SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-020595- -00000-0000

Fecha: 2013-02-04 17:23:0 Dep. 2020 DIR.NUEVASCRE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCION DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE ISOXAZOLINA COMO AGENTES ANTIPARASITARIOS.

SOLICITANTE: AH USA 42 LLC.

DIRECCIÓN: 235 East 42nd Street, New York, NY 10017. Estados Unidos de América.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 04 Febrero de 2013

P2013/000023

OLARTE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000023**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

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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

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E-mail: office@olartemoure.com

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

INVENTOR (ES) (72)

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Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2011/053355 Fecha Julio 27, 2011

Publicación Internacional No. WO 2012/017359 A1 Fecha Febrero 09, 2012

(6) **Título (54)** **DERIVADOS DE ISOXAZOLINA COMO AGENTES ANTIPARASITARIOS.**

Clasificación Internacional (51) **C07D 413/12; C07D 413/14; A01N 43/80.**

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 05, 2010	61/371,014
US	Febrero 22, 2011	61/445,221
US	Marzo 11, 2011	61/451,888
US	Mayo 17, 2011	61/486,831
US	Mayo 27, 2011	61/490,811

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

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica. Poderes, si fuere el caso.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la Regla 417(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.
- [x] 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

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Nacionalidad: Estadounidense

5

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RECIBO DE CAJA

No. 13 - 006054

Bogotá D.C., Enero 21 de 2013 - 16:28:20

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	181303194	18/01/2013	13.295.000.00

*** 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. _____

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SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

ndencia:

Fecha: ____/____/____/ (AAAA MM DD)

Recorrido:

de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐

Planilla:

cador:

No. Radicación	*Consecutivo*	*Item*
13-020595	0	

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

rvaciones:

Anexan CD

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-020595- -00000-0000
Fecha: 2013-02-04 17:23:0 Dep. 2020 DIR.NUEVASCRE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

PATENTE DE INVENCIÓN ☐ MODELO DE U...

- ☐ 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 ☑ CD 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 ☐

PCT

Print Out (Original in Electronic Form)

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 PFIZER INC. is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from CHUBB, Nathan A.L. to PFIZER INC., dated 08 March 2011 (08.03.2011)
VIII-2-1(iv)		an assignment from CHUBB, Nathan A.L. to PFIZER INC., dated 06 June 2011 (06.06.2011)
VIII-2-1(iv)		an assignment from CURTIS, Michael Paul to PFIZER INC., dated 21 March 2011 (21.03.2011)
VIII-2-1(iv)		an assignment from CURTIS, Michael Paul to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(iv)		an assignment from HOWSON, William to PFIZER INC., dated 08 March 2011 (08.03.2011)
VIII-2-1(iv)		an assignment from HOWSON, William to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(iv)		an assignment from KYNE, Graham M to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(iv)		an assignment from MENON, Sanjay Rajagopal to PFIZER INC., dated 08 March 2011 (08.03.2011)
VIII-2-1(iv)		an assignment from MENON, Sanjay Rajagopal to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(iv)		an assignment from SHEEHAN, Susan Mary Kult to PFIZER INC., dated 08 March 2011 (08.03.2011)
VIII-2-1(iv)		an assignment from SHEEHAN, Susan Mary Kult to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(iv)		an assignment from SKALITZKY, Donald James to PFIZER INC., dated 21 March 2011 (21.03.2011)
VIII-2-1(iv)		an assignment from SKALITZKY, Donald James to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(iv)		an assignment from VAILLANCOURT, Valerie Ann to PFIZER INC., dated 26 August 2010 (26.08.2010)

VIII-2-1(iv)		an assignment from VAILLANCOURT, Valerie Ann to PFIZER INC., dated 08 March 2011 (08.03.2011)
VIII-2-1(iv)		an assignment from VAILLANCOURT, Valerie Ann to PFIZER INC., dated 02 June 2011 (02.06.2011)
VIII-2-1(ii)		PFIZER INC. is entitled as employer of the inventor, WENDT, John A.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 February 2012 (09.02.2012)

PCT

(10) International Publication Number
WO 2012/017359 A1

(51) **International Patent Classification**:
C07D 413/12 (2006.01) *A01N 43/80* (2006.01)
C07D 413/14 (2006.01)

(21) **International Application Number**:
PCT/IB2011/053355

(22) **International Filing Date**:
27 July 2011 (27.07.2011)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:

61/371,014	5 August 2010 (05.08.2010)	US
61/445,221	22 February 2011 (22.02.2011)	US
61/451,888	11 March 2011 (11.03.2011)	US
61/486,831	17 May 2011 (17.05.2011)	US
61/490,811	27 May 2011 (27.05.2011)	US

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(72) **Inventors; and**

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

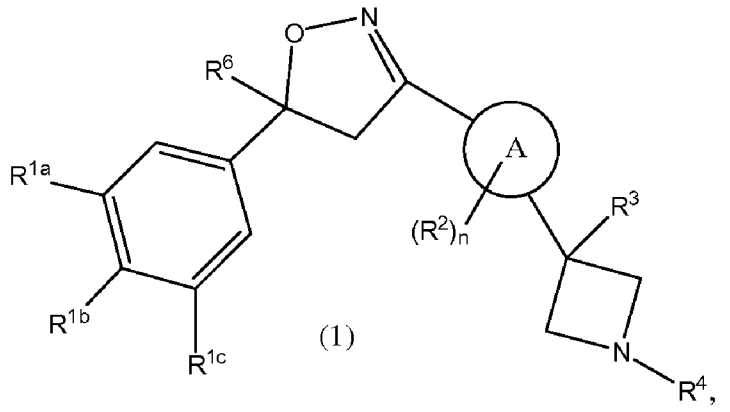
(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,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

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

[Continued on next page]

(54) **Title**: ISOXAZOLINE DERIVATIVES AS ANTIPARASITIC AGENTS



(57) **Abstract**: This invention recites isoxazoline substituted azetidine derivatives of Formula (1), stereoisomers thereof, veterinarily acceptable salts thereof, compositions thereof, and their use as a parasiticide in mammals and birds. R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, R^6, and n are as described herein.

WO 2012/017359 A1

— *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))*

ISOXAZOLINE DERIVATIVES AS ANTIPARASITIC AGENTS

FIELD OF THE INVENTION

This invention relates to isoxazoline derivatives having parasiticidal activity. The compounds of interest are isoxazoline derivatives substituted with phenyl-azetidines, naphthyl-azetidines, or heteroaryl azetidines. The invention also relates to compositions and methods of use thereof.

BACKGROUND

There is a need for improved antiparasitic agents for use with mammals, and in particular there is a need for improved insecticides and acaricides. Furthermore there is a need for improved topical and oral products with convenient administration and which contain one or more of such antiparasitic agents which can be used to effectively treat ectoparasites, such as insects (e.g., fleas, lice, and flies) and acarids (e.g., mites and ticks). Such products would be particularly useful for the treatment of companion animals, such as cats, dogs, llamas, and horses, and livestock, such as cattle, bison, swine, sheep, and goats.

The compounds currently available for insecticidal and acaricidal treatment of companion animals and livestock do not always demonstrate good activity, good speed of action, or a long duration of action. Most treatments contain hazardous chemicals that can have serious consequences, including lethality from accidental ingestion. Persons applying these agents are generally advised to limit their exposure. Pet collars and tags have been utilized to overcome some problems, but these are susceptible to chewing, ingestion, and subsequent toxicological affects to the mammal. Thus, current treatments achieve varying degrees of success which depend partly on toxicity, method of administration, and efficacy. Currently, some agents are actually becoming ineffective due to parasitic resistance.

Isoxazoline derivatives have been disclosed in the art as having insecticidal and acaricidal activity. For example, WO2007/105814 (US2009/0156643), WO2008/122375, and WO2009/035004 recite certain alkylene linked amides. Further, WO2007/075459 discloses phenyl isoxazolines substituted with 5- to 6-membered heterocycles. However, none of these citations exemplify an isoxazoline substituted phenyl azetidine, nor does the prior art indicate that such

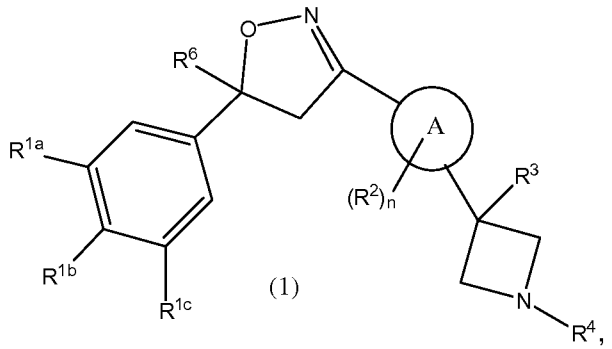
compounds would be useful against a spectrum of parasitic species, regardless of morphological lifecycle stages, in animals.

Despite the availability of effective, broad spectrum antiparasitic agents, there remains a need for a safer, convenient, efficacious, and environmentally friendly product that will overcome the ever-present threat of resistance development.

The present invention overcomes one or more of the various disadvantages of, or improves upon, the properties of existing compounds. In particular the present invention develops new isoxazoline substituted phenyl azetidines which demonstrate such properties.

SUMMARY

The present invention provides Formula (1) and Formula (XX) compounds, stereoisomers thereof, pharmaceutical or veterinarily acceptable salts thereof, which act as parasiticides, in particular, ectoparasiticides; therefore may be used to treat acarids and insect infection and infestation in animals. In addition, the invention contemplates the control and prevention endoparasites in animals. The present invention also contemplates the control and treatment of tick borne diseases, for example, Lyme disease, canine and bovine anaplasmosis, canine ehrlichiosis, canine rickettsiosis, canine and bovine babesiosis, epizootic bovine abortion, and theileriosis. Thus, according to the invention, there is provided a compound of Formula (1)



(1)

wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_0-C_3alkylC_3-C_6 cycloalkyl, C_1-C_6haloalkoxy, -C(O)NH_2, -SF_5, or –S(O)$_p$R;

R^2 is halo, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, nitro, hydroxyl, -C(O)NR^aR^b, C_2-C_6alkenyl, C_2-C_6alkynyl, -S(O)$_p$R, or -OR;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, -C(O)NH_2, nitro, -SC(O)R, -C(O)NR^aR^b, C_0-C_3alkylNR^aR^4, -$NR^aNR^bR^4$, -NR^aOR^b, -ONR^aR^b, N_3, -NHR^4, -OR, or -S(O)$_p$R;

R^4 is hydrogen, C_1-C_6alkyl, C_0-C_6alkylC_3-C_6cycloalkyl, -C(O)R^5, -C(S)R^5, -C(O)NR^aR^5, -C(O)C(O)NR^aR^5, -S(O)$_p$$R^c$, -S(O)$_2$$NR^aR^5$, -C($NR^7$)$R^5$, -C($NR^7$)$NR^aR^5$, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle;

R^5 is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_6cycloalkyl, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle;

R^6 is cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C(O)NR^aR^b, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl;

R^7 is hydrogen, C_1-C_6alkyl, hydroxyl, cyano, nitro, -S(O)$_p$$R^c$, or C_1-C_6alkoxy;

R is C_1-C_6alkyl or C_3-C_6cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1-C_6alkyl, or C_0-C_3alkylC_3-C_6cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_0-C_3alkylphenyl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or -S(O)$_p$R;

R^c is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkylC_3-C_6cycloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, C_0-C_3alkylphenyl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -S(O)$_p$R, -SH, -S(O)$_p$$NR^aR^b$, -$NR^aR^b$, -$NR^aC(O)R^b$, -SC(O)$R^b$, -SCN, or –C(O)$NR^aR^b$;

each of R^4 and R^5 C_1-C_6alkyl or C_0-C_6alkylC_3-C_6cycloalkyl can be optionally and independently substituted by at least one substituent selected from cyano,

halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -$S(O)_pR^c$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^c$, -SCN, or –$C(O)NR^aR^b$; and

wherein R^4 and R^5 C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from cyano, halo, oxo, =S, =NR^7, hydroxyl, C_1-C_6alkoxy, C_1-C_6alkyl, C_1-C_6haloalkyl, -SH, -$S(O)_pR$, and C_1-C_6haloalkoxy;

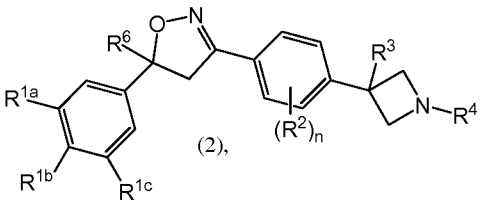
n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

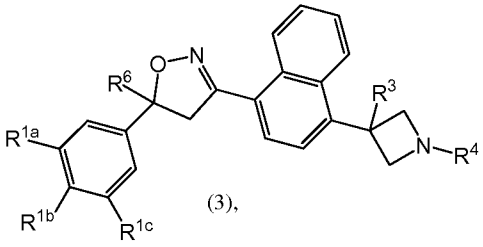
p is the integer 0, 1, or 2;

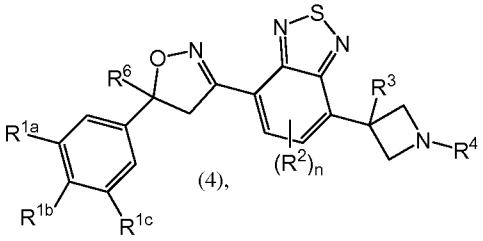
stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

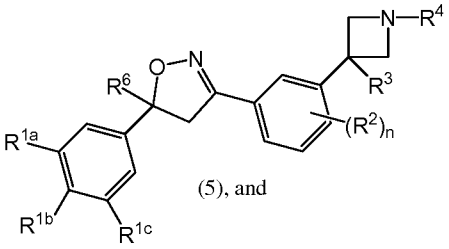
In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl pyrrolyl, furanyl, thiophenyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, benzofuranyl, benzothiophenyl, indolyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrazolyl, triazolyl, isoxazolyl, benzofuranyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrazolyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, pyridinyl, naphthyl, or benzo[1,2,5]thiadiazole. In another aspect of the invention A is phenyl or pyridinyl. In another aspect of the invention A is phenyl. In another aspect of the invention A is pyridinyl. In another aspect of the invention, A is naphthyl. In yet another aspect of the invention, A is benzo[1,2,5]thiadiazole.

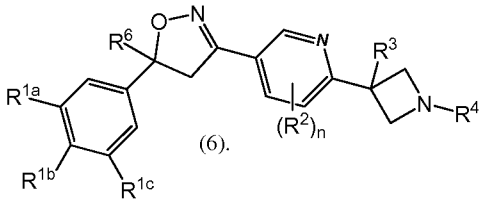
In another aspect of the invention are compounds of Formula (2), (3), (4), (5), and (6)


(2),

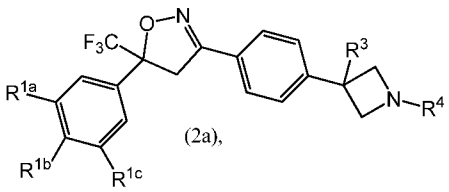

(3),

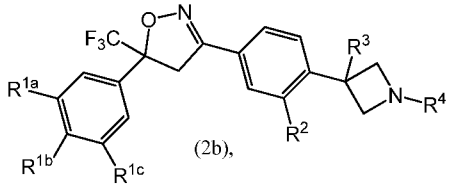

(4),

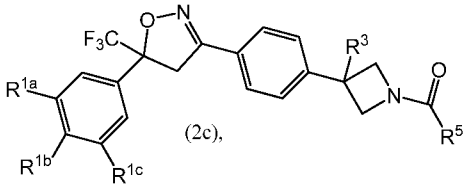

(5), and

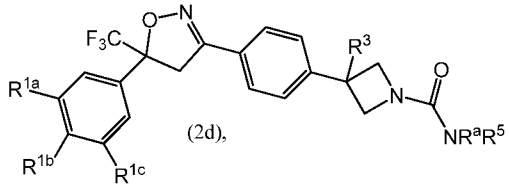

(6).

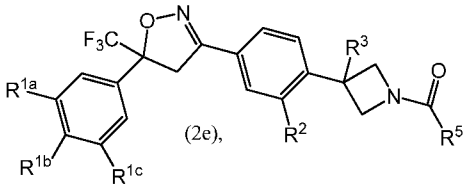
In yet another aspect of the invention are compounds of Formula (2a), (2b), (2c), (2d), (2e), (2f), (3a), (4a), (4b), (5a), (6a), and (6b).

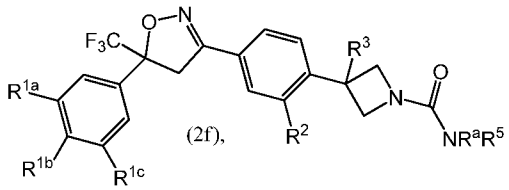

(2a),

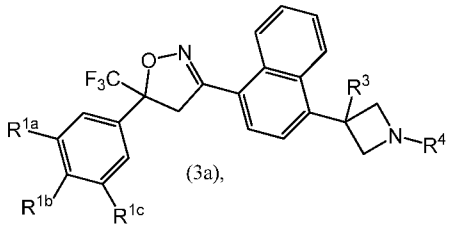

(2b),

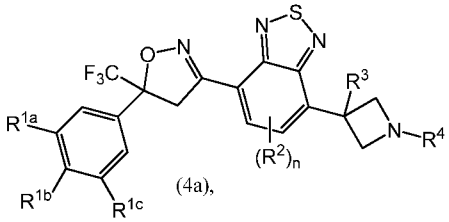

(2c),

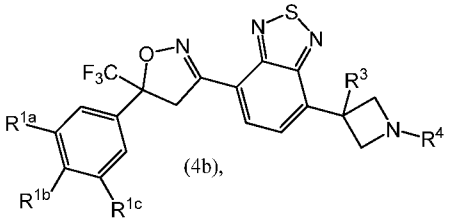

(2d),

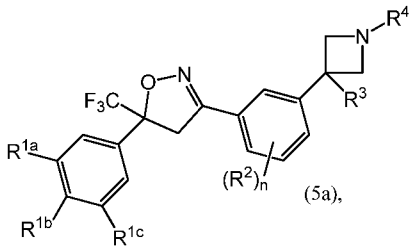

(2e),

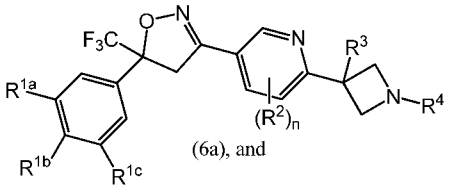

(2f),

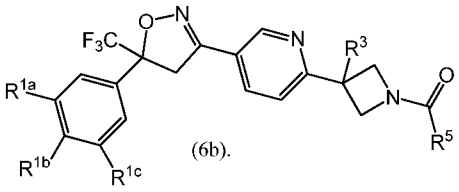

(3a),


(4a),

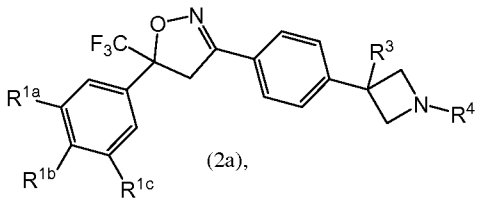

(4b),

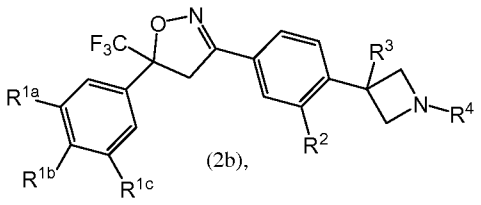

(5a),

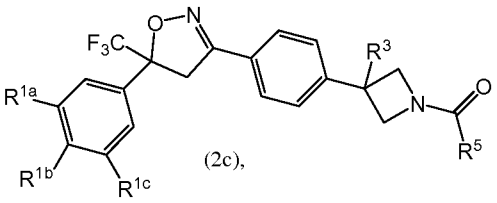

(6a), and

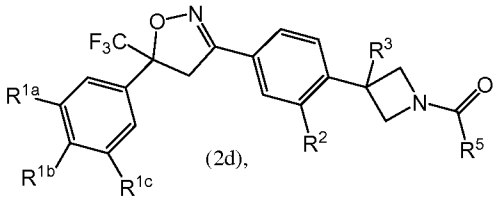

(6b).

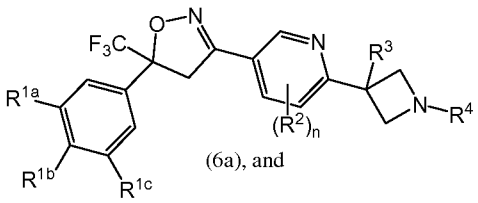
In yet another aspect of the invention are compounds of Formula (2a), (2b), (2c), (2d), (6a), and (6b).

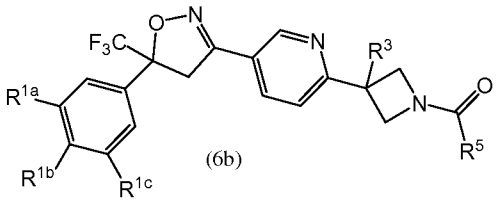

(2a),


(2b),

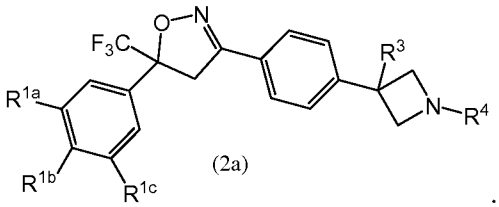

(2c),


(2d),


(6a), and

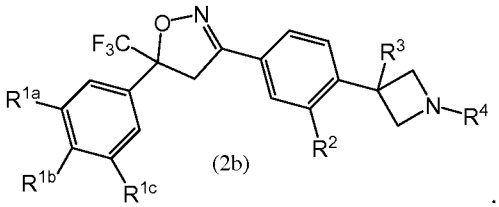

(6b)

In yet another aspect of the invention are compounds of Formula (2a)


(2a)

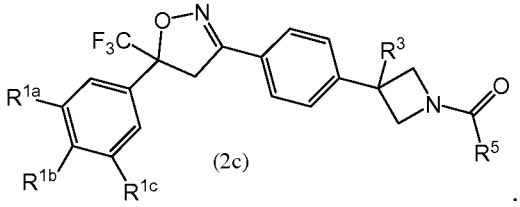
.

In yet another aspect of the invention are compounds of Formula (2b)


(2b)

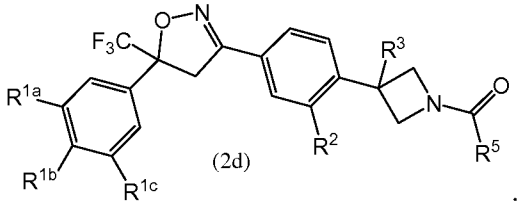
.

In yet another aspect of the invention are compounds of Formula (2c)



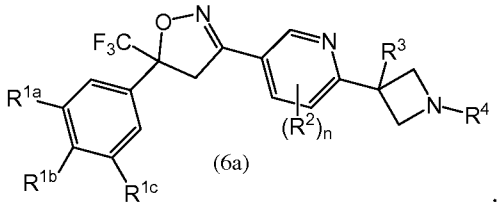
(2c)

In yet another aspect of the invention are compounds of Formula (2d)



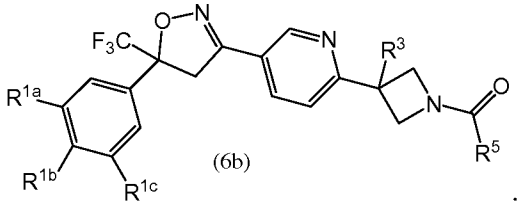
(2d)

In yet another aspect of the invention are compounds of Formula (6a)



(6a)

In yet another aspect of the invention are compounds of Formula (6b)



(6b)

In another aspect of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6 haloalkyl, C_0-C_3alkylC_3-C_6 cycloalkyl, -$S(O)_pR$, and -SF_5. In yet another aspect of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, C_1-C_6 haloalkyl, and C_0-C_3alkylC_3-C_6 cycloalkyl. In yet another aspect of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, and C_1-C_6 haloalkyl. In yet another aspect of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, cyano, and C_1-C_6 haloalkyl. In yet another aspect

of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, and C_1-C_6 haloalkyl. In yet another aspect of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, and $-CF_3$. In yet another aspect of the invention, each of R^{1a}, R^{1b}, and R^{1c} are independently selected from hydrogen, fluoro, chloro, and $-CF_3$.

In yet another aspect of the invention, the integer n of $(R^2)_n$ is 2. When the integer n is 2, then each R^2 may be identical or different from each other. In yet another aspect of the invention, the integer n of $(R^2)_n$ is 1. In yet another aspect of the invention, the integer n of $(R^2)_n$ is 0.

In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, hydroxyl, $-C(O)NR^aR^b$, C_2-C_6alkenyl, or -OR. In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, hydroxyl, $-C(O)NR^aR^b$, or -OR. In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1-C_6alkyl, $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from halo, cyano, $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from cyano or $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from cyano. In yet another aspect of the invention, R^2 is selected from $-C(O)NR^aR^b$.

In another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, $-C(O)NH_2$, -SC(O)R, $-C(O)NR^aR^b$, C_0-C_3alkylNR^aR^4, $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3, $-NHR^4$, -OR, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, C_0-C_3alkylNR^aR^4, $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3, $-NHR^4$, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, C_0-C_3alkylNR^aR^4, $-NR^aNR^bR^4$, $-NHR^4$, N_3, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, $-NHR^4$, N_3, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, $-C(O)NH_2$, or N_3.

In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, or N_3. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, or N_3. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, or N_3. In yet another aspect of the invention, R^3 is hydrogen, fluoro, chloro, bromo, N_3, hydroxyl, or cyano. In yet another aspect of the invention, R^3 is hydrogen, fluoro, N_3, hydroxyl, or cyano. In yet another aspect of the invention, R^3 is hydrogen. In yet another aspect of the invention, R^3 is fluoro. In yet another aspect of the invention, R^3 is chloro. In yet another aspect of the invention, R^3 is hydroxyl. In yet another aspect of the invention, R^3 is cyano. In yet another aspect of the invention, R^3 is N_3.

In another aspect of the invention, R^4 is C_1-C_6alkyl, C_0-C_6alkylC_3-C_6cycloalkyl, -C(O)R^5, -C(S)R^5, -C(O)NR^aR^5, -C(O)C(O)NR^aR^5, -S(O)$_p$$R^c$, -S(O)$_2$$NR^aR^5$, -C($NR^7$)$R^5$, -C($NR^7$)$NR^aR^5$, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle; wherein each of R^4 and R^5 C_1-C_6alkyl or C_0-C_6alkylC_3-C_6cycloalkyl can be optionally and independently substituted as described herein, and wherein each of R^a, R^c, R^4 and R^5 substituents can be optionally and independently substituted as described herein. In yet another aspect of the invention, R^4 is -C(O)R^5, -C(O)NR^aR^5, -S(O)$_p$$R^c$, -C(S)$R^5$, -S(O)$_2$$NR^aR^5$, -C($NR^7$)$R^5$, or -C($NR^7$)$NR^aR^5$, and wherein each of R^a, R^c, and R^5 substituents can be optionally and independently substituted as described herein.

In yet another aspect of the invention, R^4 is -C(O)R^5 or -C(O)NR^aR^5, and wherein each of R^a and R^5 substituents can be optionally and independently substituted as described herein.

In yet another aspect of the invention, when R^4 is -C(O)R^5, then R^5 is hydrogen, C_1-C_6alkyl, C_0-C_6alkylC_3-C_6cycloalkyl, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle, wherein said R^5 C_1-C_6alkyl or C_0-C_6alkylC_3-C_6cycloalkyl can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -S(O)$_p$$R^c$, -SH, -S(O)$_p$$NR^aR^b$, -$NR^aR^b$, -$NR^a$C(O)$R^b$, -SC(O)$R^c$, -SCN, or –C(O)$NR^aR^b$, where said R^5 C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, C_1-C_6alkoxy, C_1-C_6alkyl, C_1-C_6haloalkyl, -SH, -S(O)$_p$R, and C_1-C_6haloalkoxy. The R^a

and R^c substituents are also optionally substituted with at least one substituent as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is hydrogen, C_1-C_6alkyl, C_0-C_6alkylC_3-C_6cycloalkyl, or C_0-C_6alkylheteroaryl, where said C_0-C_6alkylC_3-C_6cycloalkyl or C_0-C_6alkylheteroaryl moieties are optionally substituted as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl, $-CH_2$-cyclopentyl, $-(CH_2)_2$-cyclopropyl, $-(CH_2)_2$-cyclobutyl, $-(CH_2)_2$-cyclopentyl, pyrazolyl, $-CH_2$-pyrazolyl, $-(CH_2)_2$-pyrazolyl, pyridinyl, $-CH_2$-pyridinyl, $-(CH_2)_2$-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and propyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$-cyclopropyl and $-(CH_2)_2$-cyclobutyl) can be optionally and independently substituted as defined herein.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl, $-CH_2$-cyclopentyl, $-(CH_2)_2$-cyclopropyl, $-(CH_2)_2$-cyclobutyl, $-(CH_2)_2$-cyclopentyl, pyrazolyl, $-CH_2$-pyrazolyl, $-(CH_2)_2$-pyrazolyl, pyridinyl, $-CH_2$-pyridinyl, $-(CH_2)_2$-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and propyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$-cyclopropyl and $-(CH_2)_2$-cyclobutyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, methoxy, $-CF_3$, ethoxy, $-S(O)_pR$, $-SCH_3$, $-SCH_2CH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$, -NHcyclopropyl, -NHcyclobutyl, $-NHCH_2$cyclopropyl, $-NHCH_2$cyclobutyl, $-NR^aC(O)R^b$, or $-C(O)NH_2$.

In yet another aspect of the invention, when R^4 is $-C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl, $-CH_2$-cyclopentyl, pyrazolyl, $-CH_2$-pyrazolyl, pyridinyl, $-CH_2$-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and isopropyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, $-CH_2$-cyclopropyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, $-CF_3$, $S(O)_pR$,

methoxy, ethoxy, -SCH_3, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, -NHcyclopropyl, -NHcyclobutyl, -NHC(O)H, or -$C(O)NH_2$.

In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, pyrazolyl, -CH_2-pyrazolyl, pyridinyl, -CH_2-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and isopropyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, -CH_2cyclopropyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, -CF_3, methoxy, -SCH_3, $S(O)_pR$, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, -NHcyclopropyl, -NHC(O)H, or -$C(O)NH_2$.

In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is oxetane, thiatane, azetidine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, -CH_2-oxetane, -CH_2-thiatane, -CH_2-azetidine, or -CH_2-tetrahydrofuran, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is oxetane, thiatane, azetidine, tetrahydrofuran, tetrahydrothiophene, -CH_2-oxetane, -CH_2-thiatane, or -CH_2-azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is oxetane, thiatane, azetidine, -CH_2-oxetane, -CH_2-thiatane, or -CH_2-azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is oxetane, thiatane, or azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is -CH_2-oxetane, -CH_2-thiatane, or -CH_2-azetidine, each of which are optionally substituted as defined herein.

In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, pyridine, pyridazine, pyrazine, or pyrimidine, each which are optionally substituted as defined herein.

In yet another aspect of the invention, when R^4 is -$C(O)R^5$, then R^5 is C_1-C_6alkyl, C_2-C_6alkenyl, or C_0-C_6alkylC_3-C_6cycloalkyl, wherein each of C_1-C_6alkyl or C_0-C_6alkylC_3-C_6cycloalkyl is optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, $-S(O)_pR^c$, C_1-C_6alkoxy, $-S(O)_pNR^aR^b$, or

-SC(O)R^c; pyrazole, pyridine, oxazole, pyridazine, triazole, azetidine, thiatane, wherein each heterocycle and heteroaryl moiety are optionally substituted further with at least one substituent selected from fluoro, hydroxyl, methyl, and oxo; where p, R^a, R^b, and R^c are as defined herein.

In yet another aspect of the invention, when R^4 is -C(O)NR^aR^5, then R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, -$(CH_2)_2$-cyclopropyl, -$(CH_2)_2$-cyclobutyl, or -$(CH_2)_2$-cyclopentyl; wherein the alkyl (for example methyl and propyl), cycloalkyl (for example, cyclopropyl and cyclopentyl), or the alkylcycloalkyl (for example, -CH_2-cyclopropyl, -CH_2-cyclopentyl, and -$(CH_2)_2$cyclobutyl) are optionally substituted by cyano or at least one halo substituent; and R^5 is as defined herein.

In yet another aspect of the invention, when R^4 is -C(O)NR^aR^5, then R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl; wherein the alkyl (for example methyl and propyl), cycloalkyl (for example, cyclopropyl and cyclopentyl), or the alkylcycloalkyl (for example, -CH_2-cyclopropyl and -CH_2-cyclopentyl) are optionally substituted by cyano or at least one halo substituent; and R^5 is as defined herein.

In yet another aspect of the invention, when R^4 is -C(O)NR^aR^5, then R^a is hydrogen or methyl and R^5 is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, and C_0-C_6alkylheterocycle, wherein the alkyl and alkylheterocycle moiety are each optionally substituted as described herein.

In yet another aspect of the invention, when R^4 is -$S(O)_pR^c$, the integer p is 2, and R^c is as defined herein, and said R^c substituent is optionally substituted with at least one substituent as defined herein. In yet another aspect of the invention, when R^4 is -$S(O)_pR^c$, the integer p is 2, R^c is C_1-C_6alkyl optionally substituted with at least one substituent as defined herein. In yet another aspect of the invention, when R^4 is -$S(O)_pR^c$, the integer p is 2, R^c is C_1-C_6alkyl optionally substituted with at least one substituent selected from cyano or halo. In yet another aspect of the invention, when R^4 is -$S(O)_pR^c$, the integer p is 2, and R^c is C_1-C_6alkyl.In yet another aspect of the invention, when R^4 is -$S(O)_pR^c$, the integer

p is 2, and R^c is methyl, ethyl, propyl, or isopropyl. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is methyl or ethyl.

In yet another aspect of the invention, R^6 is cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, or $-C(O)NH_2$. In yet another aspect of the invention, R^6 is cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl. In yet another aspect of the invention, R^6 is cyano, methyl, ethyl, or C_1-C_6haloalkyl. In yet another aspect of the invention, R^6 is cyano, methyl, or C_1-C_6haloalkyl. In yet another aspect of the invention, R^6 is cyano or C_1-C_6haloalkyl. In yet another aspect of the invention, R^6 is C_1-C_6haloalkyl. In yet another aspect of the invention, R^6 is $-CF_3$, $-CHF_2$, $-CH_2F$, and $-CF_2Cl$. In yet another aspect of the invention, R^6 is $-CF_3$, $-CHF_2$, and $-CH_2F$. In yet another aspect of the invention, R^6 is $-CF_3$.

In yet another aspect of the invention, R is methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, or cyclopentyl. In yet another aspect of the invention, R is methyl, ethyl, isopropyl, cyclopropyl, or cyclobutyl.

In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, or isobutyl, each alkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, or isopropyl, each alkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, or ethyl, each alkyl is optionally substituted as defined herein.

In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$-cyclopropyl, or $-CH_2$-cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, $-CH_2$-cyclopropyl, or $-CH_2$-cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $-CH_2$-cyclopropyl, or $-CH_2$-cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein.

In another aspect of the invention, R^b is hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_0-C_3alkylphenyl, or C_0-C_3alkylheteroaryl. In yet another aspect of the invention, R^b is hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, or C_0-C_3alkylheteroaryl.

In yet another aspect of the invention, R^b is hydrogen, C_1-C_6alkyl, or C_3-C_6cycloalkyl. In yet another aspect of the invention, R^b is hydrogen, methyl, ethyl, isopropyl, propyl, isobutyl, cyclopropyl, or cyclobutyl.

