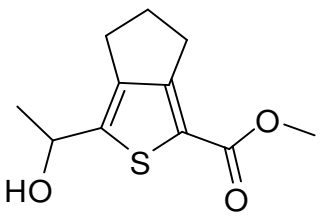
acetato de etilo en éter de petróleo) para dar acetato de 1-oxo-1-(2-oxociclopentil)propan-2-ilo como un aceite (573.4g, 2.89 mol, 72.6% por 2 etapas).

F) Síntesis de acetato de 1-cloro-1-(2-oxociclopentilidene)propan-2-ilo



Una mezcla de acetato de 1-oxo-1-(2-oxociclopentil)propan-2-ilo (8.0 g, 0.04 mol) y tributilfosfano (13.9 g, 0.069 mol) en CCl_4 (100 mL) a 60°C durante la noche. Después de la eliminación del solvente, el residuo se purificó por columna en gel de sílice (eluyendo con 1% a 2.5% de acetato de etilo en éter de petróleo) para dar una mezcla de acetato de 1-cloro-1-(2-oxociclopentilidene)propan-2-ilo y acetato de 1-(2-clorociclopent-1-enil)-1-oxopropan-2-ilo (5.47 g, 6:1 con base en HNMR) como un aceite amarillo.

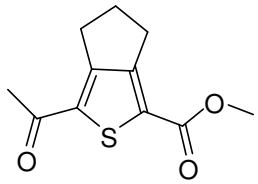
G) Síntesis de 3-(1-hidroxietil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxilato de metilo



Se agregó hidruro de sodio (60% en aceite mineral,

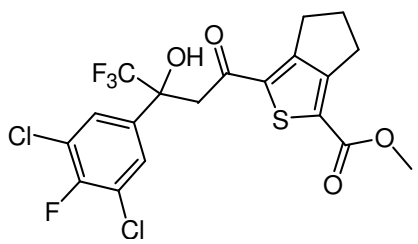
2.12 g, 0.053 mol) a una solución de éster metílico del ácido mercapto-acético (2.8 g, 0.026 mol) en tetrahidrofurano (100 mL) a -10 °C~0 °C y la mezcla se agitó a -10 °C~0 °C por 1 hora. Después se agregó una mezcla de acetato de 1-cloro-1-(2-oxociclopentilidene)propan-2-ilo y acetato de 1-(2-clorociclopent-1-enil)-1-oxopropan-2-ilo (5.47 g, 0.025 mol, 6:1) en tetrahidrofurano (15 mL) a 0 °C. Después de agitar a 0 °C durante la noche, la mezcla de reacción se diluyó con agua y extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron. El residuo y K_2CO_3 (6.9 g, 0.05 mol) en MeOH (20 mL) se calentó a 50 °C durante la noche. El solvente se eliminó. El residuo se purificó por cromatografía en gel de sílice (eluyendo con 2.5% a 10% de acetato de etilo en éter de petróleo) para dar éster metílico del ácido 3-(1-hidroxi-etil)-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico (3.2 g, 14.1 mmol, 35.6% por 2 etapas) como un aceite amarillo. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.03 (m, 1H), 3.83 (m, 3H), 2.88 (m, 2H), 2.66 (m, 2H), 2.38 (m, 2H), 2.12 (s, 1H), 1.54 (d, *J*=7.2, 3H).

H) Síntesis de 3-acetil-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxilato de metilo



Se sometió a reflujo una mezcla de éster metílico del ácido 3-(1-Hidroxi-etil)-5,6-dihidro-4H-ciclopenta[c] tiofen-1-carboxílico (3.2 g, 0.0141 mol) y dióxido de manganeso (10.8 g, 0.124 mol) en diclorometano por 2 horas. La solución de mezcla de reacción caliente se filtró y la filtración se concentró bajo vacío. El residuo se purificó por cromatografía en gel de sílice (eluyendo con 2% a 10% de acetato de etilo en éter de petróleo) para dar éster metílico del ácido 3-acetil-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico como un sólido blanco (3.0 g, 13.39 mmol, 94.5%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (s, 3H), 2.96 (m, 4H), 2.50 (s, 3H), 2.45 (m, 2H).

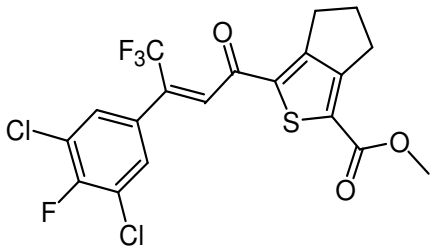
I) Síntesis de éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-3-hidroxi-butiril]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico



Se agregó una solución de LiHDMS (1M en THF, 75 mL, 75 mmol) a una suspensión de éster metílico del ácido 3-

acetil-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (14.0 g, 62.5 mmol) en THF seco (200 mL) a -78^{0}C bajo N_2. Después de agitar a temperatura ambiente por 1.5 h, se agregó 1-(3,5-dicloro-4-fluoro-fenil)-2,2,2-trifluoro-etanona (17.9 g, 68.7 mmol) en THF seco (100 mL) a la mezcla de reacción y la mezcla resultante se agitó a la misma temperatura por 2 horas adicionales. La reacción se apagó con solución acuosa saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc (100 mL×3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro y concentraron bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 15:1) para proporcionar éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-3-hidroxi-butiril]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico como un sólido anaranjado (27 g, 89.3%). MS (m/z): 486 (M+1).

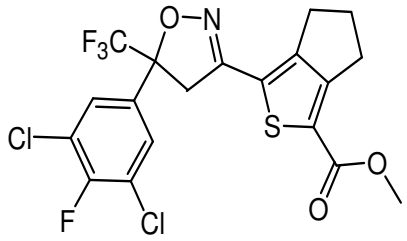
J) Síntesis de éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluorofenil)-4,4,4-trifluorobut-2-enoil]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico



Se agitó una mezcla de éster metílico del ácido 3-

[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-3-hidroxil-butiril]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (26 g, 53.7 mmol), $SOCl_2$ (12.7 g, 7.8 mL, 0.107 mmol) y piridina (42.3 g, 0.537 mmol) en DCM anhidro (300 mL) a temperatura ambiente por 3 horas. La mezcla se concentró bajo vacío. El residuo se purificó por cromatografía en gel de sílice (PE:EtOAc 12:1) para proporcionar éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-but-2-enoil]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico como un sólido amarillo pálido (25 g, 100 %). (m/z): 467 (M+1).

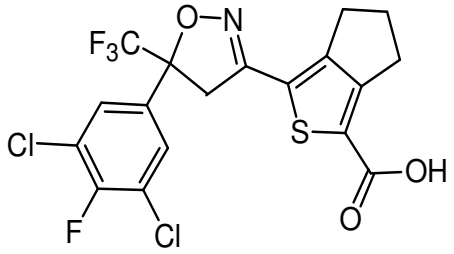
K) Síntesis de éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico



Se agitó una mezcla de éster metílico del ácido 3-[3-(3,5-Dicloro-4-fluoro-fenil)-4,4,4-trifluoro-but-2-enoil]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (25 g, 53.6 mmol), NaOH (8.6 g, 0.214 mol) y NH_2OH–HCl (7.4 g, 0.107 mmol) en agua (100 mL) y THF (200 mL) a temperatura ambiente durante la noche. Después de la eliminación del solvente bajo

vacío, la solución se diluyó con agua y extrajo con EtOAc (200 mL x 3). La capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 anhidro y concentró por vacío para proporcionar éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometilo-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico como un sólido blanco (26 g), el cual se usó directamente en la siguiente etapa sin purificación. MS (m/z): 483(M+1).

L) Síntesis de ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico

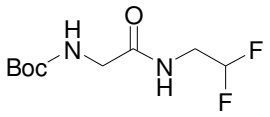


Se agitó una mezcla de éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (26 g, 54.1 mmol) y $LiOH-H_2O$ (4.54 g, 0.108 mmol) en agua (200 mL) y THF (400 mL) a 50 ^{0}C por 0.5 hora. Después de la eliminación del solvente orgánico bajo vacío, el residuo se diluyó con agua helada (100 mL). La mezcla acuosa se acidificó con HCl conc. a pH = 1, y la mezcla resultante se extrajo con EtOAc (200 mL×3). El residuo se purificó por

cromatografía en gel de sílice (EtOAc:MeOH 6:1) para proporcionar ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico como un sólido blanco (23 g, 91.7 % por 2 etapas). MS (m/z): 468 (M+1).

M) Síntesis de éster terc-butílico del ácido [(2,2-difluoro-etilcarbamoil)-metil]-carbámico

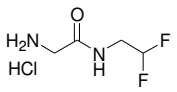
N)



A una solución del compuesto ácido *terc*-butoxicarbonilaminacético (19.6 g, 0.1 mol) en diclorometano (200 mL) se agregó *N*,*N*-diisopropiletilamina (13.2 g, 0.1 mol), 2,2-difluoroetilamina (10 g, 0.1 mol) y HATU (23 g, 0.17 mol), después de la adición la mezcla se agitó a temperatura ambiente por 1 hora. Después de ser detectada por TLC y LCMS, la mezcla de reacción se diluyó con diclorometano, después la solución se lavó con agua y salmuera, se secó sobre Na_2SO_4 anhidro, filtró, concentró y el residuo se secó en *vacío* para dar 30 g de producto crudo, el cual se usó directamente en la siguiente etapa.

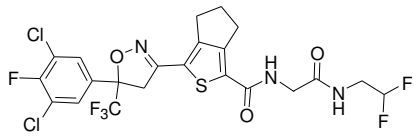
O) Síntesis de clorhidrato de 2-amino-N-(2,2-difluoro-etil)acetamida

P)



A una solución del compuesto éster terc-butílico del ácido [(2,2-difluoro-etilcarbamoil)-metil]-carbámico (30 g de producto crudo, 0.13 mol) en éster etílico del ácido acético (100 mL) se agregó 4 M HCl (100 mL, 4 mol/L en éster etílico del ácido acético) por goteo bajo un baño de agua helada. Después de la adición la mezcla de reacción se calentó a temperatura ambiente y agitó durante la noche. Lo precipitado se recolectó y secó en *vacío* para dar el producto deseado (20 g, 93 % por dos etapas) como un sólido blanco. 1H NMR (DMSO-d_6, 400 MHz): δ 8.91 (t, *J*=6.0, 1 H), 8.25 (brs, 3 H), 6.21-5.91 (m, 1 H), 3.64-3.53 (m, 4 H).

O) Síntesis de [(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico



A una solución del compuesto ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometilo-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-

carboxílico (3 g, 6.4 mmol) en acetonitrilo (30 mL) se agregó *N*,*N*-diisopropiletilamina (2.5 g, 19 mmol), clorhidrato de 2-amino-*N*-(2,2-difluoro-etil)-acetamida (1.34 g, 7.7 mmol) y HATU (3.7 g, 9.6 mmol), después de la adición la mezcla se agitó a temperatura ambiente por 1 hora. Después de ser detectada por TLC y LCMS, la mezcla de reacción se concentró y el residuo se purificó por cromatografía en columna para proporcionar el producto deseado (3 g, 88 %). MS (m/z): 588.1 (M+1).