In another aspect of the invention, are Formula (1) compounds selected from:

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone;

cyclopropyl(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;

3-fluoro-N-methyl-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide;

N-ethyl-3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide;

N-cyclopropyl-3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide;

cyclopropyl(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;

1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;

3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;

N-cyclopropyl-3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;

1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)propan-1-one;

1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)butan-1-one;

2-cyclopropyl-1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;

3-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-oxopropanenitrile;

1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methoxyethanone;
cyclobutyl(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
N-cyclopropyl-3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone;
cyclobutyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone;
3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
N-cyclopropyl-3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-hydroxyazetidine-1-carboxamide;
N-cyclopropyl-3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidine-1-carboxamide;

3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-hydroxyazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-hydroxyazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;
cyclopropyl(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
2-Cyclopropyl-1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;
3-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-oxopropanenitrile;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methoxyethanone;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)propan-1-one;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)butan-1-one;

5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,5-bis(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-acetyl-3-fluoroazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanenitrile;
1-[(3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]cyclopropanol;
1-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]cyclopropanol;
3-{4-[3-fluoro-1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-1-isobutyrylazetidin-3-ol;
1-butyryl-3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-3-ol;
5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-[3-(4-{5-[3,5-bis(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethanol;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanamide;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanamide;
1-[(3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
5-(3,5-dichlorophenyl)-3-{4-[3-fluoro-1-(3-methylbutanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-propionylazetidin-3-ol;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1H-pyrazol-3-ylcarbonyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
4-{2-[3-(4-{5-[3,5-bis(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethyl}pyridine;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-acetyl-3-fluoroazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanenitrile;
4-[(3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]pyridine;

5-[3,5-bis(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(cyclopropylcarbonyl)-3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol;
(3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
2-(1-(cyclopropanecarbonyl)-3-fluoroazetidin-3-yl)-5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)benzonitrile;
5-(3-chloro-5-(trifluoromethyl)phenyl)-3-(4-(3-fluoro-1-(methylsulfonyl)azetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-1-(cyclopropanecarbonyl)azetidine-3-carbonitrile;
1-(cyclopropanecarbonyl)-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-3-carbonitrile;
1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;
2-methyl-1-(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;
Cyclopropyl(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
Cyclopropyl(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone;
1-(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone;
1-isobutyryl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol;

3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethanol;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichlorophenyl)-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-[(3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
5-(3,5-dichlorophenyl)-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-acetylazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]-2-oxoethanol;
1-{[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]carbonyl}cyclopropanol;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]-3-oxopropanenitrile;
1-{[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]carbonyl}cyclopropanol;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-[(3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(3,3-difluoroazetidin-1-yl)carbonyl]-3-fluoroazetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-(3,3,3-trifluoropropanoyl)azetidin-3-ol;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(4-methyl-1,3-oxazol-5-yl)carbonyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
N-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]formamide;
4-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]pyridazine;
1-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]-1H-1,2,4-triazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfonyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1H-pyrazol-1-ylacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1,3-oxazol-5-ylcarbonyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-(3,5-dichloro-4-fluorophenyl)-3-{4-[1-(2,2-difluoropropanoyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-{[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]carbonyl}azetidin-3-ol;
1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-ol;
3-[4-(1-but-3-enoyl-3-fluoroazetidin-3-yl)phenyl]-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-N,N-dimethyl-2-oxoethanesulfonamide;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-{[(trifluoromethyl)thio]acetyl}azetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(2-methoxypropanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(2,2-difluorocyclopropyl)carbonyl]-3-fluoroazetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-3-oxopropan-1-ol;
(2S)-4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol;
4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol;
3-{4-[3-chloro-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[3-chloro-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3-chlorophenyl)-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[5-(3-chloro-4,5-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-(cyclopropylcarbonyl)-azetidin-3-ol;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-difluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;

(2S)-1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-1-oxopropan-2-ol;
(2R)-1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-1-oxopropan-2-ol;
(2S)-4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfinyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[3-azido-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(3-azido-1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
S-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl] ethanethioate;
5-(3-fluorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3-chlorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,4-dichlorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole;
5-(3-chloro-5-fluorophenyl)-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(cyclopropylcarbonyl)-3-{4-[(5R)-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
{[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]sulfonyl}acetonitrile;
1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-3-methanesulfonyl-propan-1-one;
1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-(2,2,2-trifluoro-ethanesulfonyl)-ethanone;
2-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-oxo-ethanesulfonic acid dimethylamide;
2-Benzenesulfonyl-1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-ethanone;
1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-propan-1-one;
cyclopropanecarboxylic acid (1-cyclopropanecarbonyl-3-{4-[5-(3,4-dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-3-yl)-amide;
(3-Amino-3-{4-[5-(3,4-dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-cyclopropyl-methanone;
3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
N-cyclopropyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
N-cyclopropyl-3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-hydroxy-N-propylazetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-hydroxy-N,N-dimethylazetidine-1-carboxamide;

N-ethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-methylazetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-methylazetidine-1-carboxamide;
3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-ethylazetidine-1-carboxamide;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-ethylazetidine-1-carboxamide;
3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-methylazetidine-1-carboxamide;
3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-cyclopropylazetidine-1-carboxamide;
N-cyclopropyl-3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
N-cyclopropyl-3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-(2,2,2-trifluoroethyl)azetidine-1-carboxamide;
3-fluoro-N,N-dimethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N,N-dimethylazetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-(3,3,3-trifluoropropyl)azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-oxetan-3-ylazetidine-1-carboxamide;
3-azido-N,N-dimethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;

2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
2-(1-acetyl-3-fluoroazetidin-3-yl)-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-propionylazetidin-3-yl)benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-isobutyrylazetidin-3-yl)benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-glycoloylazetidin-3-yl)benzonitrile;
2-(1-butyryl-3-fluoroazetidin-3-yl)-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
2-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
2-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-[3-fluoro-1-(methoxyacetyl)azetidin-3-yl]benzonitrile;
2-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-pentanoylazetidin-3-yl)benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-{3-fluoro-1-[(methylthio)acetyl]-azetidin-3-yl}benzonitrile;
2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]pyridine;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;

1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropane-1-thione;
(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
(1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-2-methanesulfonyl-ethanone; and
1-(3-{4-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone,
stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds that were shown to have biological data within at least one of the bio-assays with an ED^{100}, LD^{100}, LD^{90}, and/or ED^{80} value of ≤ 1 µg/mL or 1 µg/fly and are selected from Examples 1-60, 65-70, 72-77, 82, 84-85, 87, 89, 91, 95-101, 103-104, 106-107, 109-110, 113, 116-117, 119-121, 123-126, 128-133, 135-143, 145-146, 148, 152-155, 158, 160-165, 167-171, 173-176, 187-188, 197-199, and 200-224, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds that were shown to have biological data within at least one of the bio-assays with an ED^{100}, LD^{100}, LD^{90}, and/or ED^{80} value of ≤ 0.3 µg/mL or ≤ 0.3 µg/fly and are selected from Examples 1-17, 19-30, 32-54, 56-60, 65-70, 72-74, 76-77, 82, 84, 87, 95-99, 103-104, 117, 131, 133, 135-143, 145-146, 148, 152-155, 158, 160-161, 165, 167-171, 173-175, 187-188, 202-204, 206, 209-221, and 223, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds that were shown to have biological data within at least one of the bio-assays with an ED^{100}, LD^{100}, LD^{90}, and/or ED^{80} value of ≤ 0.1 µg/mL or ≤ 0.1 µg/fly and are selected from Examples 1-17, 19-21, 24, 26-30, 32-34, 36-48, 50-54, 56-60, 65-70, 72-74, 76-77, 84, 87, 95-99, 103-104, 117, 131, 133, 135-137, 139-143, 145-146, 148, 152-155, 158, 160, 165, 168-171, 173-175, 188, 202, 206, 209-213, 215-221, and 223, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds that were shown to have biological data within at least one of the bio-assays with an ED^{100}, LD^{100}, LD^{90}, and/or ED^{80} value of ≤ 0.03 µg/mL and are selected from Examples 1-17, 19-21, 26-28, 32-34, 36-38, 40-48, 50-54, 56, 59-60, 65-66, 68, 70, 72-74, 76, 84, 95-99, 103, 131, 133, 135, 141-143, 145-146, 155, 158, 165, 168-169, 171, 173-175, 202, 206, 209-210, 212-213, 215-216, 218-219, and 221, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds that were shown to have biological data within at least one of the bio-assays with an ED^{100}, LD^{100}, LD^{90}, and/or ED^{80} value of ≤ 0.01 µg/mL or ≤ 0.01 µg/fly and are selected from Examples 1, 5, 10-12,16, 19-21, 26-28, 33-34, 38, 40, 47, 50, 52, 54, 60, 84, 95, 99, 146, 168-169, 173-175, 202, and 221, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds that were shown to have biological data within at least one of the bio-assays with an ED^{100}, LD^{100}, LD^{90}, and/or ED^{80} value of ≤ 0.003 µg/mL and are selected from Examples 11, 19, 40, 169, and 175, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds selected from:

5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfonyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-ol;

1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;

5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole; and

(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone,

stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, are Formula (1) compounds selected from:

2,2-dichloro-1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-fluoro-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-(methylthio)propan-1-one
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-(methylsulfonyl)propan-1-one;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(thietan-3-yl)methanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoro-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-2-(methylsulfonyl)propan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)propan-1-one;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-(methylsulfonyl)cyclopropyl)methanone;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-(3-fluoro-1-(1,1,1,3,3,3-hexafluoropropan-2-yl)azetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3-difluoropropan-1-one;
2-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-N-methyl-2-oxoethanesulfonamide;
2-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-N-isopropyl-2-oxoethanesulfonamide;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(3-hydroxyazetidin-1-yl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-hydroxyphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(thietan-2-yl)methanone;

N-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-yl)acetamide;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-mercapto-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoro-2-hydroxy-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one;
3-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2,2-dimethyl-3-oxopropanenitrile;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3-difluoropropan-1-one;
S-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-yl) ethanethioate;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-2-(methylthio)propan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-2-(methylsulfonyl)propan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropane-2-sulfonamide;
1-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-yl)urea;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone

(E)-N-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)-cyanamide;

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylthio)ethanone;

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one; (3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-thietan-3-yl-methanone;

(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(1,1-dioxidothietan-3-yl)(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;

(E)-N-(1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;

1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;

1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;

1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-{4-[5-(3-Chloro-4-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;

(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;

(E)-N-(1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylthio)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-Fluoro-3-{4-[5-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-thietan-3-yl-methanone;

(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(1,1-dioxidothietan-3-yl)(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3,4-Difluoro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3-Chloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3-chloro-5-fluorophenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-Fluoro-3-{4-[5-trifluoromethyl-5-(3,4,5-trifluorophenyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-thietan-3-yl-methanone;

(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
2-(1-(cyclopropanecarbonyl)-3-fluoroazetidin-3-yl)-5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)benzonitrile; and
cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone, stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention are Formula (1) compounds selected from:
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-Fluoro-3-{5-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-azetidin-1-yl)-thietan-3-yl-methanone;
(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)methanone;

1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;

1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(4-Chloro-3-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylthio)ethanone;

1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-Fluoro-3-{5-[5-trifluoromethyl-5-(3-trifluoromethyl-phenyl)-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-azetidin-1-yl)-thietan-3-yl-methanone;
(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-{5-[5-(3,4-Difluoro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;

(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;

(E)-N-(1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

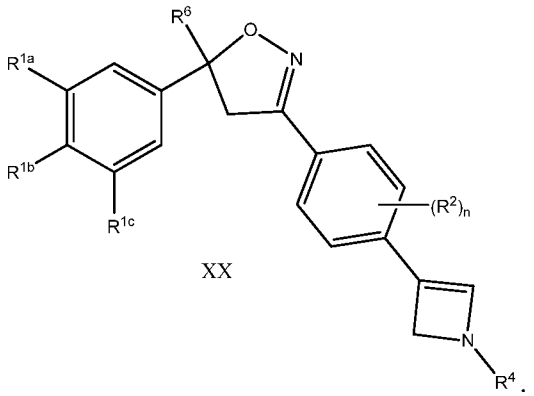
1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-{5-[5-(3-Chloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;

(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(3-Chloro-5-fluorophenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)-1,2-diazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-fluoro-3-{5-[5-trifluoromethyl-5-(3,4,5-trifluorophenyl)-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-azetidin-1-yl)-thietan-3-yl-methanone;
(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone; and
(E)-N-(1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropylidene)cyanamide,
stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

In another aspect of the invention, is a compound of Formula (XX)



XX

In yet another aspect of the invention is a composition that comprises a) a Formula (XX) compound, stereoisomers thereof, or a veterinarily or pharmaceutically acceptable salt thereof, and (b) a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. The variables R^{1a}, R^{1b}, R^{1c}, R^2, R^4, R^6, and n are as defined herein. Preferably, the composition comprises a therapeutically effective amount of a Formula (XX) compound, stereoisomer thereof, or veterinarily or pharmaceutically acceptable salt thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier.

In another aspect of the invention, is a veterinary or pharmaceutical composition that comprises a) a Formula (1) or Formula (XX) compound, stereoisomers thereof, or a veterinarily or pharmaceutically acceptable salt thereof, and (b) a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. Preferably, the composition comprises a therapeutically effective amount of a Formula (1) or Formula (XX) compound, stereoisomer thereof, or veterinarily or pharmaceutically acceptable salt thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier.

The composition may comprise at least one additional veterinary agent. Prefered additional veterinary agents include endoparasiticides, endectocides, ectoparasiticides, insecticides, and anthelmintics.

In yet another aspect of the invention is the use of a Formula (1) or Formula (XX) compound for the manufacture of a medicament.

In yet another aspect of the invention is a method for treating a parasitic infection or infestation in an animal that includes the step of administering to said animal, in need of such treatment, a therapeutically effective amount of a compound of the present invention, stereoisomer thereof, or veterinarily or pharmaceutically acceptable salt thereof. Formula (1) and Formula (XX) compounds, stereoisomers thereof, veterinarily or pharmaceutically acceptable salts thereof, or compositions thereof, may be administered orally, topically, intramuscularly, subcutaneously, and by intraperitoneal injection. Preferably, the animal is a mammal. More preferably, the mammal is a companion animal or livestock. Preferably, the companion animal is a dog, cat, or horse. Preferably, livestock is bovine, swine, or ovine. Preferably, the animal is a bird. More preferably, the bird is fowl. Preferably the animal is a fish. The compounds of the

present invention, and compositions thereof, can be admininstered to the animal by oral, topical, and intramuscular-, intraperitoneal-, and subcutaneous-injection. Preferrably, the compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically.

In yet another aspect of the invention is a method for treating a parasitic infection or infestation in an animal that includes the step of administering to said animal in need of such treatment, a therapeutically effective amount of a Formula (1) or Formula (XX) compound, stereoisomer thereof, or veterinarily or pharmaceutically acceptable salt thereof, in combination with at least one additional veterinary agent. Formula (1) or Formula (XX) compounds, stereoisomers thereof, veterinarily or pharmaceutically acceptable salts thereof, alone, with an additional veterinary agent, or composition thereof, may be administered to the animal orally, topically, or by injection (intramuscular, intraperitoneal, or subcutaneous). Prefered additional veterinary agents include endoparasiticides, endectocides, ectoparasiticides, insecticides, and anthelmintics.

Compounds of the present invention alone, or in combination with an additional veterinary agent may be administered as (a) a single veterinary composition which comprises a compound of the present invention, stereoisomer thereof, veterinarily or pharmaceutically acceptable salt thereof, and optionally, at least one additional veterinary agent as described herein and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier; or (b) two separate veterinary compositions comprising (i) a first composition comprising a compound of the present invention, stereoisomer thereof, veterinarily or pharmaceutically acceptable salt thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional veterinary agent, as described herein and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. The veterinary or pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

In another aspect of the invention are compositions comprising a Formula (1) compound, stereoisomer thereof, pharmaceutical or veterinary salt thereof,

optionally, at least one additional veterinary agent, which are useful for the control and treatment of parasites in animals.

All of the recited patent publications, patents, and priority documents herein are incorporated by reference, in their entirety.

DEFINITIONS

For purposes of the present invention, as described and claimed herein, the following terms and phrases are defined as follows:

"Additional veterinary agent(s)" as used herein, unless otherwise indicated, refers to other veterinary or pharmaceutical compounds or products that provide a therapeutically effective amount of said agents that are useful for the treatment of a parasitic infection in an animal, as described herein.

"Alkoxy", as used herein, unless otherwise indicated, refers to an oxygen moiety having a further alkyl substituent. The alkyl portion (i.e., alkyl moiety) of an alkoxy group has the same definition as below. Non-limiting examples include: $-OCH_3$, $-OCH_2CH_3$, and the like.

"Alkyl", as used herein, unless otherwise indicated, refers to saturated monovalent hydrocarbon alkane radicals of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched and may be unsubstituted or substituted. For example, the term "$(C_1$-$C_6)$ alkyl" refers to a monovalent, straight or branched aliphatic group containing 1 to 6 carbon atoms. Non-exclusive examples of $(C_1$-$C_6)$ alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, sec-butyl, t-butyl, n-propyl, n-butyl, i-butyl, s-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, 2-methylpentyl, hexyl, and the like. The alkyl moiety may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Alkyl groups are optionally substituted as described herein.

"Alkenyl" as used herein, unless otherwise indicated, refers to a straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon double bond (for example -C=C-, or $-C=CH_2$). Non-exclusive examples of alkenyl include: ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-pentenyl, and the like.

"Alkynyl" as used herein, unless otherwise indicated, refers to straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon triple bond (for example, -C≡C- or -C≡CH). Non-exclusive examples of alkynyl include: ethynyl, 2-propynyl, 1-methyl-2-propynyl, 2-butynyl, 3-butynyl, 2-methyl-3-butynyl, and the like.

"Animal", as used herein, unless otherwise indicated, refers to an individual animal that is a mammal, bird, or fish. Specifically, mammal refers to a vertebrate animal that is human and non-human, which are members of the taxonomic class Mammalia. Non-exclusive examples of non-human mammals include companion animals and livestock. Non-exclusive examples of a companion animal include: dog, cat, llama, goat, and horse. Preferred companion animals are dog, cat, and horse. More preferred is dog. Equally preferred is cat or horse. Non-exclusive examples of livestock include: swine, camel, rabbits, goat, sheep, deer, elk, bovine (cattle), and bison. Preferred livestock is cattle. Equally preferred is swine. Specifically, bird refers to a vertebrate animal of the taxonomic class Aves. Birds are feathered, winged, bipedal, endothermic, and egg-laying. Non-exclusive examples of bird include, poultry (e.g., chicken, turkey, duck, and geese), all of which are also referred to herein as fowl. Specifically, fish refers to the taxonomic class Chondrichthyes (cartilaginous fishes, e.g., sharks and rays) and Osteichthyes (bony fishes) which live in water, have gills or mucus-covered skin for respiration, fins, and may have scales. Non-exclusive examples of fish include shark, salmon, trout, whitefish, catfish, tilapia, sea bass, tuna, halibut, turbot, flounder, sole, striped bass, eel, yellowtail, grouper, and the like.

"Compounds of the present invention", as used herein, unless otherwise indicated, refers to compounds of Formula (1) or Formula (XX), stereoisomers thereof, and veterinarily or pharmaceutically acceptable salts thereof.

"Cycloalkyl", as used herein, unless otherwise indicated, includes fully saturated or partially saturated carbocyclic alkyl moieties. Non-limiting examples of partially saturated cycloalkyls include: cyclopropene, cyclobutene, cycloheptene, cyclooctene, cyclohepta-1,3-diene, and the like. Preferred cycloalkyls are 3- to 6-membered saturated monocyclic rings including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The cycloalkyl group may be attached to the chemical moiety by any one of the carbon atoms within the

carbocyclic ring. Cycloalkyl groups are optionally substituted with at least one substituent. Further when used in compound words such as alkylcycloalkyl, said alkyl and cycloalkyl moiety has the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Examples of “alkylcycloalkyl” include, methylcyclopropane (-CH_2-cyclopropane), ethylcyclopropane (-CH_2CH_2-cyclopropane), methylcyclobutane (-CH_2-cyclobutane), ethylcyclobutane (-CH_2CH_2-cyclobutane), methylcyclohexane (-CH_2-cyclohexane), and the like. Cycloalkyls are optionally substituted as described herein.

“Halogen" or “halo”, as used herein, unless otherwise indicated, refers to fluorine, chlorine, bromine and iodine. Further, when used in compound words such as "haloalkyl", “haloalkoxy”, “haloalkenyl”, or “haloalkynyl”, said alkyl, alkoxy, alkenyl, and alkynyl may be partially or fully substituted with halogen atoms which may be the same or different and said alkyl, alkoxy, alkenyl, and alkynyl moiety has the same meaning as above and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Examples of "haloalkyl" include F_3C-, $ClCH_2$-, CF_3CH_2- and CF_3CCl_2-, and the like. The term "haloalkoxy" is defined analogously to the term "haloalkyl". Examples of "haloalkoxy" include CF_3O-, CCl_3CH_2O-, $HCF_2CH_2CH_2O$- and CF_3CH_2O-, and the like. The term "haloalkenyl is defined analogously to the term "haloalkyl" except that the aliphatic chain contains at least one carbon-carbon double bond. Examples of "haloalkenyl” include $CF_3C=C$-, $CCl_3C=C$-, $HCF_2C=C$- and $CF_3C=CC$-, and the like. The term "haloalkynyl" is defined analogously to the term "haloalkyl" except that the aliphatic chain contains at least one carbon-carbon triple bond. Examples of "haloalkynyl" include $CF_3C\equiv C$-, $CCl_3C\equiv C$-, $HCF_2C\equiv C$- and $CF_3C\equiv CC$-, and the like.

“Heterocycle”, as used herein, unless otherwise indicated, refers to a partially saturated or saturated 3- to 6-membered monocyclic ring containing one or more heteroatoms each independently selected from N, O, or S, preferably from one to four heteroatoms. Non-exclusive examples of heterocycle include oxiranyl, thiaranyl, aziridinyl, oxetanyl, thiatanyl, azetidinyl, tetrahydrofuran, tetrahydrothiophene, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, tetrahydropyridinyl, 2H-azirine, 2,3-dihydro-azete, 3,4-dihydro-2H-pyrrole, and the

like. The heterocycle group may be attached to the chemical moiety by any one of the carbon atoms or heteroatoms (e.g., N, O, and S) within the monocyclic ring. Heterocycles are optionally substituted as described herein.

"Heteroaryl" or "Het", as used herein, unless otherwise indicated, refers to a 5- to 6-membered aromatic monocyclic ring or an 8- to 10-membered fused aromatic ring where said monocyclic- and fused-ring moiety contains one or more heteroatoms each independently selected from N, O, or S, preferably from one to four heteroatoms. Non-exclusive examples of monocyclic heteroaryls include pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. Non-exclusive examples of fused heteroaryls include: benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, benzo[1,2,5]thiadiazole, and the like. The heteroaryl group may be attached to the chemical moiety by any one of the carbon atoms or heteroatoms (e.g., N, O, and S) within the monocyclic or fused ring. Heteroaryls are optionally substituted as described herein.

"Optionally substituted", is used herein interchangeably with the phrase substituted or unsubstituted. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other. An optionally substituted group also may have no substituents. Therefore, the phrase "optionally substituted with at least one substituent" means that the number of substituents may vary from zero up to a number of available positions for substitution.

"Parasite(s)", as used herein, unless otherwise indicated, refers to endoparasites and ectoparasites. Endoparasites are parasites that live within the body of its host and include helminths (e.g., trematodes, cestodes, and nematodes) and protozoa. Ectoparasites are organisms of the Arthropoda phylum (e.g., arachnids, insects, and crustaceans (e.g., copepods-sea lice) which feed through or upon the skin of its host. Preferred arachnids are of the order Acarina, e.g., ticks and mites. Preferred insects are midges, fleas, mosquitos, biting flies (stable fly, horn fly, blow fly, horse fly, and the like) and lice. Preferred Compounds of the present invention can be used for the treatment of parasites, i.e., treatment of a parasitic infection or infestation.

"Therapeutically effective amount", as used herein, unless otherwise indicated, refers to an amount of the compounds of the present invention that (i) treat the particular parasitic infection or infestation, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular parasitic infection or infestation, or (iii) prevents or delays the onset of one or more symptoms of the particular parasitic infection or infestation described herein.

"Treatment", "treating", and the like, as used herein, unless otherwise indicated, refers to reversing, alleviating, or inhibiting the parasitic infection, infestation, or condition. As used herein, these terms also encompass, depending on the condition of the mammal, preventing the onset of a disorder or condition, or of symptoms associated with a disorder or condition, including reducing the severity of a disorder or condition or symptoms associated therewith prior to affliction with said infection or infestation. Thus, treatment can refer to administration of the compounds of the present invention to a mammal that is not at the time of administration afflicted with the infection or infestation. Treating also encompasses preventing the recurrence of an infection or infestation or of symptoms associated therewith as well as references to “control” (e.g., kill, repel, expel, incapacitate, deter, eliminate, alleviate, minimize, and eradicate).

"Veterinary acceptable” as used herein, unless otherwise indicated, indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, composition, and/or the mammal being treated therewith. The term “pharmaceutically” acceptable has the same meaning as that recited for “veterinarily” acceptable.

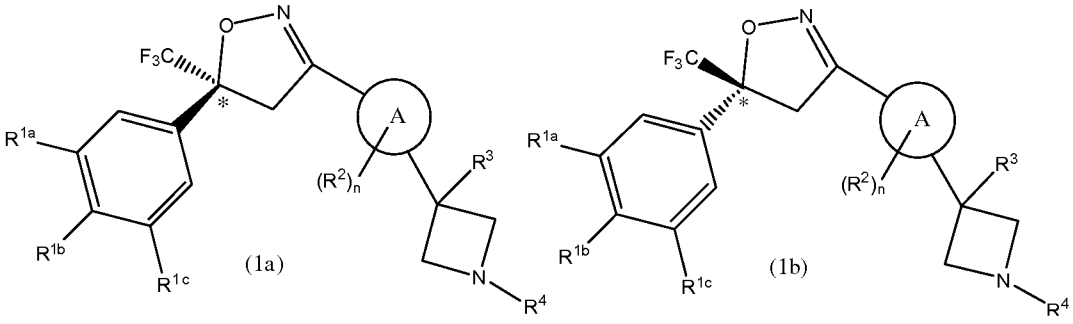
The “” as used herein, unless otherwise indicated, refers to a point of attachment.

DETAILED DESCRIPTION

The present invention provides Formula (1) compounds, stereoisomers thereof, as well as veterinary compositions that are useful as antiparasitic agents for animals and birds, in particular, compounds that act as ectoparasiticides. Further, the present invention provides Formula (XX) compounds, stereoisomers thereof, as well as veterinary compositions that are useful as antiparasitic agents for animals and birds, in particular, compounds that act as ectoparasiticides.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, "Reagents for Organic Synthesis", 1; 19, Wiley, New York (1967, 1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)).

Compounds of this invention can exist as one or more stereoisomers. The various stereo isomers include enantiomers, diastereomers and atropisomers. One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, and/or to selectively prepare said stereoisomers. The compounds of the invention may be present as a mixture of stereoisomers, individual stereo isomers or as an optically active form. For example, two possible enantiomers of Formula 1 are depicted as Formula 1a and Formula Ib involving the isoxazoline chiral center identified with an asterisk (*). Molecular depictions drawn herein follow standard conventions for depicting stereochemistry.

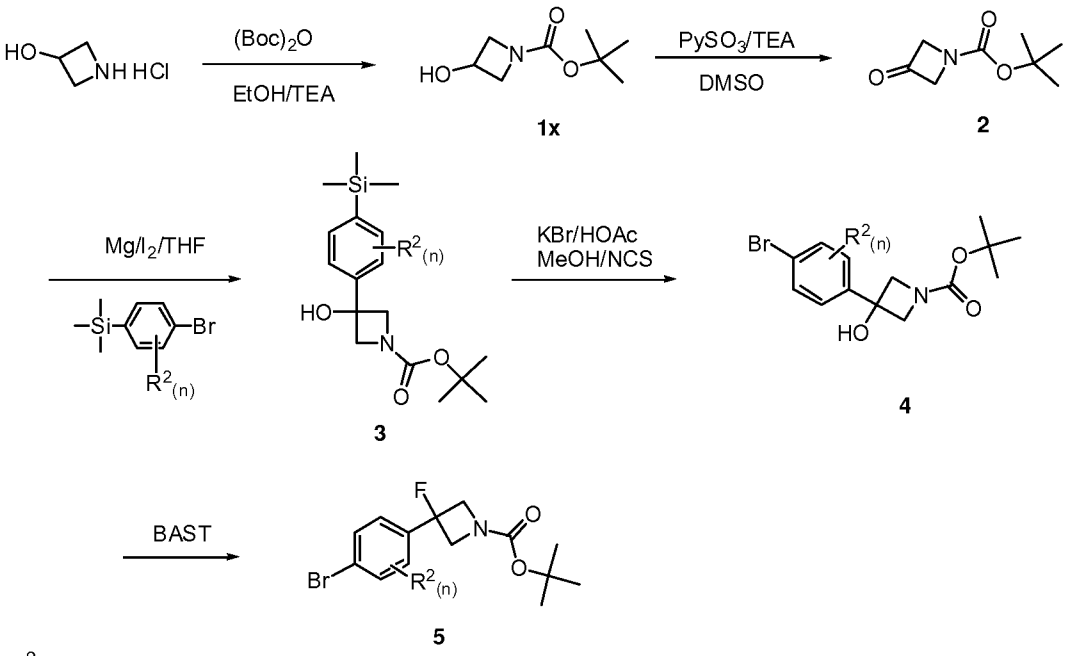


For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing key intermediates and compounds of the present invention. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate

that other suitable starting materials, reagents, and synthetic routes may be used to synthesize the intermediates and compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry. Schemes 1-17 outline the general procedures useful for the preparation of compounds of the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation.

In the Schemes and Examples below, the following catalysts/reactants include: N,N-dimethyl formamide (DMF); N-N-dimethylsulfoxide (DMSO); N-chloro-succinimide (NCS); N-bromo-succinimide (NBS); ethanol (EtOH); methanol (MeOH); tetrahydrofuran (THF); triethylamine (TEA); acetonitrile (CH_3CN, ACN); n-BuOH (n-butanol); lithium hydroxide (LiOH); hydrazine (H_2NNH_2); potassium bicarbonate ($KHCO_3$); potassium carbonate (K_2CO_3); diethyl ether (Et_2O); sodium carbonate (Na_2CO_3); hydroxylamine (NH_2OH); sulfuric acid (H_2SO_4); ammonium chloride (NH_4Cl); dichloromethane (CH_2Cl_2); hydrochloric acid (HCl); trifluoroacetic acid (TFA); methyl tert-butyl ether (MTBE); potassium acetate (KOAc); isopropyl alcohol (IPA); n-butyllithium (n-BuLi); triethylamine (Et_3N); ethyl acetate (EtOAc); sodium acetate (NaOAc); bis (triphenylphosphine) palladium II chloride ($PdCl_2(PPh_3)_2$) from Strem; N,N,N′,N′-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU); 1-hydroxybenzotriazole hydrate (HOBt); di-tert-butyl dicarbonate (Boc_2O); carbonyldiimidazole (CDI); diethylaminosulfur trioxide (DAST); 2,2'-azobis(2-methylpropionitrile) (AIBN); tetrabutylammonium fluoride (TBAF); Bis(2-methoxyethyl)aminosulfur trifluoride (BAST); tert-butyl carbonate (Boc); pyridine sulphurtrioxide ($PySO_3$); triphenylphosphine palladium ($Pd(PPh_3)_4$); 4-dimethylaminopyridine (DMAP); hexamethyldisilazide (KHMDS); (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO); and diisobutylaluminium hydride (DIBAL-H).

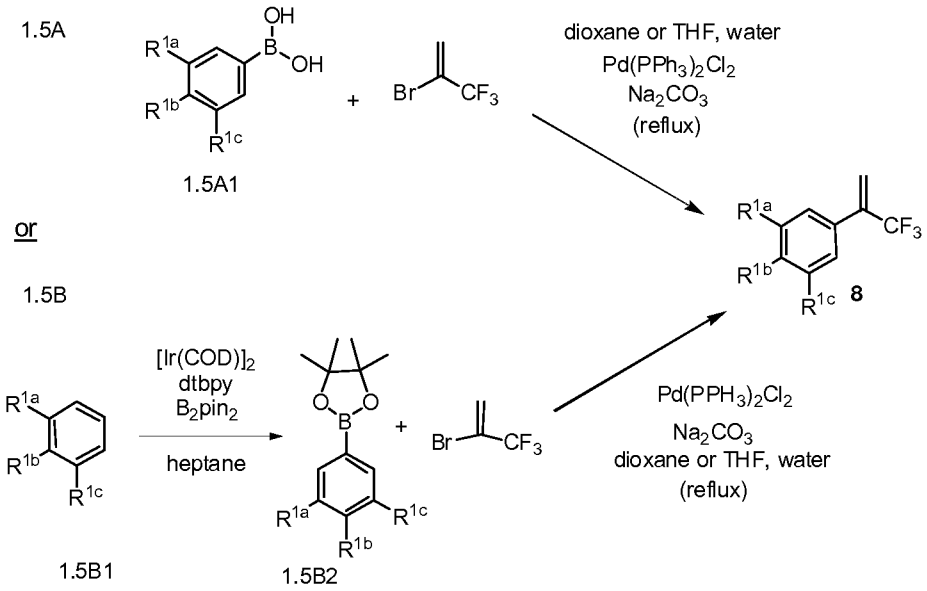
Scheme 1



R^2 and n are as defined herein.

The phenyl azetidines can be prepared as shown in Scheme 1. Boc protection of hydroxyazetidine hydrochloride followed by oxidation of the hydroxyl group gave the ketoazetidine **2**. This could be condensed with bromoaryl silanes by formation of the aryl Grignard reagent and subsequent condensation with the ketone to provide the silyl phenyl azetadine **3**. Replacement of the silane with bromine was accomplished by treatment with potassium bromide in acetic acid to give the desired bromophenyl azetidine **4**. Fluorination of the hydroxyazetidine **4** can be accomplished by treatment with BAST to provide **5**.

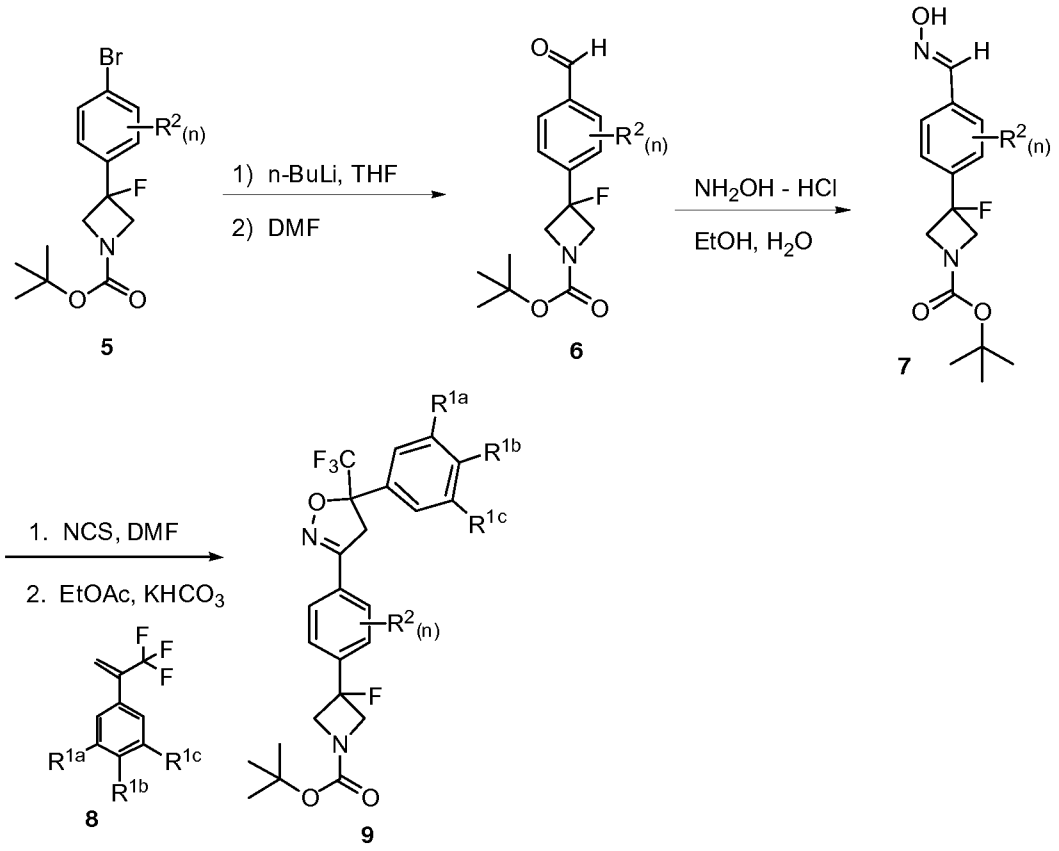
Scheme 1.5



R^{1a}, R^{1b}, and R^{1c} are as defined herein.

The aryl olefins (**8**) can be prepared according to Scheme 1.5. The requisite organoborates can be prepared as boronate ester intermediates (1.5B2) from literature methods (*Org. Lett.* 2007, *9*, 761-764) or purchased as boronic acids (1.5A1) such as 3,5-dichloroboronic acid from Aldrich. Intermediate 1.5A1 or 1.5B2 compounds can be added to dioxane or THF and water, followed by 2-bromo-3,3,3-trifluoropropene, potassium carbonate, and bis (triphenylphosphine) palladium II chloride to afford the intermediate (**8**) compounds.

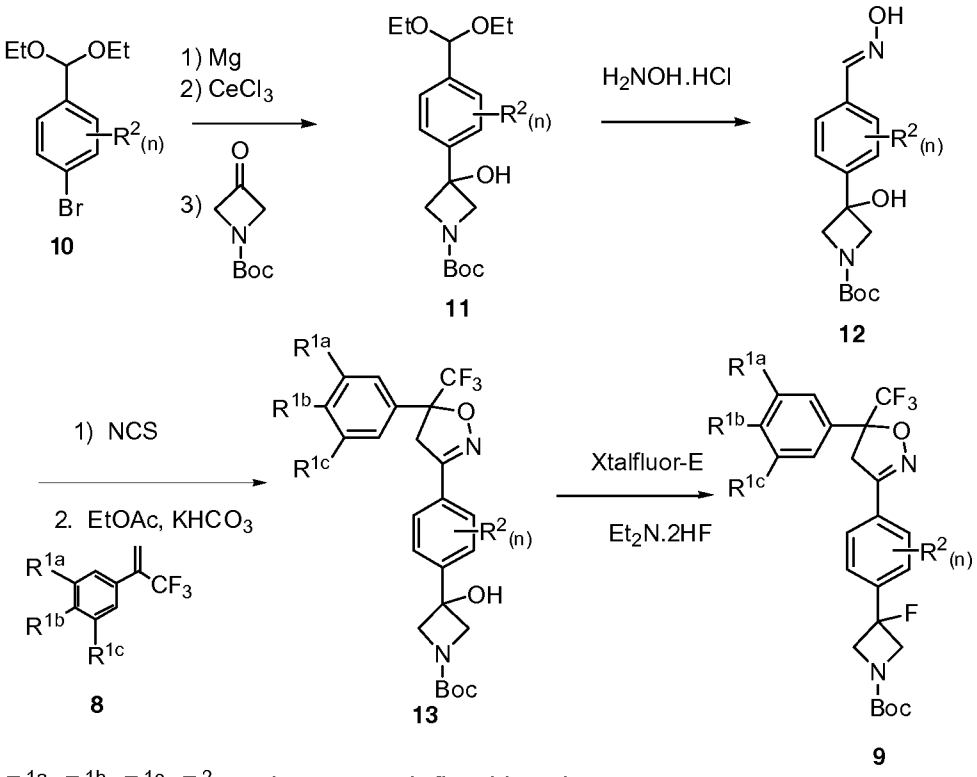
Scheme 2



R^{1a}, R^{1b}, R^{1c}, R^2, and n are as defined herein.

Scheme 2 describes the preparation of isoxazolines from the aryl bromides or aryl aldehydes.. From the bromophenyl azetidine **5**, halogen-metal exchange followed by quenching with DMF provides the aryl aldehyde **6** which can also be prepared by other methods (Schemes 3 and 4). The aldehyde is condensed with hydroxylamine to provide the oxime **7**. From the oxime, the isoxazoline ring can be prepared in a one-pot, two step process. Treatment of the oxime with N-chlorosuccinimide provides the chlorooxime which undergoes [3+2] cyclization with aryl olefins **8** to provide the isoxazoline **9**. These steps can also be done as separate reactions. Removal of the Boc protecting group on the azetidine can be accomplished by treatment with trifluoroacetic acid.

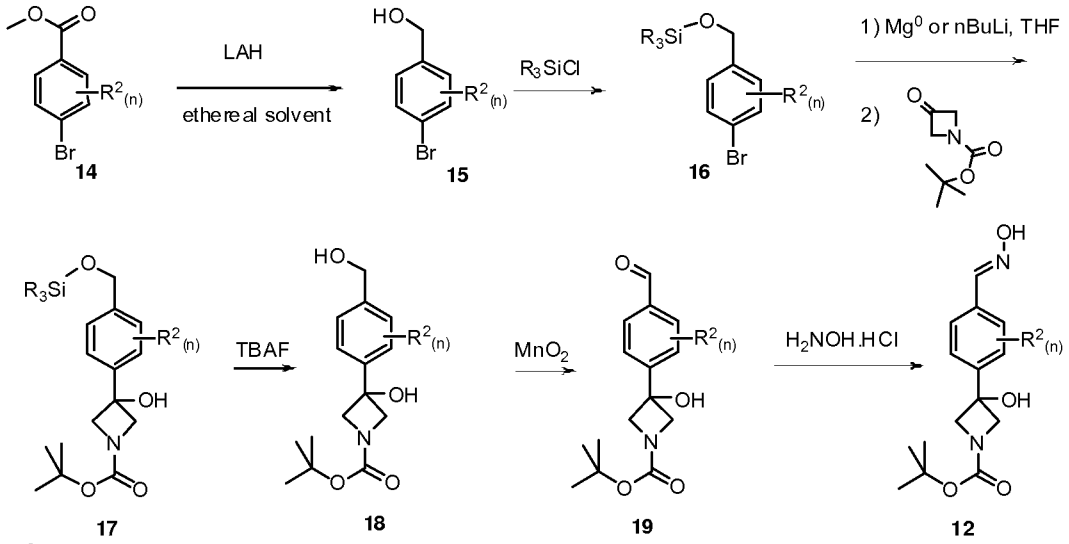
Scheme 3



R^{1a}, R^{1b}, R^{1c}, R^2, and n are as defined herein.

An alternate synthesis of the Boc-protected azetidines is shown in Scheme 3. Reaction of 4-bromobenzaldehyde diethylacetal **10** with Mg metal or iPrMgCl followed by $CeCl_3$ provides an organometallic reagent that adds to N-protected 3-azetidinone. Condensation with hydroxylamine, chlorination and cyclization as described in Scheme 2 provides the isoxazoline **13**. Fluorination of the hydroxyl group can be achieved by reaction with Xtaflor-E.

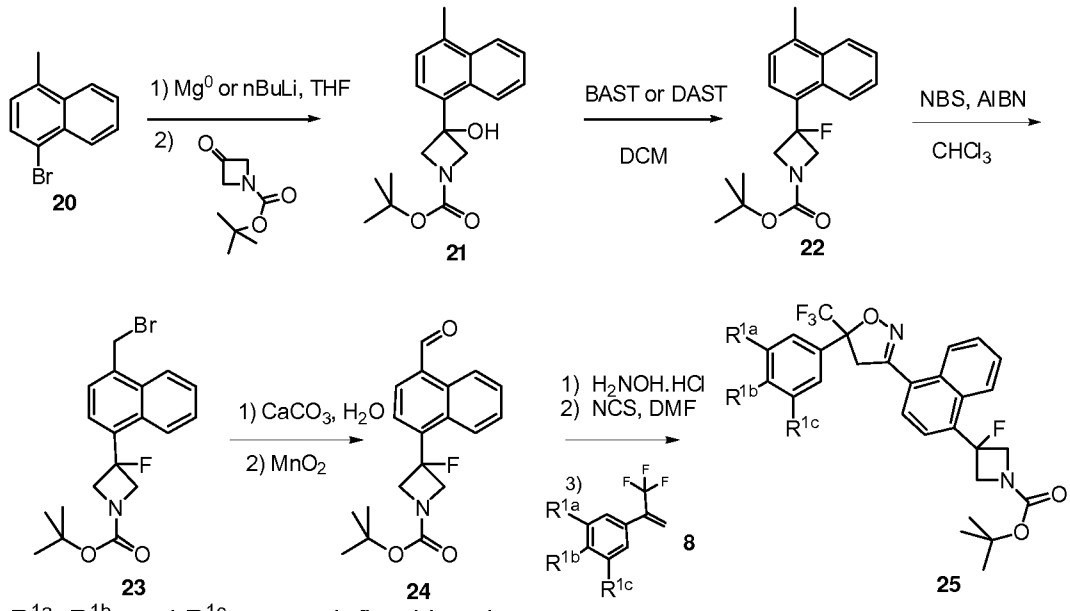
Scheme 4



R^2 and n are as defined herein.

Alternatively, the phenyl azetidines can be prepared from bromo aryl esters or bromoaryl methanols as shown in Scheme 4. Reduction of the aryl ester with lithium aluminum hydride provides the aryl methanol **15** which can be protected as a silane. Formation of the aryl Grignard with magnesium or halogen metal exchange provides the aryl anion which can condense with the N-protected azetidinone **2** to give the aryl azetidine **17**. Deprotection of the alcohol and oxidation provides the formyl phenylazetidine **19** which can undergo condensation with hydroxylamine to provide the oxime **12**.

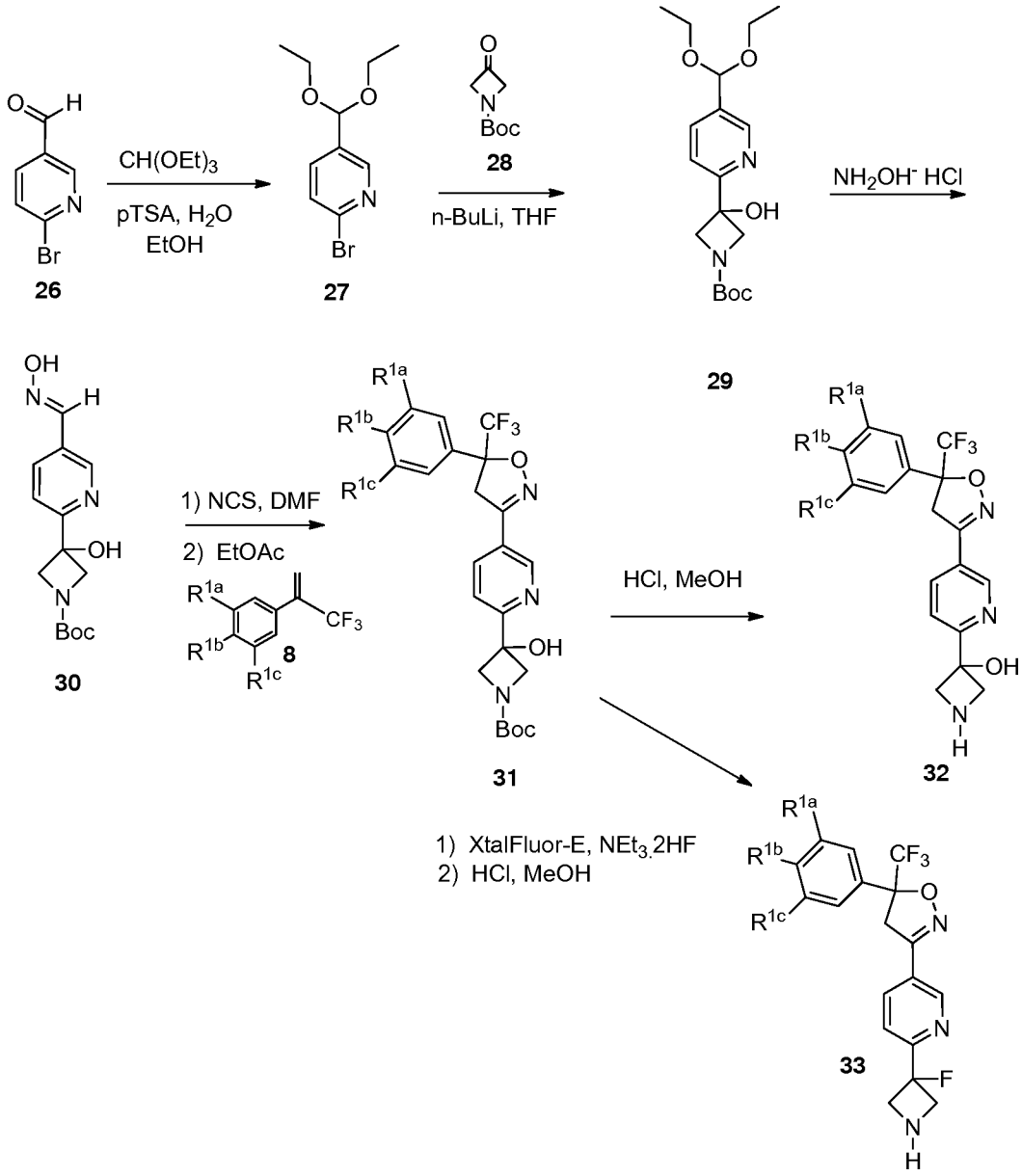
Scheme 5



R^{1a}, R^{1b}, and R^{1c} are as defined herein.

In a similar fashion, compounds in which the central phenyl ring is replaced with condensed aryl or heteroaryl groups can be prepared as shown in Scheme 5 for the naphthyl series. The desired naphthyl azetidines can be prepared from 1-bromo-4-methylnaphthalene as shown in Scheme 5. Halogen-metal exchange or formation of the Grignard reagent from the bromonaphthalene **20** provides the naphthyl anion which can condense with the ketoazetidine **2** to give the naphthyl azetidine **21**. Fluorination of the resulting alcohol can be accomplished by treatment with BAST, DAST or Xtafluor-E to give the fluoroazetidine **22**. Bromination of the methyl group followed by hydroxylation and oxidation provides the desired aldehyde **24** which can undergo oxime formation, chlorination and cyclization as described in Scheme 2 to provide the isoxazolines **25**.

Scheme 6

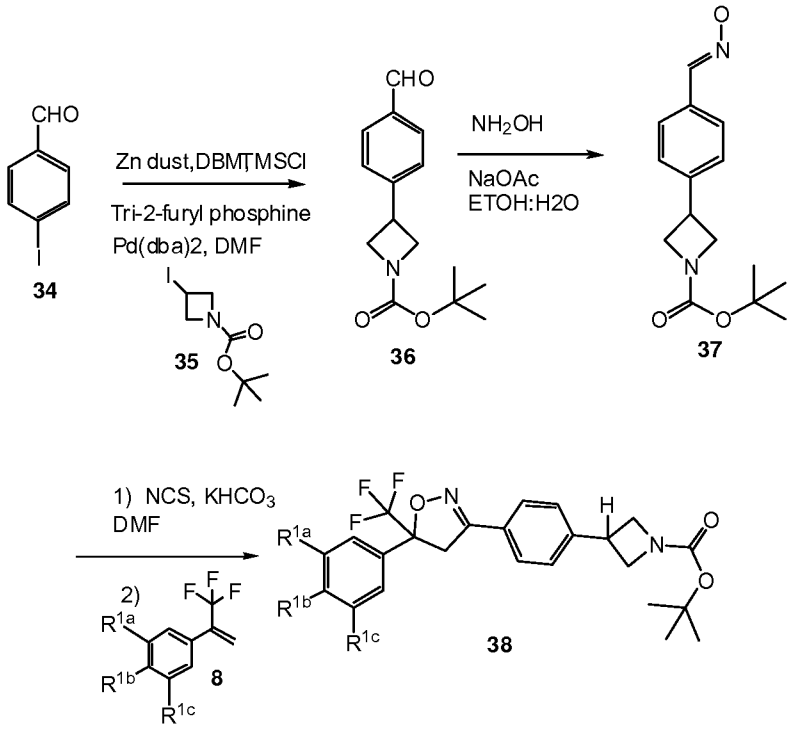


R^{1a}, R^{1b}, and R^{1c} are as defined herein.

Compounds in which the central phenyl ring is replaced with heteroaryl groups can be prepared as shown in Scheme 6 for the pyridyl series. Formation of the diethylacetal can be accomplished with ethyl formate. Treatment of the iodopyridine **27** with n-BuLi provides the organometallic reagent which adds to the N-protected 3-azetidinone **28**. Condensation of the resulting masked aldehyde with hydroxylamine followed by chlorination and cyclization provides the isoxazoline **31**. The benzhydryl protecting group can be removed by

hydrogenation or treatment with chloroethyl chloroformate to provide the hydroxyazetidine **32** or alternatively, the hydroxyazetidine **31** can be fluorinated by treatment with XtaFluor-E followed by a similar deprotection to provide the fluoroazetidine **33**.

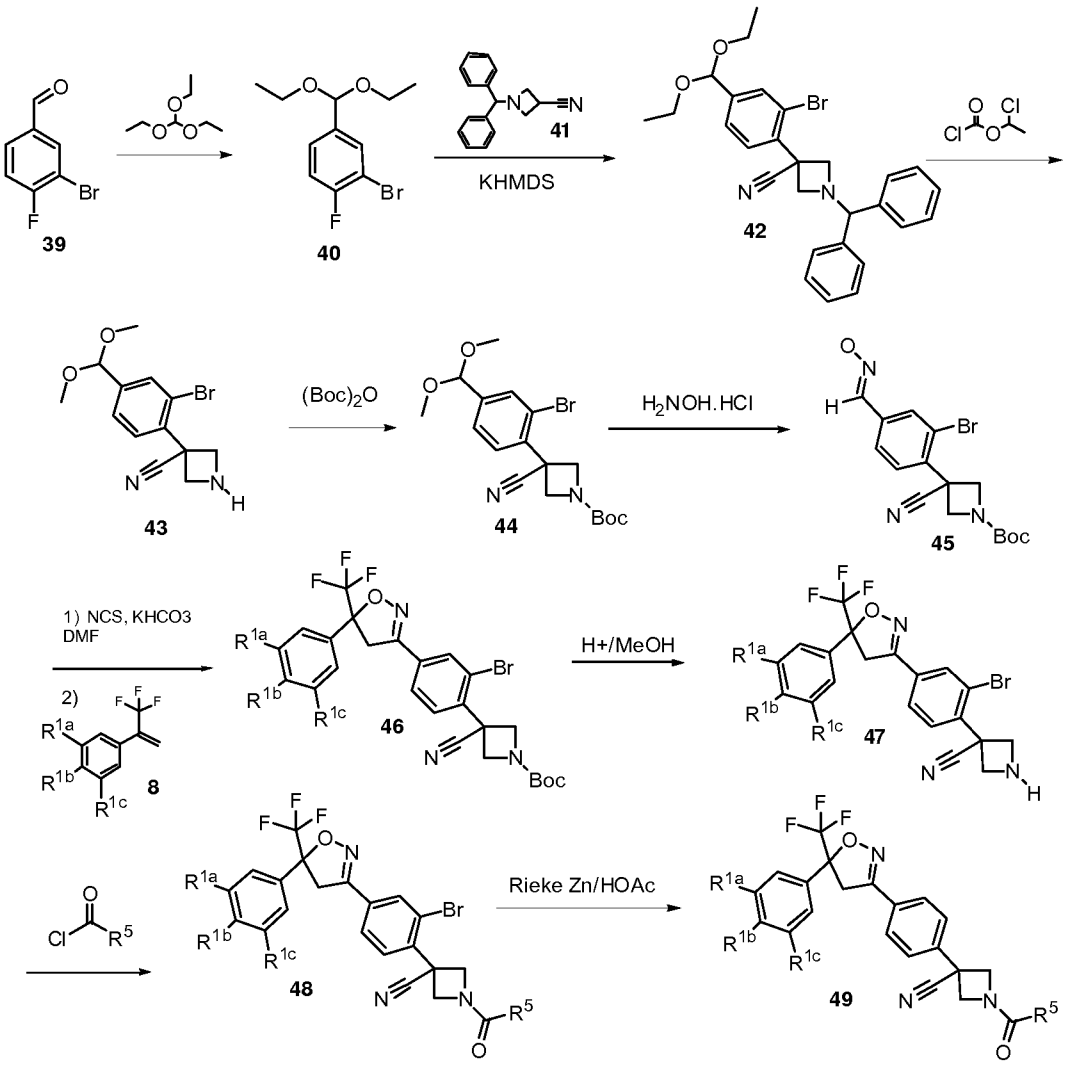
Scheme 7



R^{1a}, R^{1b}, and R^{1c} are as defined herein.

The substituent on the azetidine ring can be eliminated as shown in Scheme 7. A palladium/zinc catalyzed cross coupling reaction of the iodoaldehyde **34** with the N-protected iodoazetidine **35** provides the phenyl azetidine **36**. This aldehyde can undergo condensation with hydroxylamine, chlorination and cyclization as described in Scheme 2 to give the hydrido compound **38**.

Scheme 8

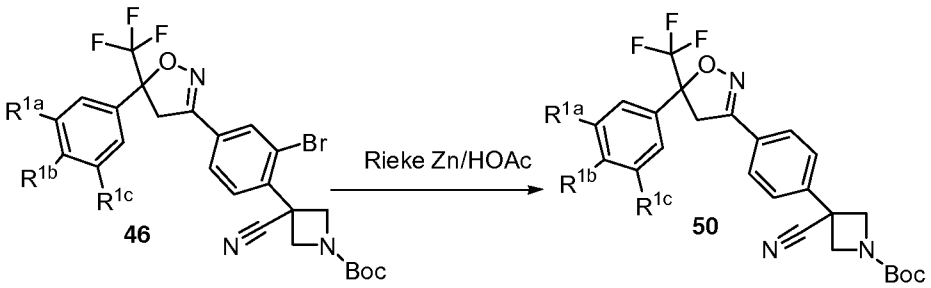


R^{1a}, R^{1b}, and R^{1c} are as defined herein.

Incorporation of a nitrile as the axial substituent of the floroazetidine can be accomplished as shown in Scheme 8. From the aldehyde **39**, formation of the acetal can be accomplished with ethyl formate. The aryl fluorine can then undergo displacement by the anion of 1-benzhydrylazetidine-3-carbonitrile to give the phenylazetidine **42**. Deprotection of the benzhydrylgroup, followed by reprotection with Boc anhydride provides the N-Boc phenylazetidne **44**. This masked aldehyde can undergo condensation with hydroxylamine, chlorination and cyclization as described in Scheme 2 to give the isoxazolines **46**. Removal of the Boc protecting group and acylation of the resulting amine gives the isoxazoline

amides **48**. The bromine on the phenyl ring can be removed by treatment with Reike Zinc in acetic acid to give the isoxazolines **49**.

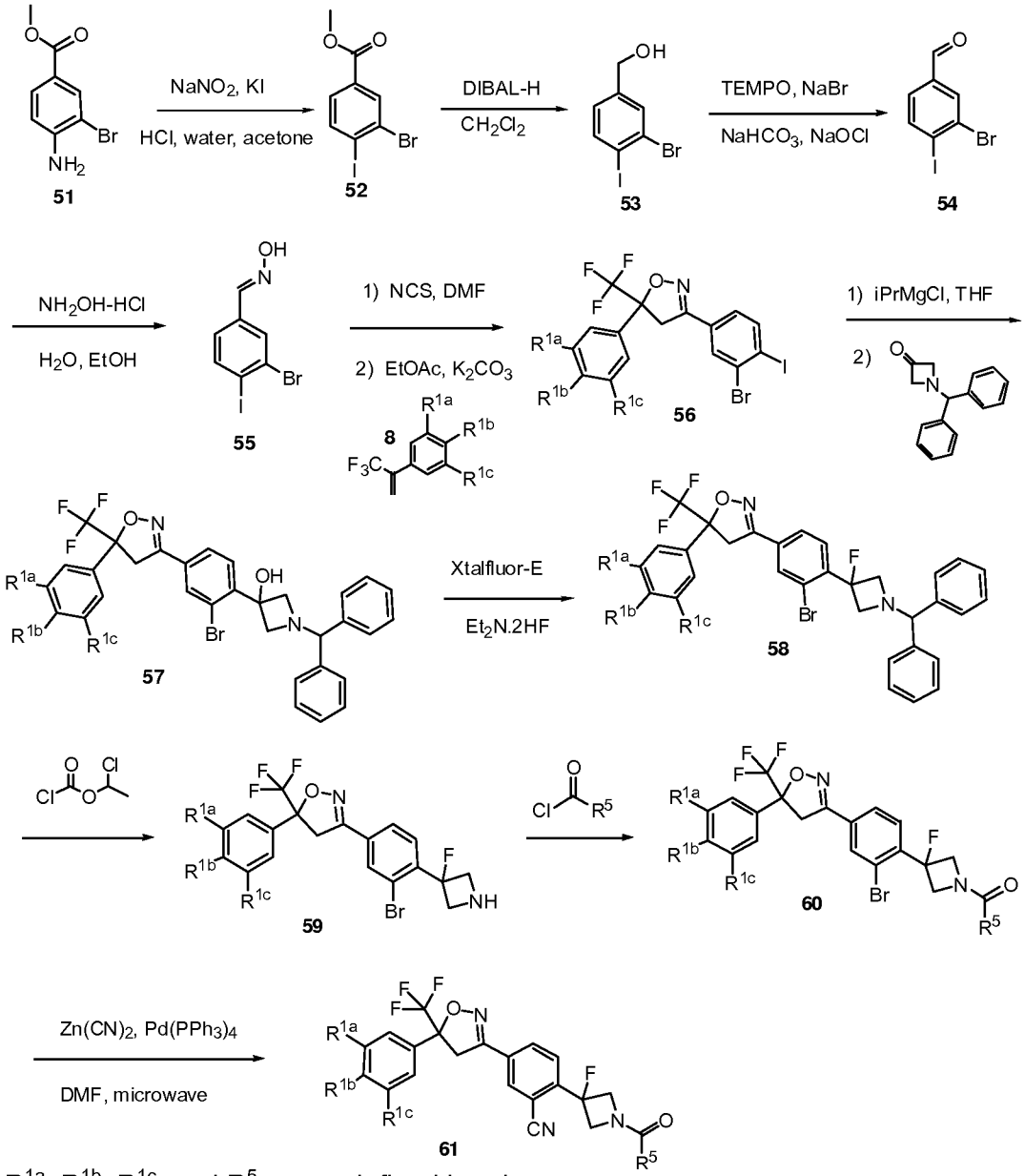
Scheme 9



R^{1a}, R^{1b}, and R^{1c} are as defined herein.

The bromine on the phenyl ring can also be removed at earlier steps in the sequence in order to form a template amenable to parallel synthesis of amides, amines, ureas, and the like.

Scheme 10

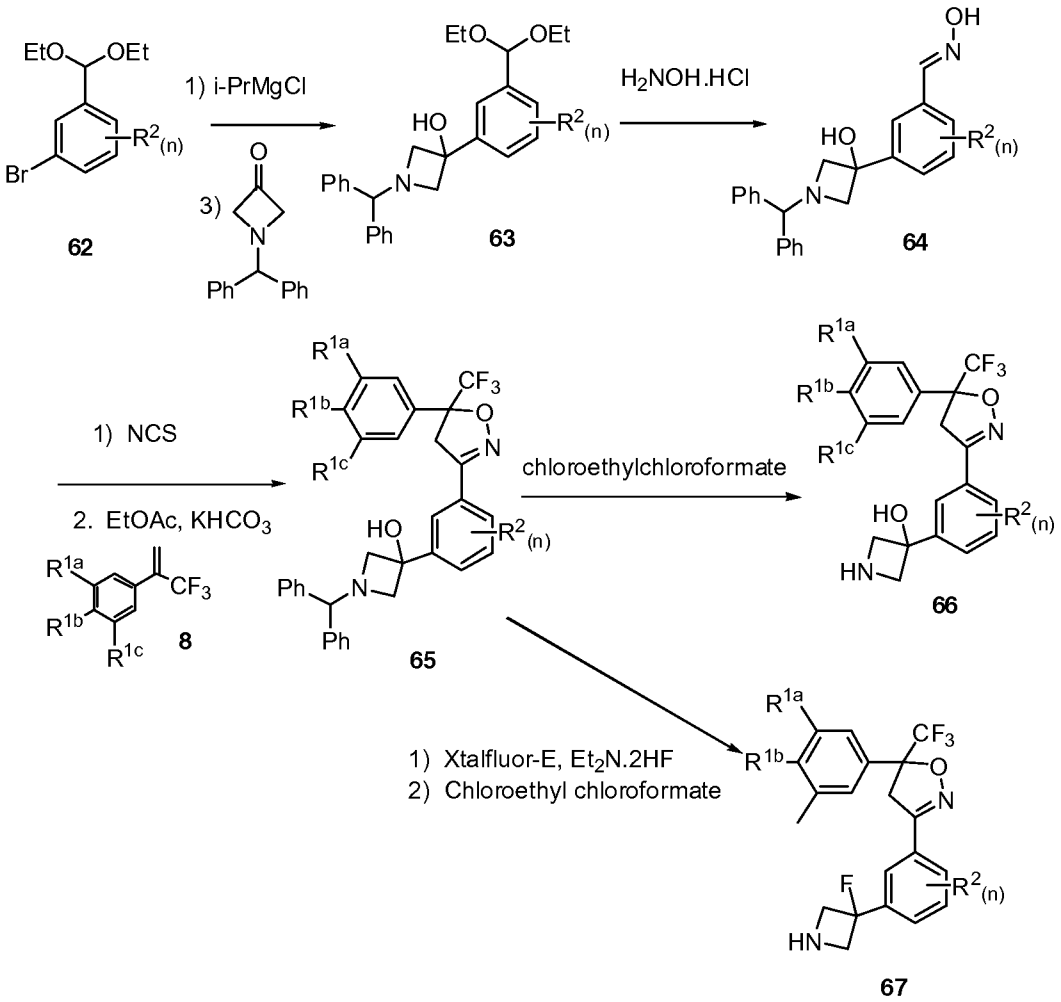


R^{1a}, R^{1b}, R^{1c}, and R^5 are as defined herein.

The identity of the R^2 substituent can be altered either by choice of starting material or by interconversion of substituents on the aryl ring as shown in Scheme 10. The iodoester **52** can be prepared by treatment of the aminoester **51** with sodium nitrite and potassium iodide. Reduction of the ester to the alcohol with diisobutylaluminum hydride followed by oxidation with TEMPO affords the iodoaldehyde **54**. This aldehyde can undergo condensation with hydroxylamine, chlorination and cyclization as described in Scheme 2 to give the isoxazoline **56**.

Grignard formation using iPrMgCl occurs selectively with the iodine and the resulting organometallic adds to the N-protected azetidinone to afford the phenylazetidine **57**. Fluroination of the azetidine can be accomplished with Xtafluro-E. Removal of the benzhydryl protecting group with chloroethylchloroformate and acylation of the resulting amine with acid chlorides or anhydrides (or coupling with desired organic acids) provides the phenylazetidine amides **60**. At this point, the bromine of the phenyl ring can undergo interconversion to other funchtional groups (i.e. nitrile as shown) by metal catalyzed cross-couplings. Alternatively, **58** can be converted to a nitrile through palladium a cross-coupling reaction, followed by benzhydral protection and acylation to form final products **61**.

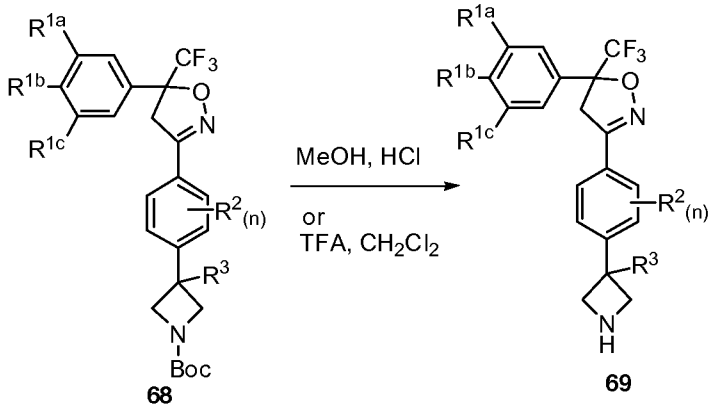
Scheme 11



R^{1a}, R^{1b}, R^{1c}, R^2, and n are as defined herein.

Analogs in which the azetidine ring is meta to the isoxazoline can be prepared from 3-bromobenzaldehyde derivatives as shown in Scheme 11. Treatment of the bromoaldehyde **62** with i-PrMgCl provides the organometallic reagent that adds to the N-protected azetinone to provide the hydroxyazetidine **63**. This masked aldehyde can undergo condensation with hydroxylamine, chlorination and cyclization as described in Scheme 2 to provide the isoxazoline **65**. Deprotection with chloroethyl chloroformate or fluorination followed by deprotection provides the requisite amines (**66** and **67**) which can be further functionalized to the desired amides, ureas, amines and sulfonamides described below.

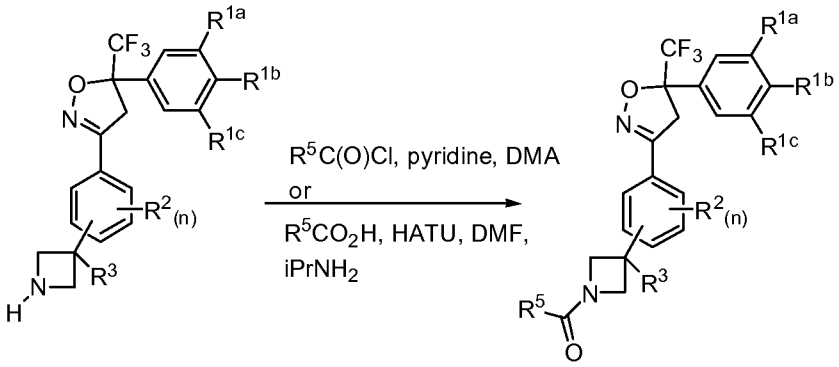
Scheme 12



R^{1a}, R^{1b}, R^{1c}, R^2, R^3, and n are as defined herein.

Removal of the Boc protecting group on the azetidines in the schemes above (e.g. structures **9, 25, 38, 50**) can be accomplished by treatment with HCl in methanol or with trifluoroacetic acid in dichloromethane.

Scheme 13

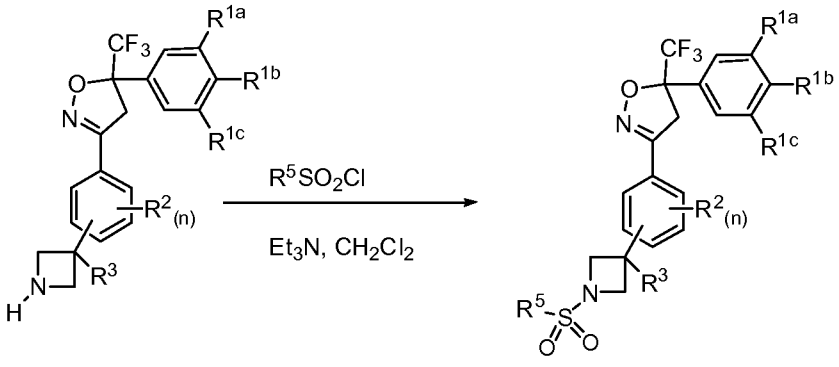


70 71

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^5, and n are as defined herein.

Amide analogs of the azetidine ring can be prepared as shown in Scheme 13. Acylation of the azetidine ring can be accomplished by reaction of the azetidine **70** with an acid chloride in pyridine/DMA or by a condensation with a carboxylic acid utilizing a condensing agent such as HATU or HOBt.

Scheme 14

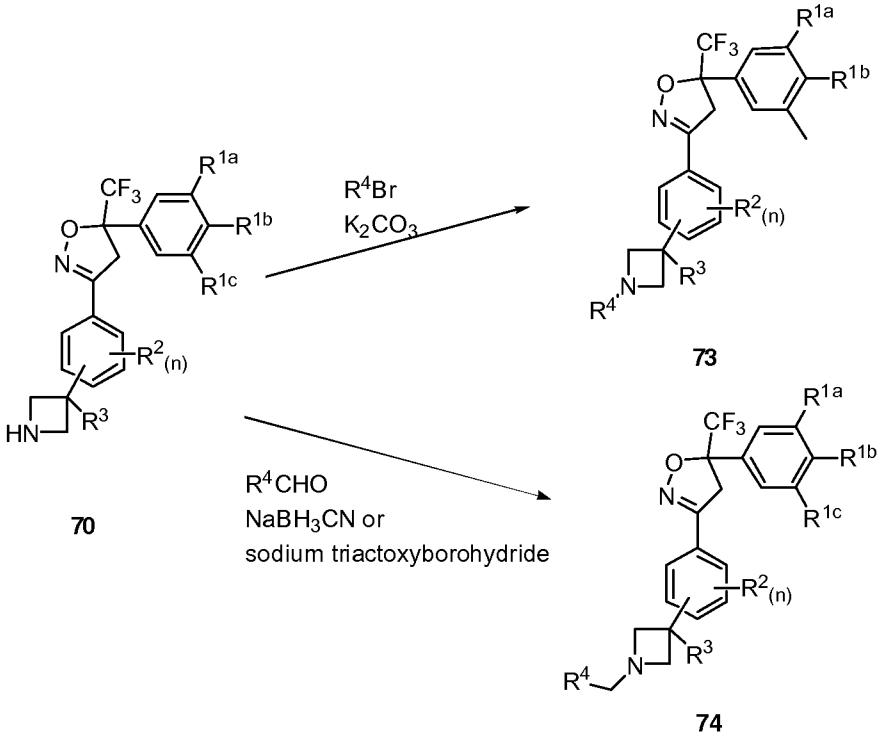


70 72

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^5, and n are as defined herein.

Sulfonamide anlogos of the azetidine ring can be prepared as shown in Scheme 14. Reaction of azetidine **70** with sulfonyl chlorides in the presence of triethylamine can give the desired sulfonamides.

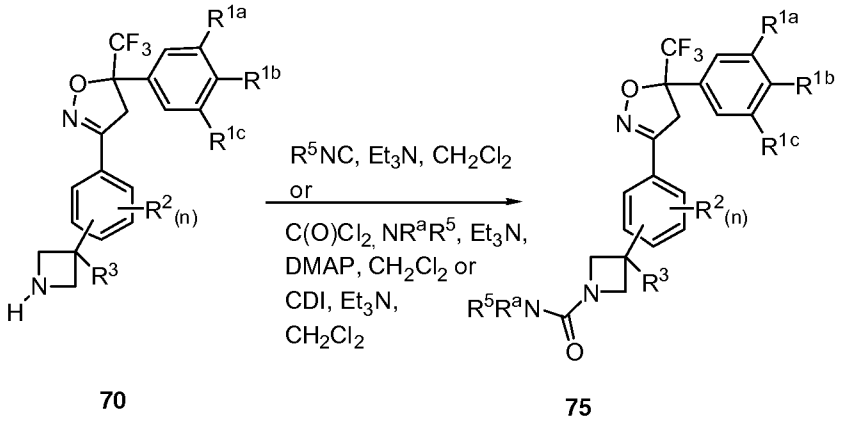
Scheme 15



R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, and n are as defined herein.

Compounds in which R^4 is alkyl or substituted alkyl can be prepared from the azetidine **70** by standard alkylation chemistry or by reductive amination with the corresponding aldehydes as shown in Scheme 15.

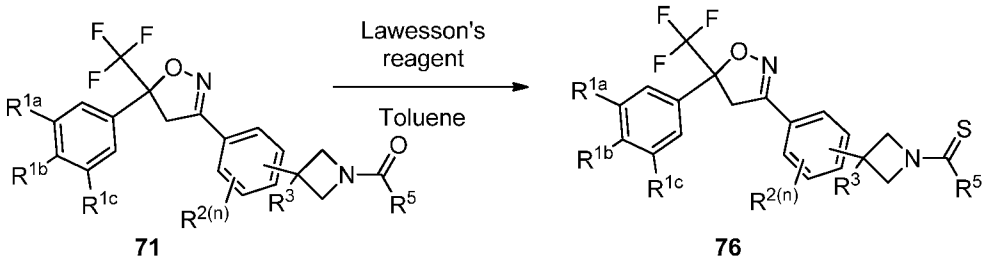
Scheme 16



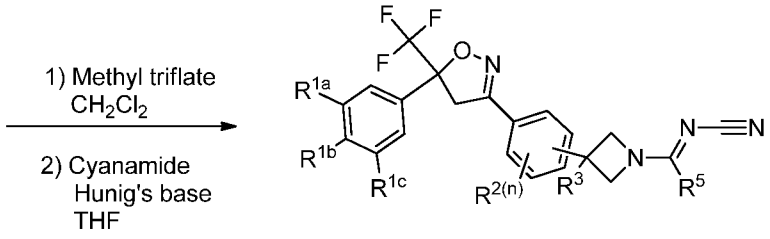
R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^a, R^5, and n are as defined herein.

Urea analogs can be prepared as shown in Scheme 16. Reaction of the azetidine **70** with an isocyanate or preformed carbamoyl chloride in the presence of a tertiary amine base provides the ureas.

Scheme 17



71 **76**



77

Thioamide **76** can be prepared by treatment of amide **71** with Lawesson's reagent in refluxing toluene. Methyl triflate can be added to thioamide **76** in a solvent such as CH_2Cl_2 to form a thioimidate intermediate as a solution. Cyanamide and Hunig's base in THF can be subsequently added directly to the thioimidate solution to afford cyanamide **77**.

One, skilled in the art will recognize that, in some cases, after the introduction of a given reagent as it is depicted in the schemes, it may be necessary to perform additional routine synthetic steps not described in detail to complete the synthesis of Formula (1) or Formula (XX) compounds.

The present invention includes all veterinarily acceptable isotopically-labelled Formula (1) and Formula (XX) compounds wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C,

^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, and sulphur, such as ^{35}S.

The skilled person will appreciate that the compounds of the present invention could be made by methods other than those herein described as incorporated herein by reference, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions).

The Formula (1) and Formula (XX) compounds are useful as ectoparasitic and endoparasitic agents, therefore, another embodiment of the present invention is a veterinary or pharmacueitcal composition comprising a therapeutically effective amount of a Formula (1) or Formula (XX) compound, stereoisomer thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent or carrier. The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

A typical formulation is prepared by mixing a Formula (1) or Formula (XX) compound with a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe to be administered to an animal. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or veterinary composition thereof) or aid

in the manufacturing of the veterinary or pharmaceutical product (i.e., medicament).

The formulations can be prepared using conventional dissolution and mixing procedures. Such compositions and methods for their preparation may be found, for example, in 'Remington's Veterinary Sciences', 19th Edition (Mack Publishing Company, 1995; and "Veterinary Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., 1980 (ISBN 0-8247-6918-X). For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more other excipients. The compounds of the present invention are typically formulated into veterinary or pharmaceutical dosage forms to provide an easily controllable dosage form for administration. Compounds of the present invention can also be admixed with animal feed.

The compounds may be administered alone or in a formulation appropriate to the specific use envisaged, the particular species of host animal being treated and the parasite involved. Generally, they will be administered as a formulation in association with one or more veterinarily or pharmaceutically acceptable salts, excipients, diluents, or carriers. The term "excipient", "diluent" or "carrier" is used herein to describe any ingredient other than the Formula (1) or Formula (XX) compounds or any additional antiparasitic agent. The choice of excipient, diluent, or carrier will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient, carrier, or diluent on solubility and stability, nature of the dosage form, and animal specie.

The methods by which the compounds of the present invention may be administered include oral, topical, and injectable (subcutaneous, intraperitoneal, and intramuscular) administration. The preferred method of administration of the Formula (1) or Formula (XX) compounds is in an oral solid dosage form or oral liquid dosage form. Equally preferred is topical administration.

The Formula (1) or Formula (XX) compounds can be administered orally by capsule, bolus, tablet, powders, lozenges, chews, multi and nanoparticulates, gels, solid solution, films, sprays, liquid form, or admixed with food. Oral administration is the preferred method of administration and as such it is desirable

to develop active Formula (1) or Formula (XX) compounds that are particularly suited to such formulations. Such formulations may be employed as fillers in soft or hard capsules, tablets, or chews, and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, N-methylpyrrolidone, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid forms include suspensions, solutions, syrups, drenches and elixirs. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. Oral drenches are commonly prepared by dissolving or suspending the active ingredient in a suitable medium. Feed admixtures can be prepared for livestock and fish. Oral formulations can comprise from about 0.5 mg/kg to 50 mg/kg of a Formula (1) or Formula (XX) compound, and preferably about 1 mg/kg to 30 mg/kg of a Formula (1) or Formula (XX) compound. Depending upon the host specie treated and the parasite being treated, dose adjustments can be made.

The compounds may be administered topically to the skin or mucosa, that is dermally or transdermally. This is a preferred method of administration and as such it is desirable to develop active Formula (1) or Formula (XX) compounds that are particularly suited to such formulations, for example liquid forms. Typical formulations for this purpose include pour-on, spot-on, multi-spot-on, stripe-on, comb-on, roll-on, dip, spray, mousse, shampoo, powder formulation, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and micro emulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, N-methyl formamide, glycol monomethyl ethers, polyethylene glycol, propylene glycol, and the like. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Pour-on or spot-on formulations may be prepared by dissolving the active ingredients in an acceptable liquid carrier vehicle such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol or a glycol ether. Alternatively, pour-on, spot-on or spray formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal, this effect may ensure that the Formula (1) or Formula (XX)

compounds have increased persistence of action and are more durable, for example they may be more water fast. Topical formulations of the combination contemplated herein can comprise from about 0.5 mg/kg to 50 mg/kg of a Formula (1) compound, and preferably about 1 mg/kg to 10 mg/kg of a Formula (1) or Formula (XX) compound. The compositions suitable for spot-on application according to the invention can be prepared by conventional mixing means. The volume of the applied composition can be from about 0.5 mL/kg to 5 mL/kg and preferably from about 1 mL/kg to 3mL/kg. Similarly, dose can be adjusted.

The compounds of the present invention can also be administered topically via a support matrix for example, a synthetic or natural resin, plastic, cloth, leather, or other such polymeric system in the shape of a collar or ear tag. Said collar or ear tag may be coated, impregnated, layered, by any means so as to provide a veterinarily or pharmaceutically acceptable amount of a compound of the present invention alone, or with a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier, and optionally an additional veterinary agent, or veterinarily or pharmaceutically acceptable salt thereof.

Agents may be added to the formulations of the present invention to improve the persistence of such formulations on the surface of the animal to which they are applied, for example to improve their persistence on the coat of the animal. It is particularly preferred to include such agents in a formulation which is to be applied as a pour-on or spot-on formulation. Examples of such agents include acrylic copolymers and in particular fluorinated acrylic copolymers. A particular suitable reagent is the trademark reagent “Foraperle” (Redline Products Inc, Texas, USA). Certain topical formulations may include unpalatable additives to minimize oral exposure.

Injectable formulations may be prepared in the form of a sterile solution, which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood. Acceptable liquid carriers include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl benzoate, isopropyl myristate and fatty acid derivatives of propylene glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending compounds of the present invention alone or with an additional veterinary agent in the liquid carrier such that

the final formulation contains from about 0.01 to 50% by weight of the active ingredients, preferably from about 0.01% to about 10% by weight of the active ingredients.

Suitable devices for injection include needle (including micro needle) injectors, needle-free injectors and infusion techniques. Subcutaneous formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dry powder form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of subcutaneous formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard veterinary techniques well known to those skilled in the art. The solubility of compounds of Formula (1) or Formula (XX) used in the preparation of subcutaneous solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice. Further, these formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection or infestation, and the body weight of the animal.