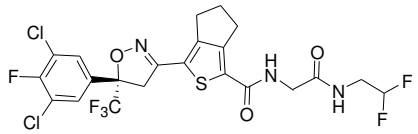
Esquema de reacción H

Separación SFC del Ejemplo 244 para proporcionar la Forma S



Ejemplo 245

[(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido (*S*)-3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico



3 g de [(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico se separó por Separación SFC para dar el producto deseado (1.4 g, 93 %).

1H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, *J*=6.0, 2 H), 6.64 (brs, 1 H), 6.40 (brs, 1 H), 6.03-5.73 (m, 1 H), 4.15 (d, *J*=5.2, 2 H), 4.01 (d, *J*=17.2, 1 H), 3.74-3.65 (m, 1 H), 3.62 (d, *J*=17.2, 1 H), 2.97 (t, *J*=7.6, 2 H), 2. 89 (t, *J*=7.6, 2 H), 2.56 (m, 2 H).

Las condiciones de SFC son como sigue:

Instrumento: Thar 350

Columna: AD 250mm*50mm, 10um

Fase móvil: A: CO_2 Supercrítico, B: EtOH, A:B =60:40 a 240ml/min

Temp. de Columna: 38 ^{0}C

Presión de Boquilla: 100Bar

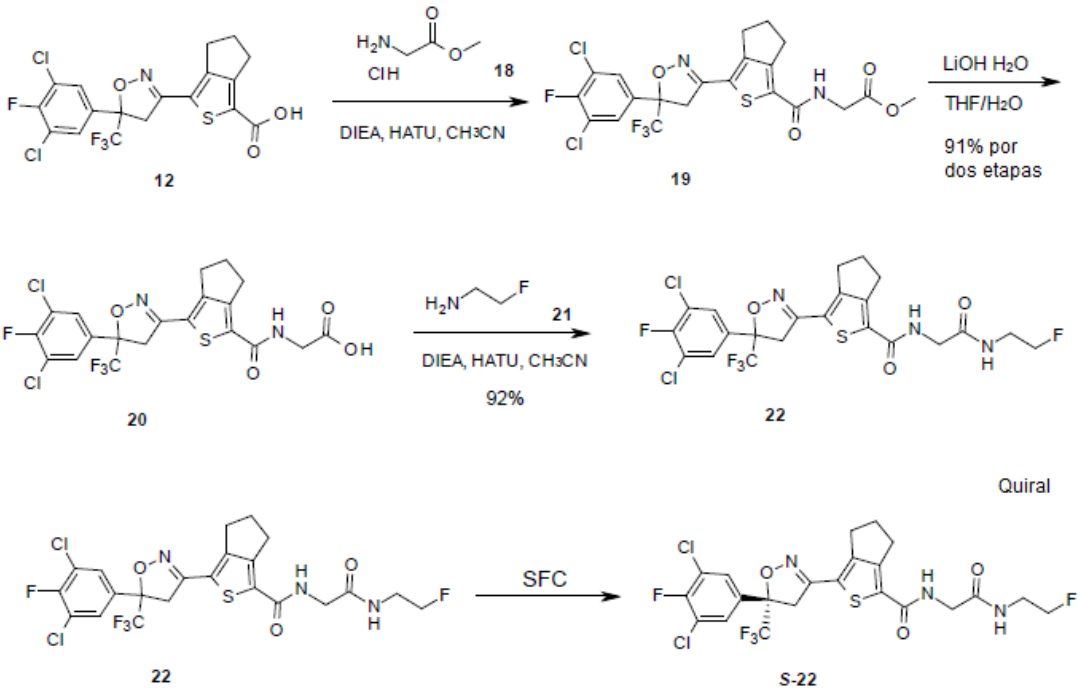
Temp. de Boquilla: 60 ^{0}C

Temp. de Evaporador: 20 ^{0}C

Compensador de Temp.: 25 ^{0}C

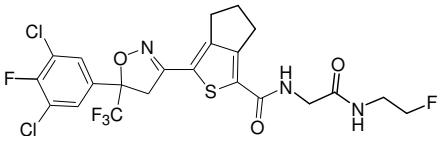
Longitud de onda: 220nm

Esquema de reacción I

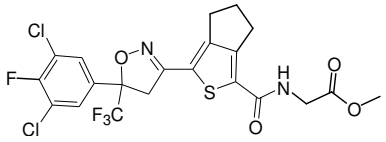


Ejemplo 246

ácido [(2-fluoro-etilcarbamoil)-metil]-amida 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico

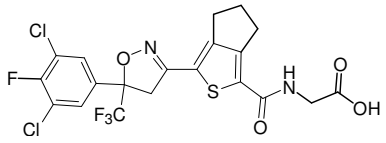


A) Síntesis de éster metílico del ácido ({3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carbonil}-amino)-acético



A una solución del compuesto ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (10.0 g, 21.4 mmol) en diclorometano (100 mL) se agregó trietilamina (6.49 g, 64.2 mmol), clorhidrato del éster metílico de glicina (3.2 g, 25.7 mmol) y HATU (12.2 g, 32.1 mmol), después de la adición la mezcla se agitó a temperatura ambiente por 1 hora. Después de ser detectada por TLC y LCMS, la mezcla de reacción se diluyó con diclorometano, después la solución se lavó con agua y salmuera, se secó sobre Na_2SO_4 anhidro, filtró, concentró y el residuo se secó en *vacío* para dar 11 g de producto crudo, el cual se usó directamente en la siguiente etapa.

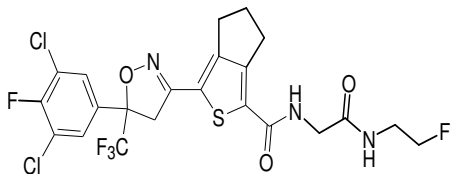
B) Síntesis de ácido ({3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carbonil}-amino)-acético



Se agitó una mezcla de éster metílico del ácido ({3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-

carbonil}-amino)-acético (11 g, 18.6 mmol) y LiOH-H_2O (1.56 g, 37.2 mmol) en THF (100 mL) y agua (50 mL) a temperatura ambiente durante la noche. Después de ser verificado con TLC, el solvente se eliminó bajo vacío, el residuo se diluyó con agua (50 mL). La mezcla acuosa se acidificó con 2M HCl a pH = 3, y la mezcla resultante se extrajo con EtOAc (100 mL×3), la capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 anhidro y concentró bajo vacío, el residuo se purificó por cromatografía en gel de sílice (PE : EtOAc 1:1) para proporcionar ácido ({3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carbonil}-amino)-acético como un sólido blanco (10.2 g, 90.7 % por dos etapas). MS (m/z): 525 (M+1).

C) Síntesis de [(2-fluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico

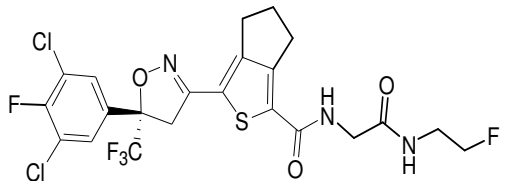


A una solución del compuesto ácido ({3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometilo-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carbonil}-amino)-acético (100 mg, 0.19 mmol) en acetonitrilo

(5 mL) se agregó *N*,*N*-diisopropiletilamina (49.3 mg, 0.38 mmol), 2-fluoro-etilamina (14.4 mg, 0.23 mmol) y HATU (108.8 mg, 0.29 mmol), después de terminada la mezcla se agitó a temperatura ambiente por 1 hora. Después de ser detectada por TLC y LCMS, la mezcla de reacción se concentró y el residuo se purificó por cromatografía en columna para proporcionar el producto deseado (100 mg, 92 %). MS (m/z): 570.1 (M+1).

Ejemplo 247

[(2-fluoro-etilcarbamoil)-metil]-amida del ácido (*S*)-3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico



100 mg de [(2-fluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico se separó por Separación SFC para dar el producto deseado (40 mg, 80 %).

1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J*=6.0, 2 H), 6.64 (brs, 1 H), 6.34 (brs, 1 H), 4.52 (t, *J*=4.8, 1 H), 4.40 (t, *J*=4.8, 1 H), 4.06 (d, *J*=4.4, 2 H), 3.94 (d, *J*=17.2, 1 H), 3.63-3.52 (m, 3 H), 2.90 (t, *J*=7.6, 2 H), 2. 81 (t, *J*=7.6, 2

H), 2.47 (m, 2 H).

Las condiciones de SFC son como sigue:

Instrumento: Thar SFC 80

Columna: AD 250mm*20mm, 20um

Fase móvil: A: O2 Supercrítico, B: EtOH (0.05%DEA) , A:B =45:55 a 80ml/min

Temp. de Columna: 38°C

Presión de Boquilla: 100Bar

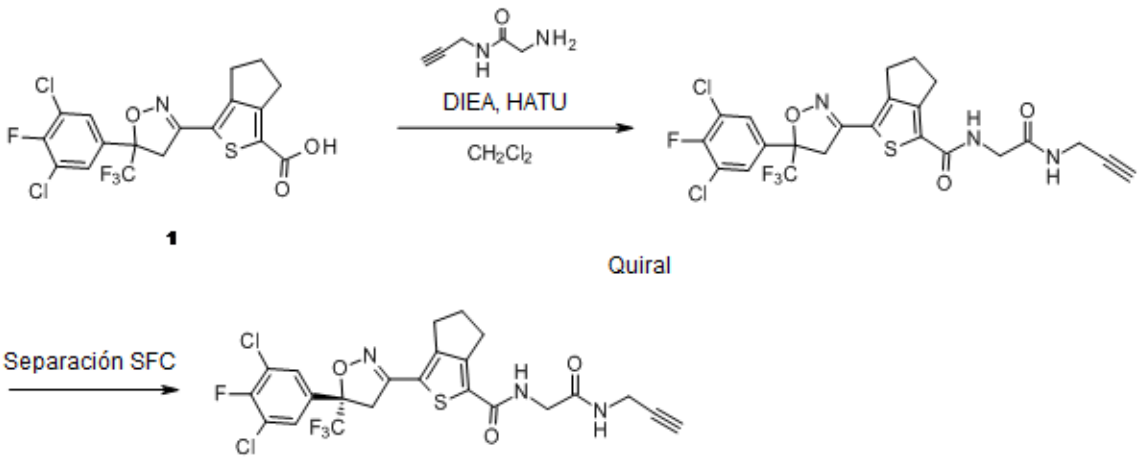
Temp. de Boquilla: 60°C

Temp. de Evaporador: 20°C

Compensador de Temp.: 25°C

Longitud de onda: 220nm

Esquema de reacción J

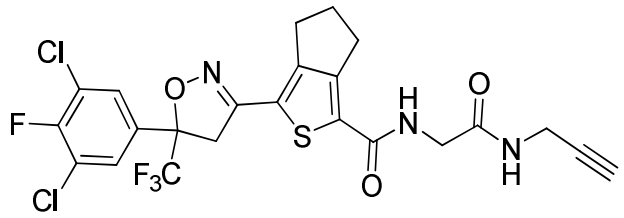


1

Quiral

Ejemplo 248

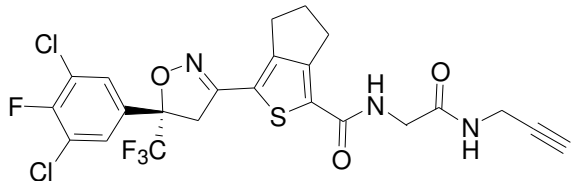
3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida



Se agitó una mezcla de ácido 3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico (0.8 g, 1.7 mmol), N,N-diisopropiletilamina (663 mg, 5.1 mmol), clorhidrato de 2-amino-N-(prop-2-in-1-il)acetamida (305 mg, 2.0 mmol) y HATU (974 g, 2.6 mmol) en CH_2Cl_2 (10 mL) a temperatura ambiente por 2 horas. La mezcla de reacción se diluyó con CH_2Cl_2 (40 mL) y se lavó con agua (10 mLx3) y salmuera. Después la capa orgánica se secó sobre Na_2SO_4 anhidro y concentró bajo vacío. El residuo se purificó por HPLC preparativa para proporcionar 3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida como un sólido blanco (850 mg, 88.4 %). MS (m/z): 584.1 (M+Na).