For fish, compounds of the present invention can be formulated for oral administration by way of feed admixture. For example, the compounds of the present invention can be formulated in a food product (e.g., pellets) that can be easily dispersed to fish as a feeding agent. Further, a compound of the present invention can be administered topically by immersing the fish into an aqueous environment containing at least one of the compounds of the present invention. For example, fish may be transferred into a tank for treatment or caused to pass from one holding zone into another. The compounds of the present invention may also be administered directly to the water containing the fish. The compound of the present invention can be in any dispersible formulation such that upon introduction to water the compound dissolves into the solution. Alternatively, the compounds of the present invention can be administered by injection. Preferable injection routes for treatment of fish are intraparitoneal or intramuscular. The

injectable formulations include any liquid suspension, such as oils, aqueous solutions, or oil and water emersions. The compounds of the present invention can also be co-administered with additional agents, antigens, adjuvants, carriers, diluents or nutrients.

The Formula (1) and Formula (XX) compounds are also active against all or individual developmental stages of animal pests showing normal sensitivity, as well as those showing resistance to widely used parasiticides.

As described herein, compounds of the present invention may be administered alone or in combination with at least one additional veterinary agent including insecticides, acaricides, anthelmintics, fungicides, nematocides, antiprotozoals, bactericides, and growth regulators to form a multi-component agent giving an even broader spectrum of veterinary utility. Thus, the present invention also pertains to a composition comprising an effective amount of a Formula (1) compound, a stereoisomer thereof, and an effective amount of at least one additional veterinary agent and can further comprise one or more of a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier.

The following list of additional veterinary agents together with which the compounds of the present invention can be used is intended to illustrate the possible combinations, but not to impose any limitation. Non-limiting examples of additional veterinary agents include: amitraz, arylpyrazoles as recited in publications WO1998/24767 and WO2005/060749, amino acetonitriles, anthelmintics (e.g., albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, octadepsipeptides, oxfendazole, oxibendazole, paraherquamide (2-desoxoparaherquamide,derquantel), parbendazole, piperazines, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel pamoate, oxantel, morantel, and the like), indoxacarb and derivatives thereof, avermectins (e.g., abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, and the like), milbemycin, milbemycin oxime, DEET, demiditraz, diethylcarbamazine, fipronil, insect growth regulators (e.g., hydroprene, kinoprene, methoprene, pyriproxyfen, and the like), metaflumizone, niclosamide, permethrin, pyrethrins, spinosad, and formamidines (e.g., demiditraz, amitraz, and the like). In certain instances, combinations of a Formula (1) or Formula (XX) compound with an additional veterinary agent(s) can result in a greater-than-additive effect.

Reducing the quantity of active ingredients released in the environment while ensuring effective pest control is always desirable.

It may be desirable to administer a compound of the present invention, stereoisomers thereof, alone or in a composition comprising a veterinarily acceptable excipient, diluent, or carrier, for example, for the purpose of treating a particular parasitic infection or infestation or condition associated therewith. It is within the scope of the present invention that two or more veterinary compositions, at least one of which contains a Formula (1) or Formula (XX) compound in accordance with the invention, and the other, an additional veterinary agent, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

The compounds of the present invention, stereoisomers thereof, and compositions comprising a therapeutically effective amount of a Formula (1) or Formula (XX) compound and a veterinarily acceptable excipient, diluent, or carrier are useful as parasiticides (endo-and ecto-parasites) for the control and treatment of infections or infestations manifested by said parasite in an animal. The compounds of the present invention have utility as an ectoparasiticide, in particular, as an acaricide and insecticide. They may, in particular, be used in the fields of veterinary medicine, livestock husbandry, fish farming, and the maintenance of public health: against acarids and insects which are parasitic upon vertebrates, particularly warm-blooded vertebrates, including companion animals, livestock, and birds. The compounds of the present invention are also parasiticides for cold-blooded fish. Some non-limiting examples of acaride and insect parasites include: ticks (e.g., *Ixodes spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Hyalomma spp., Haemaphysalis spp., Dermacentor spp., Ornithodorus spp.*, and the like); mites (e.g., *Dermanyssus spp., Sarcoptes spp., Psoroptes spp., Chorioptes spp., Demodex spp.*, and the like); chewing and sucking lice (e.g., *Damalinia spp., Linognathus spp.*, and the like); fleas (e.g., *Siphonaptera spp., Ctenocephalides spp.*, and the like); and biting flies and midges (e.g., *Tabanidae spp., Haematobia spp., Stomoxys spp., Dermatobia spp.,*

Simuliidae spp., Ceratopogonidae spp., Psychodidae spp., and the like). In another example, ectoparasites of the crustacean order copepod, more particularly of the genera Lepeophtheirus (especially the salmon louse, *Lepeoptheirus salmonis*) and/or Caligus (e.g., *C. elongates*, *C.rogercreysii*, *C. teres*, *C. flexispina*, and the like), particularly sea lice, can be treated with a compound of the present invention. The compounds of the invention can also be used for the treatment of endoparasites, for example, heartworms, roundworms, hookworms, whipworms, and tapeworms.

The compounds of the present invention and compositions comprising compounds of the present invention in conjunction with at least one other veterinary agent are of particular value in the control of ectoparasites, endoparasites, and insects which are injurious to, or spread or act as vectors of diseases in animals. The ectoparasites, insects, and endoparasites which can be treated with a combination of a Formula (1) or Formula (XX) compound and an additional veterinary agent include those as herein before described and including helminthes of the phylum platyhelminthes (e.g., trematodes, eucestoda, and cestoda), and nemathelminthes (e.g., nematodes).

Any of the compounds of the present invention, or a suitable combination of a compound of the present invention and optionally, with at least one additional veterinary agent may be administered directly to the animal and/or indirectly by applying it to the local environment in which the animal dwells. Direct administration includes contacting the skin, fur, or feathers of a subject animal or bird with the compound(s), or by feeding or injecting the compounds into the animal or bird.

The Formula (1) or Formula (XX) compounds, stereoisomers thereof, and combinations with at least one additional veterinary agent, as described herein, are of value for the treatment and control of the various lifecycle stages of insects and parasites including egg, nymph, larvae, juvenile and adult stages.

The present invention also relates to a method of administering a compound of the present invention alone or in combination with at least one additional veterinary agent, and optionally a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier, to animals in good health comprising the application to said animal to reduce or eliminate the potential for human parasitic

infection or infestation from parasities carried by the animal and to improve the environment in which the animal and human inhabit.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents *via* syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel 60 F 254 precoated plates and eluted with appropriate solvent ratios (v/v). Reactions were assayed by TLC or LCMS and terminated as judged by the consumption of starting material. Visualization of the TLC plates was done with UV light (254 nM wavelength) or with an appropriate TLC visualizing solvent and activated with heat. Flash column chromatography (Still et al., J. Org. Chem. 43, 2923, (1978) was performed using silica gel (RediSep Rf) or various MPLC systems, such as Biotage or ISCO purification system.

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography (TLC), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compound structures in the examples below were confirmed by one or more of the following methods: proton magnetic resonance spectroscopy, and mass spectroscopy. Proton magnetic resonance (^{1}H NMR) spectra were determined using a Bruker spectrometer operating at a field strength of 400 megahertz (MHz). Chemical shifts are reported in parts per million (PPM, δ) downfield from an internal tetramethylsilane standard. Mass spectra (MS) data were obtained using Agilent mass spectrometer with atmospheric pressure chemical ionization. Method: Acquity HPLC with chromatography performed on a Waters BEH C18 column (2.1 x 50 mm, 1.7 μm) at 50°C. The mobile phase was

a binary gradient of acetonitrile (containing 0.1% trifluoroacetic acid) and water (5–100%).

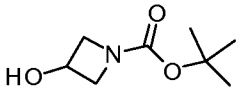
Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

One skilled in the art will also recognize that Formula (1) or Formula (XX) compounds and the intermediates described herein can be subjected to various electrophilic, nucleophilic, radical, organometallic, oxidation, and reduction reactions to add substituents or modify existing substituents.

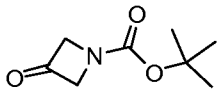
The following examples provide a more detailed description of the process conditions. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation.

Preparation 1: tert-butyl-3-hydroxyazetidine-1-carboxylate



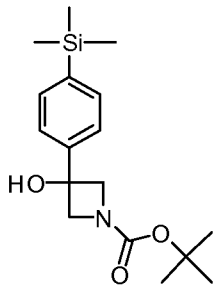
To a stirred cold (0°C) solution of 3-hydroxyazetidine hydrochloride (75 g, 0.68 mol) in ethanol (1300 mL) was added triethylamine (208g/280mL, 2.05mol) followed by Boc_2O (164 g, 0.75 mol). The resultant solution was stirred at ambient temperature for 16 hours. GC/MS analysis of the reaction mixture revealed complete reaction. Volatiles were removed in vacuo and the residue was diluted with EtOAc (1300 mL) and washed with 10% citric acid (700 mL), water (700 mL) and brine (700 mL). The organics were dried over sodium sulfate filtered, and concentrated to give the desired product (100.8 g, 85% yield). ^1H NMR ($CDCl_3$) δ 4.6 (m, 1 H), 4.2 (m, 2 H), 3.8 (m, 2 H), 1.4 (s, 9 H).

Preparation 2: tert-butyl 3-oxoazetidine-1-carboxylate



A 5L-3-neck flask equipped with mechanical stirrer, thermocouple, addition funnel and nitrogen inlet was charged with Py-SO_3 (277 g, 1.74 mol) and DMSO (900 mL) and cooled to 10°C in ice-bath. TEA (177 g/244 mL, 1.74 mol) was added. A solution of tert-butyl-3 hydroxyazetidine-1-carboxylate (Preparation 1, 100.8 g, 0.58 mol) in DMSO (500 mL) was added slowly via addition funnel at 10°C. The reaction was stirred at ambient temperature overnight. GC/MS analysis of the reaction mixture reveals that the reaction was completed. The reaction was quenched with brine (1L). Solids were filtered and the aqueous was extracted with ethyl acetate (3 x 1 L). The combined organics were washed with saturated aqueous NaHCO3 (1.5 L), brine (1.5 L), dried over sodium sulfate, filtered, and concentrated to give the desired product (94 g, 95% yield). ^{1}H NMR ($CDCl_3$) δ 4.6 (s, 4 H), 1.4 (s, 9 H).

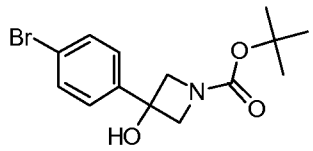
Preparation 3: tert-butyl 3-hydroxy-3-(4-(trimethylsilyl)phenyl)azetidine-1-carboxylate



A 2L-3neck flask equipped with mechanical stirrer, thermocouple, addition funnel and nitrogen inlet was charged with (4-bromophenyl)trimethylsilane (80.4 g, 0.35 mol), THF (600 mL), Mg (8.5 g), and I_2 (catalytic amount). The suspension was refluxed at 68°C for 1.5 hours until all magnesium disappeared. The solution was cooled to 0°C in ice-bath. Then, a solution of tert-butyl 3-oxoazetidine-1-carboxylate (Preparation 2, 30 g, 0.17 mol) in THF (200 mL) was added slowly via addition funnel. The solution was stirred at 0°C for 3 hours. LC/MS indicated the formation of desired product. The reaction was quenched with brine at 0°C. The aqueous layer was extracted with EtOAc (2 x 800 mL). The combined organics

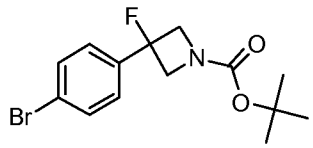
were dried over sodium sulfate, filtered and concentrated to give the desired product (47.4 g, 84% yield). ^{1}H NMR ($CDCl_3$) δ 7.3 (d, 2 H), 7.2 (d, 2 H), 4.0 (d, 2 H), 3.9 (d, 2 H), 2.9 (s, 1 H), 1.2 (s, 9 H), 0.0 (s, 9 H).

Preparation 4: tert-butyl 3-(4-bromophenyl)-3-hydroxyazetidine-1-carboxylate



A mixture of tert-butyl 3-hydroxy-3-(4-(trimethylsilyl)phenyl)azetidine-1-carboxylate (Preparation 3, 45 g, 0.14 mol) and KBr (25 g, 0.21 mol) in acetic acid (1L) and MeOH (100 mL) was heated at 60°C for 20 minutes. Then N-chlorosuccinimide (22.4 g, 0.17 mol) was added to the reaction mixture and stirred at 60°C for 2 hours. LC/MS indicated the reaction was complete (only product peak). After cooling to ambient temperature, the mixture was poured into ice-water (1 L). The mixture was extracted with $CHCl_3$ (2 x 800 mL). The combined organics were washed with 3M NaOH (2 x 600 mL), water (600 mL), dried over sodium sulfate, filtered and concentrated. The crude product was washed with ether to afford the desired product (35 g, 76% yield). ^{1}H NMR ($CDCl_3$) δ 7.5 (d, 2 H), 7.4 (d, 2 H), 4.2 (s, 4 H), 3.4 (s, 1 H), 1.4 (s, 9 H).

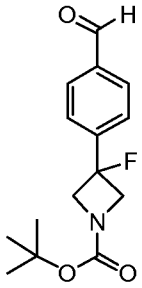
Preparation 5: tert-butyl-3-(4-bromophenyl)-3-fluoroazetidine-1-carboxylate



Tert-butyl-3-(4-bromophenyl)-3-hydroxyazetidine-1-carboxylate (Preparation 4, 25 g, 0.076 mol) in CH_2Cl_2 (500 mL) was cooled to –78°C. To this slurry was slowly added BAST (20.2 g, 0.09 mol) via addition funnel. The temperature of the reaction was increased slowly from –78°C to ambient temperature. The mixture was stirred at ambient temperature overnight. LC/MS indicated that the reaction was complete. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (500 mL) and 1M NaOH (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 800 mL). The combined organics were washed with aqueous citric

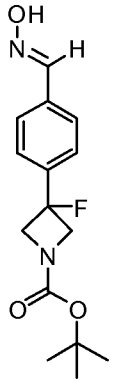
acid (2 x 700 mL), dried over Na_2SO_4, filtered, and concentrated to afford the desired product as tan solid (24.4 g, 97% yield). ^1H NMR ($CDCl_3$) δ 7.5 (d, 2 H), 7.3 (d, 2 H), 4.4 (m, 2 H), 4.2 (m, 2 H), 1.4 (s, 9 H).

Preparation 6: tert-butyl 3-fluoro-3-(4-formylphenyl)azetidine-1-carboxylate



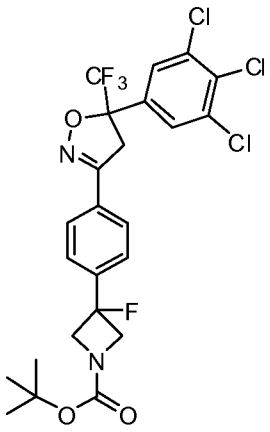
To a solution of tert-butyl-3-(4-bromophenyl)-3-fluoroazetidine-1-carboxylate (Preparation 5, 1.0 g, 3 mmol) in THF (10 mL) at -78°C was slowly added n-BuLi (2.1 mL of 1.6M solution in hexanes). The reaction was stirred at -78°C for 15 minutes at which time DMF (0.5 mL, 6 mmol) was added. Reaction mixture was allowed to warm to room temperature and stir for additional 1 hour. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. Crude product was chromatographed on silica (12 g column) using a gradient of 0-30% EtOAc/hexanes in a 12 minute run. Yield 460 mg. LC/MS retention time = 3.004 minutes; MS calculated for ($C_{15}H_{18}FNO_3$) 279.127, found 180.2 M-BOC. ^1H NMR ($CDCl_3$) δ 10.0 (s, 1 H), 8.0 (d, 2 H), 7.7 (d, 2 H), 4.5 (m, 2 H), 4.2 (m, 2 H), 1.6 (s, 9 H).

Preparation 7: tert-butyl 3-fluoro-3-(4-((hydroxyimino)methyl)phenyl)azetidine-1-carboxylate



To a solution of tert-butyl 3-fluoro-3-(4-formylphenyl)azetidine-1-carboxylate (Preparation 6, 460 mg, 1.65 mmol) in ethanol (30 mL) was added $NH_2OH{\cdot}HCl$ (127 mg, 1.8 mmol) and water (2.5 mL). The solution was heated to 50°C for 1 hour and then allowed to stir at room temperature for 2 hours. The reactants were concentrated under vacuum to remove the ethanol. Water (5 mL) was added to the remaining residue and extracted with EtOAc (2 x 10 mL). Combined organic phases were dried (Na_2SO_4) and concentrated under vacuum to afford the intermediate as a solid. Yield 485 mg. ^1H NMR ($CDCl_3$) δ 8.17 (s, 1 H), 7.65 (d, 2 H), 7.50 (d, 2 H), 5.32 (s, 1 H), 4.37 - 4.50 (m, 2 H), 4.28 (m, 2 H), 1.45 - 1.55 (m, 9 H). LC/MS retention time = 2.926 minutes; MS calculated for ($C_{15}H_{19}FN_2O_3$) 294.13, found 195.0 M-Boc.

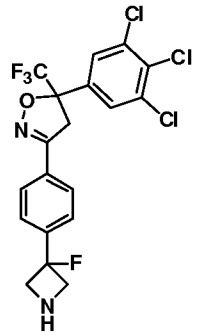
Preparation 8: tert-butyl 3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxylate



To a DMF (8 mL) solution of tert-butyl 3-fluoro-3-(4-((hydroxyimino)methyl)-phenyl)azetidine-1-carboxylate (Preparation 7, 486 mg, 1.65 mmol) was added

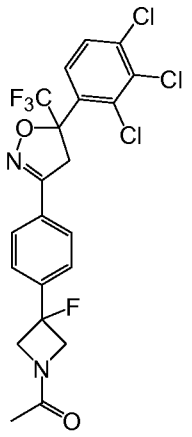
NCS (232 mg, 1.65 mmol) in two portions over 10 minutes. The reaction was stirred at room temperature overnight. The reaction was diluted with EtOAc (8 mL) and 1,2,3-trichloro-5-(1,1,1-trifluoroprop-2-en-2-yl)benzene (546 mg, 1.98 mmol) was added, followed by potassium bicarbonate (248 mg, 2.48 mmol). The reaction was stirred at room temperature for 3 days. The reaction was concentrated under vacuum. The residue was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (3X50 mL). The combined organic layers were dried and condensed. The crude material was adsorbed on silica and chromatographed on a 40 g silica column eluting with a gradient of 0%-40% EtOAc/hexanes over 20 minutes. Fractions containing the desired material were combined and concentrated to yield 526 mg of a white solid. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H), 7.67 (s, 2 H), 7.56 (d, 2 H), 4.39 - 4.51 (m, 2 H), 4.24 (m 2 H), 4.12 (d, 1 H), 3.72 (d, 1 H), 1.5 (s, 9 H).

Preparation 9: 3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



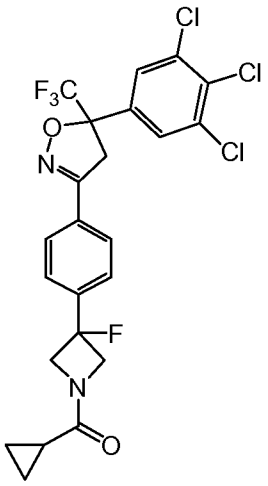
To a solution of 250 mg of tert-butyl 3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxylate (Preparation 8) in 2 mL CH_2Cl_2 was added 1 mL of trifluoroacetic acid. The reaction was stirred overnight under a positive pressure of nitrogen. The reaction was concentrated. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted 2x with EtOAc (20 mL). The combined organics were dried over Na_2SO_4 and condensed to yield 188 mg of a film. TLC shows much more polar spot. The crude product was carried on to the next reactions. MS calculated for ($C_{19}H_{13}Cl_3F_4N_2O$) 466.00, found 467.9 M+H

Example 1: 1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone



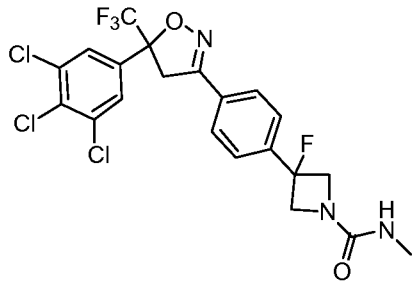
To a solution of 3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 9, 94 mg) in 2 mL CH_2Cl_2 was added pyridine (0.05 mL) followed by acetyl chloride (31 mg). The reaction was allowed to stir at room temperature for 1 hour. Water (3 mL) was added. The reaction was diluted with 3 mL of CH_2Cl_2, stirred for 30 minutes and poured through a phase extractor. The CH_2Cl_2 layer was collected and concentrated. The crude product from the reaction was adsorbed onto silica and chromatographed on a 12 g silica column eluting with a gradient of 50% EtOAc/hexanes to 100% EtOAc/hexanes to yield 90 mg of the desired compound as a white foam. ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2 H). 7.67 (s, 2 H), 7.56 (d, 2 H), 4.71 - 4.31 (m, 4 H), 4.12 (d, 1 H), 3.72 (d, 1 H), 2.01 (s, 3 H). LC/MS retention time = 3.591 minutes; MS calculated for ($C_{21}H_{15}Cl_3F_4N_2O_2$) 509.714, found 511 M+H.

Example 2: cyclopropyl(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone



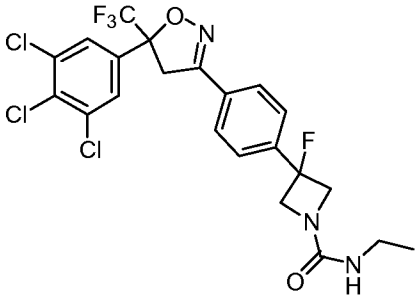
To a solution of the 3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 9, 94 mg) in 2 mL CH_2Cl_2 was added pyridine (0.05 mL) followed by cyclopropane carbonyl chloride (31 mg). The reaction was allowed to stir at room temperature for 1 hour. Water (10 mL) was added. The reaction was diluted with an additional 10 mL of CH_2Cl_2, stirred for 30 minutes at room temperature then passed through a phase separation tube. The CH_2Cl_2 layer was collected and condensed. The crude material was adsorbed on silica and chromatographed on a 12 g silica column, eluting with a gradient of 20% EtOAc/hexane to 80% EtOAc/hexane. Fractions containing the desired material were combined and concentrated. Et_2O (~½ mL) was added to the resulting film. Placing the flask on high vac overnight resulted in formation of the product as a white foam (87 mg). ^1H NMR ($CDCl_3$) δ ppm 7.76 (d, 2 H), 7.67 (s, 2 H), 7.58 (d, 2 H), 4.8 - 4.7 (m, 1 H), 4.6 - 4.2 (m, 3 H), 4.12 (d, 1 H), 3.72 (d, 1 H), 1.5 - 1.4 (m, 1 H), 1.08 (m, 2 H), 0.86 (m, 2 H). LC/MS retention time = 3.710 minutes, MS calculated for ($C_{23}H_{17}Cl_3F_4N_2O_2$) 534.03, found 535.0 M+H.

Example 3: 3-fluoro-N-methyl-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide



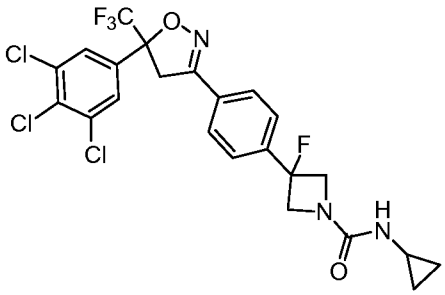
The compound was prepared using a procedure similar to that of Example 2 using methyl isocyanate in place of cyclopropane carbonyl chloride. Yield 124 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.66 (s, 2 H), 7.56 (d, 2 H), 4.49 - 4.40 (m, 2 H), 4.28 - 4.17 (m, 3 H), 4.10 (d, 1 H), 3.70 (d, 1 H), 2.86 (d, 3 H). LC/MS retention time = 3.559 minutes, MS calculated for ($C_{21}H_{16}Cl_3F_4N_3O_2$) 523.02, found 524.0 M+H.

Example 4: N-ethyl-3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide



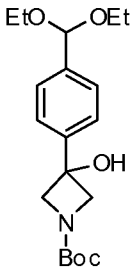
The compound was prepared using a procedure similar to that of Example 2 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 130 mg (96%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.66 (s, 2 H), 7.56 (d, 2 H), 4.49 - 4.38 (m, 2 H), 4.27 - 4.15 (m, 3 H), 4.10 (d, 1 H), 3.70 (d, 1 H), 3.31 (m, 2 H), 1.18 (t, 3 H). LC/MS retention time = 3.638 minutes, MS calculated for ($C_{22}H_{18}Cl_3F_4N_3O_2$) 537.04, found 538.0 M+H.

Example 5: N-cyclopropyl-3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide



The compound was prepared using a procedure similar to that of Example 2 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 130 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.66 (s, 2 H), 7.56 (d, 2 H), 4.55 - 4.40 (m, 3 H), 4.28 - 4.19 (m, 2 H), 4.10 (d, 1 H), 3.70 (d, 1 H), 2.65 (m, 1 H), 0.78 (m, 2 H), 0.55 (m, 2 H). LC/MS retention time = 3.647 minutes, MS calculated for ($C_{23}H_{18}Cl_3F_4N_3O_2$) 549.04, found 550.0 M+H.

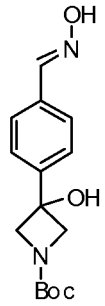
Preparation 10: tert-butyl 3-(4-(diethoxymethyl)phenyl)-3-hydroxyazetidine-1-carboxylate



Cerium chloride (71.4g, 290mmoles) was slurried in tetrahydrofuran (600mL) and heated to 65°C for 2.5 hours, then cooled to room temperature In a separate flask, 4-bromobenzaldehyde diethylacetal (100g, 386mmoles) was dissolved in tetrahydrofuran (750mL). Magnesium turnings (5.9g, 241mmoles) and dibromoethane (0.5mL) were added and the mixture heated to reflux for 2.5 hours, until all the magnesium had reacted. Heating was removed and the Grignard solution cooled in an ice bath. The cerium chloride/tetrahydrofuran slurry was cooled in an ice bath to 0°C. The Grignard solution was added, portionwise, and the mixture stirred at 0°C for 45 minutes. N-(t-butoxycarbonyl)azetidinone (41.3g, 241mmoles) dissolved in tetrahydrofuran (200mL) was added portionwise and the reaction allowed to stir at 0°C for 30 minutes. The reaction was quenched with saturated sodium carbonate solution (500mL) and then diluted with ethyl acetate

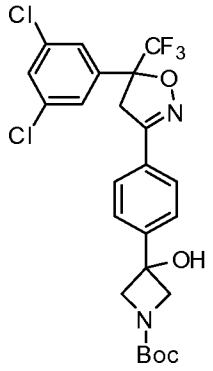
(2000mL). The organic phase was washed with water (3 x 500mL), separated, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to give a yellow oil weighing 120g which was purified using normal phase chromatography (600g SiO_2 column, loaded as a solution in 25mL of dichloromethane, linear gradient of 10% tert-butylmethylether in n-heptane to 100% tert-butylmethylether over 60 minutes, 150mL/minutes, 55mL fractions using the 'Threshold OR Slope' method) to give a light yellow oil weighing 65g, which NMR suggests is the desired acetal product. ^{1}HNMR ($CDCl_3$) δ ppm: 7.50 (4H), 5.50 (1H), 4.15 (2H), 4.30 (2H), 3.55 (4H), 1.50 (9H), 1.25 (6H); m/z (ESI) 252 $[M+H\text{-}Boc]^+$.

Preparation 11: (E)-tert-butyl 3-hydroxy-3-(4-((hydroxyimino)methyl)phenyl)-azetidine-1-carboxylate



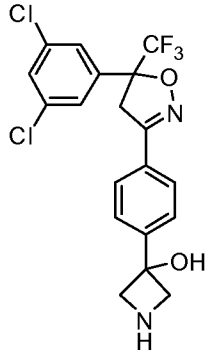
The product of Preparation 10 (54g, 195mmoles) was dissolved in methanol (800mL) and water (400mL). Hydroxylamine hydrochloride (14g, 200mmoles) was added portionwise and the mixture stirred at room temperature for 60 minutes. The reaction mixture was evaporated to remove excess methanol. The aqueous residue was extracted with ethyl acetate (3000 mL), separated, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to give a thick yellow syrup weighing 49g ^{1}HNMR ($CDCl_3$) δ ppm: 8.15 (1H), 7.60 (2H), 7.50 (2H), 4.20 (4H), 1.52 (9H); m/z (ESI) 193 $[M+H\text{-}Boc]^+$.

Preparation 12: tert-butyl 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidine-1-carboxylate



The product of Preparation 11 (56g, 192mmoles) was dissolved in ethyl acetate (1000mL) and stirred at room temperature. N-chlorosuccinimide (29.9g, 224mmoles) was added portionwise. After 60 minutes, to the reaction mixture was added potassium bicarbonate (57.5g, 575mmoles), water (5mL) and 1,3-dichloro-2-fluoro-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (49.7g, 192mmoles). The mixture was stirred overnight at room temperature. The reaction was quenched with water (750mL), diluted with ethyl acetate (1500mL), layers shaken to dissolve all the solids, separated, organic phase dried over anhydrous magnesium sulphate, filtered and evaporated to a slurry (approx 1 litre in volume). Hexanes (1 litre) were added and the mixture shaken and filtered to give a white filter cake which was washed through with a further 300mL of hexanes and dried at the pump to give a white solid weighing 52g ^{1}HNMR (DMSO-D6) δ ppm: 7.80 (2H), 7.75 (2H), 7.62 (2H), 4.32 (2H), 4.05 (4H), 1.40 (9H); m/z (ESI) 449 $[M+H-Boc]^+$, 547 $[M-H]^+$

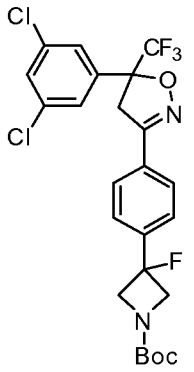
Preparation 13: 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol



To a slurry of the product of Preparation 12 (52g, 95mmoles) in methanol (650mL) was added concentrated aqueous hydrochloric acid (38mL). The mixture was

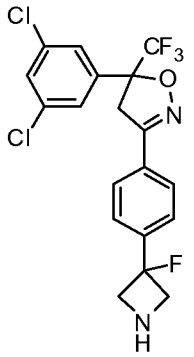
heated with stirring. At around 50°C, the slurry started to dissolve - forming a solution at reflux. After refluxing for 2 hours, the reaction was cooled to room temperature and evaporated under reduced pressure, chasing with toluene to give a white solid which was slurried with toluene (1000mL) and filtered under reduced pressure. The filter cake was washed with hexanes (500mL) and then dried in the vacuum oven at 50°C to give a white solid weighing 42g. ^{1}HNMR (DMSO-D6) δ ppm: 7.80 (6H), 4.30 (4H), 4.12 (2H); m/z (ESI) 449 $[M+H]^+$, 447 $[M-H]^+$

Preparation 14: tert-butyl 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxylate



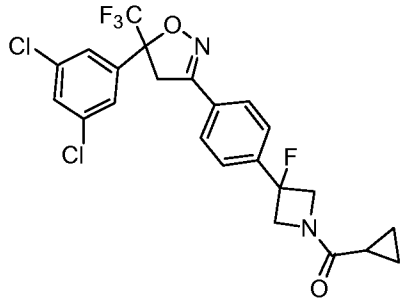
Reference: J. Org. Chem. 2010, 75, 3401-3411. Triethylamine trihydrofluoride (5.3g, 32.8mmoles) was dissolved in dichloromethane (97mL). Triethylamine (2.3mL, 16.4mmoles) was added and the solution cooled to -78°C. To the cooled mixture was added XtalFluor-E (5.6g, 24.6mmoles) and then the product of Preparation 12 (9g, 16.4mmoles). This resulted in a thick slurry. Cooling was removed and the mixture allowed to warm to room temperature, with stirring. The slurry dissolved to give a light brown solution. After stirring at room temperature, overnight, the reaction was quenched by addition of saturated aqueous sodium carbonate solution (100mL) and dichloromethane (100mL). The layers were then separated. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to give a brown oil weighing 9g ^{1}HNMR ($CDCl_3$) δ ppm: 7.75 (2H), 7.60 (2H), 7.55 (2H), 4.45 (2H), 4.25 (2H), 4.15 (1H), 3.70 (1H), 1.50 (9H); m/z (ESI) 451 $[M+H\text{-}Boc]^+$, 549 $[M-H]^+$

Preparation 15: 5-(3,5-dichlorophenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



To a solution of tert-butyl 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxylate (Preparation 14) in methanol (10 mL) was added a methanolic solution of HCl (10 mL of 1.25 M). Reaction mixture warmed to 65°C for 1.5 hours. Reaction concentrated via rotavap to yield a viscuous oil. CH_2Cl_2 was added and a precipitate formed. Volatiles removed under reduced pressure to yield 573 mg of the title compound as a white solid. ^{1}H NMR (DMSO – d_6) δ 9.8 – 9.6 (br s, 2 H) 7.9 – 7.8 (m, 3 H), 7.75 (d, 2 H), 7.63 (d, 2 H), 4.64 - 4.29 (m, 6 H).). LC/MS retention time = 3.039 minutes, MS calculated for ($C_{19}H_{14}Cl_2F_4N_2O$) 432.04, found 433.0 M+H.

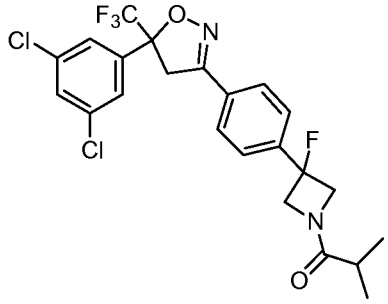
Example 6: cyclopropyl(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone



To a solution of the 5-(3,5-dichlorophenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 15, 65 mg) in 2 mL CH_2Cl_2 was added triethyl amine (50µL) followed by cyclopropane carbonyl chloride (19 mg). The reaction was allowed to stir at room temperature for 30 minutes. Water (5 mL) was added. The reaction was diluted with an additional 5 mL of CH_2Cl_2,

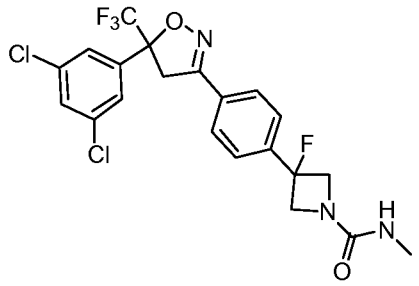
stirred for 5 minutes at room temp then passed through a phase separation tube. The CH_2Cl_2 layer was collected and condensed. The crude material was adsorbed on silica and chromatographed on a 12 g silica column, eluting with a gradient of 0% to 100% ethyl acetate in heptane. Fractions containing the desired material were combined and concentrated. Et_2O (~½ mL) was added to the resulting film. Placing the flask on high vacuum overnight resulted in formation of a white foam. Yield 67 mg (98%) of the desired product. ^1H NMR ($CDCl_3$) δ ppm 7.76 (d, 2 H), 7.63 – 7.51 (s, 4 H), 7.45 (s, 1 H), 4.8 - 4.7 (m, 1 H), 4.6 - 4.3 (m, 3 H), 4.12 (d, 1 H), 3.74 (d, 1 H), 1.6 - 1.4 (m, 1 H), 1.07 (m, 2 H), 0.86 (m, 2 H). LC/MS retention time = 3.654 minutes, MS calculated for ($C_{23}H_{18}Cl_2F_4N_2O_2$) 500.07, found 501.0 M+H.

Example 7: 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one



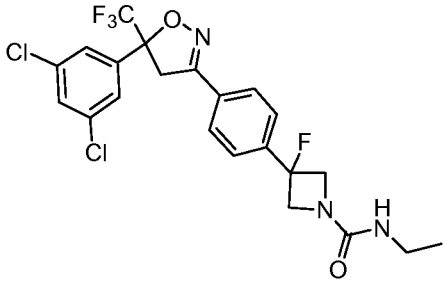
The compound was prepared using a procedure similar to that of Example 6 using of isobutyroyl chloride in place of cyclopropane carbonyl chloride. Yield 146 mg (95%). ^1H NMR ($CDCl_3$) δ 7.76 (d, 2 H), 7.58 – 7.51 (m, 4 H), 7.45 (m, 1 H), 4.71 - 4.58 (m, 1 H), 4.56 – 4.32 (m 3 H), 4.12 (d, 1 H), 3.73 (d, 1 H), 2.53 (m, 1 H), 1.22 – 1.14 (m, 6 H). LC/MS retention time = 3.660 minutes, MS calculated for ($C_{23}H_{20}Cl_2F_4N_2O_2$) 502.08, found 503.0 M+H.

Example 8: 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide



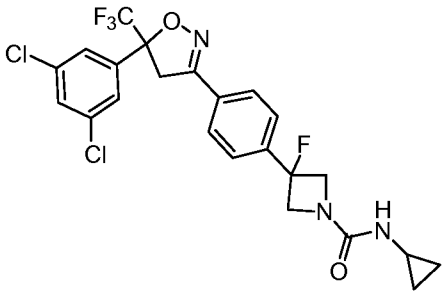
The compound was prepared using a procedure similar to that of Example 6 using methyl isocyanate in place of cyclopropane carbonyl chloride. Yield 118 mg (96%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.61 – 7.51 (m, 4 H), 7.44 (m, 1 H), 4.50 - 4.39 (m, 2 H), 4.28 - 4.16 (m, 3 H), 4.10 (d, 1 H), 3.71 (d, 1 H), 2.87 (d, 3 H). LC/MS retention time = 2.965 minutes, MS calculated for ($C_{21}H_{17}Cl_2F_4N_3O_2$) 489.06, found 490.0 M+H.

Example 9: 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide



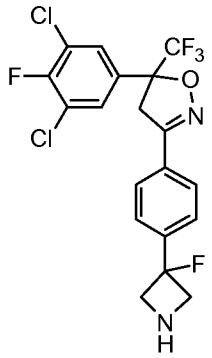
The compound was prepared using a procedure similar to that of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 123 mg (97%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.59 – 7.50 (m, 4 H), 7.44 (m, 1 H), 4.50 - 4.38 (m, 2 H), 4.27 - 4.14 (m, 3 H), 4.10 (d, 1 H), 3.71 (d, 1 H), 3.31 (m, 2 H), 1.18 (t, 3 H). LC/MS retention time = 3.018 minutes, MS calculated for ($C_{22}H_{19}Cl_2F_4N_3O_2$) 503.08, found 504.0 M+H.

Example 10: N-cyclopropyl-3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide



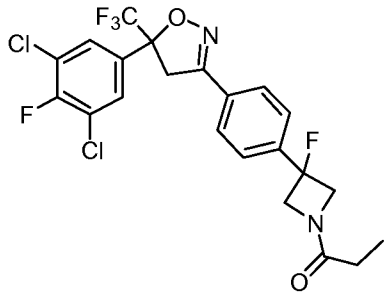
The compound was prepared using a procedure similar to that of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 124 mg (96%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.58 – 7.51 (m, 4 H), 7.44 (m, 1 H), 4.55 - 4.39 (m, 3 H), 4.29 - 4.19 (m, 2 H), 4.10 (d, 1 H), 3.71 (d, 1 H), 2.65 (m, 1 H), 0.77 (m, 2 H), 0.55 (m, 2 H). LC/MS retention time = 3.026 minutes, MS calculated for ($C_{23}H_{19}Cl_2F_4N_3O_2$) 515.08, found 516.0 M+H.

Preparation 16: 5-(3,5-dichloro-4-fluorophenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



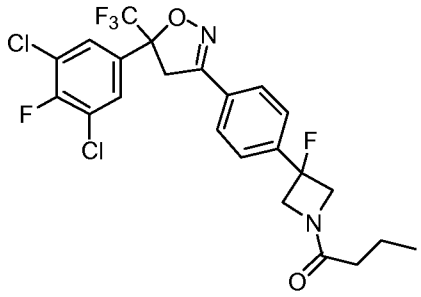
The product was prepared according to the methods of Preparation 12, 14, and 15 using 1,3-dichloro-2-fluoro-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene. ^{1}H NMR (DMSO – d_6) δ 10.0 – 9.6 (br s, 2 H) 7.9 – 7.7 (m, 6 H), 4.68 - 4.24 (m, 6 H). LC/MS retention time = 3.020 minutes, MS calculated for ($C_{19}H_{13}Cl_2F_5N_2O$) 450.03, found 450.9 M+H.