Ejemplo 249

(S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida



850 mg de 3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida se separó por SFC para dar (S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida (400 mg, 94 % de rendimiento, 99.7% de ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J*=6.0, 2 H), 6.76 (t, *J*=4.8, 1 H), 6.46 (t, *J*=4.8, 1 H), 4.14 (m, 4 H), 4.03 (d, *J*=17.2, 1 H), 3.64 (d, *J*=17.2, 1 H), 2.99 (t, *J*=7.6, 2 H), 2.90 (t, *J*=7.6, 2 H), 2.56 (m, 2 H), 2.29 (t, *J*=2.8, 1 H). MS (m/z): 584.1 (M+Na).

Condición de análisis SFC: Columna: Chiralcel AS-H 150×4.6mm I.D., 5um. Fase móvil: EtOH en CO_2 de 5% a 40% más 8 minutos. Velocidad de flujo: 3 mL/min. Longitud de onda:

220 nm. El isómero-S eluye a 4.00 minutos.

Instrumento: Thar SFC 200; Columna: AS 250mm*50mm,10um; Fase móvil: A: CO_2 Supercrítico, B: EtOH, A:B =45:55 a 200ml/min; Temp. de Columna: 38 ^{0}C; Presión de Boquilla: 100Bar; Temp. de Boquilla: 60 ^{0}C; Temp. de Evaporador: 20 ^{0}C; Compensador de Temp.: 25 ^{0}C; Longitud de onda: 220nm.

Ensayo de Helminto *in vitro*

Los compuestos pueden ser evaluados contra una o más etapas de vida de helmintos para medir la actividad antelmíntica. Los compuestos pueden ser evaluados en una concentración única seguidos por dilución serial con el fin de determinar la concentración efectiva mínima. Típicamente, los gusanos son expuestos a compuestos en una solución líquida por un periodo de tiempo predeterminado. La actividad se midió a través de una o más variables, las cuales pueden incluir un efecto en la motilidad del gusano (*por ejemplo,* movimiento contra no movimiento) o viabilidad (*por ejemplo,* vivo contra muerto).

Actividad *in vivo* Contra Nemátodos

Los compuestos pueden ser evaluados contra una o más etapas de vida de infestación de helmintos en un animal para medir la actividad antelmíntica *in vivo*. Los compuestos

pueden ser evaluados con una dosis única, administrados en una base de miligramo por kilo gramo de peso corporal, seguido por titulación de dosis con el fin de determinar la dosis de punto efectiva mínima. En un modelo antelmíntico de roedor, por ejemplo, gerbilos adultos de Mongolia (*Meriones unguiculates*) infectados con una o más especies de nemátodos Estrongilidos (por ejemplo, *Haemonchus contortus* y/o *Trichostrongilus colubriformis*) son dosificadas con compuestos, administrados vía alimentación forzada oral. Los gerbilos son necropsiados y el límite del gusano del tracto gastrointestinal es medido y comparado a gerbilos de control infectados, no tratados, para determinar el grado de actividad antelmíntico. Las pruebas similares pueden ser conducidas en especies superiores (*por ejemplo,* perros, gatos, ovejas, vacas), de este modo la carga del nemátodo en animales tratados se compara con la carga en animales infectados no tratados, para medir la potencia y duración de actividad antelmíntica.

Microensayo de Inmersión Lavar *in vitro* (LIM)

El microensayo de inmersión larval puede ser conducido como se describe en White, *et al.*, J. Med. Entomol. 41: 1034-1042 (2004). Brevemente, los artículos de ensayo experimental son formulados en dimetilsulfóxido (DMSO) para preparar una solución base a una concentración de 10mM.

Usando placas microtituladoras de 96 cavidades, una alícuota de la muestra de 10 mM es subsecuentemente diluida en una solución a base de agua que contiene 1% de etanol y 0.2% de Triton X-100, para obtener la concentración deseada (típicamente 0.3mM o inferior) del artículo de ensayo experimental en un volumen de 0.1ml (mínimo n = 3 replicados por compuesto o concentración). Aproximadamente 30-50 larvas de garrapata Lone star (*Amblyomma americanum*) son sumergidas en cada cavidad que contiene artículos de prueba experimental. Después de un periodo de inmersión de 30 minutos, las larvas son removidas con una punta de pipeta de agujero amplio en 0.05ml de fluido, dispensadas en una bolsa de biopsia de tejido de papel comercial la cual es sellada en la parte superior con un sujetador de diálisis de plástico, invertida y dejada secar al aire por 60 minutos. Las bolsas que contienen larvas son después incubadas a aproximadamente 27°C y >90% de humedad relativa. Después de 24 horas, las bolsas son abiertas, las larvas vivas y muertas son contadas y el porcentaje de mortalidad larval se calcula como sigue: % de Eficacia = (# de larvas muertas)/(# de larvas totales) X 100.

Los siguientes Ejemplos presentan eficacia, y en un nivel de ≥ 80% de eficacia cuando se prueban en este ensayo a 300 micromolares: 32, 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, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87b, 94, 95, 96, 230, 231, 232, 233, 236, 237, 240, 241, 243, 244, 245, 246, 247, y 249.

Prueba de Acaricida en Roedores *in vivo* (RAT)

La evaluación de artículos de prueba experimentales puede ser conducida usando una versión modificada del ensayo como se describe en Gutierrez *et al*., J. Med. Entomol. 43(3): 526–532(2006). El ensayo puede ser modificado usando una especie de garrapata diferente (la referencia describe garrapatas de *Amblyomma americanum*) tales como garrapatas *Dermacentor variabilis*. Además, la referencia describe usar administración tópica, pero puede ser usada la administración oral. Brevemente, los artículos de prueba experimentales son formulados en una solución de polietilen glicol–300, propilen glicol y agua a la concentración deseada, típicamente 1 – 25 mg/ml, dependiendo de la solubilidad y dosis de punto deseado. Las unidades contenedoras de garrapata (comprendidas de un chupón para beber, parte superior de tapa roscada ventilada y arandela de goma reforzada) son unidas al dorso de ratas adultas Sprague–Dawley. Después de la unión de las unidades contenedoras, aproximadamente 10 garrapatas de perro Americano de etapa ninfal no alimentadas (*Dermacentor variabilis*) son colocadas dentro de cada unidad contenedora.

Aproximadamente 24 horas después de la infestación, las formulaciones del artículo de prueba son administradas a las ratas vía alimentación oral forzada. Las ratas de control negativo reciben polietilen glicol-300, propilen glicol y agua sola. Dependiendo de la disponibilidad del compuesto, un mínimo de tres (3) y un máximo de cinco (5) ratas son utilizadas por grupo de tratamiento. Cuarenta y ocho (48) horas post-tratamiento, las unidades contenedoras son removidas y las garrapatas vivas y muertas son contadas. Los conteos de garrapatas vivas son transformados usando la transformación de logaritmo natural más uno (conteo Ln + 1); la adición de uno a cada conteo sirve para ajustar los conteos que fueron cero. Los conteos de garrapatas del grupo de media geométrica (GM) se obtuvieron vía transformación posterior de los conteos transformados de la media del grupo y una substracción. El grupo de control no tratado es usado para comparación con los grupos que reciben artículos de prueba experimental para el cálculo de porcentaje de eficacia (% de reducción en conteos de garrapatas vivas). La eficacia de los tratamientos se calcula comparando el número de media geométrica (GM) de garrapatas vivas observado en ratas tratadas con el número GM de garrapatas vivas contadas en las ratas de control negativo, usando la siguiente fórmula:

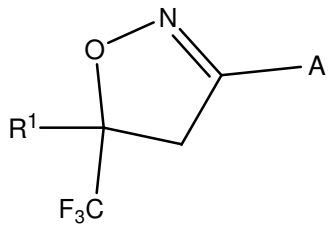
$$\% \text{ de Eficacia} = \frac{(\text{GM \# de control de garrapatas vivas} - \text{GM \# garrapatas vivas tratadas})}{\text{GM \# control de garrapatas vivas}} \times 100$$

Los siguientes Ejemplos presentan ≥ 50% de eficacia cuando se prueban en este ensayo a una dosis de no más de 25 mpk: 32, 36, 38, 39, 41, 42, 43, 45, 46, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 87b, 95, 96, 234, 235, 240, 241, 243, 244, 245, 246, 247, y 249.

La actividad en los ensayos anteriores demuestra que los compuestos de la invención son útiles para controlar las infestaciones de ecto o endoparásitos.

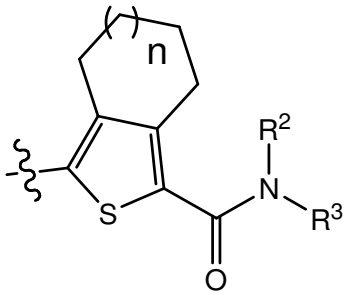
Las siguientes son modalidades de la invención y son no limitantes.

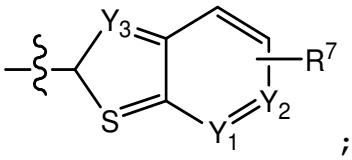
1. Un compuesto, o una sal del mismo, de fórmula I



I

en donde A es



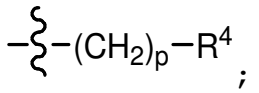
o


;

n es 0 o 1;

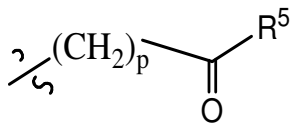
R^1 es tienilo o fenilo, tal tienilo o fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo;

R^2 es en cada caso independientemente hidrógeno, alquilo C_1–C_5, cicloalquilo C_3–C_6, o haloalquilo C_1–C_5;

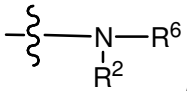
R^3 es 

;

p es en cada caso independientemente 0 o 1;

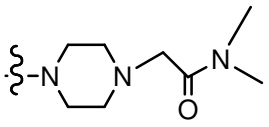
R^4 es alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, cicloalquilo C_3–C_6 opcionalmente sustituido con hidroxi, halo, o alquilo C_1–C_5: Cicloheteroalquilo C_3–C_5 opcionalmente sustituido con alquilo C_1–C_5, cicloalquilo C_3–C_6, o haloalquilo C_1–C_5: fenilo, tienilo, piridinilo, o 

, en donde uno de los carbonos en tales cicloalquilos, independientemente, o cicloheteroalquilo puede formar un grupo carbonilo, y en donde tal fenilo, tienilo, o piridinilo es opcionalmente sustituido con un grupo halo o carbamoilo;

R^5 es hidroxi, –O–(alquilo C_1–C_5), o  ;

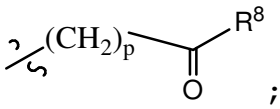
R^6 es hidrógeno, alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, o alquinilo C_2–C_5;

o R^2 y R^3 se combinan para formar, con el nitrógeno al cual están unidos,

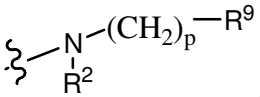
 ;

Y_1, Y_2, y Y_3 son carbono o nitrógeno con a lo sumo solamente uno de Y_1, Y_2, y Y_3 siendo nitrógeno, y cuando Y_1, Y_2, o Y_3 es un carbono, cada uno puede ser sustituido por alquilo C_1–C_5;

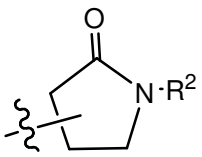
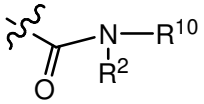
R^7 es hidrógeno, halo, alquilo C_1–C_5, o

 ;

R^8 es hidroxi, –O–(alquilo C_1–C_5), o

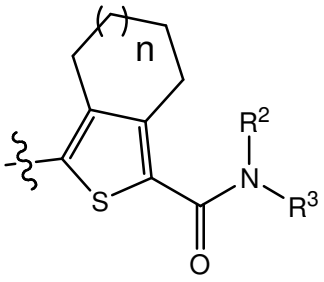
 ;

R^9 es alquilo C_1–C_5,

 o  ; y

R^{10} es hidrógeno, alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, o alquinilo C_2–C_5.

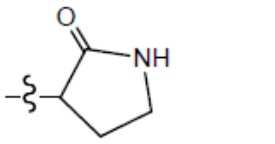
2. Un compuesto de la cláusula 1, en donde A es

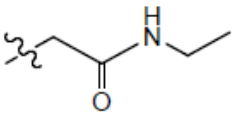


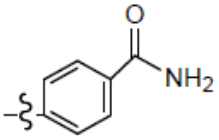
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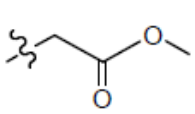
3. Un compuesto de conformidad con cualquiera de la cláusulas 1-2, en donde R^2 es hidrógeno y n es 1.

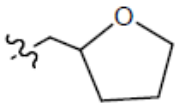
4. Un compuesto of de conformidad con cualquiera de la cláusulas 1-3, en donde R^3 es

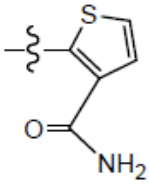


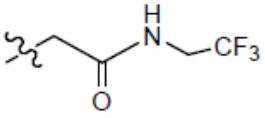


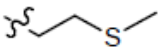




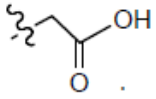




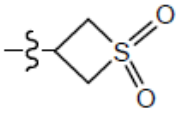


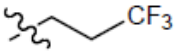


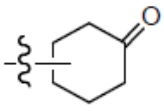
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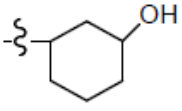


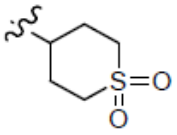
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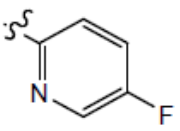


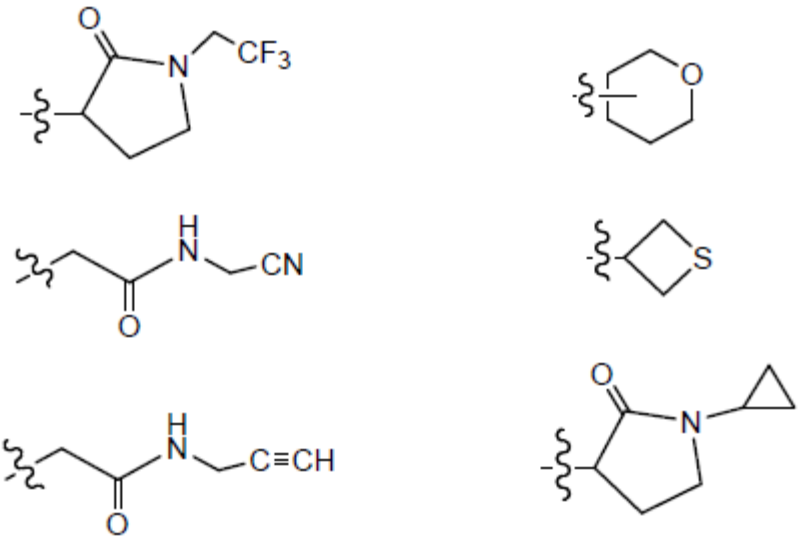












5. Un compuesto de conformidad con cualquiera de la cláusulas 1 a 4, o sal del mismo, que es

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N,N-Dimetil-2-(4-{3-[5-(3,4,5-tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-piperazin-1-il)-acetamida;

éster metílico del ácido ({3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético;

éster metílico del ácido ({3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

(1,1-dioxo-tietan-3-il)-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3-oxociclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(1,1-dioxo-hexahidro-1l6-tiopiran-4-il)-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

[2-oxo-1-(2,2,2-trifluoro-etil)-pirrolidin-3-il]-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-

dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-((R)-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-((R)-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-(etilamino)-2-oxoetil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((tetrahidrofuran-2-il)metil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-(metiltio)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3,3,3-trifluoropropil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3-hidroxiciclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(5-fluoropiridin-2-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tietan-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-4-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-

triclorotiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(1,1-dioxo-hexahidro-tiopiran-4-il)-amida del ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(tetrahidro-2H-piran-4-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(1,1-dioxo-tietan-3-il)-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

(1,1-dioxo-hexahidro-tiopiran-4-il)-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

3-(5-(3,5-dicloro-4-fluorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(4-oxociclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-4-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(4-oxociclohexil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-((R)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-((S)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(4-carbamoilfenil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(3-carbamoil-tiofen-2-il)-amida del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 2-(3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamido)acético;

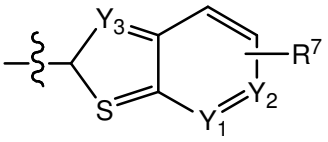
ácido ({3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida; o

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorotiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida.

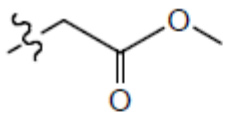
6. Un compuesto de la cláusula 1 en donde A es

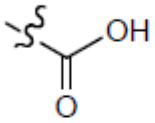


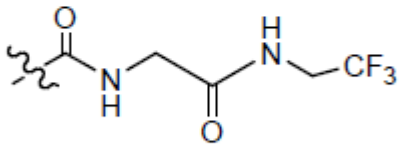
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7. Un compuesto de la cláusula 1 o 6, en donde Y_1 es nitrógeno.

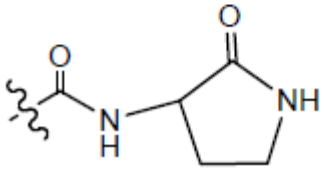
8. Un compuesto de conformidad con cualquiera de la cláusulas 1, 6, o 7, en donde R^7 es







o



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9. Un compuesto de conformidad con cualquiera de la cláusulas 6-8, o sal del mismo, siendo

3-(4-clorobenzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-c]piridina;

5-Bromo-2-[5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-b]piridina;

2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-b]piridina;

3-(benzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(benzo[d]tiazol-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-diclorofenil)-3-(3-metilbenzo[b]tiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-diclorofenil)-3-(5-metilbenzo[b]tiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(5-clorobenzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)tieno[2,3-b]piridina-5-carboxilato de metilo;

ácido 2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-*il*]-tieno[2,3-b]piridina-5-carboxílico;

2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)tieno[2,3-b]piridina-5-carboxamida; o

2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)tieno[2,3-

b]piridina-5-carboxamida.

10. Un compuesto, o sal del mismo, que es

(S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

[(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico;

[(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido (*S*)-3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico;

[(2-fluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

[(2-fluoro-etilcarbamoil)-metil]-amida del ácido (*S*)-3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-

carboxamida; o

(S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida.

11. Una formulación que comprende un compuesto o sal de cualquiera de la cláusulas 1-10, y uno o más portadores aceptables.

12. La formulación de la cláusula 11, en donde además comprende al menos un ingrediente activo adicional.

13. La formulación de la cláusula 11 o cláusula 12, en donde es una formulación farmacéutica humana.

14. La formulación de la cláusula 11 o cláusula 12, en donde es una formulación farmacéutica veterinaria.

15. Un método para controlar una infestación de parásitos en o sobre un animal en necesidad del mismo que comprende administrar una cantidad efectiva de un compuesto o sal de cualquiera de la cláusulas 1-10, a tal animal.

16. El método de la cláusula 15, en donde al menos otro ingrediente activo es administrado a tal animal.

17. El método de la cláusula 15 o cláusula 16, en donde tal animal es un humano.

18. El método de la cláusula 15 o cláusula 16, en donde tal animal es un animal de compañía.

19. El método de la cláusula 17 o cláusula 18, en

donde tal animal de compañía es un perro o gato.

20. El método de conformidad con cualquiera de la cláusulas 15-19, en donde tal parásito es una garrapata.

21. El método de la cláusula 15, en donde tal animal es un animal de ganado.

22. Un método para prevenir o tratar enfermedades transmitidas a través de parásitos que comprende administrar una cantidad efectiva de un compuesto de cualquiera de la cláusulas 1-10, a un animal en necesidad del mismo.

23. El método de la cláusula 22, en donde al menos otro ingrediente activo es administrado a tal animal.

24. El método de la cláusula 22 o cláusula 23, en donde tal animal es un humano.

25. El método de la cláusula 22, en donde tal animal es un animal de compañía.

26. El método de la cláusula 25, en donde tal animal de compañía es un perro o gato.

27. El método de conformidad con cualquiera de la cláusulas 22-26, en donde tal parásito es una garrapata.

28. El método de la cláusula 22 o cláusula 23, en donde tal animal es un animal de ganado.

29. Un método para controlar parásitos, caracterizado porque un compuesto de cualquiera de las cláusulas 1-10, se deja actuar en las plagas o su hábitat, o ambos.

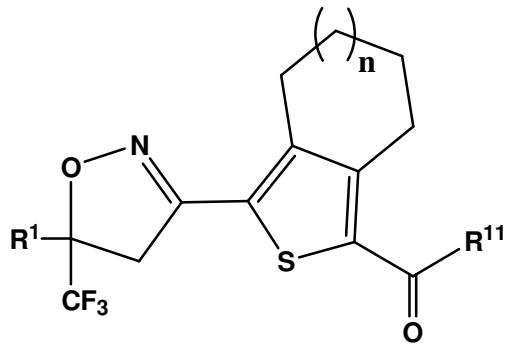
30. El método de la cláusula 29, en donde el compuesto es colocado en una planta o un animal.

31. Uso de compuestos o sales de los mismos de cualquiera de la cláusulas 1–10, para controlar parásitos.

32. Un compuesto o sal de conformidad con cualquiera de la cláusulas 1–10, para uso en terapia.

33. Un compuesto o sal de conformidad con cualquiera de la cláusulas 1–10, para uso en el control de una infestación de ectoparásitos.

34. Un compuesto, o sal del mismo, de fórmula II



II

en donde n es 0 o 1;

R^1 es tienilo o fenilo, tal tienilo o fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo; y

R^{11} es hidroxi, –O–(alquilo C_1–C_4), o un átomo de halo.