Example 11: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)propan-1-one



The compound was prepared from the compound of preparation 16 according to the method of Example 6 using propionyl chloride in place of cyclopropane carbonyl chloride. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H), 7.60 (d, 2 H), 7.54 (d, 2 H), 4.66 - 4.30 (m, 4 H), 2.22 (m, 1 H), 1.19 (m, 3 H). LC/MS retention time = 3.611 minutes, MS calculated for ($C_{22}H_{17}Cl_2F_5N_2O_2$) 506.6, found 507.0 M+H.

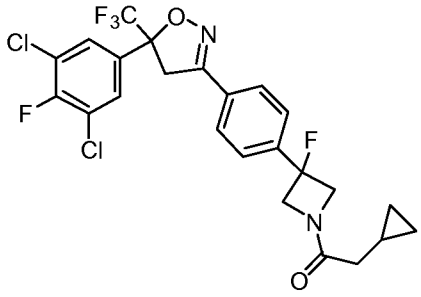
Example 12: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)butan-1-one



To a solution of butyric acid (50 mg) in DMF (5 mL) was added HATU (200 mg) then triethyl amine (150 µL). The resulting solution was stirred at ambient temperature for 15 minutes then 5-(3,5-dichloro-4-fluorophenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole hydrochloride (Preparation 16 100 mg) was added in one portion. Reaction stirred at ambient temperature for 16 hours. Solvent was removed in vacuo and the residue partitioned between water (10 mL) and CH_2Cl_2 (10 mL). Organic phase collected and condensed. The crude material was adsorbed on silica and chromatographed on a 12 g silica column, eluting with a gradient of 0% to 100% ethyl acetate in heptane. Fractions containing the desired material were combined and concentrated. Et_2O (~½mL) was added to the resulting film. Placing the flask on high vacuum overnight resulted in formation of a white foam. Yield 86 mg (80%). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2 H), 7.61 (d, 2 H), 7.55 (d, 2 H), 4.68 - 4.33 (m, 4 H),

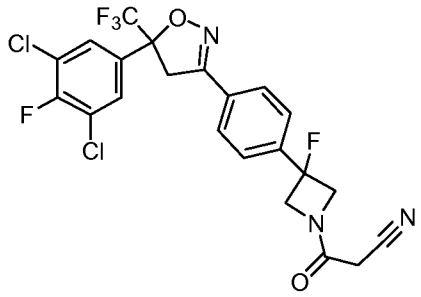
4.12 (d, 1 H), 3.72 (d, 1 H), 2.19 (m, 2 H), 1.73 (m, 2 H), 1.01 (m, 3 H). LC/MS retention time = 3.688 minutes, MS calculated for ($C_{23}H_{19}Cl_2F_5N_2O_2$) 520.07, found 521.0 M+H.

Example 13: 2-cyclopropyl-1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone



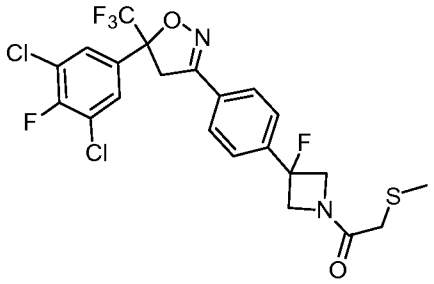
The compound was prepared from the compound of Preparation 16 according to the method of Example 12 using cyclopropyl acetic acid in place of butyric acid. Yield 73 mg (67%). ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H), 7.60 (d, 2 H), 7.54 (d, 2 H), 4.67 - 4.33 (m, 4 H), 4.10 (d, 1 H), 3.70 (d, 1 H), 2.03 (m, 2 H), 1.09 (m, 1 H), 0.61 (m, 2 H), 0.20 (m, 2 H). LC/MS retention time = 3.694 minutes, MS calculated for ($C_{24}H_{19}Cl_2F_5N_2O_2$) 532.07, found 533.0 M+H.

Example 14: 3-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-oxopropanenitrile



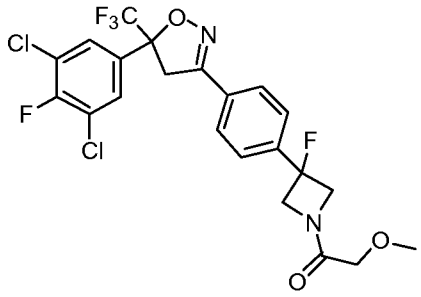
The compound was prepared from the compound of Preparation 16 according to the method of Example 12 using cyanoacetic acid in place of butyric acid. Yield 88 mg (55%). ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2 H), 7.60 (d, 2 H), 7.55 (d, 2 H), 4.79 (m, 1 H), 4.71 - 4.40 (m, 3 H), 4.11 (d, 1 H), 3.71 (d, 1 H), 3.40 (s, 2 H). LC/MS retention time = 3.533 minutes, MS calculated for ($C_{22}H_{14}Cl_2F_5N_3O_2$) 517.04, found 539.9 M+H+Na^+.

Example 15: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone



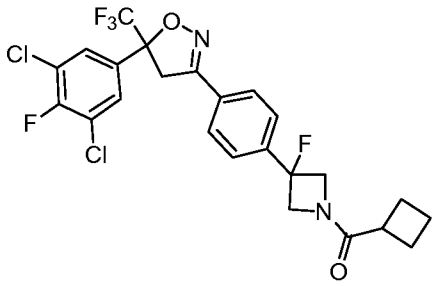
The compound was prepared from the compound of Preparation 16 according to the method of Example 12 using 2-(methylthio)acetic acid in place of butyric acid. Yield 208 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2 H), 7.60 (d, 2 H), 7.55 (d, 2 H), 4.72 (m, 1 H), 4.61 - 4.34 (m, 3 H), 4.11 (d, 1 H), 3.71 (d, 1 H), 3.15 (s, 2 H) , 2.26 (s, 3 H). LC/MS retention time = 3.637 minutes, MS calculated for ($C_{22}H_{17}Cl_2F_5N_2O_2S$) 538.03, found 538.9 M+H+.

Example 16: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methoxyethanone



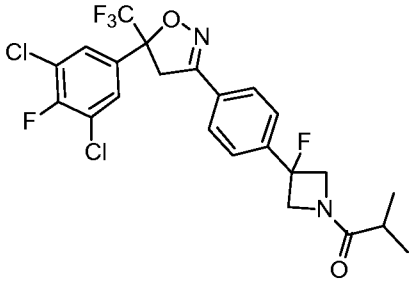
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using methoxy acetyl chloride in place of cyclopropane carbonyl chloride. Yield 114 mg (88%). ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H), 7.60 (d, 2 H), 7.54 (d, 2 H), 4.82 - 4.68 (m, 1 H), 4.66 - 4.34 (m, 3 H), 4.15 - 4.04 (m, 3 H), 3.71 (d, 1 H), 3.42 (s, 3 H). LC/MS retention time = 3.543 minutes, MS calculated for ($C_{22}H_{17}Cl_2F_5N_2O_3$) 522.05, found 523.0 M+H.

Example 17: cyclobutyl(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone



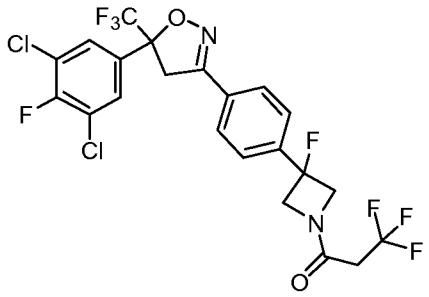
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using cyclobutanecarbonyl chloride in place of cyclopropane carbonyl chloride. Yield 115 mg (88%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.59 (d, 2 H), 7.51 (d, 2 H), 4.59 - 4.26 (m, 4 H), 4.10 (d, 1 H), 3.71 (d, 1 H), 3.12 (m, 1 H), 2.38 (m, 2 H), 2.16 (m, 2 H), 2.07 – 1.87 (m, 2 H). LC/MS retention time = 3.743 minutes, MS calculated for ($C_{24}H_{19}Cl_2F_5N_2O_2$) 532.07, found 533.0 M+H.

Example 18: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one



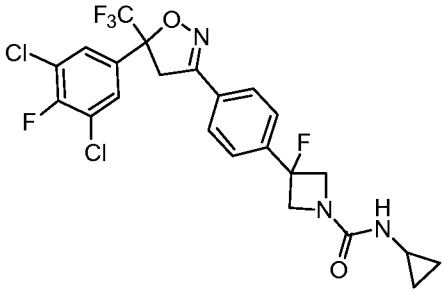
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using isobutyroyl chloride in place of cyclopropane carbonyl chloride. Yield 166 mg (90%). ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H), 7.60 (d, 2 H), 7.53 (d, 2 H), 4.70 - 4.29 (m, 4 H), 4.10 (d, 1 H), 3.71 (d, 1 H), 2.51 (m, 1 H), 1.17 (m, 6 H). LC/MS retention time = 3.685 minutes, MS calculated for ($C_{23}H_{19}Cl_2F_5N_2O_2$) 520.07, found 521.0 M+H.

Example 19: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one



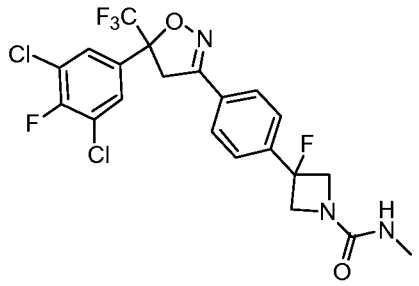
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using 3,3,3-trifluoropropanoyl chloride in place of cyclopropane carbonyl chloride. Yield 96 mg (70%). ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2 H), 7.60 (d, 2 H), 7.53 (d, 2 H), 4.76 - 4.65 (m, 1 H), 4.61 - 4.38 (m, 3 H), 4.10 (d, 1 H), 3.71 (d, 1 H), 3.09 (m, 2 H). LC/MS retention time = 3.712 minutes, MS calculated for ($C_{22}H_{14}Cl_2F_8N_2O_2$) 560.03, found 561.0 M+H.

Example 20: N-cyclopropyl-3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide



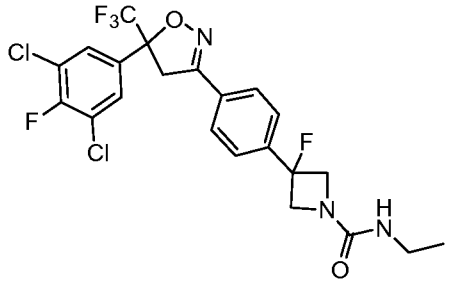
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 126 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2 H), 7.60 (d, 2 H), 7.56 (d, 2 H), 4.56 - 4.39 (m, 3 H), 4.29 - 4.18 (m, 2 H), 4.10 (d, 1 H), 3.70 (d, 1 H), 2.65 (m, 1 H), 0.78 (m, 2 H), 0.55 (m, 2 H). LC/MS retention time = 3.233 minutes, MS calculated for ($C_{23}H_{18}Cl_2F_5N_3O_2$) 533.07, found 534.0 M+H.

Example 21: 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide



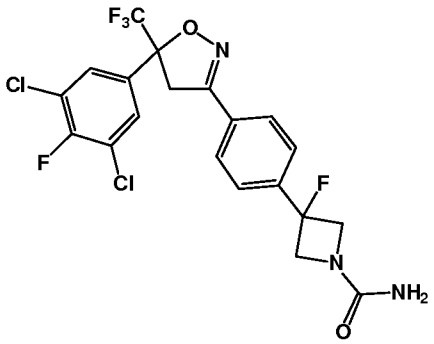
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using methyl isocyanate in place of cyclopropane carbonyl chloride. Yield 44 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2 H), 7.59-7.53 (m, 4 H), 4.45 (d, 1 H), 4.39 (d, 1 H), 4.23 (d, 1 H), 4.21 (d, 1 H), 4.24-4.17 (m, 3 H), 4.08 (d, 1 H), 3.68 (d, 1 H), 2.83 (d, 3 H). LC/MS retention time = 3.001 minutes, MS calculated for ($C_{21}H_{16}Cl_2F_5N_3O_2$) 507, found 508 M+H.

Example 22: 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide



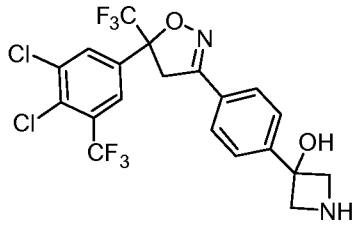
The compound was prepared from the compound of preparation 16 according to the method of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 44 mg (91%). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2 H), 7.59-7.53 (m, 4 H), 4.44 (d, 1 H), 4.39 (d, 1 H), 4.24-4.17 (m, 3 H), 4.08 (d, 1 H), 3.68 (d, 1 H), 3.33-3.26 (m, 2 H), 1.16 (t, 3 H). LC/MS retention time = 3.531 minutes, MS calculated for ($C_{22}H_{18}Cl_2F_5N_3O_2$) 521, found 522 M+H.

Example 23: 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide



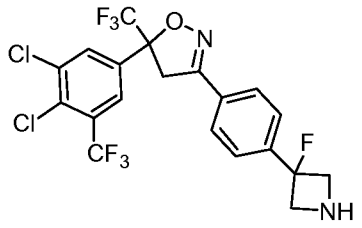
Triethylamine (0.070 mL, 0.492 mmol) was added to a suspension of azetidine hydrochloride salt (Preparation 16, 0.200 g, 0.410 mmol) in CH_2Cl_2 (5 mL). Subsequently, trimethylsilyl isocyanate (0.308 mL, 2.05 mmol) was added and the reaction mixture was stirred at room temperature overnight. A saturated aqueous solution of Na_2CO_3 (5 mL) was added and the reaction mixture was stirred for 5 minutes. The organic phase was separated, washed with brine and dried (anhydrous Na_2SO_4). Solvent was evaporated under reduced pressure to yield an off-white solid. The residue was purified by chromatography [Teledyne Isco CombiFlash Rf system, 24 g silica gel RediSep Rf cartridge, CH_2Cl_2 to CH_2Cl_2-MeOH (95:5) over 10 CV gradient elution] to afford the purified desired compound as a white solid (0.089 g, 44%). LC/MS R_t = 3.378 minutes, *m/z* 494 $[M+H]^+$

Preparation 17: 3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol



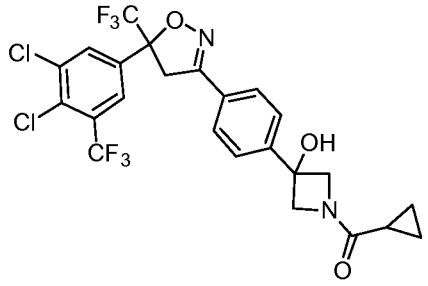
Prepared according to the methods of Preparation 12 and Preparation 13 using 1,2-dichloro-3-(trifluoromethyl)-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene.

Preparation 18: 5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole.



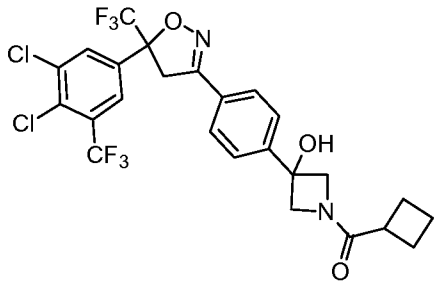
Prepared according to the methods of Preparations 12, 14 and 15 using 1,2-dichloro-3-(trifluoromethyl)-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene. ^{1}H NMR (DMSO-d_6) δ ppm: 8.20 (1H), 7.93 (1H), 7.86 (2H), 7.75 (2H), 4.62-4.36 (6H); m/z (Cl) 501 ($[M+H]^+$.

Example 24: cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone



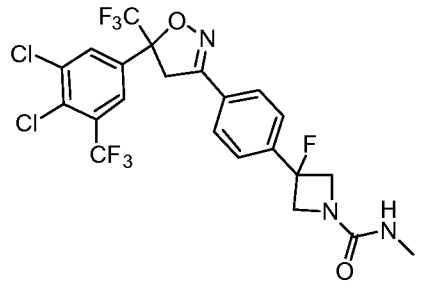
The compound was prepared from the compound of preparation 17 according to the method of Example 6 using cycloproplylcarboxyl chloride in place of cyclopropane carbonyl chloride. Yield 112 mg (88%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1 H), 7.85 (d, 1 H), 7.71 (m, 2 H), 7.62 (m, 2 H), 4.51 (m, 2 H), 4.29 (m, 2 H), 4.16 (d, 1 H), 3.95 (s, 1 H), 3.73 (d, 1 H), 1.47 (m, 1 H), 1.01 (m, 2 H), 0.82 (m, 2 H). LC/MS retention time = 3.564 minutes, MS calculated for ($C_{24}H_{18}Cl_2F_6N_2O_3$) 566.06, found 567.0 M+H.

Example 25: cyclobutyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone



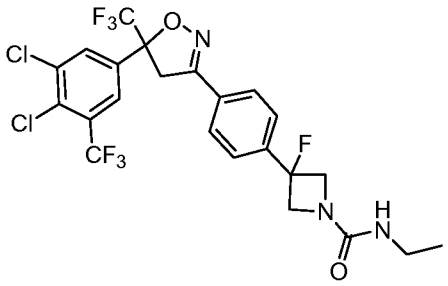
The compound was prepared from the compound of preparation 17 according to the method of Example 6 using cyclobutanecarbonyl chloride in place of cyclopropane carbonyl chloride. Yield 111 mg (85%). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1 H), 7.85 (d, 1 H), 7.70 (m, 2 H), 7.58 (m, 2 H), 4.37 – 4.21 (m, 4 H), 4.15 (m, 1 H), 4.04 (d, 1 H), 3.72 (m, 1 H), 3.10 (m, 1 H), 2.33 (m, 2 H), 2.12 (m, 2 H), 2.06 – 1.83 (m, 2 H). LC/MS retention time = 3.650 minutes, MS calculated for ($C_{25}H_{20}Cl_2F_6N_2O_3$) 580.08, found 581.0 M+H.

Example 26: 3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide



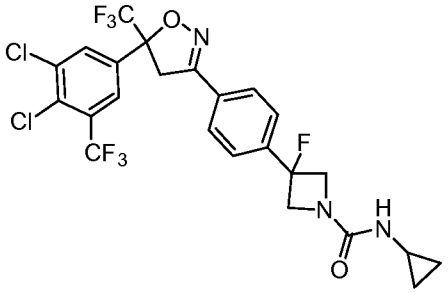
The compound was prepared from the compound of preparation 18 according to the method of Example 6 using methyl isocyanate in place of cyclopropane carbonyl chloride. Yield 132 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 1 H), 7.85 (m, 1 H), 7.73 (d, 2 H), 7.57 (d, 2 H), 4.50 - 4.39 (m, 2 H), 4.28 - 4.11 (m, 4 H), 3.72 (d, 1 H), 2.86 (d, 3 H). LC/MS retention time = 3.090 minutes, MS calculated for ($C_{22}H_{16}Cl_2F_7N_3O_2$) 557.05, found 558.0 M+H.

Example 27: 3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide



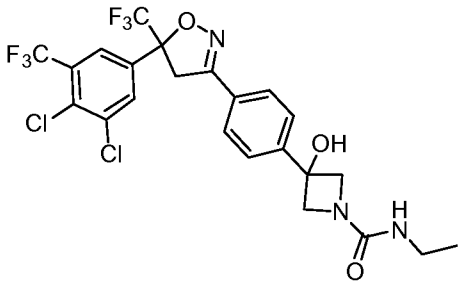
The compound was prepared from the compound of preparation 18 according to the method of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 141 mg (98%). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 1 H), 7.85 (m, 1 H), 7.74 (d, 2 H), 7.57 (d, 2 H), 4.49 - 4.38 (m, 2 H), 4.27 - 4.11 (m, 4 H), 3.72 (d, 1 H), 3.31 (m, 2 H), 1.18 (t, 3 H). LC/MS retention time = 3.133 minutes, MS calculated for ($C_{23}H_{18}Cl_2F_7N_3O_2$) 571.01, found 572.0 M+H.

Example 28: N-cyclopropyl-3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide



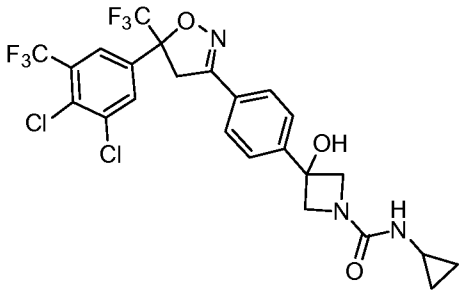
The compound was prepared from the compound of preparation 18 according to the method of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 142 mg (97%). ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 1 H), 7.85 (m, 1 H), 7.74 (d, 2 H), 7.56 (d, 2 H), 4.55 - 4.38 (m, 3 H), 4.29 - 4.19 (m, 2 H), 4.16 (d, 1 H), 3.72 (d, 1 H), 2.64 (m, 1 H), 0.78 (m, 2 H), 0.55 (m, 2 H). LC/MS retention time = 3.152 minutes, MS calculated for ($C_{24}H_{18}Cl_2F_7N_3O_2$) 583.07, found 584.0 M+H.

Example 29: 3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-hydroxyazetidine-1-carboxamide



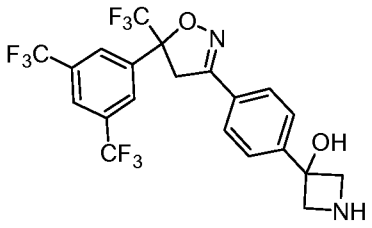
The compound was prepared from the compound of preparation 17 according to the method of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 50 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H), 7.83 (s, 1 H), 7.68 (d. 2 H), 7.62 (d, 2 H) 4.21-4.11 (m, 6 H), 3.90 (s, 1H), 3.70 (d, 1 H), 3.26 (q, 2H), 1.13 (t, 3 H). LC/MS retention time = 3.179 minutes, MS calculated for ($C_{23}H_{19}Cl_2F_6N_3O_3$) 569, found 570 M+H.

Example 30: N-cyclopropyl-3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidine-1-carboxamide



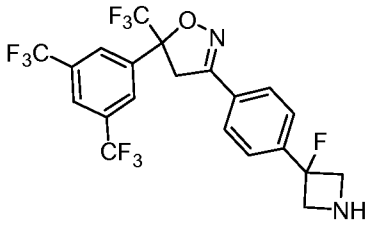
The compound was prepared from the compound of preparation 17 according to the method of Example 6 using cyclopropane carbonyl chloride. Yield 51 mg (94%). ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H), 7.83 (s, 1 H), 7.68 (d, 2 H), 7.62 (d, 2 H), 4.49 (s, 1 H) 4.23-4.18 (m, 4 H), 4.13 (d, 1 H), 3.70 (d, 1 H), 3.3.8 (s, 1 H), 2.63-2.59 (m, 1 H), 0.76-0.72 (m, 2 H), 0.53-0.49 (m, 2 H). LC/MS retention time = 3.481 minutes, MS calculated for ($C_{24}H_{19}Cl_2F_6N_3O_3$) 581, found 582 M+H.

Preparation 19: 3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol



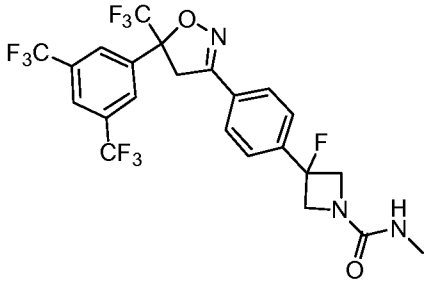
Prepared according to the methods of Preparation 12 and Preparation 13 using 1,3-bis(trifluoromethyl)-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene.

Preparation 20: 5-(3,5-bis(trifluoromethyl)phenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole.



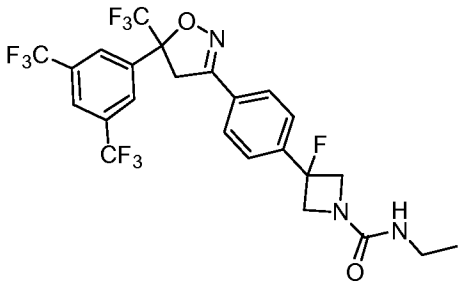
Prepared according to the methods of Preparations 12, 14 and 15 using 1,3-bis(trifluoromethyl)-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene. ^{1}H NMR (DMSO-d_6) δ ppm: 8.36 (1H), 8.22 (2H), 7.87 (2H), 7.76 (2H), 4.62-4.42 (6H); m/z (CI) 501 ($[M+H]^+$.

Example 31: 3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide



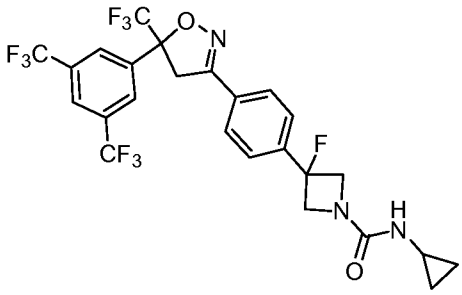
The compound was prepared from the compound of Preparation 20 according to the method of Example 6 using methyl isocyanate in place of cyclopropane carbonyl chloride. Yield 131 mg (94%). ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 2 H), 7.98 (s, 1 H), 7.75 (d, 2 H), 7.57 (d, 2 H), 4.50 - 4.39 (m, 2 H), 4.28 - 4.17 (m, 4 H), 3.76 (d, 1 H), 2.86 (d, 3 H). LC/MS retention time = 3.015 minutes, MS calculated for ($C_{23}H_{17}F_{10}N_3O_2$) 557.12, found 558.0 M+H.

Example 32: 3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide



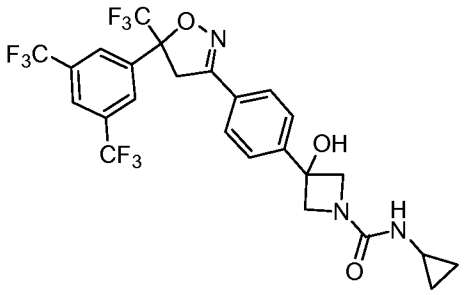
The compound was prepared from the compound of Preparation 20 according to the method of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 131 mg (92%). ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 2 H), 7.98 (s, 1 H), 7.75 (d, 2 H), 7.57 (d, 2 H), 4.50 - 4.39 (m, 2 H), 4.27 - 4.16 (m, 4 H), 3.76 (d, 1 H), 3.31 (m, 2 H), 1.18 (t, 3 H). LC/MS retention time = 3.089 minutes, MS calculated for ($C_{24}H_{19}F_{10}N_3O_2$) 571.13, found 572.0 M+H.

Example 33: 3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-fluoroazetidine-1-carboxamide



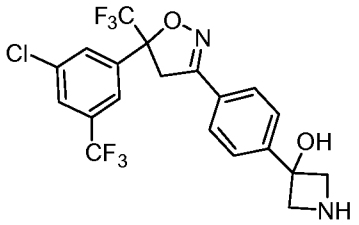
The compound was prepared from the compound of Preparation 20 according to the method of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 141 mg (96%). ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 2 H), 7.98 (s, 1 H), 7.75 (d, 2 H), 7.57 (d, 2 H), 4.55 - 4.39 (m, 3 H), 4.28 - 4.18 (m, 3 H), 3.77 (d, 1 H), 2.65 (m, 1 H), 0.78 (m, 2 H), 0.55 (m, 2 H). LC/MS retention time = 3.086 minutes, MS calculated for ($C_{25}H_{19}F_{10}N_3O_2$) 583.13, found 584.0 M+H.

Example 34: 3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-hydroxyazetidine-1-carboxamide



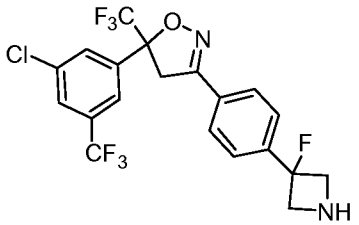
The compound was prepared from the compound of Preparation 19 according to the method of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 119 mg (89%). ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 2 H), 7.97 (s, 1 H), 7.71 (m, 2 H), 7.64 (m, 2 H), 4.57 (d, 1 H), 4.28 - 4.16 (m, 6 H), 3.77 (d, 1 H), 2.61 (m, 1 H), 0.74 (m, 2 H), 0.52 (m, 2 H). LC/MS retention time = 2.989 minutes, MS calculated for ($C_{25}H_{20}F_9N_3O_3$) 581.14, found 582.0 M+H.

Preparation 21: 3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol



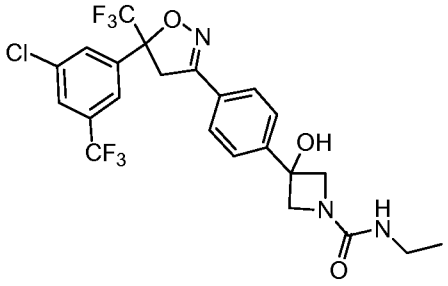
Prepared according to the methods of Preparation 12 and Preparation 13 using 1-chloro-3-(trifluoromethyl)-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene.

Preparation 22: 5-(3-chloro-5-(trifluoromethyl)phenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole.



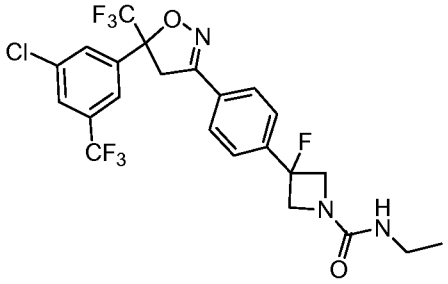
Prepared according to the methods of Preparations 12, 14 and 15 using 1-chloro-3-(trifluoromethyl)-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene. . ^{1}H NMR (DMSO-d_6) δ ppm: 8.10 (1H), 7.99 (1H), 7.87-7.85 (3H), 7.75 (2H), 4.62-4.37 (6H); m/z (CI) 467 ($[M+H]^+$.

Example 35: 3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-hydroxyazetidine-1-carboxamide



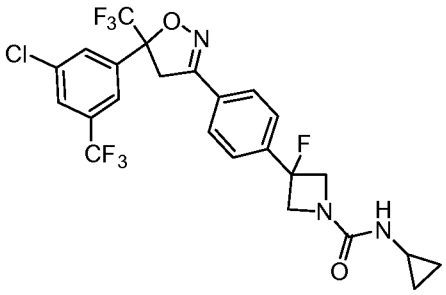
The compound was prepared from the compound of Preparation 21 according to the method of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 121 mg (90%). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.77 (m, 1 H), 7.74 – 7.68 (m, 3 H), 7.66 – 7.62 (m, 2 H), 4.22 – 4.13 (m, 6 H), 3.74 (d, 1 H), 3.30 (m, 2 H), 1.16 (t, 3 H). LC/MS retention time = 3.312 minutes, MS calculated for ($C_{23}H_{20}ClF_6N_3O_3$) 535.11, found 536.0 M+H.

Example 36: 3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide



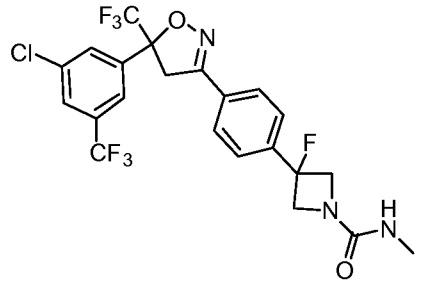
The compound was prepared from the compound of Preparation 22 according to the method of Example 6 using ethyl isocyanate in place of cyclopropane carbonyl chloride. Yield 133 mg (99%). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.79 – 7.68 (m, 4 H), 7.57 (d, 2 H), 4.49 - 4.38 (m, 2 H), 4.27 - 4.12 (m, 4 H), 3.74 (d, 1 H), 3.32 (m, 2 H), 1.18 (t, 3 H). LC/MS retention time = 3.571 minutes, MS calculated for ($C_{23}H_{19}ClF_7N_3O_2$) 537.11, found 538.0 M+H.

Example 37: 3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-fluoroazetidine-1-carboxamide



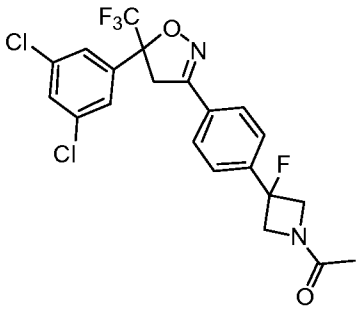
The compound was prepared from the compound of Preparation 22 according to the method of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield 131 mg (95%). ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1 H), 7.79 – 7.68 (m, 4 H), 7.56 (d, 2 H), 4.55 - 4.39 (m, 3 H), 4.29 - 4.20 (m, 2 H), 4.16 (d, 1 H), 3.74 (d, 1 H), 2.65 (m, 1 H), 0.78 (m, 2 H), 0.55 (m, 2 H). LC/MS retention time = 3.574 minutes, MS calculated for ($C_{22}H_{17}ClF_7N_3O_2$) 549.11, found 550.0 M+H.

Example 38: 3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide



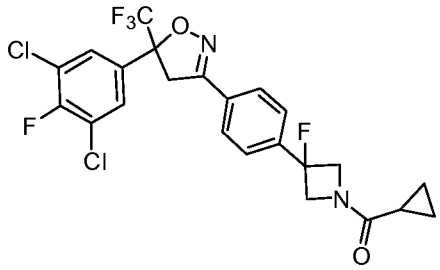
The compound was prepared from the compound of Preparation 22 according to the method of Example 6 using methyl isocyanate in place of cyclopropane carbonyl chloride. Yield 126 mg (96%). ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1 H), 7.79 – 7.68 (m, 4 H), 7.57 (d, 2 H), 4.50 - 4.39 (m, 2 H), 4.28 - 4.12 (m, 4 H), 3.74 (d, 1 H), 2.86 (d, 3 H). LC/MS retention time = 3.487 minutes, MS calculated for ($C_{22}H_{17}ClF_7N_3O_2$) 523.09, found 524.0 M+H.

Example 39: 1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone



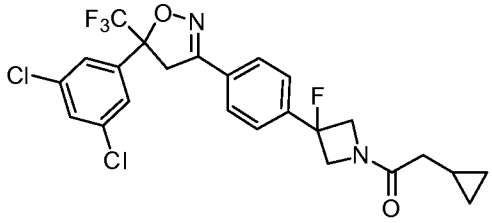
To a solution of 5-(3,5-dichlorophenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 15, 200 mg, 0.462 mMol) in dichloromethane (3 mL) was added triethylamine (0.192 mL) followed by acetic anhydride (50.2 µL). The reaction was allowed to stir at room temperature overnight. The solution was diluted with water and allowed to stir for 10 minutes. The mixture was passed through an ISCO Phase Separator. A stream of nitrogen was blown onto the organics then placed under high vacuum to form a white foam 200 mg (91% yield) ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.01 (s, 3 H) 3.73 (d, 1 H) 3.92 (qd, 1 H) 4.12 (d, 1 H) 4.32 - 4.56 (m, 3 H) 4.59 - 4.70 (m, 1 H) 7.46 (t, 1 H) 7.52 - 7.59 (m, 4 H) 7.76 (d, 2 H), LC/MS retention time = 3.510 min; MS calculated for ($C_{21}H_{16}Cl_2F_4N_2O_2$) 474.052, found 475.0 M+H.

Example 40: cyclopropyl(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone



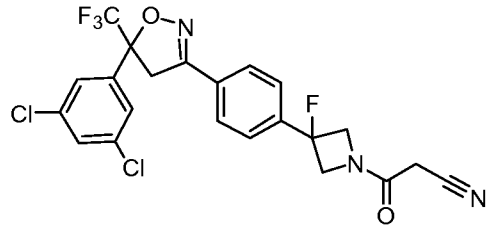
The compound was prepared from the compound of Preparation 16 according to the method of Example 6 using cyclopropyl isocyanate in place of cyclopropane carbonyl chloride. Yield: 87% of a glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 0.85 (t, Hz, 2 H) 1.06 (dd, 2 H) 1.42 - 1.51 (m, 1 H) 3.71 (d, 1 H) 4.11 (d, 1 H) 4.28 - 4.82 (m, 4 H) 7.53 - 7.64 (m, 4 H) 7.75 (d, 2 H) LC/MS retention time = 3.675 minutes; MS calculated for ($C_{23}H_{17}Cl_2F_5N_2O_2$) 518.059, found 519 M+H.

Example 41: 2-Cyclopropyl-1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone



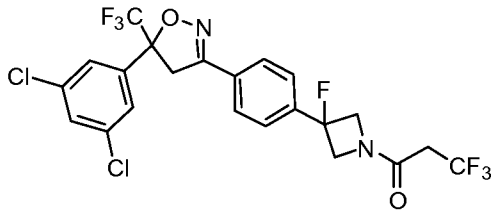
The compound was prepared from the compound of preparation 15 according to the method of Example 12 using 2-cyclopropylacetic acid in place of butyric acid. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm -0.04 - 0.04 (m, 2 H) 0.41 (d, 2 H) 0.86 - 0.92 (m, 1 H) 1.95 (d, 2 H) 3.51 (d, 1 H) 3.90 (d, 1 H) 4.12 - 4.46 (m, 4 H) 7.24 (t, 1 H) 7.30 - 7.37 (m, 4 H) 7.54 (d, 2 H), LC/MS retention time = 3.682 minutes; MS calculated for ($C_{24}H_{20}Cl_2F_4N_2O_2$) 514.084, found 515.0 $[M+H]^+$.

Example 42: 3-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-oxopropanenitrile



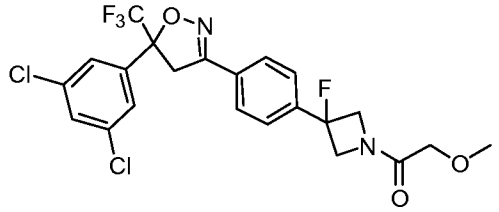
The compound was prepared from the compound of preparation 15 according to the method of Example 12 using 2-cyanoacetic acid in place of butyric acid to provide a glassy solid . ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.41 (s, 1 H) 3.73 (d, 1 H) 4.12 (d, 1 H) 4.41 - 4.72 (m, 4 H) 4.76 - 4.86 (m, 1 H) 7.46 (t, 1 H) 7.54 - 7.58 (m, 4 H) 7.78 (d, 2 H); MS calculated for ($C_{22}H_{15}Cl_2F_4N_3O_2$) 499.048, found 500.0 $[M+H]^+$.

Example 43: 1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one



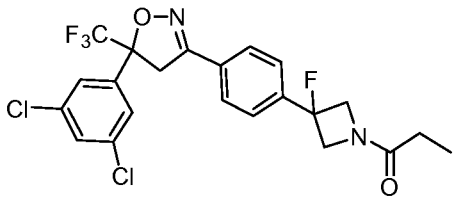
The compound was prepared from the compound of Preparation 15 according to the method of Example 6 using 3,3,3-trifluoropropanoyl chloride in place of cyclopropane carbonyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.09 (q, 2 H) 3.64 (d, 1 H) 4.10 (d, 1 H) 4.39 - 4.63 (m, 4 H) 7.37 (t, 1 H) 7.44 - 7.46 (m, 4 H) 7.76 (d, 2 H); MS calculated for ($C_{22}H_{15}Cl_2F_7N_2O_2$) 543.266, found 544.0 $[M+H]^+$.

Example 44: 1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methoxyethanone



The compound was prepared from the compound of Preparation 15 according to the method of Example 6 using 2-methoxyacetyl chloride in place of cyclopropane carbonyl chloride to provide a white solid. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.44 (s, 3 H) 3.73 (d, 1 H) 4.09 - 4.14 (m, 3 H) 4.37 - 4.63 (m, 3 H) 4.65 - 4.85 (m, 1 H) 7.43 - 7.49 (m, 1 H) 7.51 - 7.60 (m, 4 H) 7.76 (d, 2 H); MS calculated for ($C_{22}H_{18}Cl_2F_4N_3O_3$) 505.295, found m/z (ESI) 506.0 $[M+H]^+$.