35. El compuesto de 34, en donde R^1 es fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo.

36. El compuesto de conformidad con las cláusulas 34 o 35, en donde R^{11} es hidroxi.

37. El compuesto de conformidad con cualquiera de la cláusulas 34-36, en donde es

éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

cloruro de 3-(5-(3,5-diclorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carbonilo; o

cloruro de 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonilo.

38. Un compuesto de conformidad con la cláusula 34, en donde es ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico.

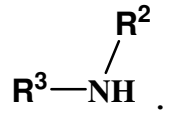
39. Un compuesto de conformidad con la cláusula 34 en donde es ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico.

40. Un compuesto de conformidad con la cláusula 34 en donde es ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico.

41. Un compuesto de conformidad con la cláusula 34 en donde es ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico.

42. Un proceso para preparar un compuesto de conformidad con las cláusulas 1-5 o 10, que comprende modificar sintéticamente un compuesto de conformidad con cualquiera de las cláusulas 34-41.

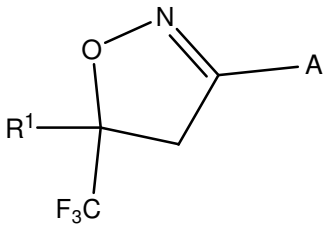
43. El proceso de la cláusula 42, en donde un compuesto de conformidad con cualquiera de la cláusulas 34-41 se hace reaccionar con un compuesto de la fórmula



REIVINDICACIONES

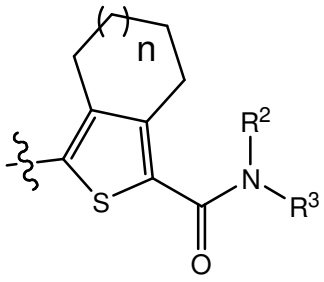
Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes.

1. Un compuesto, o una sal del mismo, caracterizado porque es de fórmula I

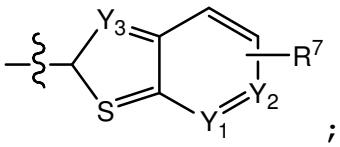


I

en donde A es



o



;

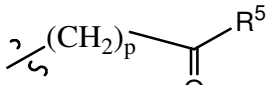
n es 0 o 1;

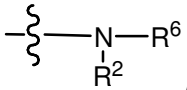
R^1 es tienilo o fenilo, tal tienilo o fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo;

R^2 es en cada caso independientemente hidrógeno, alquilo C_1–C_5, cicloalquilo C_3–C_6, o haloalquilo C_1–C_5;

R^3 es $-\!\!\!\sim\!\!\!-(CH_2)_p-R^4$;

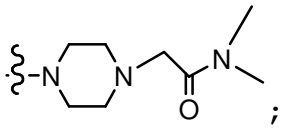
p es en cada caso independientemente 0 o 1;

R^4 es alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, cicloalquilo C_3–C_6 opcionalmente sustituido con hidroxi, halo, o alquilo C_1–C_5: Cicloheteroalquilo C_3–C_5 opcionalmente sustituido con alquilo C_1–C_5, cicloalquilo C_3–C_6, o haloalquilo C_1–C_5: fenilo, tienilo, piridinilo, o  , en donde uno de los carbonos en tales cicloalquilos, independientemente, o cicloheteroalquilo puede formar un grupo carbonilo, y en donde tal fenilo, tienilo, o piridinilo es opcionalmente sustituido con un grupo halo o carbamoilo;

R^5 es hidroxi, –O–(alquilo C_1–C_5), o  ;

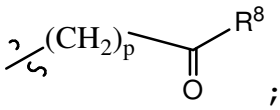
R^6 es hidrógeno, alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, o alquinilo C_2–C_5;

o R^2 y R^3 se combinan para formar, con el nitrógeno al cual están unidos,

 ;

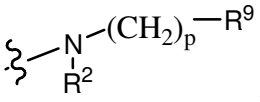
Y_1, Y_2, y Y_3 son carbono o nitrógeno con a lo sumo solamente uno de Y_1, Y_2, y Y_3 siendo nitrógeno, y cuando Y_1, Y_2, o Y_3 es un carbono, cada uno puede ser sustituido por alquilo C_1–C_5;

R^7 es hidrógeno, halo, alquilo C_1–C_5, o



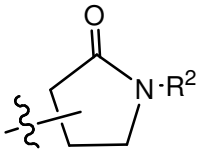
;

R^8 es hidroxi, –O–(alquilo C_1–C_5), o

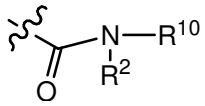


;

R^9 es alquilo C_1–C_5,



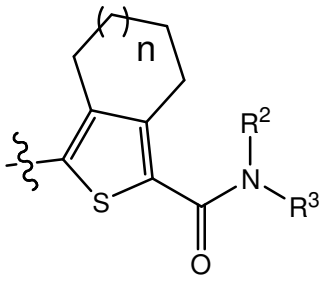
o



; y

R^{10} es hidrógeno, alquilo C_1–C_5, haloalquilo C_1–C_5, cianoalquilo C_1–C_5, alquiltio C_1–C_5, o alquinilo C_2–C_5.

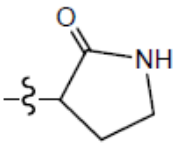
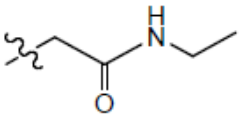
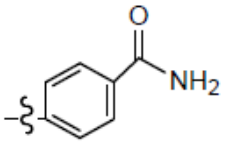
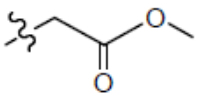
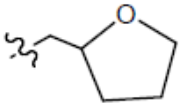
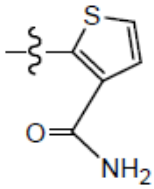
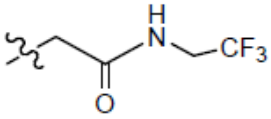
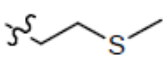
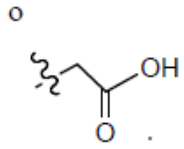
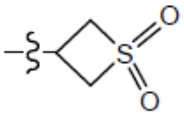
2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque A es

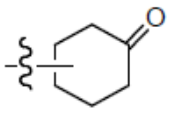
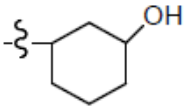
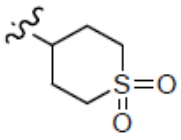
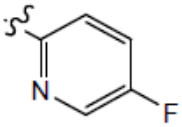
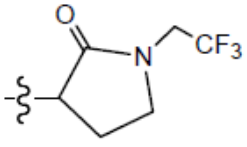
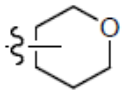
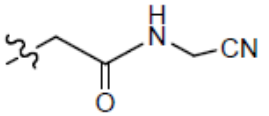
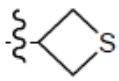
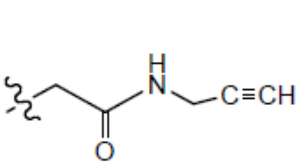
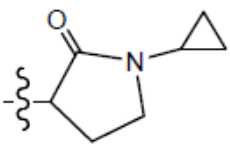


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3. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R^2 es hidrógeno y n es 1.

4. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R^3 es

.

5. Un compuesto de conformidad con la reivindicación 1, o sal del mismo, caracterizado porque es

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N,N-Dimetil-2-(4-{3-[5-(3,4,5-tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-piperazin-1-il)-acetamida;

éster metílico del ácido ({3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético;

éster metílico del ácido ({3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

(1,1-dioxo-tietan-3-il)-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3-oxociclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(1,1-dioxo-hexahidro-1l6-tiopiran-4-il)-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

[2-oxo-1-(2,2,2-trifluoro-etil)-pirrolidin-3-il]-amida del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-((R)-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-

4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-((R)-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-

5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-

trifluoroetil)pirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-(etilamino)-2-oxoetil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((tetrahidrofuran-2-il)metil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-(metiltio)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3,3,3-trifluoropropil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(3-hidroxiciclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(5-fluoropiridin-2-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tietan-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-piran-4-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(2-oxo-2-(prop-2-inilamino)etil)-3-(5-(3,4,5-triclorotiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(1,1-dioxo-hexahidro-tiopiran-4-il)-amida del ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-

carboxamida;

N-(tetrahidro-2H-piran-4-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(1,1-dioxo-tietan-3-il)-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

(1,1-dioxo-hexahidro-tiopiran-4-il)-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(4-oxociclohexil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(tetrahidro-2H-

piran-4-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(1-ciclopropil-2-oxopirrolidin-3-il)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(4-oxociclohexil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-1-(2,2,2-trifluoroetil)pirrolidin-3-il)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

3-((R)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-((S)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

N-(4-carbamoilfenil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

(3-carbamoil-tiofen-2-il)-amida del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 2-(3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamido)acético;

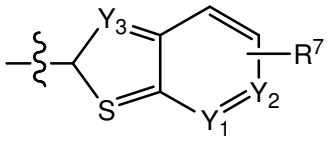
ácido ({3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonil}-amino)-acético;

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida;

3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida; o

N-(2-(cianometilamino)-2-oxoetil)-3-(5-(3,4,5-triclorotiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carboxamida.

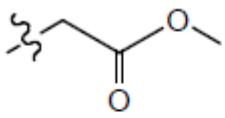
6. Un compuesto de conformidad con la reivindicación 1, caracterizado porque A es

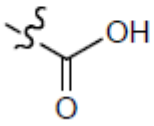


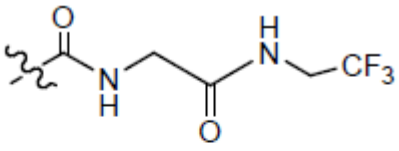
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7. Un compuesto de conformidad con la reivindicación 6, caracterizado porque Y_1 es nitrógeno.

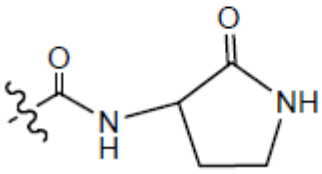
8. Un compuesto de conformidad con la reivindicación 6, caracterizado porque R^7 es







o



9. Un compuesto de conformidad con la reivindicación 6, o sal del mismo, caracterizado porque es

3-(4-clorobenzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-c]piridina;

5-Bromo-2-[5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-b]piridina;

2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-tieno[2,3-b]piridina;

3-(benzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(benzo[d]tiazol-2-il)-5-(3,5-diclorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-diclorofenil)-3-(3-metilbenzo[b]tiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-diclorofenil)-3-(5-metilbenzo[b]tiofen-2-il)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(5-clorobenzo[b]tiofen-2-il)-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)tieno[2,3-b]piridina-5-carboxilato de metilo;

ácido 2-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-*il*]-tieno[2,3-b]piridina-5-carboxílico;

2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)tieno[2,3-b]piridina-5-carboxamida; o

2-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-((R)-2-oxopirrolidin-3-il)tieno[2,3-b]piridina-5-carboxamida.

11. Un compuesto, o sal del mismo, caracterizado porque es

(S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(2,2,2-trifluoroetilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida;

[(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico;

[(2,2-difluoro-etilcarbamoil)-metil]-amida del ácido (*S*)-3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4*H*-ciclopenta[*c*]tiofen-1-carboxílico;

[(2-fluoro-etilcarbamoil)-metil]-amida del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

[(2-fluoro-etilcarbamoil)-metil]-amida del ácido (*S*)-3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida; o

(S)-3-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-N-(2-oxo-2-(prop-2-inilamino)etil)-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxamida.

11. Una formulación caracterizada porque comprende

un compuesto o sal de conformidad con la reivindicación 1 y uno o más portadores aceptables.

12. La formulación de conformidad con la reivindicación 11, caracterizada porque además comprende al menos un ingrediente activo adicional.

13. La formulación de conformidad con la reivindicación 11, caracterizada porque es una formulación farmacéutica humana.

14. La formulación de conformidad con la reivindicación 11, caracterizada porque es una formulación farmacéutica veterinaria.

15. Un método para controlar una infestación de parásitos en o sobre un animal en necesidad del mismo, caracterizado porque comprende administrar una cantidad efectiva de un compuesto o sal de conformidad con la reivindicación 1 a tal animal.

16. El método de conformidad con la reivindicación 15, caracterizado porque al menos otro ingrediente activo es administrado a tal animal.

17. El método de conformidad con la reivindicación 15, caracterizado porque tal animal es un humano.

18. El método de conformidad con la reivindicación 15, caracterizado porque tal animal es un animal de compañía.

19. El método de conformidad con la reivindicación 18, caracterizado porque tal animal de compañía es un perro o

gato.

20. El método de conformidad con la reivindicación 15, caracterizado porque tal parásito es una garrapata.

21. El método de conformidad con la reivindicación 15, caracterizado porque tal animal es un animal de ganado.

22. Un método para prevenir o tratar enfermedades transmitidas a través de parásitos caracterizado porque comprende administrar una cantidad efectiva de un compuesto de conformidad con la reivindicación 1 a un animal en necesidad del mismo.

23. El método de conformidad con la reivindicación 22, caracterizado porque al menos otro ingrediente activo es administrado a tal animal.

24. El método de conformidad con la reivindicación 22, caracterizado porque tal animal es un humano.

25. El método de conformidad con la reivindicación 22, caracterizado porque tal animal es un animal de compañía.

26. El método de conformidad con la reivindicación 25, caracterizado porque tal animal de compañía es un perro o gato.

27. El método de conformidad con la reivindicación 22, caracterizado porque tal parásito es una garrapata.

28. El método de conformidad con la reivindicación 22, caracterizado porque tal animal es un animal de ganado.

29. Un método para controlar parásitos,

caracterizado porque un compuesto de conformidad con la reivindicación 1 se deja actuar en las plagas o su hábitat, o ambos.

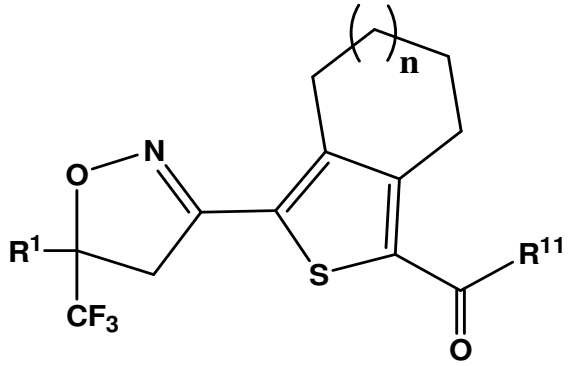
30. El método de conformidad con la reivindicación 29, caracterizado porque el compuesto es colocado en una planta o un animal.

31. Uso de compuestos, o sales de los mismos, de conformidad con la reivindicación 1, para controlar parásitos.

32. Un compuesto, o sal del mismo, de conformidad con la reivindicación 1, para uso en terapia.

33. Un compuesto, o sal del mismo, de conformidad con la reivindicación 1, para uso en el control de una infestación de ectoparásitos.

34. Un compuesto, o sal del mismo, caracterizado porque es de fórmula II



II

en donde n es 0 o 1;

R^1 es tienilo o fenilo, tal tienilo o fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo; y

R^{11} es hidroxi, -O-(alquilo C_1-C_4), o un átomo de halo.

35. El compuesto de conformidad con la reivindicación 34, caracterizado porque R^1 es fenilo sustituido con 2 o 3 de los mismos o diferentes átomos de halo.

36. El compuesto de conformidad con la reivindicación 34, caracterizado porque R^{11} es hidroxi.

37. El compuesto de conformidad con la reivindicación 34, caracterizado porque es

éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

éster metílico del ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

ácido 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico;

ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-

trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico;

cloruro de 3-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)-4,5,6,7-tetrahidrobenzo[c]tiofen-1-carbonilo; o

cloruro de 3-[5-(3,4,5-Tricloro-tiofen-2-il)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carbonilo.

38. Un compuesto de conformidad con la reivindicación 34, caracterizado porque es ácido 3-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico.

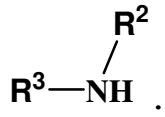
39. Un compuesto de conformidad con la reivindicación 34, caracterizado porque es ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-5,6-dihidro-4H-ciclopenta[c]tiofen-1-carboxílico.

40. Un compuesto de conformidad con la reivindicación 34, caracterizado porque es ácido 3-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico.

41. Un compuesto de conformidad con la reivindicación 34, caracterizado porque es ácido 3-[5-(3,4,5-Tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-4,5,6,7-tetrahidro-benzo[c]tiofen-1-carboxílico.

42. Un proceso para preparar un compuesto de conformidad con la reivindicación 1, caracterizado porque comprende modificar sintéticamente un compuesto de conformidad con la reivindicación 34.

43. El proceso de conformidad con la reivindicación 42, caracterizado porque un compuesto de conformidad con la reivindicación 34 se hace reaccionar con un compuesto de la fórmula



.

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos de dihidroisoxazol útiles para controlar parásitos tanto en animales como en la agricultura. Además se proporcionan métodos para controlar infestaciones de parásitos de un animal administrando una cantidad efectiva de un compuesto como se describe anteriormente, o una sal del mismo farmacéuticamente aceptable, a un animal, así como también formulaciones para controlar infestaciones de parásitos usando los compuestos descritos anteriormente o una sal del mismo aceptable, y un portador aceptable. También se proporcionan compuestos y procesos útiles para elaborar los compuestos de dihidroisoxazol.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Reply Due 19 Mar 2013

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2012/036883	08.05.2012	19.05.2011

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/04 C07D413/14 C07D495/04 A01N43/80

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Gettins, Marc Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/036883

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-43
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-43
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-43
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Relevant prior art is provided by:

D1 WO 2008/154528 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; WAGERLE TY [US]; XU MING [US]) 18 December 2008 (2008-12-18)

D2 WO 2012/038851 A1 (PFIZER [US]; CURTIS MICHAEL PAUL [US]; ELLSWORTH EDMUND LEE [US]) 29 March 2012 (2012-03-29)

D3 WO 2010/079077 A1 (NOVARTIS AG [CH]; NANCHEN STEVE [CH]; GAUVRY NOELLE [FR]; PAUTRAT FRAN) 15 July 2010 (2010-07-15)

D4 WO 2007/079162 A1 (DU PONT [US]; LAHM GEORGE PHILIP [US]; SHOOP WESLEY LAWRENCE [US]; XU) 12 July 2007 (2007-07-12)

1.1 On the assumption that the current application is entitled to the priority date of 19.05.2011 D2 has not been taken into account for the PCT examination. For the sake of completeness it is pointed out that the current application differs from D2 on account of the A substituent.

2 Claims 15-31 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv) /67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3 The current application is novel vis-à-vis D1, D3-D4 on account of the A substituent.

4 The current application addresses the problem of providing further isoxazoline derivatives for use as pesticides. The solution proposed uses (as the A group) a benzothiophene substituent. The closest prior art is represented by D1 which also uses a benzo thiophene. The difference lies in the fact that in D1 the attachment is to the benzo group whereas in the current application it is to the thiophene ring. The skilled person seeking to solve the given problem would not have regarded this as being an obvious modification to make. The compounds I of the current application as well as the intermediates II of claim 34 used to make them are therefore considered to be inventive.

Re Item VI

Certain documents cited

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2012/038851	29.03.2012	08.09.2011	24.09.2010

Re Item VII

Certain defects in the international application

1 The second possibility for A in claim 1 is drawn inaccurately (see also claim 6) since it has a 3 valent sulphur atom. Presumably the double bonds should be drawn differently- see e.g. example 240 on page 65. Search and examination has been carried out on the assumption that example 240 provides an accurate interpretation i.e. in terms of the double bonds in the general definition of A.

Re Item VIII

Certain observations on the international application

1 Claim 42 is a process for converting II to I where no technical information whatsoever is provided as to how this is to be done. The claim is therefore a result to be achieved. However, the description does not provide support and disclosure in the sense of Article 6 and 5 PCT for any such compound/ process having the said property or effect and there is no common general knowledge of this kind available to the person skilled in the art. The claim should therefore be deleted or made more specific by incorporating claim 43 into it.

2 The current application appears to use "preparations" and "examples" in different sometimes interchangeable ways. Examples 240-247 are clearly embodiments falling within the scope of the claims and several "preparations" such as 1-17 are clearly not compounds falling within the scope of claim 1. However, several "preparations" such as 18-86 appear to actually be examples of the current application. The Applicant should clarify this point and clearly identify all examples of the current application so as to distinguish them from "preparations".

3 The passage "and are non-limiting" on page 87, line 24 should be deleted.

4 The prior art documents D1-D4 should be cited (Rule 5.1 (a) (ii) PCT).

TRATADO DE COOPERACION EN MATERIA DE PATENTES

De la
AUTORIDAD DE BÚSQUEDA INTERNACIONAL

Para:

Véase forma PCT/ISA/220

PCT

OPINION ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL
(Regla 43bis.1 del PCT)

	Fecha de envío *(día/mes/año)* véase forma PCT/ISA/210 (segunda hoja)
Referencia de archivo del solicitante o mandatario Véase forma PCT/ISA/220	**PARA ACCIÓN ADICONAL** (véase párrafo 2 abajo)

No. de solicitud internacional:	Fecha de presentación internacional *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT/US2012/036883	08.05.2012	19.05.2011

Clasificación de Patente Internacional (IPC) o Clasificación nacional e IPC
INV. C07C413/00 C07D413/14 C07D495/04 A01N43/80

Solicitante

ELI LILLY AND COMPANY

1. Esta opinión contiene las indicaciones que están relacionadas con los siguientes ítems:
   - ☒ Cuadro No. I Base de la opinión
   - ☒ Cuadro No. II Prioridad
   - ☐ Cuadro No. III Ningún establecimiento del reporte con respecto a la novedad, paso de la invención, o aplicabilidad industrial
   - ☐ Cuadro No. IV Carencia de unidad de la invención
   - ☒ Cuadro No. V Establecimiento razonado bajo la Regla 43bis.1(a)(i) con respecto a la novedad, paso de la invención o aplicabilidad industrial; las citas y explicaciones que soportan tal establecimiento o fundamento.
   - ☒ Cuadro No. VI Ciertos documentos citados
   - ☒ Cuadro No. VII Ciertos defectos en la solicitud internacional
   - ☒ Cuadro No. VIII Ciertas observaciones en la solicitud internacional.

2. **CONTINUACIÓN DE LA TRAMITACIÓN**
   Si se hace una petición de examen preliminar internacional, esta opinión se considerará como una opinión escrita de la administración encargada del examen preliminar internacional ("IPEA") salvo en aquellos casos en los que el solicitante elija una Administración distinta a ésta y, la IPEA elegida haya notificado a la Oficina Internacional según lo previsto en la Regla 66.1*bis*(b) que las opiniones escritas de esta Administración encargada de la búsqueda internacional no serán consideradas como tales.