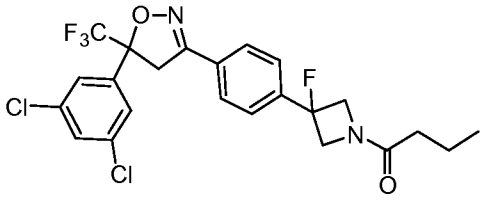
Example 45: 1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)propan-1-one



The compound was prepared from the compound of Preparation 15 according to the method of Example 6 using propionyl chloride in place of cyclopropane carbonyl chloride to provide a white solid ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.14

- 1.25 (m, 3 H) 2.24 (m, 2 H) 3.73 (d, 1 H) 4.11 (d, 1 H) 4.32 - 4.67 (m, 4 H) 7.46 (t, 1 H) 7.52 - 7.60 (m, 4 H) 7.76 (d, 2 H); MS calculated for ($C_{22}H_{18}Cl_2F_4N_2O_2$) 489.296, found m/z (ESI) 490.0 $[M+H]^+$.

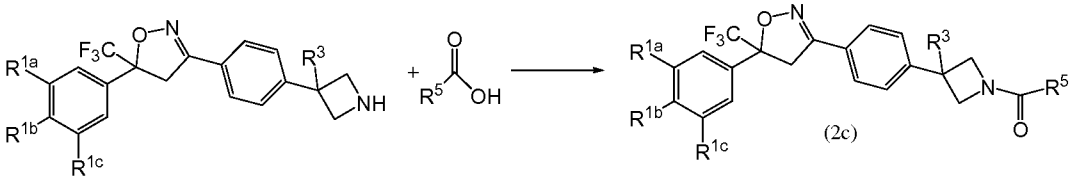
Example 46: 1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)butan-1-one



The compound was prepared from the compound of Preparation 15 according to the method of Example 6 using butyryl chloride in place of cyclopropane carbonyl chloride to provide a white solid. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.01 (t, 3 H) 1.73 (m, 2 H) 2.19 (m, 2 H) 3.73 (d, 1 H) 4.11 (d, 1 H) 4.33 - 4.66 (m, 4 H) 7.46 (t, 1 H) 7.53 - 7.58 (m, 4 H) 7.76 (d, 2 H); MS calculated for ($C_{23}H_{20}Cl_2F_4N_2O_2$) 503.323, found m/z (ESI) 503.0 $[M+H]^+$.

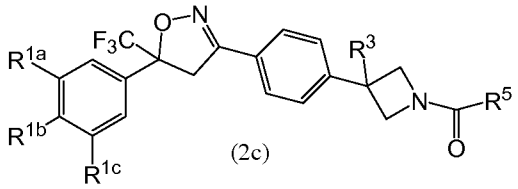
Examples 47-82

The Examples in Table 1 below were prepared under the following conditions



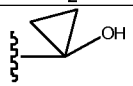
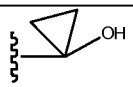
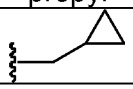
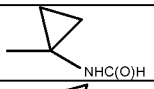
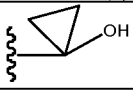
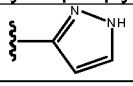
The isoxazoline phenyl azetidine (0.05 mmol) was dissolved in dimethyl formamide (0.5 mL). This was added to the respective acid (0.2 mmol), followed by a solution of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (0.10 mmol) in dimethyl formamide (0.5 mL) and Et_3N (0.5mmol). The resulting mixture was shaken at ambient temperature for 16 hours. The solvent was removed by distillation under vacuum, and the crude product purified by preparative HPLC. (Waters,Gemini NX C18 21x100mm 5µm, mobile phase A = 0.1%TFA in H_2O, mobile phase B = acetonitrile, linear gradient 30%B to 100% in 8 minutes, hold for 1 minute, 20 mL/minute, peaks collected by mass.). Retention times (RT) quoted below were obtained with the following

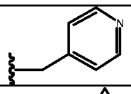
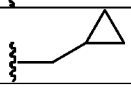
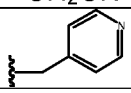
analytical method: Agilent 1200, Column = Gemini NX C18 4.6x50mm 3µm, mobile phase A = 0.1%TFA in H_2O, mobile phase B = acetonitrile, linear gradient 30%B to 100% in 5 minutes, holding for 1 minute, 1.5mL/minute.



(2c)

Table 1

Example No.	R^{1a}	R^{1b}	R^{1c}	R^3	R^5	m/z (ESI) [M+H]+	RT (minutes)
47	CF_3	H	CF_3	F	cyclobutyl	583	4.66
48	CF_3	H	CF_3	F	cyclopropyl	569	4.45
49	CF_3	H	CF_3	F	isopropyl	571	4.55
50	CF_3	H	Cl	F	propyl	538	4.55
51	CF_3	H	Cl	F	ethyl	524	4.34
52	CF_3	H	Cl	F	methyl	510	4.07
53	CF_3	H	Cl	F	$-CH_2CN$	535	4.21
54	Cl	H	Cl	F		517	3.98
55	Cl	F	Cl	F		535	4.04
56	Cl	Cl	Cl	F	$-CH_2OCH_3$	539	4.43
57	Cl	Cl	CF_3	OH	isopropyl	569	8.75
58	Cl	Cl	CF_3	OH	propyl	569	8.77
59	CF_3	H	CF_3	F		583	4.55
60	CF_3	H	CF_3	F	$-CH_2OH$	559	3.83
61	CF_3	H	Cl	F	$-CH_2SCH_3$	556	4.44
62	CF_3	H	Cl	F	cyclobutyl	550	4.66
63	CF_3	Cl	Cl	F	$-CH_2C(O)NH_2$	586	5.15
64	Cl	F	Cl	F		562	3.71
65	Cl	Cl	Cl	F		551	4.29
66	Cl	H	Cl	F	isobutyl	517	9.61
67	Cl	Cl	Cl	F	$-CH_2SCH_3$	555	9.59
68	Cl	F	Cl	OH	ethyl	505	7.76
69	CF_3	H	Cl	F	cyclopropyl	536	4.44
70	Cl	F	Cl	F		545	4.03

71	CF_3	H	CF_3	F		620	2.75
72	CF_3	H	Cl	F		550	4.53
73	CF_3	Cl	Cl	F	ethyl	557	7.31
74	CF_3	Cl	Cl	F	cyclopropyl	569	7.58
75	CF_3	Cl	Cl	F	methyl	543	6.67
76	CF_3	Cl	Cl	F	isopropyl	571	7.84
77	CF_3	Cl	Cl	F	$-CH_2CN$	568	6.72
78	Cl	Cl	Cl	F		572	7.40
79	CF_3	H	CF_3	F	ethyl	557	4.36
80	CF_3	Cl	Cl	F	cyclopentyl	597	8.66
81	CF_3	Cl	Cl	F	$-CH_2SCH_3$	589	7.56
82	Cl	F	Cl	OH	cyclopropyl	517	8

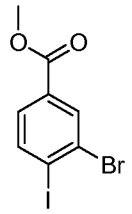
~~~~~~~~is the point of attachment, RT = retention time

The following IUPAC names for Examples (47-82) of Table 1 include: 5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (47); 5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (48); 5-[3,5-bis(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (49); 3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (50); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (51); 3-[4-(1-acetyl-3-fluoroazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (52); 3-[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanenitrile (53); 1-[(3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]cyclopropanol (54); 1-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]cyclopropanol (55); 3-{4-[3-fluoro-1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (56); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-1-isobutyrylazetidin-3-ol (57); 1-butyryl-3-(4-{5-[3,4-
~~~~~~~~

dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-3-ol (58); 5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (59); 2-[3-(4-{5-[3,5-bis(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethanol (60); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (61); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (62); 3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanamide (63); 3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanamide (64); 1-[(3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol (65); 5-(3,5-dichlorophenyl)-3-{4-[3-fluoro-1-(3-methylbutanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (66); 3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (67); 3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-propionylazetidin-3-ol (68); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (69); 5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1H-pyrazol-3-ylcarbonyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (70); 4-{2-[3-(4-{5-[3,5-bis(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethyl}pyridine (71); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (72); 5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (73); 3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (74); 3-[4-(1-acetyl-3-fluoroazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (75); 5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-

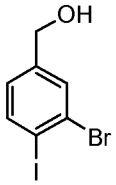
(trifluoromethyl)-4,5-dihydroisoxazole (76); 3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanenitrile (77); 4-[(3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]pyridine (78); 5-[3,5-bis(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (79); 3-{4-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (80); 5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (81); and 1-(cyclopropylcarbonyl)-3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol (82).

Preparation 23: Methyl 3-bromo-4-iodobenzoate



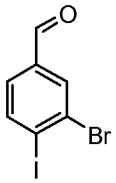
A solution of 4-amino-3-bromo-benzoic acid methyl ester (5.0g, 22.0mmol from Aldrich) in acetone (35mL) was treated with 6M HCl (35mL). The solution was cooled to 0°C and treated dropwise with $NaNO_2$ (1.84g, 26.1mmol) dissolved in 10mL water. After stirring for 2 hours at 0°C, the reaction was slowly treated with potassium iodide (5.47g, 32.6mmol) dissolved in 20mL water. The reaction mixture was allowed to warm to room temperature and stir for 1 hour. Reaction mixture was dilted with water and extracted with EtOAc (2 x 150mL). The combined organic phase was dried (Na_2SO_4) and concnetrated under vacuum The residue was chromatographed (80g Redi-Sep column) eluting from 100% heptane to 20:80 EtOAc:heptane to afford the intermediate (4.1g, 55%) as a solid. ^{1}HNMR ($CDCl_3$): 8.27 (1H), 7.98 (1H), 7.64 (1H), 3.94 (3H).

Preparation 24: (3-bromo-4-iodophenyl)methanol



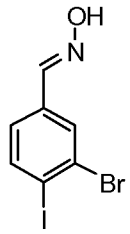
A solution of methyl 3-bromo-4-iodobenzoate (Preparation 23, 4.3g, 12.6mmol) in CH_2Cl_2 was cooled, under N_2, to -78°C. DIBAL-H was added slowly to the solution, which was stirred at -78°C for 45 minutes and then allowed to come to room temperature. Next, the reaction mixture was diluted with 1M HCL (40mL) and stirred for 30 minutes. The reaction was further diluted with water and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated under vacuum to afford the intermediate (3.2g, 82%) as a solid. ^{1}HNMR ($CDCl_3$): 7.85 (1H), 7.67 (1H), 7.02 (1H), 4.65 (2H), 1.76 (1H, OH).

Preparation 25: 3-bromo-4-iodobenzaldehyde



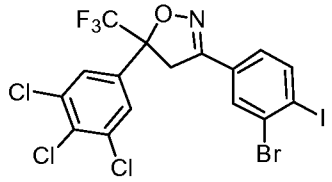
A solution of (3-bromo-4-iodophenyl)methanol (Preparation 24, 3.1g, 9.9mmol) in CH_2Cl_2/water (2:1, 225mL) was treated with $NaHCO_3$ (915mg, 10.9mmol), NaBr (1060mg, 10.2mmol) and TEMPO free radical (40mg, 0.2mmol). The resulting mixture was cooled to 0°C and NaOCl solution (0.8mL, 10% aqueous) was added dropwise. The reaction mixture was left to come to room temperature while stirring. TLC after 30 minutes showed approximately 50% conversion to less polar spot. Sequence repeated using same equivalent of reagents. TLC 25:75 EtOAc:heptane still showed unreacted starting material. The reaction mixture was separated and the organic phase was treated with 1.0x Dess-Martin periodinane (2.1g, 4.9mmol) while stirring. TLC after 10 minutes showed complete conversion to less polar spot. The organic phase was washed with sat $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to give an orange solid. The crude material was chromatographed (80g Redi-Sep column) eluting from 100% heptane to 50:50 EtOAc/heptane to give the intermediate (2.7g, 87%) as a white solid. ^{1}HNMR ($CDCl_3$): 9.94 (1H), 8.10 (2H), 7.50 (1H).

Preparation 26: (*E/Z*)-3-bromo-4-iodobenzaldehyde oxime



To a solution of 3-bromo-4-iodobenzaldehyde (Preparation 25, 1000mg, 3.2mmol) in EtOH (50mL) was added $NH_2OH.HCl$ (345mg, 4.8mmol) and water (10mL). The reaction was heated to 50°C for 1 hour and then allowed to stir for 18 hours at room temperature. The reaction mixture was concentrated under vacuum to remove EtOH. Water was added to residue and extracted with EtOAc (2 x 75mL). The combined organic phase was dried (Na_2SO_4) and concentrated under vacuum to afford the intermediate (1035mg, 98%) as a glass. M/z (CI) = 326 $[M+H]^+$.

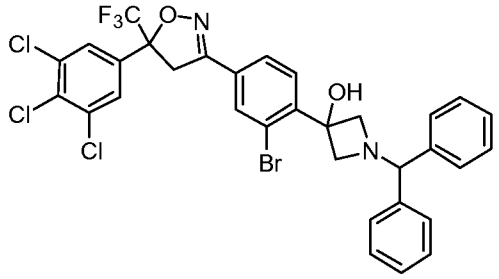
Preparation 27: 3-(3-bromo-4-iodophenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



To a DMF (25 mL) solution of (*E/Z*)-3-bromo-4-iodobenzaldehyde oxime (1000mg, 3.1mmol) was added NCS (Preparation 26, 500mg, 3.7mmol) portionwise. The reaction was stirred at room temperature for 18 hours. TLC 50:50 EtOAc:heptane shows slightly less polar spot, no starting material. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 x 50mL). The organic phase was dried over sodium sulfate and concentrated to give the chlorooxime intermediate (1056mg, 96%) as a solid. Next, to an ethyl acetate (70 mL) solution of the chlorooxime (1000mg, 2.8mmol) and 1,2,3-trichloro-5-(1,1,1-trifluoroprop-2-en-2-yl)benzene (765mg, 2.8mmol) was added potassium bicarbonate (310mg, 3.1mmol). The mixture was allowed to stir at room temperature for at least 48 hours. Reaction mixture filtered and concentrated under vacuum. The residue was chromatographed (80g Redi-Sep column) eluting from 100% heptane to

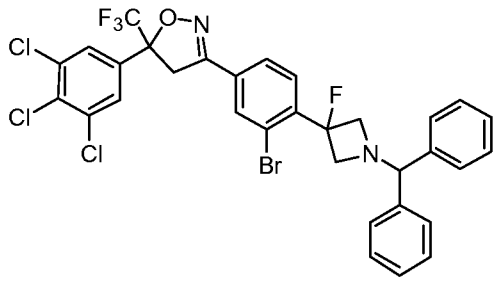
20:80 EtOAc:heptane to afford the intermediate (1.53g, 92%) as a solid. ^{1}HNMR ($CDCl_3$): 7.95 (1H), 7.88 (1H), 7.65 (2H), 7.33 (1H), 4.07 (1H), 3.67 (1H).

Preparation 28: 1-benzhydryl-3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol



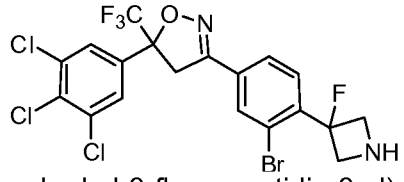
In an oven-dried flask containing 3-(3-bromo-4-iodophenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 27, 1000mg, 1.67mmol) in THF (25mL) at -40°C was slowly added isopropyl magnesium chloride (1.7mL of 2.0M solution). The reaction was stirred at approx. -40°C for 1.5 under nitrogen. 1-benzhydrylazetidin-3-one (520mg in 4mL THF) was slowly added. The reaction was stirred at -40°C for an additional 30 minutes and allowed to warm to room temperature. Stirring was continued for 2 hours at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (2 x 75mL). The combined organic phase was dried (Na_2SO_4) and concentrated under vacuum. The crude material was chromatographed (40g Redi-Sep column) eluting from 100% heptane to 60:40 EtOAc:heptane, collecting the intermediate (615mg, 52%) as a glass. ^{1}HNMR ($CDCl_3$): 7.87 (1H), 7.66-7.63 (3H), 7.45 (4H), 7.36-7.21 (7H), 4.39 (1H), 4.07 (1H), 3.73-3.58 (5H), 3.06 (1H); m/z (CI) 711 ($[M+H]^+$.

Preparation 29: 3-(4-(1-benzhydryl-3-fluoroazetidin-3-yl)-3-bromophenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



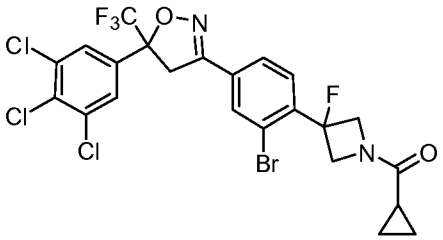
Triethylamine trihydrofluoride (0.3mL, 1.7mmol) and triethylamine (0.11mL, 0.8mL) were dissolved in dichloromethane (30mL) and cooled to -78°C. To the cooled mixture was added XtalFluor-E (310mg, 1.4mmol) and then 1-benzhydryl-3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol (Preparation 28, 600mg, 0.8mmol). Cooling was removed and the mixture was allowed to warm to room temperature with stirring for 2 hours. The reaction was poured into saturated aqueous sodium carbonate solution (100mL) and the organic phase was separated, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Crude material was chromatographed (40G Redi-Sep Column) eluting from 100%heptane to 20:80 EtOAc:heptane to afford the intermediate (523mg, 87%) as a glass. ^{1}HNMR ($CDCl_3$) δ ppm: 7.90 (1H), 7.69-7.66 (3H), 7.47-7.21 (11H), 4.46 (1H), 4.08 (1H), 3.90-3.66 (5H); m/z (CI) 713 ($[M+H]^+$.

Preparation 30: 3-(3-bromo-4-(3-fluoroazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



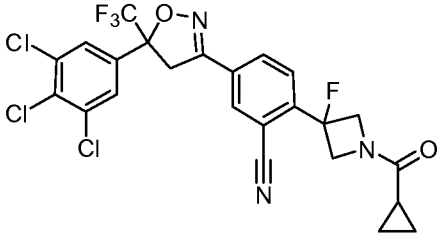
To a solution of 3-(4-(1-benzhydryl-3-fluoroazetidin-3-yl)-3-bromophenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 29, 515mg, 0.76mmol) in MeCN/DCM (5:1, 60mL) at 0°C was added 1-chloroethyl chloroformate (275uL, 2.5mmol). The reaction was heated to reflux for 3 hours then allowed to cool to room temperature while stirring for 18 hours. Next, the reaction mixture was concentrated under vacuum, re-dissolved in anhydrous MeOH (50mL), and refluxed for 1 hour. The reaction was cooled, concentrated under reduced pressure, and diethyl ether was added to residue. The resulting precipitate was filtered, rinsed with diethyl ether, and air dried to afford the intermediate (365mg, 87%) as a solid. M/z (CI) 713 ($[M+H]^+$.

Example 83: (3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone



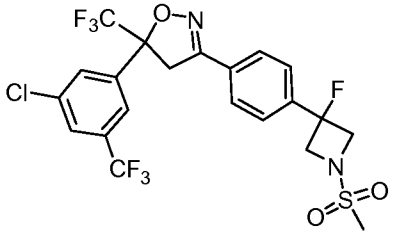
Prepared from the compound of Preparation 30, according to the method of Example 6. ^{1}H NMR ($CDCl_3$) δ ppm: 7.98 (1H), 7.71 (1H), 7.66 (2H), 7.53 (1H), 4.96-4.46 (4H), 4.09 (1H), 3.70 (1H), 1.49 (1H), 1.11-0.77 (4H); m/z (CI) 615 ($[M+H]^+$.

Example 84: 2-(1-(cyclopropanecarbonyl)-3-fluoroazetidin-3-yl)-5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)benzonitrile



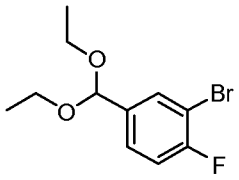
To a solution of (3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone (Example 83, 35mg, 0.06mmol) in DMF was added ZnCN (15mg, 0.12mmol) and the reaction was degassed with N_2 purge. $Pd(PPh_3)_4$ (4mg, 0.003mmol) was added and the reaction mixture was heated under microwave irradiation at 150°C for 15 minutes. Next, the reaction mixture was diluted with water and extracted with EtOAc (75mL). The organic phase was dried (Na_2SO_4) and concentrated under vacuum. Crude product was chromatographed (12g Redi-Sep column) eluting from 100% heptane to 60:40 EtOAc:heptane to afford the final product (18mg, 56%) as a solid. ^{1}H NMR ($CDCl_3$) δ ppm: 8.08 (1H), 8.00 (1H), 7.70 (1H), 7.66 (2H), 4.98-4.52 (4H), 4.12 (1H), 3.73 (1H), 1.49 (1H), 1.10-0.81 (4H); m/z (CI) 560 ($[M+H]^+$.

Example 85: 5-(3-chloro-5-(trifluoromethyl)phenyl)-3-(4-(3-fluoro-1-(methylsulfonyl)azetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole



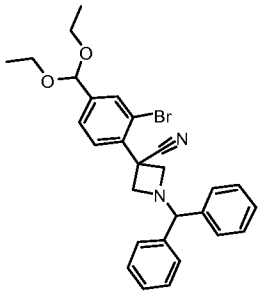
To a solution of 5-(3-chloro-5-(trifluoromethyl)phenyl)-3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (Preparation 22, 95mg, 0.2mmol) in CH_2Cl_2 (5mL) was added triethylamine (0.15mL, 1.1mmol) and DMAP (5mg, 0.04mmol). Contents were stirred for 30 minutes at which time mesyl chloride (25mg, 0.2mmol) was added and the reaction was stirred for 18 hours at room temperature. Next, the reaction was concentrated to ~3mL under nitrogen purge and injected directly onto a 24g Redi-Sep column. The crude material was chromatographed eluting from 100%heptane to 30:70 EtOAc:heptane to afford the final product (95mg, 94%) as a solid. ^{1}HNMR ($CDCl_3$) δ ppm: 7.85 (1H), 7.79-7.77 (3H), 7.72 (1H), 7.64 (2H), 4.50-4.42, (2H), 4.34-4.27 (2H), 4.18 (1H), 3.76 (1H), 3.03 (3H); m/z (CI) 545 ($[M+H]^+$.

Preparation 31: 2-bromo-4-(diethoxymethyl)-1-fluorobenzene



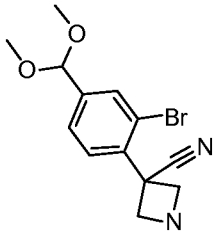
A 10mL vial equipped with stir bar was charged with 1g of 3-bromo-4-fluoro-benzaldehyde, 2mL of triethyl orthoformate, and 5mL of anhydrous ethanol. 50mgs of tetrabutylammonium tribromide was then added, and the reaction mixture was stirred at ambient temperature overnight. TLC shows complete conversion to slightly less polar product. The crude reaction is poured into $NaHCO_3$, and extracted with ethyl acetate (2x 25mL). Combined organics are dried over MgSO4, and filtered over a pad of silica. The solvents are reduced under vacuum and a colorless oil (1g) is isolated. The diethyl acetal intermediate is used as such in the next step. 74% yield.

Preparation 32: 1-benzhydryl-3-(2-bromo-4-(diethoxymethyl)phenyl)azetidine-3-carbonitrile



2-bromo-4-(diethoxymethyl)-1-fluorobenzene (Preparation 31, 1g) and 1-benzhydrylazetidine-3-carbonitrile (2.7g) were dissolved in anhydrous THF (4mL). KHMDS (2.2g) was then added all at once. The solution became dark brown instantaneously. The reaction was stirred at room temperature overnight. An LC-Ms confirms complete conversion into the desired product: [433] ~ 3.31 minutes and [505] ~ 3.62 min. Both peaks correspond to desired product: one is the aldehyde, and the other is the acetal. The crude reaction mixture was concentrated to an oil, and loaded on a 80g SiO_2 cartridge, then eluted with a gradient 0-100% ethylacetate in heptane. The desired fractions were collected and concentrated in vacuum. The resulting oil was suspended in methanol and sonicated for 30sec, and the resulting white powder is filtered and used as such in the next step. 55% yield. LC-MS [505].

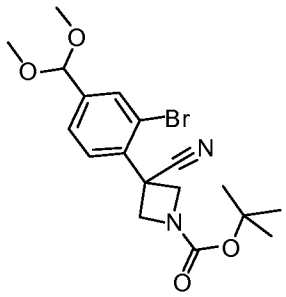
Preparation 33: 3-(2-bromo-4-(dimethoxymethyl)phenyl)azetidine-3-carbonitrile



The product from Preparation 32 (500 mg) was dissolved in acetonitrile and the reaction mixture was cooled to 0°C, then chloroethylchloroformate (0.2 mL) was added all at once. The reaction mixture was heated to reflux for 2 hours. LC-MS shows desired peak forming ~ 2.329 minutes [339], but some starting material left. Another equivalent of chloroethylchloroformate was added, and the reaction mixture is left stirring for another hour at reflux. TLC shows completion. The crude

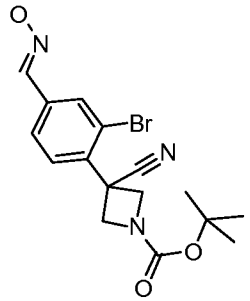
reaction was concentrated in vacuum, and the resulting yellow oil was dissolved in MeOH, and re-heated to reflux for 30 minutes. TLC shows complete conversion to a baseline spot. The reaction was concentrated to an oil, and 20 mL diethylether was added. The gum was then sonicated for 15 minutes, and the solid is filtered and analysed. LC-MS ([311] ~ 2.036min) confirms desired product, although the ethylacetal is now a methylacetal due to reflux in methanol. Used as such in the next step. Assumed quantitative yield.

Preparation 34: tert-butyl 3-(2-bromo-4-(dimethoxymethyl)phenyl)-3-cyanoazetidine-1-carboxylate



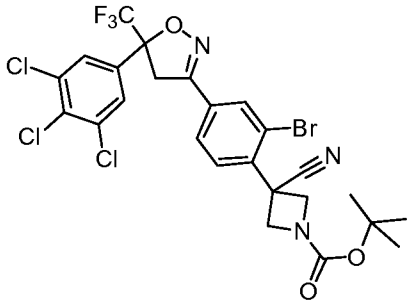
The product of Preparation 33 (300 mg) and boc anhydride (252 mg) were mixed in CH_2Cl_2 (4 mL), and Hunig's base was added (500 μL). The reaction mixture was left stirring at room temperature for 1 hour, then a TLC was taken (50/50 ethylacetate/heptane) and shows completion. The crude mixture was concentrated to an oil and was chromatographed on a 25g SiO_2 column, eluting with a gradient 0-100% ethylacetate in heptane. The desired fractions were collected, and concentrated in vacuum. LC-MS and NMR confirms desired product [m/z 411], used as such in the next step. Mixture of the aldehyde and dimethoxyacetal.

Preparation 35: tert-butyl 3-(2-bromo-4-((hydroxyimino)methyl)phenyl)-3-cyanoazetidine-1-carboxylate



The product of Preparation 34 (320 mg) was added to 4mL MeOH and 1 mL water was added, followed by hydroxylamine hydrochloride (85 mg). The reaction mixture was stirred at room temp, and after 30 minutes, LC-MS shows new peak forming 2.976 minutes, no ionisation. After 60 minutes, LC-MS shows little progress so the mixture was heated to 65°C for 10 minutes. LC-MS now shows clean conversion to desired mass [446] ~ 3.165 min. The crude reaction was concentrated to a minimum (white suspension), then extracted with ethylacetate / $NaHCO_3$. The ethylacetate layer is dried over $MgSO_4$, filtered and concentrated in vacuum, and the resulting gum is analysed by NMR. Shows desired product. 300 mg, used as such in the next step.

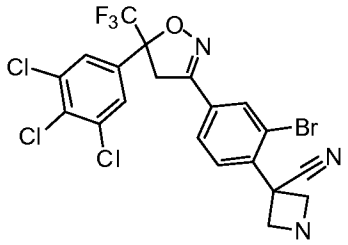
Preparation 36: tert-butyl 3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-cyanoazetidine-1-carboxylate



The oxime from Preparation 35 (130 mg) was mixed with N-chlorosuccinimide (50 mg) in ethyl acetate, and the reaction mixture was stirred at 55°C for 15 minutes. LC-MS confirms desired product formed (starting material was all gone). To the reaction trichlorostyrene (95 mg) was added, followed by $KHCO_3$ (63 mg). The reaction mixture was left stirring at room temperature overnight. LC-MS shows completion. The mixture was filtered over a pad of $MgSO_4$, and the yellow solution was concentrated to yield a solid. LC-MS confirms desired mass [553] ~ 4.059

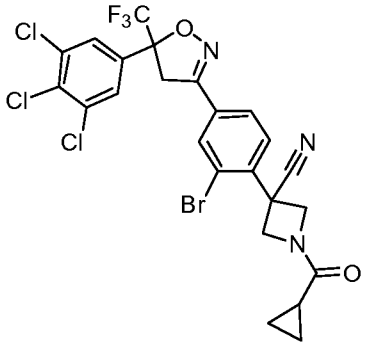
minutes. The solid was loaded on a 25g silica column and eluted with 0-100% gradient ethylacetate/heptane. The desired fractions were concentrated, and a white powder collected. 95 mg. 46% yield.

Preparation 37: 3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-3-carbonitrile



The product from Preparation 36 (90mgs) was dissolved in anhydrous methanol. A methanolic solution of HCl was added (300 μL), and warmed to 65°C. After 3 hours, LC-MS shows desired product [m/z 553] ~ 3.195min. The mixture was then concentrated to dryness and diethyl lether (6 mL) was added to the solid. The resulting suspension was sonicated for 10 minutes, and a fine white powder was then filtered. It was used as such in the next step. LC-MS confirms desired product [553].75mgs. 98% yield.

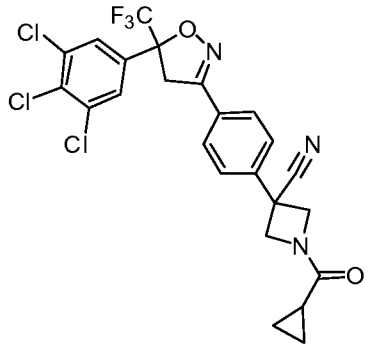
Example 86: 3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-1-(cyclopropanecarbonyl)azetidine-3-carbonitrile



The product of Preparation 37 (75 mg) was dissolved in CH_2Cl_2 (5 mL) and Hunig's base (74 mg, 97 μL) was added. Reaction was stirred at room temperature for 1 minute, then cyclopropanecarbonyl chloride (18.4 mg, 16 μL) was added and the mixture was stirred for 15 minutes. LC-MS shows desired product formed [m/z 621] ~ 3.73 min. The mixture was concentrated and loaded

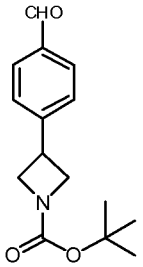
on a 25g SiO_2 column, and eluted with a gradient of ethyl acetate in heptane (0-50% over 8 CV). The desired fractions were isolated and concentrated in vacuum. 60 mg, 62% yield. NMR 400Mhz δ ppm: 7.99 (s, 1H), 7.74 (d, 1H), 7.64 (s, 2H), 7.49 (d, 1H), 5.05 (m, 1H), 4.73 (m, 2H), 4.65 (m, 1H), 4.08 (d, 1H), 3.68 (d, 1H), 1.41 (m, 1H), 1.10-1.06 (m, 2H), 0.91-0.86 (m, 2H); LC-MS: [m/z 621] @ 3.73 minutes.

Example 87: 1-(cyclopropanecarbonyl)-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-3-carbonitrile



The compound of Example 86 (60 mg) was dissolved in THF (2 mL) and Rieke Zn in THF was then added dropwise (2 mL of a 0.7N solution). The mixture was then sonicated for 5 minutes. LC-MS (THF + a few drops of acetic acid) shows about 50% conversion. Another 4 equivalents of Zn was added, and again 15 minutes sonication. LC-MS shows the reaction mixture is gone to about 90% conversion. About 200 μL of acetic acid was then added, the reaction mixture was stirred for 2 minutes, then filtered over celite. The solution was concentrated under vacuum and the remaining oil dissolved in ethyl acetate and washed with $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated in vacuum. The remaining oil is purified via reverse phase chromatography. Yield 55 mg. LC-MS confirms desired product [m/z 542]. NMR 400MHz δ ppm: 7.78(d, 2H), 7.67(d, 2H), 7.66(s, 2H), 4.99(m, 1H), 4.71(m, 1H), 4.53(m, 1H), 4.39(m, 1H), 4.10(d, 1H), 3.71(d, 1H), 1.45-1.39(m, 1H), 1.10-1.06(m, 2H), 0.91-0.86(m, 2H).

Preparation 38: 3-(4-Formyl-phenyl)-azetidine-1-carboxylic acid tert-butyl ester:

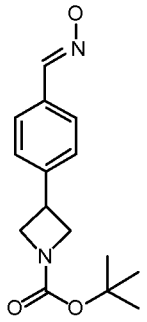


To a stirred suspension of activated zinc (5.636g, 86.19mmol, 2 equivalents) in dry DMF (20mL) was added pre-dissolved dibromomethane (1.89g, 10.77mmol, 0.25 equivalents) in dry DMF (5mL) and reaction mixture was heated at 70°C for 30 minutes under nitrogen atmosphere. After 30 minutes reaction was cooled to room temperature. To the resulting reaction mixture was added pre-dissolved chlorotrimethylsilane (1.12g, 10.77 mmol, and 0.25 equivalents) in dry DMF (5mL) and stirred for 15 minutes followed by addition of pre-dissolved 3-Iodo-N-Boc-Azetidine (15.24g, 53.86mmol, 1.25eq) in dry DMF (30mL) and the reaction mixture was heated at 40 °C for 30 minutes under nitrogen atmosphere. Reaction mixture was sonicated for 30 minutes, during sonication zinc dust was uniformLy suspended to leave the hazy reaction mixture. To the sonicated reaction mixture (Zincate) was added pre-dissolved 4-Iodo benzaldehyde (10g, 43.099mmol, 1eq) in dry DMF(42mL) followed byaddition of Tri-2-furyl phosphine (1.1g, 4.73 mmol, 0.1eq), and Tris (dibenzylidene-acetone) dipalladium(0) (1.18g, 1.292mmol, 0.03 equivalents). The resulting reaction mixture was heated at 70°C for 18 hours under nitrogen atmosphere. Progress of the reaction was monitored by TLC using 10% ethyl acetate in hexane and visualized in UV light (254nm). Reference of new spot and starting material was 0.3 and 0.7 respectively. After maximum consumption of starting material (18 hours), reaction mixture was quenched with saturated ammonium chloride (100mL) and extracted by ethyl acetate (3x100mL). Combined organic layer was dried over sodium sulphate and concentrated in *vacuo* to afford brown colored liquid (15g, crude). Crude compound was purified by column chromatography using 100-200 mesh size silica gels. Desired compound was eluted in 10% ethyl acetate in hexanes to afford 6.5g (57.79%) brown colored liquid. ^{1}H NMR and LC-MS was consistent. ^{1}H NMR (400 MHz, DMSO-d_6)δ: 1.40 (s, 9 H), 3.86-3.89(m, 3 H), 4.26-4.29(m, 2 H), 7.57(d, *J*

=8.04Hz, 2H), 7.90(d, *J* =8.16Hz, 2H), 9.99(s, 1 H). LC-MS (m/z): = 262.30 (M+H).

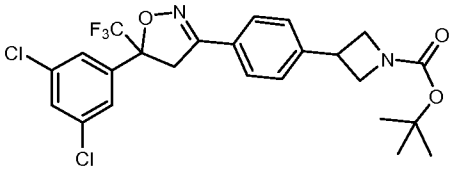
***Activation of zinc: Zinc powder (5g) was stirred with 10% HCl solution (20mL) for 5 minutes at room temperature and decanted. This procedure was repeated twice and filtered through Buchner funnel, washed with water (3x25mL), acetone (2x20mL), well dried in *vacuo* to afford activated zinc (2g).

Preparation 39: 3-[4-(Hydroxyimino-methyl)-phenyl]-azetidine-1-carboxylic acid tert-butyl ester



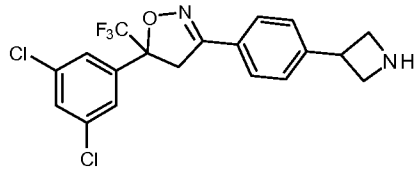
To a stirred suspension of 3-(4-Formyl-phenyl)-azetidine-1-carboxylic acid tert-butyl ester (Preparation 38, 6.5g, 24.904mmol, 1 equivalents) in ethanol:water (1:1, 120mL) was added hydroxyl amine hydrochloride (2.5g, 37.356mmol, 1.5 equivalents) followed by sodium acetate (3.67g, 44.82mol, 1.8eq). Resulting reaction mixture was stirred at room temperature for 0.5 hours. Progress of the reaction was monitored by TLC using 20% ethyl acetate in hexane and visualized in UV light (254 nm). Reference of new spot and starting material was 0.32 and 0.67 respectively. After consumption of starting material, solvents was evaporated under reduced pressure and extracted with DCM (3x25mL). Evaporation of volatiles provided light yellow solid (6.5g, 94.51%). LC-MS and ^{1}H NMR was consistent. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (s, 9 H), 3.81 (broad s, 3 H), 4.42 (broad s, 2 H), 7.36 (d, *J* = 8 Hz, 2 H), 7.57 (d, *J* = 8 Hz, 2 H), 8.12 (s, 1 H), 11.19 (s, 1 H). LC-MS (m/z): = 277.30 (M+H).

Preparation 40: 3-{4-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidine-1-carboxylic acid tert-butyl ester:



To a stirred solution of 3-[4-(Hydroxyimino-methyl)-phenyl]-azetidine-1-carboxylic acid tert-butyl ester (Preparation 39, 1g, 3.62mmol, 1.0 equivalents) in DMF (6.0 mL) was added NCS (725.26mg, 5.43 mmol, 1.5 equivalents) and heated to 50°C for 1 hour. Progress of the reaction was monitored by TLC using 5% methanol in dichloromethane. After complete consumption of starting material, reaction was cooled to 0°C followed by the addition of potassium hydrogen carbonate (543.18mg, 5.43mmol, 1.5 equivalents) and pre-dissolved solution of 1,3-Dichloro-5-(1-trifluoromethyl-vinyl)-benzene (1.04g, 4.345mmol, 1.2 equivalents) in DMF (4.0 mL). Resulting reaction was stirred at room temperature for 16 hours under nitrogen atmosphere. Progress of the reaction was monitored by TLC using 20% ethyl acetate in hexane and visualized in UV light (254 nm). Reference of required product was 0.6 and 0.5 for starting material. After consumption of starting material, reaction mixture was quenched with water (40 mL) extracted with diethyl ether (3 x 50 mL). Combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulphate and concentrated in *vacuo* to afford (1.50g, crude). Further purification by column chromatography (on neutral alumina) using 10% ethyl acetate in hexane as eluent afforded off white solid 1.3g (69.84 %). ^{1}H NMR and LC-MS were consistent. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (s, 9 H), 3.84 (m, 3 H), 4.25-4.38 (m, 4 H), 7.47 (d, J = 8 Hz, 2 H), 7.62 (d, J = 1 Hz, 2 H), 7.71 (d, J = 8 Hz, 2 H), 7.81 (t, J = 2 Hz, 1 H). LC-MS (*m/z*): =513(M-H).