   Si esta opinión es, como se indica más arriba, considerada como una opinión escrita de la IPEA, se invita al solicitante a que presente ante la IPEA una respuesta por escrito junto con modificaciones, en su caso, antes de la expiración del plazo de 3 meses a contar desde la fecha de envío del formulario PCT/ISA/220 o antes de la expiración del plazo de 22 meses a contar desde la fecha de prioridad, aplicándose el plazo que expire más tarde.

   Para otras opciones, consultar el formulario PCT/ISA/220.

3. Para más detalles, ver las notas del formulario PCT/ISA/220.

Nombre y dirección de envío de la IPEA/US	Fecha de terminación de esta opinión	Oficial autorizado
Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Véase forma PCT/ISA/210	Gettins, Marc Teléfono No. +49 89 2399-0

Cuadro No. I Bases de esta opinión

1. Por lo que respecta al **idioma** esta opinión se ha establecido sobre la base de

☒ la solicitud internacional en el idioma en el cual se depositó

☐ una traducción de la solicitud internacional en , que es el idioma de una traducción proporcionada a los fines de la búsqueda internacional (según las Reglas 12.3 y 23.1 b)).

2. ☐ Esta opinión se ha establecido tomando en cuenta la rectificación de un error obvio autorizado por o notificado a esta Autoridad bajo la Regla 91 (Regla 43bis.1(a))

3. En lo que se refiere a **las secuencias de nucleótidos y/o de aminoácidos** divulgadas en la solicitud internacional y necesarias para la invención reivindicada, esta opinión se ha establecido sobre la base de:

a. (medios)

☐ por escrito

☐ en soporte legible por ordenador

b. (tiempo)

☐ contenido en la solicitud internacional tal y como se presentó

☐ presentado junto con la solicitud internacional en forma electrónica

☐ presentado posteriormente a esta Administración a los fines de la búsqueda

4. ☐ Además, en caso de que se haya presentado más de una versión o copia de una lista de secuencias y/o tabla relacionada con ella, se ha entregado la declaración requerida de que la información contenida en las copias subsiguientes o adicionales es idéntica a la de la solicitud tal y como se presentó o no va más allá de lo presentado inicialmente.

5. Comentarios adicionales:

Cuadro No. II Prioridad

1. ☒ No se ha considerado la validez de la reivindicación de prioridad porque la Administración encargada de la búsqueda internacional no dispone de una copia de la solicitud anterior cuya prioridad se ha reivindicado, o en su caso, de una traducción de dicha solicitud anterior. Sin embargo, se ha establecido esta opinión asumiendo que la fecha pertinente (Reglas 43bis.1 y 64.1) es la fecha de prioridad reivindicada

2. ☐ La presente opinión se ha formulado como si no se hubiese reivindicado ninguna prioridad, debido a que no se ha considerado válida la reivindicación de prioridad (Reglas 43bis.1 y 64.1). En consecuencia, a los efectos de la presente opinión, se considera como fecha pertinente la fecha de presentación internacional indicada más arriba.

3. Observaciones complementarias, si procede:

Cuadro V. Declaración razonada bajo la Regla 43bis.1(a)(i) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que soportan la declaración

1. Declaración

Novedad (N)	SI	Reivindicaciones	1-43
	NO	Reivindicaciones	
Actividad inventiva (AI)	SI	Reivindicaciones	1-43
	NO	Reivindicaciones	
Aplicación industrial (AI)	SI	Reivindicaciones	1-43
	NO	Reivindicaciones	

2. Citas y explicaciones

Véase hoja separada

Cuadro No. VI Ciertos documentos citados

1. Ciertos documentos publicados (Reglas 43bis.1 y 70.10)

y/o

2. Descripciones no escritas (Reglas 43bis.1 y 70.9)

Véase forma 210

Cuadro No. VII Ciertos defectos en la solicitud internacional

Se han notado los siguientes defectos en la forma o contenidos de la solicitud internacional

Véase hoja separada

Cuadro No. VIII Ciertas observaciones en la solicitud internacional

Se hacen las siguientes observaciones en la claridad de las reivindicaciones, descripción y dibujos o en la cuestión si las reivindicaciones son completamente soportadas:

Véase hoja separada

Punto V

Declaración razonada con respecto a novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que soporta la declaración

1) Se hace referencia a los siguientes documentos:

D1 WO 2008/154528 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; WAGERLE TV [US]; XU MING [US]) 18 Diciembre 2008 (2008-12-18)

D2 WO 2012/038851 A1 (PFIZER [US]; CURTIS MICHAEL PAUL [US] ; ELLSWORTH EDMUND LEE [US]) 29 Marzo 2012 (2012-03-29)

D3 WO 2010/079077 A1 (NOVARTIS AG [CH]; NANCHEN STEVE [CH] ; GAUVRY NOELLE [FR] PAUTRAT FRAN) 15 Julio 2010 (2010-07-15)

D4 WO 2007/079162 A1 (DU PONT [US]; LAHM GEORGE PHILIP [US]; SHOOP WESLEY LAWRENCE [US]; XU) 12 Julio 2007 (2007-07-12)

1.1 En el supuesto que la actual solicitud es tiene el derecho de la fecha de prioridad del 19.05.2011, el documento D2 no se ha tomado en cuenta para el examen del PCT. En aras de la exhaustividad, se señala que la solicitud difiere de D2 en cuenta del sustituyente A.

2 Las reivindicaciones 15-31 se refieren a la materia objeto considerada por esta Autoridad para ser cubierta por la provisión de la Regla 39.1(iv)/67.1(iv) del PCT. La patentabilidad puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como reivindicaciones patentables al uso de un compuesto en tratamiento médico, pero puede permitir reivindicar un producto, en particular sustancias o composiciones para uso un primer tratamiento médico o subsecuente. La patentabilidad puede ser dependiente de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como reivindicaciones patentables al uso de un compuesto en tratamiento médico, pero puede permitir reivindicar un producto, en particular sustancias o composiciones para uso en un primer tratamiento médico o subsecuente.

3 La actual solicitud es nueva vis-à-vis D1, D3-D4 en cuenta del sustituyente A.

4 La actual solicitud se dirige al problema de proporcionar derivados de isoxazolina adicionales para uso como pesticidas. La solución propuesta utiliza (como en el grupo A) un sustituyente de benzotiofeno. La técnica anterior más cercana es representada por D1 el cual también utiliza un benzo tiofeno. La diferencia se encuentra en el hecho que en D1 la unión es al grupo benzo mientras que en la actual solicitud es al anillo tiofeno. La persona experta pretende resolver el problema proporcionado que puede no ser contemplado esto como una modificación obvia para elaborar. Los compuestos I de la actual solicitud, así como también los intermediarios II de la reivindicación 34 usados para elaborarlos son por lo tanto considerados inventivos.

Re punto VI

Ciertos documentos citados

Solicitud No. Patente No.	Fecha de publicación (día/mes/año)	Fecha de presentación (día/mes/año)	Fechad de prioridad (reivin. Válida) (día/mes/año)
WO2012/038851	29.03.2012	08.09.2011	24.09.2010

Re punto VII

Ciertos defectos en la solicitud internacional

1 La segunda posibilidad para A en la reivindicación 1 se elabora incorrectamente (véase también reivindicación 6) ya que tiene un átomo de azufre de 3 valencias. Presumiblemente, los enlaces dobles deben ser elaborados diferentemente, véase por ejemplo, ejemplo 240 en la página 65. Se ha llevado a cabo búsqueda y examen en la presunción que el ejemplo 240 proporciona una interpretación exacta, es decir, en términos de los enlaces dobles en la definición general de A.

Re punto VIII

Ciertas observaciones en la solicitud internacional

1 La reivindicación 42 es un proceso para convertir II a I en donde no se proporciona en absoluto información técnica en cuanto a como se elabora. La reivindicación es por lo tanto un resultado a ser logrado. Sin embargo, la descripción no proporciona soporte y describe en la opinión del Artículo 6 y 5 del PCT por cualquiera de esto compuesto/procesos que tienen esta propiedad o efecto y no es conocimiento general común de este tipo disponible a una persona experta en la técnica. La reivindicación debe por lo tanto ser eliminada o hecha más especifica incorporando la reivindicación 43 en ella.

2 La actual solicitud parece usar “preparaciones” y “ejemplos” en diferentes maneras en un algún momento. Los ejemplos 240-247 son claramente modalidades que caen dentro del alcance de las reivindicaciones y varias “preparaciones” tales como 1-17 claramente no son compuestos que caen dentro del alcance de la reivindicación 1. Sin embargo, varias “preparaciones” tales como 18-86 parecer actualmente ser ejemplos de la actual solicitud. El Solicitante debe clarificar este punto y claramente identificar todos los ejemplos de la actual solicitud de forma que se distinguirlos de las “preparaciones”.

3 El pasaje “y no son limitantes” en la página 87, línea 24 debe ser suprimido.

4 Los documentos de la técnica anterior D1-D4 deben ser citados (Regla 5.1(a)(ii) del PCT).

TRATADO DE COOPERACIÓN DE PATENTES

PCT

REPORTE DE BÚSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia al expediente del solicitante o del mandatario	**PARA ACCIÓN ADICIONAL**	Véase Forma PCT/ISA/220) así como, en donde aplique el inciso 5 posterior
X19158		
No. de solicitud internacional	Fecha de presentación internacional *(día/mes/año)*	(Fecha de Prioridad) (La más cercana) (*día/mes/año*)
PCT/US20129/036883	08/05/2012	19/05/2011
Solicitante		
ELI LILLY AND COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de conformidad con el Artículo 18. Se transmite una copia a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 4 hojas

☒ También está acompañado de una copia de cada documento de la técnica anterior citado en este reporte.

1. **Bases del Reporte**

a. Con respecto al **lenguaje,** la búsqueda internacional se realizó en las bases de
☒ la solicitud internacional en el lenguaje en el cual se presentó.

☐ una traducción de la solicitud internacional en _____, la cual está en el idioma de una traducción proporcionada para el propósito de búsqueda internacional (Reglas 12.3(a) y 23.1(b))

b. ☐ Este reporte internacional se ha establecido tomando en cuenta la rectificación de un error obvio autorizado por o notificado a esta Autoridad bajo la Regla 91 (Regla 43.6bis(a)).

c. ☐ Con respecto a cualquier **secuencia de nucleótido y/o aminoácido** descrita en la solicitud internacional, véase, Cuadro No. I

2. ☐ **Se encontró que ciertas reivindicaciones no son localizables** (ver el Cuadro II).

3. ☐ **La unidad de la invención es deficiente** (ver el Cuadro III).

4. Con respecto al **título**,

☐ el texto se aprueba tal como lo presentó el solicitante,
☒ esta Autoridad ha establecido que el texto sea como sigue:

COMPUESTOS DE DIHIDROISOXAZOL PARASITICIDAS

5. Con respecto al **resumen,**
☒ el texto se aprueba tal como lo presentó el solicitante.
☐ Esta Autoridad ha establecido el texto, de acuerdo con la Regla 38.2(b), tal como aparece en el Cuadro IV. El solicitante puede, dentro de un mes a partir de la fecha de envío por correo de este reporte de búsqueda internacional, proporcional comentarios a esta autoridad.

6. Con respecto a los dibujos
a. La figura de los **dibujos** que se va a publicar con el resumen es la Figura No. _____.

☐ como lo sugirió el solicitante.
☐ porque al solicitante le faltó sugerir una figura.
☐ porque esta figura caracteriza mejor la invención.

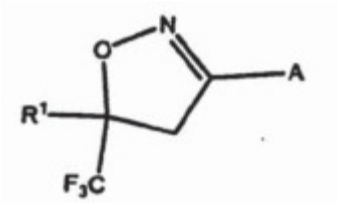
b. ☐ ninguna de las figuras es para ser publicada con el resumen.

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de Solicitud Internacional
PCT/US2012/036883

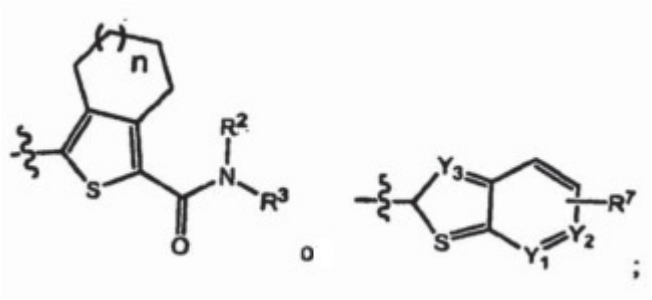
Cuadro No. IV Texto del resumen (Continuación del punto 5 de la primera hoja)

Se proporcionan compuestos de dihidroisoxazol I útiles para el control de parásitos tanto en animales como en agricultura. Además se proporcionan métodos para controlar infestaciones de parásitos de un animal administrando una cantidad efectiva de un compuesto como se describe anteriormente, o una sal del mismo farmacéuticamente aceptable, a un animal, así como a formulaciones para controlar infestaciones de parásitos usando los compuestos descritos anteriormente o una sal del mismo farmacéuticamente aceptable, y un portador. También se proporcionan compuestos y procesos útiles para elaborar los compuestos de dihidroisoxazol.



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REPORTE DE BÚSQUEDA INTERNACIONAL

No. de Solicitud Internacional
PCT/US2012/036883

A. CLASIFICACION DEL ASUNTO RELACIONADO
INV. C07D413/04 C07D413/14 C07D495/04 A01N43/80

De acuerdo con la Clasificación Internacional de Patentes (IPC) o tanto la clasificación nacional como la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)
C07D

Documentación buscada diferente de la documentación mínima, al grado que estos documentos se incluyen en los campos buscados.

Base de datos, electrónica, consultada durante la búsqueda internacional (nombre de la base de datos, donde se puede practicar, términos de búsqueda usados).
EPO-Interno, Datos WPI

C. DOCUMENTOS QUE SE CONSIDERAN PERTINENTES

Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la reivindicación No.
X	WO 2008/154528 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; WAGERLE TV [US]; XU MING [US]) 18 Diciembre 2008 (2008-12-18) reivindicaciones 1,8; tabla 17	1-43
A,P	WO 2012/038851 A1 (PFIZER [US]; CURTIS MICHAEL PAUL [US] ; ELLSWORTH EDMUND LEE [US]) 29 Marzo 2012 (2012-03-29) reivindicaciones 1,13	1-43
A	WO 2010/079077 A1 (NOVARTIS AG [CH]; NANCHEN STEVE [CH] ; GAUVRY NOELLE [FR] PAUTRAT FRAN) 15 Julio 2010 (2010-07-15) reivindicaciones 1,15	1-43
A	WO 2007/079162 A1 (DU PONT [US]; LAHM GEORGE PHILIP [US]; SHOOP WESLEY LAWRENCE [US]; XU) 12 Julio 2007 (2007-07-12) reivindicaciones 1,18	1-43

☐ Documentos adicionales se listan en la continuación del cuadro C. ☒ Los miembros de la familia de patentes se listan en el anexo

* Categoría especial de los documentos citados:

"A" Documento que define el estado general de la técnica, que no se considera que es de pertinencia particular

"E" Documento anterior, pero publicado en o después de la fecha de presentación internacional

"L" Documento que puede crear dudas de la reivindicación(es) de prioridad o que se cita para establecer la fecha de publicación de otra situación u otra razón especial (como se especifique)

"O" Documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" Documento publicado antes de la fecha de presentación internacional, pero después de la fecha de prioridad reivindicada

"T" Documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad, y que no provoca conflicto con la solicitud, pero se cita para entender el principio o teoría que trata la invención

"X" Documento de pertinencia particular; la invención reivindicada no se puede considerar nueva o no se puede considerar que comprende un paso inventivo cuando el documento se toma solo

"Y" Documento de pertinencia particular; la invención reivindicada no se puede considerar que comprende un paso inventivo cuando el documento se combina con uno o más de estos documentos, estas combinaciones son obvias para una persona experta en la técnica

"&" Documento miembro de la familia de patentes

Fecha de la actual terminación de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
13 Junio 2012	20/06/2012

Nombre y dirección de envío I SA/	Funcionario autorizado
Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL- 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax. (+31-70) 340-3016	Gettins, Marc

REPORTE DE BÚSQUEDA INTERNACIONAL

Información sobre los miembros de familia de patentes

Solicitud Internacional No.:
PCT/US2012/036883

Documento de la patente citado en el reporte de búsqueda	Fecha de publicación	Miembros de la familia de patentes	Fecha de publicación
WO 2008154528 A2	18-12-2008	AU 2008261793 A1	18-12-2008
		CA 2684671 A1	18-12-2008
		CN 101815706 A	25-08-2010
		EP 2155701 A2	24-02-2010
		JP 2010529989 A	02-09-2010
		US 2010179195 A1	15-07-2010
		WO 2008154528 A2	18-12-2008
WO 2012038851 A1	29-03-2012	US 2012077765 A1	29-03-2012
		UY 33622 A	30-04-2012
		WO 2012038851 A1	29-03-2012
WO 2010079077 A1	15-07-2010	CA 2747060 A1	15-07-2010
		EP 2379544 A1	26-10-2011
		US 2011245274 A1	06-10-2011
		WO 2010079077 A1	15-07-2010
WO 2007079162 A1	12-07-2007	AR 058896 A1	27-02-2008
		AT 496900 T	15-02-2011
		AU 2006332749 A1	12-07-2007
		BR PI0621171 A2	29-11-2011
		CA 2632694 A1	12-07-2007
		CN 101351456 A	21-01-2009
		DK 1973888 T3	16-05-2011
		EP 1973888 A1	01-10-2008
		ES 2358683 T3	12-05-2011
		HR 20110223 T1	30-06-2011
		JP 2009522282 A	11-06-2009
		KR 20080094015 A	22-10-2008
		KR 20120013453 A	14-02-2012
		MA 30070 B1	01-12-2008
		MD 20080171 A	31-07-2009
		NZ 568026 A	29-10-2010
		PT 1973888 E	22-02-2011
		RS 51670 B	31-10-2011
		RS 20060699 A	07-08-2008
		SI 1973888 T1	30-06-2011
		US 2010234219 A1	16-09-2010
		US 2011263641 A1	27-10-2011
		UY 30069 A1	31-07-2007
		WO 2007079162 A1	12-07-2007
		ZA 200804384 A	26-08-2009

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X19158	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2012/036883	International filing date *(day/month/year)* 08/05/2012	(Earliest) Priority Date *(day/month/year)* 19/05/2011
Applicant ELI LILLY AND COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

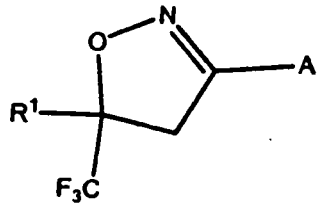
   PARASITICIDAL DIHYDROISOXAZOLE COMPOUNDS

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

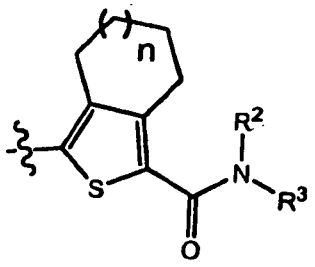
Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Provided are dihydroisoxazole compounds I useful for controlling parasites both in animals and agriculture. Further provided are methods for controlling parasite infestations of an animal by administering an effective amount of a compound as described above, or a pharmaceutically acceptable salt thereof, to an animal, as well as formulations for controlling parasite infestations using the compounds described above or an acceptable salt thereof, and an acceptable carrier. Also provided are compounds and processes useful for making the dihydroisoxazole compounds.

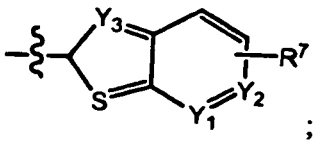


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or



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/036883

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 C07D495/04 A01N43/80
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/154528 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; WAGERLE TY [US]; XU MING [US]) 18 December 2008 (2008-12-18) claims 1,8; table 17	1-43
A,P	WO 2012/038851 A1 (PFIZER [US]; CURTIS MICHAEL PAUL [US]; ELLSWORTH EDMUND LEE [US]) 29 March 2012 (2012-03-29) claims 1,13	1-43
A	WO 2010/079077 A1 (NOVARTIS AG [CH]; NANCHEN STEVE [CH]; GAUVRY NOELLE [FR]; PAUTRAT FRAN) 15 July 2010 (2010-07-15) claims 1,15	1-43
A	WO 2007/079162 A1 (DU PONT [US]; LAHM GEORGE PHILIP [US]; SHOOP WESLEY LAWRENCE [US]; XU) 12 July 2007 (2007-07-12) claims 1,18	1-43

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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
13 June 2012	20/06/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gettins, Marc

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/036883

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008154528 A2	18-12-2008	AU 2008261793 A1	18-12-2008
		CA 2684671 A1	18-12-2008
		CN 101815706 A	25-08-2010
		EP 2155701 A2	24-02-2010
		JP 2010529989 A	02-09-2010
		US 2010179195 A1	15-07-2010
		WO 2008154528 A2	18-12-2008
WO 2012038851 A1	29-03-2012	US 2012077765 A1	29-03-2012
		UY 33622 A	30-04-2012
		WO 2012038851 A1	29-03-2012
WO 2010079077 A1	15-07-2010	CA 2747060 A1	15-07-2010
		EP 2379544 A1	26-10-2011
		US 2011245274 A1	06-10-2011
		WO 2010079077 A1	15-07-2010
WO 2007079162 A1	12-07-2007	AR 058896 A1	27-02-2008
		AT 496900 T	15-02-2011
		AU 2006332749 A1	12-07-2007
		BR PI0621171 A2	29-11-2011
		CA 2632694 A1	12-07-2007
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		DK 1973888 T3	16-05-2011
		EP 1973888 A1	01-10-2008
		ES 2358683 T3	12-05-2011
		HR 20110223 T1	30-06-2011
		JP 2009522282 A	11-06-2009
		KR 20080094015 A	22-10-2008
		KR 20120013453 A	14-02-2012
		MA 30070 B1	01-12-2008
		MD 20080171 A	31-07-2009
		NZ 568026 A	29-10-2010
		PT 1973888 E	22-02-2011
		RS 51670 B	31-10-2011
		RS 20060699 A	07-08-2008
		SI 1973888 T1	30-06-2011
		US 2010234219 A1	16-09-2010
		US 2011263641 A1	27-10-2011
		UY 30069 A1	31-07-2007
		WO 2007079162 A1	12-07-2007
		ZA 200804384 A	26-08-2009