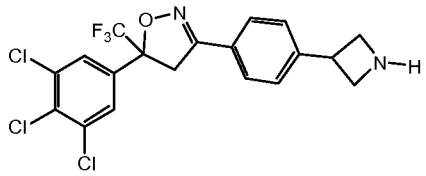
Preparation 41: 3-(4-Azetidin-3-yl-phenyl)-5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazole hydrochloride salt



To a stirred solution of 3-{4-[5-(3,5-Dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidine-1-carboxylic acid tert-butyl ester (Preparation 40, 1g, 1.94mmol, 1eq) in MeOH (10mL) was purged HCl (g) at 0°C for 0.5 hours and

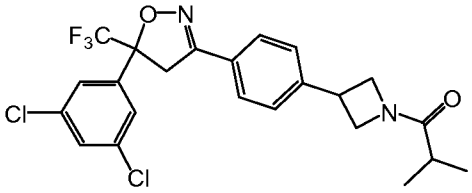
then reaction mixture was refluxed at 70°C for 0.5 hours. Progress of reaction was monitored by TLC, after complete consumption of starting material reaction mixture was evaporated under reduced pressure to dryness to give 1.15g (crude) Which was washed with methyl t-butyl ether (10mL X 2) to afforded 1.1g (95.21%). ^{1}H-NMR and LC-MS were consistent. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.05 (t, *J* = 8 Hz, 2 H), 4.15-4.21 (m, 1 H), 4.24-4.39 (m, 4 H), 7.55 (d, *J* = 8 Hz, 2 H), 7.62 (d, *J* = 1 Hz, 2 H), 7.74 (d, *J* = 8 Hz, 2 H), 7.81 (t, *J* = 2 Hz, 1 H), 8.99 (bs, 2 H). LC-MS (*m/z*): =415(M+H).

Preparation 42: 3-(4-(azetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole hydrochloride salt



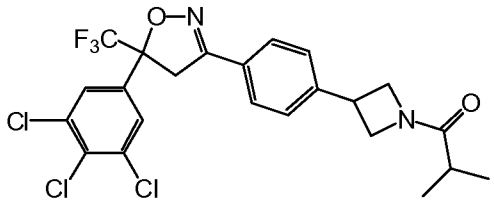
Prepared from the compound of Preparation 39 using procedures similar to Preparations 40 and 41 using 1,2,3-trichloro-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene instead of 1,3-dichloro-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.06 (t, *J* = 17 Hz, 2 H), 4.15-4.19 (m, 1 H), 4.24-4.29 (m, 2 H), 4.35 (t, *J* = 18 Hz, 2 H), 7.55 (d, *J* = 8 Hz, 2 H), 7.74 (d, *J* = 8 Hz, 2 H), 7.84 (s, 2 H), 9.004 (bs, 2 H). LC-MS (*m/z*): =488.90(M+H).

Example 88: 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one



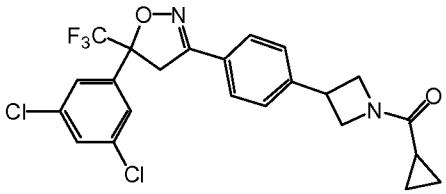
The compound was prepared from the compound of preparation 41 using a procedure similar to that of Example 6 using isobutyryl chloride in place of cyclopropane carbonyl chloride. ^{1}HNMR (DMSO-d6) δ ppm: 7.81 (1H), 7.72 (2H), 7.63 (2H), 7.49 (2H), 4.59-3.81 (8H), 1.0 (6H); m/z (ES+APCI Positive) 485 $[M+H]^+$.

Example 89: 2-methyl-1-(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one



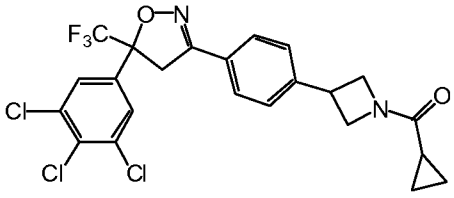
The compound was prepared from the compound of Preparation 42 using a procedure similar to that of Example 6 using isobutyryl chloride in place of cyclopropane carbonyl chloride. ^{1}HNMR (DMSO-d6) δ ppm: 7.84 (2H), 7.72 (2H), 7.50 (2H), 4.59-3.84 (8H),1.0 (6H); m/z (ES+APCI Positive) 519 $[M+H]^+$.

Example 90: Cyclopropyl(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone



The compound was prepared from the compound of Preparation 41 using a procedure similar to that of Example 6 using isobutyryl chloride in place of cyclopropane carbonyl chloride. ^{1}HNMR (DMSO-d6) δ ppm: 7.81 (1H), 7.72 (2H), 7.63 (2H), 7.51 (2H), 4.66-3.16 (8H), 0.72 (4H); m/z (ES+APCI Positive) 483 $[M+H]^+$.

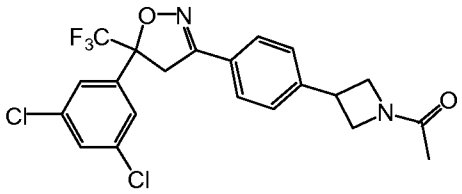
Example 91: Cyclopropyl(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone



The compound was prepared from the compound of Preparation 42 using a procedure similar to that of Example 6 using isobutyryl chloride in place of

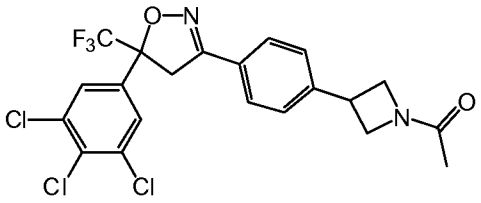
cyclopropane carbonyl chloride. ^{1}HNMR ($CDCl_3$) δ ppm: 7.84 (2H), 7.71 (2H), 7.51 (2H), 4.69-3.18 (8H), 0.72 (4H); m/z (ES+APCI Positive) 517 $[M+H]^+$.

Example 92: 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone



The compound was prepared from the compound of Preparation 41 using a procedure similar to that of Example 1. ^{1}HNMR ($CDCl_3$) δ ppm 7.81 (1H), 7.72 (2H), 7.63 (2H), 7.51 (2H), 4.53-3.80 (7H), 1.80 (3H); m/z (ES+APCI Positive) 457 $[M+H]^+$.

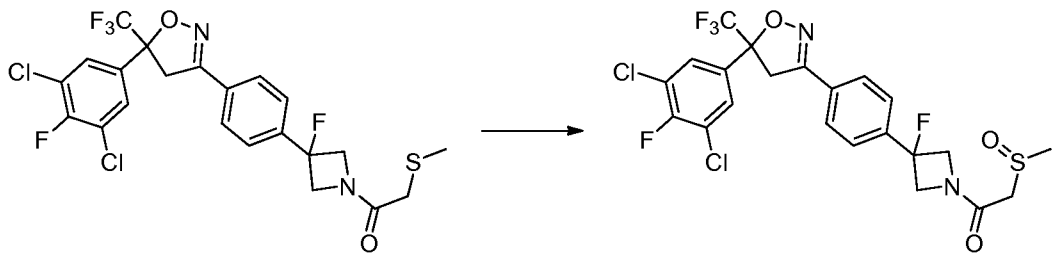
Example 93: 1-(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone



The compound was prepared from the compound of Preparation 42 using a procedure similar to that of Example 1. ^{1}HNMR ($CDCl_3$) δ ppm: 7.84 (2H), 7.71 (2H), 7.50 (2H), 4.53-3.83 (7H), 1.80 (3H); m/z (ES+APCI Positive) 491 $[M+H]^+$.

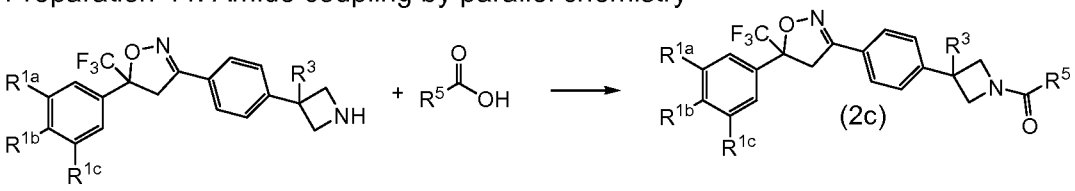
Preparation 43 - oxidation of sulfide to sulfoxide:

1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone (Example 162)

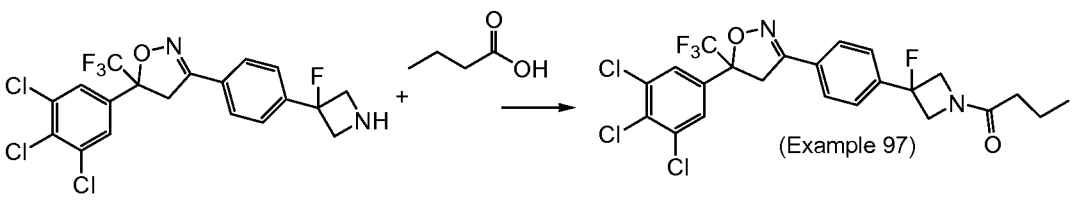


A solution of sodium (meta)periodate (49 mg, 0.23 mmol) in 1:1 methanol/water (6 mL) was cooled with a ice bath and a solution of 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone (102 mg, 0.19 mmol) in methanol (~2 mL) was added drop wise via pipette. A precipitate forms and the reaction was allowed to stir with the ice bath in place slowly warming to ambient overnight. When complete, the reaction was partitioned between water (5 mL) and CH_2Cl_2 (5 mL). Aqueous extracted with additional CH_2Cl_2 (2 x 5 mL). Organic phase collected and condensed. The crude material was adsorbed on silica and chromatographed on a 12 g silica column, eluting with a gradient of 0% to 100% ethyl acetate in heptane. Fractions containing the desired material were combined and concentrated. CH_2Cl_2 (~100 µL) was added to the resulting film. Placing the flask on high vacuum overnight resulted in formation of a white foam. Yield 90 mg (86%). LC/MS retention time = 3.317 minutes, MS calculated for ($C_{22}H_{17}Cl_2F_5N_2O_3S$) 554.03, found 555.0 M+H+.

Preparation 44: Amide coupling by parallel chemistry

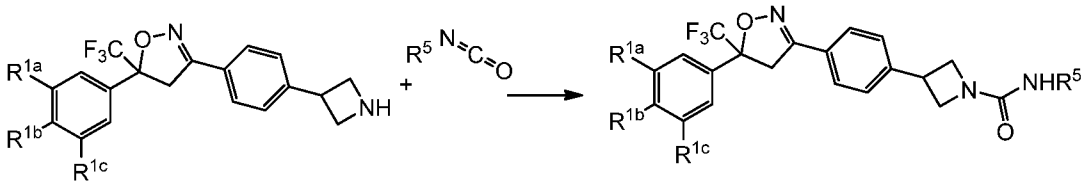


The isoxazoline phenyl azetidine (0.05mmol) was dissolved in dimethyl formamide (0.5ml); this was added to the respective acid (0.1mmol), followed by a solution of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexa-fluorophosphate in dimethyl formamide (0.5ml), and triethylamine (0.5mmol). The resulting mixture was shaken at ambient temperature for 16 hours. The solvent was removed by distillation under vacuum, and the crude product purified by preparative HPLC. An example as prepared by this preparatory method is shown below:

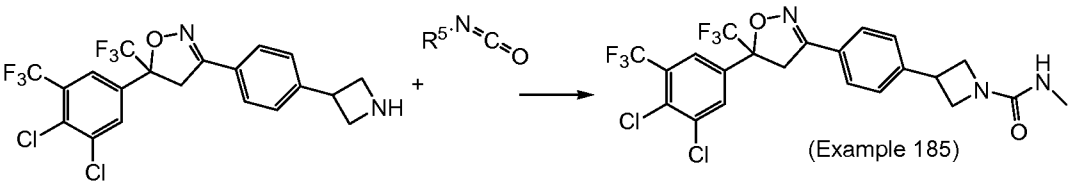


3-(4-(3-fluoroazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (0.05mmol) was dissolved in dimethyl formamide (0.5mL); this was added to butyric acid (0.1mmol), followed by a solution of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate in dimethyl formamide (0.5mL), and triethylamine (0.5mmol). The resulting mixture was shaken at ambient temperature for 16 hours. The solvent was removed by distillation under vacuum, and the crude product purified by preparative HPLC to give 3.2 mg of 1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)butan-1-one. MH+ 537; retention time 9.83 minutes.

Preparation 45: Urea formation by parallel chemistry.



A solution of the isoxazoline phenyl azetidine (0.05mmol) in DMF (1mL) was treated with triethylamine (0.20mmol). A solution of the respective isocyanate (0.055mmol) in DMF (0.5mL) was added and the reaction mixture stirred at ambient temperature for 16 hours. The solvent was removed under reduced pressure, and the crude product purified by preparative HPLC. An example prepared by this preparatory method is shown below:

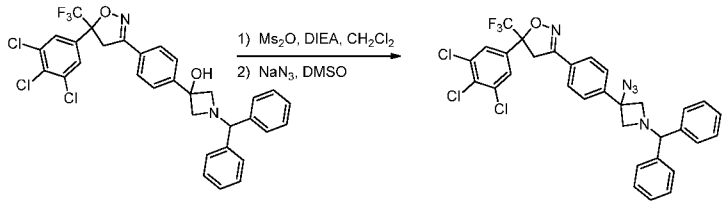


3-(4-(azetidin-3-yl)phenyl)-5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (0.05mmol) was dissolved in DMF (1mL); triethylamine (0.20mmol) was added, followed by a solution isocyanatomethane. The resulting solution was stirred at ambient temperature for 16 hours. The solvent was removed under reduced pressure and the crude product purified by preparative HPLC to give 3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-

(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-methylazetidine-1-carboxamide (11.2mg) MH+ 540.1; retention time 6.14 minutes.

Preparation 46: Azido formation

Azide intermediates can be prepared according to the following procedure for 3-(4-(3-azido-1-benzhydrylazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (intermediate for Example 163).



To a solution of 1.19 grams (1.88 mmole, 1.0 eq) of 1-benzhydryl-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-ol in 17 mL of CH_2Cl_2 was added 500µL (2.8 mmole, 1.5 eq) of diisopropyl-ethylamine, neat via syringe, followed by 438mg (2.5 mmole, 1.3 eq) of methylsulfonic anhydride solid. After stirring 3.5 hours at room temperature an aliquot of the reaction mixture was placed in 1.0mL of methanol and analyzed via LC/MS. The chromatograph indicated the starting material was consumed. The reaction with diluted with 20mL of CH_2Cl_2 and 20mL of saturated $NaHCO_3$ solution. After stirring for 2 hours the layers were separated via a Biotage Phase Separator cartridge. The organic layer was concentrated under reduced pressure to give 1.29 grams (96% yield) of intermediate 1-benzhydryl-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-yl methanesulfonate as light yellow solid. A 227mg sample of 1-benzhydryl-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-3-yl methanesulfonate (0.35mmole, 1.0 eq) and 72.1mg of sodium azide (1.1mmole, 3.1eq) were weighed into a 100mL flask, to this was added 3mL of anhydrous DMSO. After stirring for 1.5 hours at room temperature the reaction was diluted with 30mL of CH_2Cl_2 and 15mL of saturated $NaHCO_3$ solution. After stirring this mixture for 1 hour the layers were separated via a Biotage Phase Separator cartridge. The water layer was rinsed with additional CH_2Cl_2 and the combined organic layers were concentrated by evaporation utilizing a stream of

N_2 gas. The resulting crude oil was purified via silica gel column chromatography eluting with 100% CH_2Cl_2. Evaporation of the appropriate fractions gave 144.5mg of product, 3-(4-(3-azido-1-benzhydrylazetidin-3-yl)phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole, (63% yield) as a glassy yellow solid. ms 656 [M+H], HPLC retention time: 3.600 minutes.

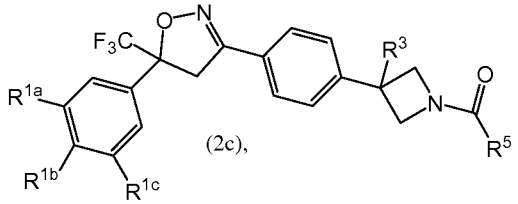
Preparation 47: Chiral Separation of Enantiomers:

As an example for separating a single enantiomer from a racemic mixture, racemic Example 18 was separated on a chiral column to provide Example 177 according to the following HPLC chiral resolution: Berger analytical SFC, column-Chiral IC 4.6 x 250mm 5µ, mobile phase (A) was CO_2 and mobile phase (B) was 0.1% TEA in methanol. Linear gradient 5% B to 65% B in 12 minutes, 3mL/minute at 100 bar. The preparatory SFC was conducted on a Berger Multigram with a IC 30x250mm 5µ column, with mobile phase (A) CO_2 and mobile phase (B) methanol, isocratic 25%B, at a 100mL/minute and 120bar. Example 172 is a single enatiomer from racemate Example 19. Example 176 is a single enantiomer from racemate 24.

The HPLC conditions used to obtain the retention times and mass of the Examples of Tables 2, 3, and 4 were based on the following methods. Each retention time in the corresponding tables is listed with an “a”, “b”, “c”, “d”, “e”, or “f”. Each alphabetic symbol refers to separate HPLC conditions and methods. For Method “a”, mass spectra (MS) data were obtained using Agilent mass spectrometer with atmospheric pressure chemical ionization. Method: Acquity HPLC with chromatography performed on a Waters BEH C18 column (2.1 x 50 mm, 1.7 µm) at 50°C. The mobile phase was a binary gradient of water (containing 0.1% trifluoroacetic acid) and acetonitrile (5–100% acetonitrile in a 5 minute run time), at 254nm. For Method “b”, HPLC with chromatography was performed on a Gemini NX-50X4.60mm, 5µ column. The mobile phase was a binary gradient of 10mM ammonium acetate buffer (pH=4.6) and acetonitrile (10-100% acetonitrile gradient in a 12 minute run time with a flow rate of 1 mL/minute) at 254nm. For Method “c”, HPLC with chromatography was performed on a Gemini NX-50X4.60mm, 5µ column. The mobile phase was a binary gradient of

10mM ammonium acetate buffer(pH=4.6) and acetonitrile (50–100% acetonitrile gradient in a 4.5 minute run time with a flow rate of 1 mL/minute) at 254nm. For Method "d", HPLC with chromatography performed on a Waters Alliance 2795 with ZQ MS-ESI+ with a Gemini NX C18 4.6 x 100, 5μ column. The mobile phase was a binary gradient of water (containing 0.05% trifluoroacetic acid) and acetonitrile (50–95% acetonitrile gradient in a 12 minute run time, flow rate 1 mL/min) at 254nm. For Method "e", HPLC with chromatography performed on a Waters Alliance 2795 with ZQ MS-ESI+ with a Gemini NX C18 4.6 x 150, 5μ column. The mobile phase was a binary gradient of water (containing 0.1% trifluoroacetic acid) and acetonitrile (50–95% acetonitrile gradient in a 12 minute run time, flow rate 1 mL/min) at 254nm. For Method "f", SFC chromatography was performed on a Berger 2-EP 5μm 4.6x250mm column. The mobile phase was a binary gradient of CO_2 and 0.1%triethylamine in MeOH (5–65% 0.1%TEA in MeOH gradient in a 9 minute run time, flow rate 3 mL/min).

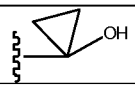
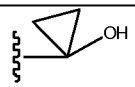
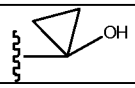
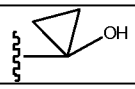
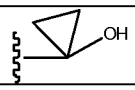
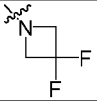
Using procedures similarly described herein, compounds (Examples 94-185) of Formula (2c) were prepared and are presented in Table 2.

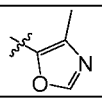
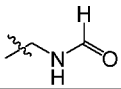
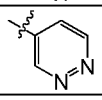
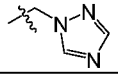
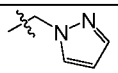
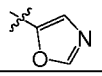
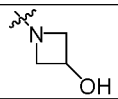
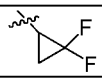
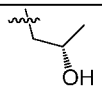
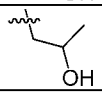


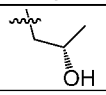
(2c),

Table 2

Example No.	R^{1a}	R^{1b}	R^{1c}	R^3	R^5	m/z (ESI) [M+H]+	Retention Time (minutes)
94	Cl	Cl	Cl	OH	isopropyl	535	10.05e
95	Cl	Cl	Cl	F	CH_2CF_3	577	11.19e
96	Cl	Cl	Cl	F	CH_2-cyclopropyl	549	11.35e
97	Cl	Cl	Cl	F	propyl	537	9.83d
98	Cl	Cl	Cl	F	isopropyl	537	9.8d
99	Cl	Cl	Cl	F	ethyl	523	9.44d
100	CF_3	H	Cl	F	isopropyl	537.1	4.53d
101	CF_3	H	Cl	F	CH_2OH	525.1	3.76d
102	CF_3	H	Cl	F	cyclopentyl	563.1	4.85d
103	CF_3	Cl	Cl	F	propyl	571.1	7.86d

104	Cl	H	Cl	H	ethyl	471.1	6.2d
105	Cl	H	Cl	H		499.1	5.27d
106	Cl	H	Cl	H	CH_2OCH_3	487.1	5.62d
107	CF_3	Cl	Cl	H	CH_2-cyclopropyl	565.1	7.69d
108	CF_3	Cl	Cl	H	CH_3	525	7.11d
109	CF_3	Cl	Cl	H	ethyl	539.1	7.2d
110	CF3	H	Cl	H	propyl	519.1	6.96d
111	CF_3	Cl	Cl	H	propyl	553.1	7.82d
112	CF_3	Cl	Cl	H	CH_2OH	541	5.53d
113	CF_3	Cl	Cl	H		567.1	6.24d
114	CF_3	Cl	Cl	H	CH_2SCH_3	571	7.42d
115	CF_3	H	Cl	H	CH_2-cyclopropyl	531.1	6.97d
116	CF_3	H	Cl	H	CH_2OCH_3	521.1	5.72d
117	CF_3	Cl	Cl	H	CH_2CN	550	6.72d
118	CF_3	H	Cl	H		533.1	5.39d
119	CF_3	Cl	Cl	H	CH_2OCH_3	555.1	6.58d
120	CF_3	H	Cl	H	ethyl	505.1	6.34d
121	Cl	Cl	Cl	H	propyl	519.1	7.82d
122	CF_3	H	Cl	H	isopropyl	519.1	6.94d
123	Cl	Cl	Cl	H		533	6.14d
124	Cl	Cl	Cl	H	ethyl	505	7.17d
125	Cl	Cl	Cl	H	CH_2SCH_3	537	7.41d
126	Cl	Cl	Cl	H	CH_2OCH_3	521	6.42d
127	Cl	Cl	Cl	H	CH_2-cyclopropyl	531.1	7.82d
128	Cl	F	Cl	H	CH_2SCH_3	521	6.55d
129	Cl	F	Cl	H	CH_2OCH_3	505.1	5.74d
130	Cl	F	Cl	H		517.1	5.41d
131	Cl	F	Cl	H	ethyl	489.1	6.4d
132	Cl	F	Cl	H	isopropyl	503.1	7.03d
133	Cl	F	Cl	F		570	3.674a

134	Cl	F	Cl	OH	CH_2CF_3	559	3.483a
135	CF_3	Cl	Cl	F	CH_2CF_3	611	3.2a
136	Cl	F	Cl	F		560	7.42d
137	Cl	F	Cl	F		536	5.28d
138	Cl	F	Cl	F		557	6.13d
139	Cl	F	Cl	F		560.1	5.7d
140	Cl	F	Cl	F	$CH_2S(O)_2CH_3$	571	6.51d
141	Cl	F	Cl	F		559.1	6.7d
142	Cl	F	Cl	F		546	6.71d
143	Cl	F	Cl	F	CF_2CH_3	543	8.54d
144	CF_3	Cl	Cl	F		600	3.295a
145	Cl	F	Cl	F	$C(OH)(CH_3)_2$	537.1	6.74d
146	Cl	F	Cl	F	$CH_2CH=CH_2$	519.1	7.23d
147	Cl	F	Cl	F	$CH_2S(O)_2N(CH_3)_2$	600	6.99d
148	Cl	F	Cl	F	CH_2SCF_3	592.9	3.54a
149	Cl	F	Cl	F	$CH(OCH_3)CH_3$	537.1	6.93d
150	Cl	F	Cl	F		555	7.32d
151	Cl	F	Cl	F	$CH(CH_3)CH_2OH$	537.1	6.39d
152	Cl	F	Cl	F		537.1	6.43d
153	Cl	F	Cl	F		537.1	6.44d
154	Cl	F	Cl	Cl	cyclopropyl	nd	Nd-a
155	CF_3	Cl	Cl	Cl	cyclopropyl	nd	Nd-a
156	Cl	H	H	F	cyclopropyl	466.90	5.88b
157	Cl	F	F	OH	cyclopropyl	498.80[M-H]	5.58b
158	CF_3	F	F	F	cyclopropyl	534.60[M-H]	6.16b
159	Cl	F	Cl	F		523	3.419a

160	Cl	F	Cl	F		523	3.406a
161	Cl	F	Cl	F		537	3.414a
162	Cl	F	Cl	F	$CH_2S(O)CH_3$	555	3.317a
163	Cl	Cl	Cl	N_3	cyclopropyl	558	3.176a
164	Cl	Cl	Cl	N_3	ethyl	546	3.271a
165	Cl	F	Cl	F	$CH_2SC(O)CH_3$	567	3.604a
166	F	H	H	F	ethyl	436.90 [M-H]	2.38c
167	Cl	H	H	F	ethyl	455.20	2.60c
168	Cl	Cl	H	F	ethyl	486.70 [M-H]	6.11b
169	CF_3	H	H	F	cyclopropyl	498.90 [M-H]	5.90b
170	Cl	H	F	F	cyclopropyl	482.90 [M-H]	5.45b
171	F	F	H	F	cyclopropyl	467.00 [M-H]	2.55c
172^	Cl	F	Cl	F	CH_2CF_3	nd	nd-a
173	Cl	H	Cl	F		516	3.562a
174	Cl	Cl	Cl	F		552	3.667a
175	Cl	F	Cl	F		534.0	3.58a
176^	CF_3	Cl	Cl	OH	cyclopropyl	nd	nd-a
177^	Cl	F	Cl	F	isopropyl	nd	nd-a
178	Cl	F	Cl	F	$CH_2S(O)_2CH_2CN$	596	3.55d
179	Cl	F	Cl	F	$CH_2CH_2S(O)_2CH_3$	585	3.43d
180	Cl	F	Cl	F	$CH_2S(O)_2CH_2CF_3$	639	3.66d
181	Cl	F	Cl	F	$CH_2S(O)_2N(CH_3)_2$	600	3.55d
182	Cl	F	Cl	F	$CH_2S(O)_2$Phenyl	633	3.65d
183	Cl	F	Cl	F	$CHCH_3S(O)_2CH_3$	585	3.51d
184	CF_3	Cl	Cl	NHC(O)-cyclopropyl	cyclopropyl	634	6.315f
185	CF_3	Cl	Cl	NH_2	cyclopropyl	567	6.23f

~~~~ is the point of attachment.
^ represents single enantiomer resolved on chiral column,
nd = not determined
HPLC methods a, b, c, d, and e are as defined herein.

The following names for Examples (94-185) of Table 2 include:
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1-isobutyryl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol (94); 3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (95); 3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (96); 3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (97); 3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (98); 3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (99); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (100); 2-[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethanol (101); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (102); 3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (103); 5-(3,5-dichlorophenyl)-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (104); 1-[(3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol (105); 5-(3,5-dichlorophenyl)-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (106); 3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (107); 3-[4-(1-acetylazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (108); 5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (109); 3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (110); 3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (111); 2-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]-2-oxoethanol (112); 1-{[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]carbonyl}cyclopropanol (113); 5-[3,4-dichloro-5-

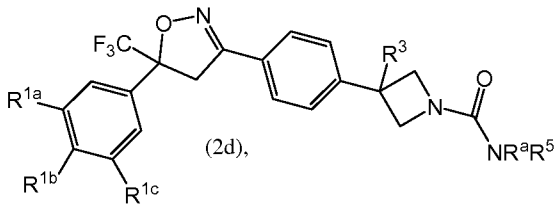
(trifluoromethyl)phenyl]-3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (114); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (115); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (116); 3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]-3-oxopropanenitrile (117); 1-{[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]carbonyl}cyclopropanol (118); 5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (119); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (120); 3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (121); 5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (122); 1-[(3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol (123); 3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (124); 3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (125); 3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (126); 3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (127); 5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (128); 5-(3,5-dichloro-4-fluorophenyl)-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (129); 1-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol (130); 5-(3,5-dichloro-4-fluorophenyl)-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (131); 5-(3,5-dichloro-4-fluorophenyl)-3-[4-(1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (132); 5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(3,3-difluoroazetidin-1-yl)carbonyl]-3-fluoroazetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (133); 3-{4-[5-(3,5-dichloro-4-fluorophenyl)-

5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-(3,3,3-trifluoropropanoyl)azetidin-3-ol (134); 5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (135); 5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(4-methyl-1,3-oxazol-5-yl)carbonyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (136); N-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]formamide (137); 4-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]pyridazine (138); 1-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]-1H-1,2,4-triazole (139); 5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfonyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (140); 5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1H-pyrazol-1-ylacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (141); 5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1,3-oxazol-5-ylcarbonyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (142); 5-(3,5-dichloro-4-fluorophenyl)-3-{4-[1-(2,2-difluoropropanoyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (143); 1-{[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]carbonyl}azetidin-3-ol (144); 1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-ol (145); 3-[4-(1-but-3-enoyl-3-fluoroazetidin-3-yl)phenyl]-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (146); 2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-N,N-dimethyl-2-oxoethanesulfonamide (147); 5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-{[(trifluoromethyl)thio]acetyl}azetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (148); 5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(2-methoxypropanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (149); 5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(2,2-difluorocyclopropyl)carbonyl]-3-fluoroazetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (150); 3-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-

yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-3-oxopropan-1-ol (151); (2S)-4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol (152); 4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol (153); 3-{4-[3-chloro-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (154); 3-{4-[3-chloro-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (155); 5-(3-chlorophenyl)-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (156); 3-{4-[5-(3-chloro-4,5-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-(cyclopropylcarbonyl)-azetidin-3-ol (157); 3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-difluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (158); (2S)-1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-1-oxopropan-2-ol (159); (2R)-1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-1-oxopropan-2-ol (160); (2S)-4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol (161); 5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfinyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (162); 3-{4-[3-azido-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (163); 3-[4-(3-azido-1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (164); S-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl] ethanethioate (165); 5-(3-fluorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (166); 5-(3-chlorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (167); 5-(3,4-dichlorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (168); 3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole (169); 5-(3-chloro-5-fluorophenyl)-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole (170); 3-{4-

[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (171); 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one (172); 3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (173); 3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (174); 3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (175); 1-(cyclopropylcarbonyl)-3-{4-[(5R)-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol (176); 5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole (177), {[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]sulfonyl}acetonitrile (178), 1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-3-methanesulfonyl-propan-1-one (179), 1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-(2,2,2-trifluoro-ethanesulfonyl)-ethanone (180), 2-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-oxo-ethanesulfonic acid dimethylamide (181), 2-Benzenesulfonyl-1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-ethanone (182), 1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-propan-1-one (183), cyclopropanecarboxylic acid (1-cyclopropanecarbonyl-3-{4-[5-(3,4-dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-3-yl)-amide (184), and (3-Amino-3-{4-[5-(3,4-dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-cyclopropyl-methanone (185).

Using procedures similarly described herein, compounds (Examples 186-205) of Formula (2d) were prepared and are presented in Table 3.



(2d),

Table 3

Example No.	R^{1a}	R^{1b}	R^{1c}	R^a	R^3	R^5	m/z (ESI) [M+H]+	Retention Time (minutes)
186	Cl	Cl	Cl	H	F	H	nd	nd a
187	Cl	Cl	Cl	H	H	cyclopropyl	532	6.68d
188	Cl	H	Cl	H	H	cyclopropyl	498.1	5.8d
189	CF_3	Cl	Cl	H	OH	propyl	nd	nd a
190	CF_3	Cl	Cl	methyl	OH	methyl	570	3.0a
191	Cl	Cl	Cl	H	H	ethyl	520	6.69d
192	Cl	F	Cl	H	H	methyl	490.1	5.32d
193	CF3	Cl	Cl	H	H	methyl	540.1	6.14d
194	Cl	H	Cl	H	H	ethyl	486.1	5.8d
195	Cl	F	Cl	H	H	ethyl	504.1	5.94d
196	CF_3	H	Cl	H	H	methyl	506.1	5.32d
197	CF_3	H	Cl	H	H	cyclopropyl	532.1	5.91d
198	Cl	F	Cl	H	H	cyclopropyl	516.1	5.94d
199	CF_3	Cl	Cl	H	H	cyclopropyl	566.1	6.74d
200	CF_3	Cl	Cl	H	F	CH_2CF_3	626	3.461a
201	Cl	Cl	Cl	methyl	F	methyl	538	3.278a
202	CF_3	Cl	Cl	methyl	F	methyl	572	3.422a
203	CF_3	Cl	Cl	H	F	$CH_2CH_2CF_3$	640	3.238a
204	CF_3	Cl	Cl	H	F		600	3.305a
205	Cl	Cl	Cl	methyl	N_3	methyl	561	3.724a

~~~~~~~~ is the point of attachment
nd = not deteremined
HPLC methods a, b, c, d, and e are as defined herein

The following IUPAC names for Examples (186-205) of Table 3 include: 3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (186); N-cyclopropyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (187); N-cyclopropyl-3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-
~~~~~~~~

4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (188); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-hydroxy-N-propylazetidine-1-carboxamide (189); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-hydroxy-N,N-dimethylazetidine-1-carboxamide (190); N-ethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (191); 3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-methylazetidine-1-carboxamide (192); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-methylazetidine-1-carboxamide (193); 3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-ethylazetidine-1-carboxamide (194); 3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-ethylazetidine-1-carboxamide (195); 3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-methylazetidine-1-carboxamide (196); 3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-cyclopropylazetidine-1-carboxamide (197); N-cyclopropyl-3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (198); N-cyclopropyl-3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidine-1-carboxamide (199); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-(2,2,2-trifluoroethyl)azetidine-1-carboxamide (200); 3-fluoro-N,N-dimethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (201); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N,N-dimethylazetidine-1-carboxamide (202); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-(3,3,3-trifluoropropyl)azetidine-1-carboxamide (203); 3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-oxetan-3-ylazetidine-1-carboxamide (204); and 3-azido-N,N-dimethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide (205).

Using procedures similarly described herein, compounds (Examples 206-218) of Formula (2e) were prepared and are presented in Table 4.

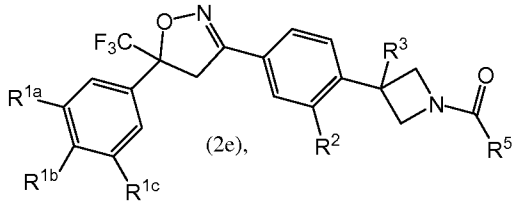


Table 4

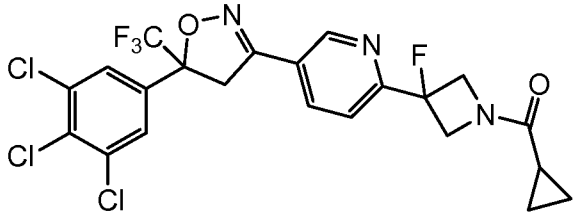
Example No.	R^{1a}	R^{1b}	R^{1c}	R^2	R^3	R^5	m/z (ESI) [M+H]+	Retention Time (minutes)
206	Cl	F	Cl	CN	F	cyclopropyl	544	3.573a
207	Cl	F	Cl	CN	F	methyl	518	3.046a
208	Cl	F	Cl	CN	F	CH_2CF_3	586	3.206a
209	Cl	F	Cl	CN	F	ethyl	532	3.534a
210	Cl	F	Cl	CN	F	isopropyl	546	3.657a
211	Cl	F	Cl	CN	F	CH_2OH	534	6.19d
212	Cl	F	Cl	CN	F	propyl	546.1	7.17d
213	Cl	F	Cl	CN	F	cyclobutyl	558.1	7.3d
214	Cl	F	Cl	CN	F	cyclopentyl	572.1	7.54d
215	Cl	F	Cl	CN	F	CH_2OCH_3	548	6.74d
216	Cl	F	Cl	CN	F	CH_2-cyclopropyl	558.1	7.15d
217	Cl	F	Cl	CN	F	n-butyl	560.1	7.44d
218	Cl	F	Cl	CN	F	CH_2SCH_3	564	7.02d

HPLC methods a, b, c, d, and e are as defined herein

The following IUPAC names for Examples (206-218) of Table 4 include: 2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile (206); 2-(1-acetyl-3-fluoroazetidin-3-yl)-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile (207); 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]benzonitrile (208); 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-propionylazetidin-3-yl)benzonitrile (209); 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-isobutyrylazetidin-3-

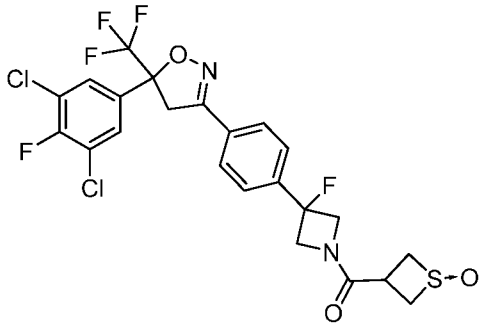
yl)benzonitrile (210); 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-glycoloylazetidin-3-yl)benzonitrile (211); 2-(1-butyryl-3-fluoroazetidin-3-yl)-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile (212); 2-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile (213); 2-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile (214); 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-[3-fluoro-1-(methoxyacetyl)azetidin-3-yl]benzonitrile (215); 2-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile (216); 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-pentanoylazetidin-3-yl)benzonitrile (217); and 5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-{3-fluoro-1-[(methylthio)acetyl]-azetidin-3-yl}benzonitrile (218).

Example 219: 2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]pyridine



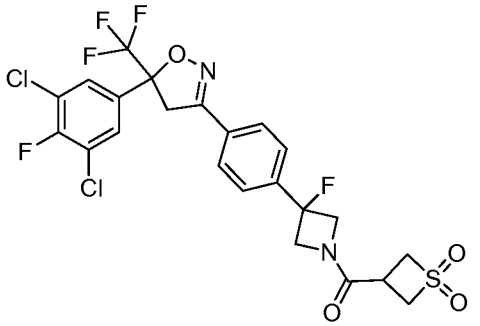
Using procedures described above, 2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]pyridine was prepared from 6-bromonicotinaldehyde and tert-butyl 3-oxoazetidine-1-carboxylate. ms 533.80[M-H], HPLC retention time 6.41 minutes. HPLC method "b". ^{1}H NMR (400 MHz, $CDCl_3$) d 0.79-0.86 (m, 2 H), 1.03-1.05(m, 2 H), 1.44-1.47 (m, 1 H), 3.70 (d, *J* = 16.88 Hz, 1H), 4.10 (d, *J* = 17.28Hz, 1H), 4.34-4.52 (m, 2 H), 4.61 (dd, *J* = 9.48, 22.36Hz, 1H), 4.84 (dd, *J* = 9.56, 20.32 Hz, 1H), 7.63 (s, 2H), 7.65 (s, 1H), 8.07-8.11 (m, 1H), 8.85 (s,1 H).

Example 220: (3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone



The compound was prepared from the compound of Preparation 16 according to the method of Example 12 using thietane-3-carboxylic acid 1-oxide in place of butyric acid. Yield 133 mg (70%). ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2 H), 7.58 (d, 2 H), 7.47 (m, 2 H), 4.67 - 4.32 (m, 4 H), 4.09 (d, 1 H), 3.91 – 3.64 (m, 4 H), 3.60 – 3.33 (m, 2 H). LC/MS retention time = 3.355 minutes, MS calculated for ($C_{23}H_{17}Cl_2F_5N_2O_3S$) 566.03, found 567.0 M+H+.

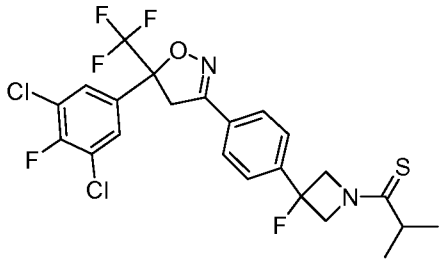
Example 221: (3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone



A solution of (3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone (30 mg) in methanol (2 mL) was added to a solution of oxone (160 mg) in water (1 mL) cooled with an ice bath. Reaction allowed to warm slowly to ambient then stirred at ambient temperature for 16 hours. Majority of methanol removed under reduced pressure then remaining aqueous extracted with DCM (2 x 5 mL). Organic phase collected and condensed. The crude material was adsorbed on

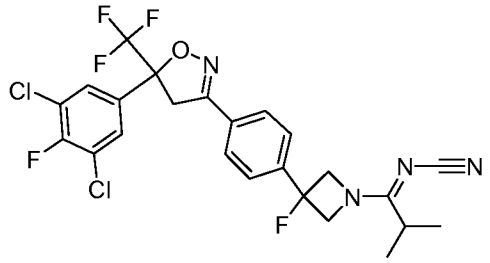
silica and chromatographed on a 4 g silica column, eluting with a gradient of 0% to 100% ethyl acetate in heptane. Fractions containing the desired material were combined and concentrated. Placing the flask on high vacuum overnight resulted in formation of a white foam. Yield 15.7 mg (51%). ^{1}H NMR (DMSO-D6) δ 7.82 (m, 4 H), 7.69 (m, 2 H), 4.67 (d, 2 H), 4.46 - 4.29 (m, 8 H), 3.56 – 3.43 (m, 1 H). LC/MS retention time = 3.455 minutes, MS calculated for ($C_{23}H_{17}Cl_2F_5N_2O_4S$) 582.02, nd M+H+.

Example 222: 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropane-1-thione



1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one (500mg, 1.9mmol) was dissolved in toluene (35mL). Lawesson's reagent (790mg, 1.9mmol) was added and the reaction mixture was heated to reflux for 2 hours, then cooled to room temperature and allowed to stir overnight. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The crude residue from the filtrate was chromatographed (40g Redi-Sep column) eluting from 100% heptane to 25:75 EtOAc:heptane to afford the product (415mg, 80%) as a solid. ^{1}HNMR ($CDCl_3$): 7.77 (2H), 7.61 (2H), 7.54 (2H), 4.68 (4H), 4.12 (1H), 3.72 (1H), 2.88 (1H), 1.28 (6H); m/z (CI) 537 ($[M+H]^+$.

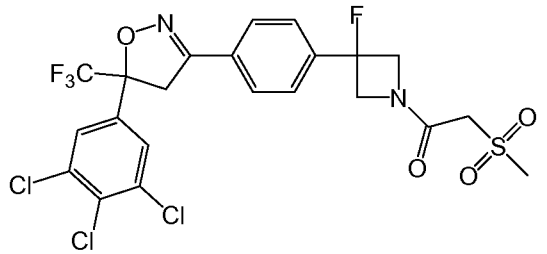
Example 223: (1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide



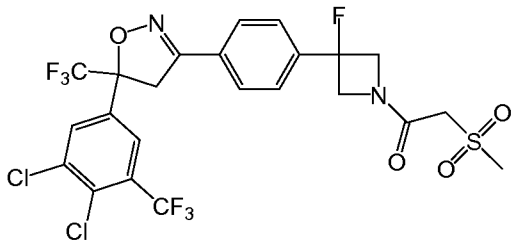
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropane-1-thione (325mg, 0.6mmol) was dissolved in CH_2Cl_2 (15mL) at 0°C and methyl triflate (130µL, 1.2mmol) was added. The reaction was allowed to warm to room temperature and stirred for 3 hours. Next, the solution was cooled to 0°C and a solution of cyanimide (54mg, 1.2mmol) and Hunig's base (220µL, 1.2mmol) in THF was added dropwise. The reaction was allowed to warm to room temperature and stirred for 1 hour. Water was added to the solution and the reaction was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The crude material was chromatographed (24g Redi-Sep column) eluting from 100% heptane to 50:50 EtOAc:heptane to afford the product (104mg, 31%) as a solid. ^{1}HNMR ($CDCl_3$): 7.79 (2H), 7.61 (2H), 7.54 (2H), 4.68 (4H), 4.12 (1H), 3.72 (1H), 3.44 (1H), 1.38 (6H); m/z (CI) 545 ($[M+H]^+$.

Examples 224 and 225 were prepared according to the methods and schemes as described herein.

Example 224: (1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-2-methanesulfonyl-ethanone



Example 225: 1-(3-{4-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone



NMR data for select compounds as described herein are presented in Table 5.

Table 5. NMR data for select compounds

Compound No.	Solvent	^{1}H NMR (δ ppm)
54	$CDCl_3$	7.76 (d, 2 H), 7.61 – 7.52 (d, 4 H), 7.46 (t, 1 H), 5.17 - 4.18 (m, 4 H), 4.12 (d, 1 H), 3.73 (d, 1 H), 2.46 (s, 1 H), 1.43 (q, 2 H), 1.08 (q, 2 H)
55	$CDCl_3$	7.75 (d, 2 H), 7.61 (d, 2 H), 7.57 (m, 2 H), 5.15 - 4.20 (m, 4 H), 4.12 (d, 1 H), 3.72 (d, 1 H), 2.95 (s, 1 H), 1.41 (q, 2 H), 1.07 (q, 2 H)
57	$CDCl_3$	7.97 (d, 1 H), 7.87 (d, 1 H), 7.72 (m, 2 H), 7.61 (m, 2 H), 4.49 - 4.12 (m, 5 H), 3.84 – 3.69 (m, 2 H), 2.52 (m, 1 H), 1.15 (d, 6 H)
58	$CDCl_3$	7.97 (d, 1 H), 7.86 (d, 1 H), 7.72 (m, 2 H), 7.61 (m, 2 H), 4.46 - 4.12 (m, 5 H), 4.01 (d, 1 H), 3.74 (m, 1 H), 2.16 (t, 2 H), 1.68 (m, 2 H) 0.98 (t, 3 H)
68	DMSO-d_6	7.82 (d, 2 H), 7.74 (d, 2 H), 7.64 (d, 2 H), 6.53 (s, 1 H), 4.40 - 4.22 (m, 4 H), 4.03 (m, 2 H), 2.15 (q, 2 H), 1.00 (t, 2 H)
133	$CDCl_3$	7.75 (d, 2 H), 7.61 (d, 2 H), 7.55 (d, 2 H), 4.48 (m, 2 H), 4.38 - 4.24 (m, 6 H), 4.11 (d, 1 H), 3.72 (d, 1 H)
134	$CDCl_3$	7.72 (d, 2 H), 7.66 - 7.53 (m, 4 H), 4.56 - 4.28 (m, 4 H), 4.12 (d, 1 H), 3.90 (s, 1 H), 3.72 (d, 1 H), 3.07 (m, 2 H)
135	$CDCl_3$	7.97 (m, 1 H), 7.86 (m, 1 H), 7.78 (d, 2 H), 7.55 (d, 2 H), 4.78 - 4.66 (m, 1 H), 4.63 – 4.39 (m, 3 H), 4.17 (d, 1 H), 3.74 (d, 1 H), 3.11 (m, 2 H)
137	$CDCl_3$	8.29 (d, 1 H), 7.77 (d, 2 H), 7.61 (d, 2 H), 7.55 (d, 2 H), 6.58 (br s, 1 H), 4.73 - 4.39 (m, 4 H), 4.18 - 3.93 (m, 3 H), 3.72 (d, 1 H)
140	$CDCl_3$	7.77 (d, 2 H), 7.60 (m, 4H), 4.81 (d, 2 H), 4.57 (m, 1 H), 4.44 (m, 1 H), 4.11 (d, 1 H), 3.90 (s, 2 H), 3.72 (d, 1 H), 3.20 (s, 3 H)
141	$CDCl_3$	7.73 (d, 2 H), 7.64 - 7.57 (m, 4H), 7.50 (d, 2 H), 6.39 (m, 1 H), 4.96 (m, 2 H), 4.59 - 4.48 (m, 1 H), 4.46 - 4.33 (m, 2 H), 4.28 - 4.17 (m, 1 H), 4.14 – 4.07 (m, 1 H), 3.71 (d, 1 H)
144	$CDCl_3$	7.96 (m, 1 H), 7.85 (m, 1 H), 7.75 (d, 2 H), 7.58 (d, 2 H), 4.72 - 7.61 (m, 1 H), 4.49 - 4.38 (m, 2 H), 4.29 - 4.19 (m, 4 H), 4.15 (d, 1 H), 3.92 - 3.87 (m, 2 H), 3.72 (d, 1 H), 2.57 (m, 1 H)
145	$CDCl_3$	7.76 (d, 2 H), 7.61 (d, 2 H), 7.55 (d, 2 H), 4.95 - 4.33 (m, 4 H), 4.12 (d, 1 H), 3.72 (d, 1 H), 2.99 (s, 1 H), 1.50 (s, 6 H)
153	$CDCl_3$	7.76 (d, 2 H), 7.61 (d, 2 H), 7.55 (d, 2 H), 4.71 - 4.35 (m, 4 H), 4.34 - 4.23 (m, 1 H), 4.12 (d, 1 H), 3.72 (d, 2 H), 2.41 – 2.21 (m, 2 H), 1.28 (d, 3 H)
165	DMSO-	7.85 – 7.79 (m, 4 H), 7.69 (d, 2 H), 4.82 - 4.69 (m, 2 H), 4.44 - 4.30 (m,

	d_6	4 H), 3.70 (d, 2 H), 2.38 (s, 3 H)
178	$CDCl_3$	7.8 (2H), 7.5-7.7 (4H), 4.2-4.9 (6H), 4.0-4.2 (3H), 3.7 (1H)
179	$CDCl_3$	7.8 (2H), 7.6-7.7 (4H), 4.3-4.8 (4H), 4.0-4.2 (1H), 3.7-3.8 (1H), 3.3-3.6 (2H), 3.05 (3H), 2.7-2.9 (2H)
180		7.8 (2H), 7.5-7.7 (4H), 4.65-4.9 (2H), 4.3-4.65 (2H), (3.9-4.3 (5H), 3.6-3.8 (1H)
181	DMSO-d_6	7.8-7.9 (4H), 7.7 (2H), 4.7-4.9 (2H), 4.3-4.5 (4H), 4.15 (2H), 2.85 (6H)
182	$CDCl_3$	8.0 (2H), 7.7-7.8 (3H), 7.5-7.7 (6H), 4.7-4.9 (2H), 4.3-4.6 (2H), 3.9-4.2 (3H), 3.7-3.8 (1H)
183	$CDCl_3$	7.8 (2H), 7.5-7.7 (4H), 4.9-5.2 (1H), 4.3-4.8 (3H), 4.0-4.2 (1H), 3.6-3.9 (2H), 3.0 (3H), 1.7 (3H).
187	$CDCl_3$	7.69 - 7.64 (m, 4 H), 7.41 (d, 2 H), 4.43 - 4.34 (m, 3 H), 4.11 (d, 1 H), 3.98 (m, 2 H), 3.86 - 3.77 (m, 1 H), 3.70 (d, 1 H), 2.68 - 2.61 (m, 1 H), 0.76 (m, 2 H) 0.54 (m, 2 H)
188	$CDCl_3$	7.67 (m, 2 H), 7.54 (d, 2 H), 7.45 (t, 1 H), 7.41 (d, 2 H), 4.44 - 4.35 (m, 3 H), 4.10 (d, 1 H), 3.97 (m, 2 H), 3.85 – 3.76 (m, 1 H), 3.71 (d, 1 H), 2.68 – 2.60 (m, 1 H), 0.76 (m, 2 H) 0.54 (m, 2 H).
190	$CDCl_3$	7.98 (d, 1 H), 7.87 (d, 1 H), 7.70 (m, 4 H), 4.27 (m, 4 H), 4.17 (d, 1 H), 3.73 (d, 1 H), 3.62 (s, 1 H), 2.92 (s, 6 H)
200	$CDCl_3$	7.97 (s, 1 H), 7.86 (s, 1 H), 7.76 (d, 2 H), 7.56 (d, 2 H), 4.85 (m, 1 H), 4.60 - 4.43 (m, 2 H), 4.40 – 4.25 (m, 2 H), 4.18 (d, 1 H), 3.92 (m, 2 H), 3.75 (d, 1 H)
201	$CDCl_3$	7.72 (d, 2 H), 7.66 (s, 2 H), 7.57 (d, 2 H), 4.51 - 4.41 (m, 2 H), 4.31 - 4.21 (m, 2 H), 4.10 (d, 1 H), 3.70 (d, 1 H), 2.92 (s, 6 H)
202	$CDCl_3$	7.96 (m, 1 H), 7.85 (m, 1 H), 7.73 (d, 2 H), 7.58 (d, 2 H), 4.51 - 4.41 (m, 2 H), 4.31 - 4.21 (m, 2 H), 4.15 (d, 1 H), 3.72 (d, 1 H), 2.92 (s, 6 H)
203	$CDCl_3$	7.96 (m, 1 H), 7.85 (m, 1 H), 7.74 (d, 2 H), 7.56 (d, 2 H), 4.52 - 4.40 (m, 3 H), 4.29 – 4.20 (m, 2 H), 4.16 (d, 1 H), 3.72 (d, 1 H), 3.54 (m, 2 H), 2.46 – 2.33 (m, 2 H)
204	$CDCl_3$	7.96 (m, 1 H), 7.85 (m, 1 H), 7.75 (d, 2 H), 7.56 (d, 2 H), 5.05 – 4.92 (m, 3 H), 4.85 (d, 1 H), 4.54 - 4.47 (m, 3 H), 4.44 (d, 1 H), 4.32 – 4.22 (m, 2 H), 4.16 (d, 1 H), 3.73 (d, 1 H)
213	$CDCl_3$	8.07 (s, 1 H), 7.99 (m, 1H), 7.68 (m, 1H), 7.60 (d, 2 H), 4.74 - 4.47 (m, 4 H), 4.11 (d, 1 H),), 3.73 (d, 1 H). 3.14 (m, 1 H), 2.45 - 2.29 (m, 2 H), 2.27 - 1.86 (m, 4 H)
216	$CDCl_3$	8.06 (s, 1 H), 7.98 (m, 1 H), 7.68 (m, 1 H), 7.58 (d, 2 H), 4.80 - 4.48 (m, 4 H), 4.10 (d, 1 H), 3.72 (d, 1 H), 2.15 (d, 2 H), 1.12 - 1.02 (m, 1 H), 0.59 (m, 2 H), 0.18 (m, 2 H)
224	$CDCl_3$	7.77 (d, 2 H), 7.67 (s, 2 H), 7.59 (d, 2 H), 4.81 (d, 2 H), 4.63 – 4.38 (m, 2 H), 4.11 (d, 1 H), 3.90 (s, 2 H), 3.72 (d, 1 H), 3.20 (s, 3 H)
225	$CDCl_3$	.97 (m, 1 H), 7.86 (m, 1 H), 7.77 (d, 2 H), 7.59 (d, 2 H), 4.81 (d, 2 H), 4.64 – 4.39 (m, 2 H), 4.17 (d, 1 H), 3.90 (s, 2 H), 3.73 (d, 1 H), 3.20 (s, 3 H)

In addition to the previous 225 Examples, the following compounds can be prepared according to the aforementioned Schemes and preparations and are

herein encompassed by the instant invention. These compounds of Formula (1) include:
2,2-dichloro-1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-fluoro-2-methylpropan-1-one; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-(methylthio)propan-1-one; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-(methylsulfonyl)propan-1-one; (3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(thietan-3-yl)methanone; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoro-2-methylpropan-1-one; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-2-(methylsulfonyl)propan-1-one; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)propan-1-one; (3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-(methylsulfonyl)cyclopropyl)methanone; 5-(3,5-dichloro-4-fluorophenyl)-3-(4-(3-fluoro-1-(1,1,1,3,3,3-hexafluoropropan-2-yl)azetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3-difluoropropan-1-one; 2-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-N-methyl-2-oxoethanesulfonamide; 2-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-N-isopropyl-2-oxoethanesulfonamide; 1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(3-hydroxyazetidin-1-yl)ethanone; 1-(3-(4-(5-(3,5-dichloro-4-hydroxyphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one; (3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(thietan-2-yl)methanone;

N-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-yl)acetamide;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-mercapto-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoro-2-hydroxy-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one;
3-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2,2-dimethyl-3-oxopropanenitrile;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3-difluoropropan-1-one;
S-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-yl) ethanethioate;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-2-(methylthio)propan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-2-(methylsulfonyl)propan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropane-2-sulfonamide;
1-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-yl)urea;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone

(E)-N-(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;
3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one; (3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-thietan-3-yl-methanone;
(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;

1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-{4-[5-(3-Chloro-4-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;

(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;

(E)-N-(1-(3-(4-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylthio)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-Fluoro-3-{4-[5-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-thietan-3-yl-methanone;

(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(1,1-dioxidothietan-3-yl)(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3,4-Difluoro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3-Chloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{4-[5-(3-chloro-5-fluorophenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(4-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-Fluoro-3-{4-[5-trifluoromethyl-5-(3,4,5-trifluorophenyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-thietan-3-yl-methanone;

(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
2-(1-(cyclopropanecarbonyl)-3-fluoroazetidin-3-yl)-5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)benzonitrile;
cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;

(E)-N-(1-(3-(5-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;

3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)propan-1-one;

1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylthio)ethanone;

1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-Fluoro-3-{5-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-azetidin-1-yl)-thietan-3-yl-methanone;

(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(1,1-dioxidothietan-3-yl)(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;

(E)-N-(1-(3-fluoro-3-(5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)methanone;

1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;

1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;

1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(4-Chloro-3-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-Fluoro-3-{5-[5-trifluoromethyl-5-(3-trifluoromethyl-phenyl)-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-azetidin-1-yl)-thietan-3-yl-methanone;
(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
(E)-N-(1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
cyclopropyl(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-{5-[5-(3,4-Difluoro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;

(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;

(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;

(E)-N-(1-(3-(5-(5-(3,4-difluoro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;

(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;

1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;

(3-{5-[5-(3-Chloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;

(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3-chloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-{5-[5-(3-Chloro-5-fluorophenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-3-fluoro-azetidin-1-yl)-thietan-3-yl-methanone;
(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
(E)-N-(1-(3-(5-(5-(3-chloro-5-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropan-1-one;

cyclopropyl(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)propan-1-one;
1-(3-fluoro-3-(4-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)-1,2-diazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfinyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(methylsulfonyl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-(1H-pyrazol-1-yl)ethanone;
1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-hydroxy-2-methylpropan-1-one;
(3-fluoro-3-{5-[5-trifluoromethyl-5-(3,4,5-trifluorophenyl)-4,5-dihydro-isoxazol-3-yl]-pyridin-2-yl}-azetidin-1-yl)-thietan-3-yl-methanone;
(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(1,1-dioxidothietan-3-yl)(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)methanone; and
(E)-N-(1-(3-fluoro-3-(5-(5-(trifluoromethyl)-5-(3,4,5-trifluorophenyl)-4,5-dihydroisoxazol-3-yl)pyridin-2-yl)azetidin-1-yl)-2-methylpropylidene)cyanamide,
stereoisomers thereof, pharmaceutical or veterinarily acceptable salts thereof.

BIOLOGICAL ASSAYS

The biological activity of the compounds of the present invention were tested against fleas, ticks, flies, and or sea lice using the test methods described below.

Horn Fly (*Haematobia irritans*) Feed Assay

Formula (1) compounds were dissolved in DMSO and aliquots were added to citrated bovine blood in a membrane covered Petri dish. Approximately ten horn flies were placed onto each Petri dish and covered. The flies were allowed

to feed on the treated blood cell. Flies were held at approximately 80°F with a minimum of approximately 50% relative humidity. Flies were examined for knockdown and mortality at approximately 2 and 24 hours. Endpoint data were recorded as a lethal dose 90% (LD^{90}) in µg/mL. In this assay, Examples 8-10, 28, 32-34, 36, 38, 54, 160, 168-69, 171, 209, and 221 demonstrated an LD^{90} of ≤ 0.3 µg/mL. Further in this assay, Examples 3-5, 11, 13-16, 20-22, 26-27, 31, 37, 40, 42, 45, 56, 59, 84-85, 87, 95, 99, 117, 137, 141, 145, 148, 152-53, 158, 162, 200, 206-07, 220, and 224 demonstrated an LD^{90} of ≤ 1 µg/mL. Further in this assay, Examples 1, 2, 6,12, 46, 60, 65, 69, 77, 98, 108, 112, 133, 135, 138, 140, 142-44, 147, 154, 163, 170, 179, 187, 193, 197, 199, 201-02, 204, 216, 219, 222, and 225 demonstrated an LD^{90} of ≤ 3 µg/mL .

Stable Fly (*Stomoxys calcitrans*) Topical Assay

Formula (1) compounds were dissolved in acetone, and 1 µL was placed on the thorax of an anesthetized fly (n=10). The flies were allowed to recover, and were incubated for 24 hours at room temperature. Flies were examined for knockdown and mortality at 2 and 24 hours. Endpoint data was recorded as lethal dose 90% (LD^{90}) in µg/fly. In this assay, Examples 1 and 11 demonstrated an LD^{90} of ≤ 0.01 µg/fly. Further in this assay, Examples 2, 9, 12, and 99 demonstrated an LD^{90} of ≤ 0.03 µg/fly. Further in this assay, Examples 6, 16, 26, 28, 33, 36, 37, and 98 demonstrated an LD^{90} of ≤ 0.1 µg/fly. Further in this assay, Examples 3, 14, 19, 27, 46, 84, 91, and 188 demonstrated an LD^{90} of ≤ 1 µg/fly.

Flea (*Ctenocephalides felis)* Membrane Feed Assay-Adult

Formula (1) compounds were dissolved in DMSO and aliquots were added to citrated bovine blood in a membrane covered Petri dish pre-warmed to 37°C. Feeding tubes containing approximately 30-35 adult fleas were placed onto the Petri dishes. The fleas were allowed to feed for approximately 2 hours. Fleas were observed for knockdown and/or death at approximately 2 and 24 hours. Endpoint data were recorded as a lethal dose 90% (LD^{90}) in µg/mL. In this assay, Example 10 demonstrated an LD^{90} of ≤ 0.03 µg/mL. Further in this assay, Examples 27 and 36 demonstrated an LD^{90} of ≤ 0.1 µg/mL. Further in

this assay, Examples 4-5, 11, 19, 23, 28, 32-33, 38, 84, 104, 117, 131, 137, 141, 160-161, 167-169, 175, 215-216, and 221 demonstrated an LD^{90} of ≤ 0.3 μg/mL. Further, in this assay, Examples 1-3, 6-8, 12-16, 20-22, 26, 31, 37, 40-41, 43, 45-56, 59-60, 68, 72-77, 82, 91, 95-101, 103, 106-107, 109-110, 113, 116, 119-121, 123-126, 128-130, 132-133, 135, 138, 140, 145-146, 148, 152-153, 158, 162-164, 170, 173-174, 176, 197-199, 201-202, 205-210, 212-213, 218-220, and 222-223 demonstrated an LD^{90} of ≤ 1 μg/mL. Further, in this assay, Examples 17, 24-25, 29-30, 34-35, 39, 42, 44, 57-58, 61-65, 67, 69-70, 79-81, 87, 89, 94, 102, 105, 108, 111-112, 114-115, 118, 122, 127, 134, 136, 139, 142-144, 147, 154-157, 165-166, 171, 179, 186-196, 200, 203-204, 211, 214-215, 217, and 224-225 demonstrated an LD^{90} of ≤ 3 μg/mL.

Soft Tick (*Ornithidorus turicata*) Blood Feed Assay

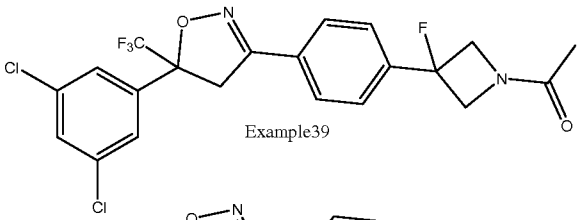
Formula (1) compounds were dissolved in dimethylsulfoxide (DMSO) and aliquots were added to citrated bovine blood in a membrane covered Petri dish. The Petri dish was then placed on a warming tray. Approximately 5 nymph stage ticks were placed onto the membrane, covered, and left to feed. Fed ticks were removed and placed into a Petri dish with sand. Fed ticks were observed at approximately 24, 48 and 72 hours for paralysis and/or death. Endpoint data was recorded as an ED^{100} and/or an LD^{100} in μg/mL. Positive control was fipronil and DMSO was used for the negative control. In this assay, Examples 11, 19, 40, 169, and 175 demonstrated an ED^{100} of ≤ 0.003 $\mu g/cm^2$. Further, In this assay, Examples 2-8, 10-17, 20-21, 26-28, 32-34, 36-38, 41-48, 50-54, 56, 59-60, 65-66, 68, 70, 72-74, 76, 84, 95-99, 103, 131, 133, 135, 141-143, 145-146, 155, 158, 165, 168, 171, 173-174, 202, 206, 209-210, 212-213, 215-216, 218-219, and 221 demonstrated an ED^{100} of ≤ 0.03 $\mu g/cm^2$. In this assay, Examples 1, 9, 22,-25, 29-31, 35, 39, 49, 55, 57-58, 67, 69, 71, 75, 77, 82, 87, 104, 117, 136-140, 144, 148, 152-154, 160, 170, 187-188, 203-204, 207, 211, 214, 217, 220, and 223 demonstrated an ED^{100} of ≤ 0.3 $\mu g/cm^2$. Further, in this assay, Examples 18, 89, and 91 demonstrated an ED^{100} of ≤1 $\mu g/cm^2$. Further, in this assay, Example 86 demonstrated an ED^{100} of ≤3 $\mu g/cm^2$.

Copepod (*Lepeophtheirus salmonis*) BioAssay

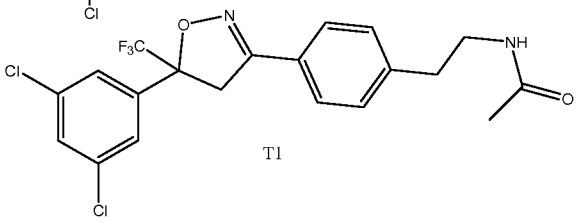
Two Formula (1) compounds were dissolved in sea water. Negative control was sea water and positive control was emamectin benzoate. Ten pre-adult/adult salmon lice were exposed for 24 hours. Lice were monitored for motility and endpoint data was recorded as an Effective Concentration 100% (EC^{100}) based on immotility. In this assay, Examples 19 and 177 had an EC^{100} value of 50 ppb.

Comparative Data: Flea Feed Assay

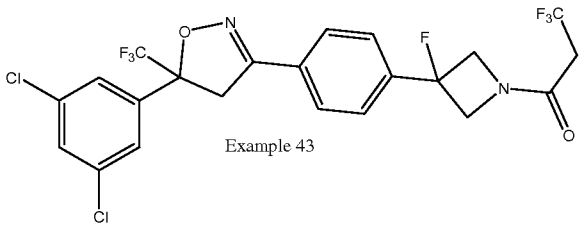
Comparator compounds T1 and T2 were tested in the flea feed assay, as described above, and are compared to Examples 39 and 43, respectively. The compounds T1 (WO2008/122375) and T2 (US2009/0156643) represent the closet exemplified art. The data represents the 24 hour time period. Endpoint data were recorded as an lethal dose 90% (LD^{90}) in µg/mL. In this assay, Example 39 and 43 had an LD^{90} of ≤ 3 and ≤ 1 $\mu g/cm^2$, respectively. Comparator compounds T1 and T2 both had LD^{90} values of > 30 $\mu g/cm^2$.



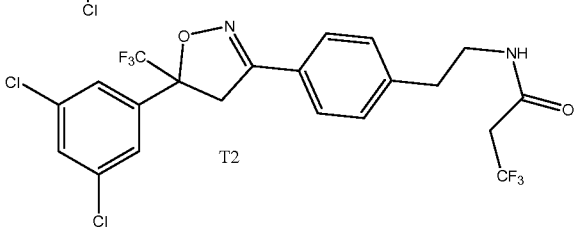
Example39



T1



Example 43

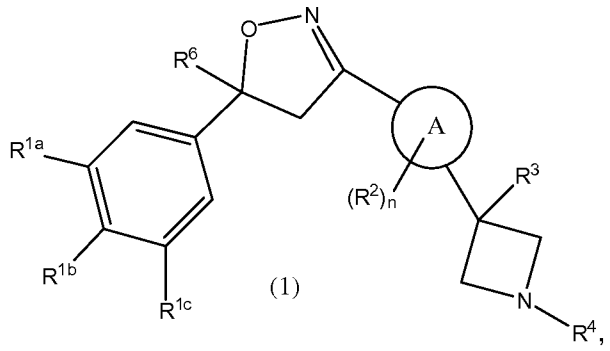


T2

5

We claim:

1. A compound of Formula (1)



(1)

wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_0-C_3alkylC_3-C_6 cycloalkyl, C_1-C_6haloalkoxy, -C(O)NH_2, -SF_5, or –$S(O)_pR$;

R^2 is halo, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, nitro, hydroxyl, -C(O)NR^aR^b, C_2-C_6alkenyl, C_2-C_6alkynyl, -$S(O)_pR$, or -OR;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, -C(O)NH_2, nitro, -SC(O)R, -C(O)NR^aR^b, C_0-C_3alkylNR^aR^4, -$NR^aNR^bR^4$, -NR^aOR^b, -ONR^aR^b, N_3, -NHR^4, -OR, or -$S(O)_pR$;

R^4 is hydrogen, C_1-C_6alkyl, C_0-C_6alkylC_3-C_6cycloalkyl, -C(O)R^5, -C(S)R^5, -C(O)NR^aR^5, -C(O)C(O)NR^aR^5, -$S(O)_pR^c$, -$S(O)_2NR^aR^5$, -C(NR^7)R^5, -C(NR^7)NR^aR^5, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle;

R^5 is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_6cycloalkyl, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle;

R^6 is cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C(O)NR^aR^b, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl;

R^7 is hydrogen, C_1-C_6alkyl, hydroxyl, cyano, nitro, -$S(O)_pR^c$, or C_1-C_6alkoxy;

R is C_1-C_6alkyl or C_3-C_6cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1-C_6alkyl, or C_0-C_3alkylC_3-C_6cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_0-C_3alkylphenyl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or -$S(O)_pR$;

R^c is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkylC_3-C_6cycloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, C_0-C_3alkylphenyl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -$S(O)_pR$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^b$, -SCN, or –$C(O)NR^aR^b$;

each of R^4 and R^5 C_1-C_6alkyl or C_0-C_6alkylC_3-C_6cycloalkyl can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -$S(O)_pR^c$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^c$, -SCN, or –$C(O)NR^aR^b$; and

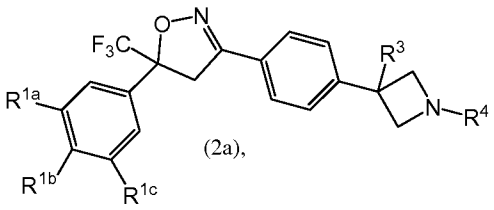
wherein R^4 and R^5 C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from cyano, halo, oxo, =S, =NR^7, hydroxyl, C_1-C_6alkoxy, C_1-C_6alkyl, C_1-C_6haloalkyl, -SH, -$S(O)_pR$, and C_1-C_6haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

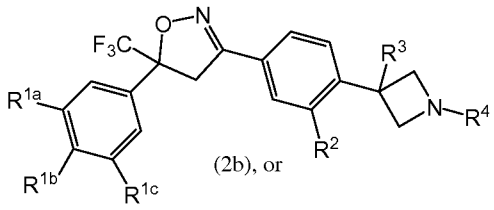
p is the integer 0, 1, or 2;

and pharmaceutically or veterinarily acceptable salts thereof.

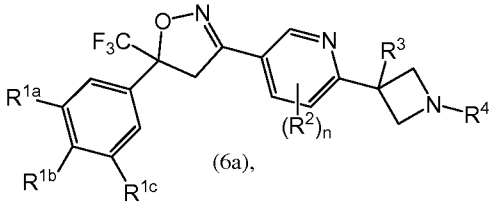
2. The compound of Claim 1 having Formula (2a), (2b), or (6a)



(2a),



(2b), or



(6a),

wherein

R^{1a}, R^{1b}, and R^{1c} are each independently selected from hydrogen, halo, hydroxyl, and C_1-C_6 haloalkyl;

R^2 is halo, cyano, hydroxyl, -C(O)NR^aR^b, or -OR; and

R^3 is hydrogen, halo, hydroxyl, N_3, or cyano;

and pharmaceutically or veterinarily acceptable salts thereof.

3. The compound of claim 1 or 2 wherein

R^{1a}, R^{1b}, and R^{1c} are each independently selected from hydrogen, flouro, chloro, bromo, and $-CF_3$;

R^2 is halo, cyano, hydroxyl, or -C(O)NR^aR^b;

R^3 is hydrogen, flouro, chloro, hydroxyl, N_3, or cyano; and

R^4 is -C(O)R^5, -C(O)NR^aR^5, -S(O)$_pR^c$, -C(S)R^5, -S(O)$_2NR^aR^5$, -C(NR^7)R^5, or -C(NR^7)NR^aR^5, and veterinary salts thereof.

4. The compound of any one of claims 1 to 3 wherein

R^2 is cyano or -C(O)NR^aR^b;

R^3 is hydrogen, fluoro, hydroxyl, N_3, or cyano;

R^4 is -C(O)R^5, -C(O)NR^aR^5, or -C(NR^7)R^5; and

pharmaceutically or veterinarily acceptable salts thereof.

5. A compound of claim 1 selected from the group consisting of:

1-(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone;
cyclopropyl(3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
3-fluoro-N-methyl-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide;
N-ethyl-3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide;
N-cyclopropyl-3-fluoro-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-1-carboxamide;
cyclopropyl(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
N-cyclopropyl-3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)propan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)butan-1-one;
2-cyclopropyl-1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;
3-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-oxopropanenitrile;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylthio)ethanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methoxyethanone;

cyclobutyl(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
N-cyclopropyl-3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
cyclopropyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone;
cyclobutyl(3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidin-1-yl)methanone;
3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
N-cyclopropyl-3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-hydroxyazetidine-1-carboxamide;
N-cyclopropyl-3-(4-(5-(3,4-dichloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-hydroxyazetidine-1-carboxamide;
3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;

3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-hydroxyazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-hydroxyazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-ethyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-N-cyclopropyl-3-fluoroazetidine-1-carboxamide;
3-(4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoro-N-methylazetidine-1-carboxamide;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;
cyclopropyl(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)methanone;
2-Cyclopropyl-1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)ethanone;
3-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3-oxopropanenitrile;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methoxyethanone;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)propan-1-one;
1-(3-(4-(5-(3,5-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)butan-1-one;
5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-[3,5-bis(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-acetyl-3-fluoroazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanenitrile;
1-[(3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]cyclopropanol;
1-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]cyclopropanol;
3-{4-[3-fluoro-1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-1-isobutyrylazetidin-3-ol;
1-butyryl-3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-3-ol;
5-[3,5-bis(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-[3-(4-{5-[3,5-bis(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethanol;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanamide;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanamide;

1-[(3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
5-(3,5-dichlorophenyl)-3-{4-[3-fluoro-1-(3-methylbutanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-propionylazetidin-3-ol;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1H-pyrazol-3-ylcarbonyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
4-{2-[3-(4-{5-[3,5-bis(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethyl}pyridine;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-acetyl-3-fluoroazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-3-oxopropanenitrile;
4-[(3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]pyridine;
5-[3,5-bis(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-(4-{3-fluoro-1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(cyclopropylcarbonyl)-3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol;
(3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(cyclopropyl)methanone;
2-(1-(cyclopropanecarbonyl)-3-fluoroazetidin-3-yl)-5-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)benzonitrile;
5-(3-chloro-5-(trifluoromethyl)phenyl)-3-(4-(3-fluoro-1-(methylsulfonyl)azetidin-3-yl)phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(2-bromo-4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-1-(cyclopropanecarbonyl)azetidine-3-carbonitrile;
1-(cyclopropanecarbonyl)-3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidine-3-carbonitrile;
1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)-2-methylpropan-1-one;
2-methyl-1-(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)propan-1-one;
Cyclopropyl(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
Cyclopropyl(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)methanone;
1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone;
1-(3-(4-(5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)azetidin-1-yl)ethanone;
1-isobutyryl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol;
3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]-2-oxoethanol;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyryl-3-fluoroazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichlorophenyl)-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-[(3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
5-(3,5-dichlorophenyl)-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-acetylazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]-2-oxoethanol;

1-{[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]carbonyl}cyclopropanol;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]-3-oxopropanenitrile;
1-{[3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidin-1-yl]carbonyl}cyclopropanol;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(1-butyrylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-[3-chloro-5-(trifluoromethyl)phenyl]-3-[4-(1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-[(3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylacetyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(methylthio)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;

5-(3,5-dichloro-4-fluorophenyl)-3-{4-[1-(methoxyacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-1-yl)carbonyl]cyclopropanol;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(3,3-difluoroazetidin-1-yl)carbonyl]-3-fluoroazetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-(3,3,3-trifluoropropanoyl)azetidin-3-ol;
5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(4-methyl-1,3-oxazol-5-yl)carbonyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
N-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]formamide;
4-[(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)carbonyl]pyridazine;
1-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]-1H-1,2,4-triazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfonyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1H-pyrazol-1-ylacetyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(1,3-oxazol-5-ylcarbonyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[1-(2,2-difluoropropanoyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-{[3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoroazetidin-1-yl]carbonyl}azetidin-3-ol;

1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-1-oxopropan-2-ol;
3-[4-(1-but-3-enoyl-3-fluoroazetidin-3-yl)phenyl]-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-N,N-dimethyl-2-oxoethanesulfonamide;
5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-{[(trifluoromethyl)thio]acetyl}azetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-{4-[3-fluoro-1-(2-methoxypropanoyl)azetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{1-[(2,2-difluorocyclopropyl)carbonyl]-3-fluoroazetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-methyl-3-oxopropan-1-ol;
(2S)-4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol;
4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol;
3-{4-[3-chloro-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[3-chloro-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3-chlorophenyl)-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[5-(3-chloro-4,5-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-1-(cyclopropylcarbonyl)-azetidin-3-ol;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-[3,4-difluoro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
(2S)-1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-1-oxopropan-2-ol;
(2R)-1-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-1-oxopropan-2-ol;

(2S)-4-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-4-oxobutan-2-ol;
5-(3,5-dichloro-4-fluorophenyl)-3-(4-{3-fluoro-1-[(methylsulfinyl)acetyl]azetidin-3-yl}phenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[3-azido-1-(cyclopropylcarbonyl)azetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-[4-(3-azido-1-propionylazetidin-3-yl)phenyl]-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
S-[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl] ethanethioate;
5-(3-fluorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3-chlorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
5-(3,4-dichlorophenyl)-3-[4-(3-fluoro-1-propionylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-5-[3-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole;
5-(3-chloro-5-fluorophenyl)-3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4-difluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-3,3,3-trifluoropropan-1-one;
3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
3-{4-[1-(azetidin-1-ylcarbonyl)-3-fluoroazetidin-3-yl]phenyl}-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole;
1-(cyclopropylcarbonyl)-3-{4-[(5R)-5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidin-3-ol;

5-(3,5-dichloro-4-fluorophenyl)-3-[4-(3-fluoro-1-isobutyrylazetidin-3-yl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazole;

{[2-(3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-3-fluoroazetidin-1-yl)-2-oxoethyl]sulfonyl}acetonitrile;

1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-3-methanesulfonyl-propan-1-one;

1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-(2,2,2-trifluoro-ethanesulfonyl)-ethanone;

2-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-oxo-ethanesulfonic acid dimethylamide;

2-Benzenesulfonyl-1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-ethanone;

1-(3-{4-[5-(3,5-Dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-propan-1-one;

cyclopropanecarboxylic acid (1-cyclopropanecarbonyl-3-{4-[5-(3,4-dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-3-yl)-amide;

(3-Amino-3-{4-[5-(3,4-dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-cyclopropyl-methanone;

3-fluoro-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;

N-cyclopropyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;

N-cyclopropyl-3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;

3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-hydroxy-N-propylazetidine-1-carboxamide;

3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-hydroxy-N,N-dimethylazetidine-1-carboxamide;

N-ethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;

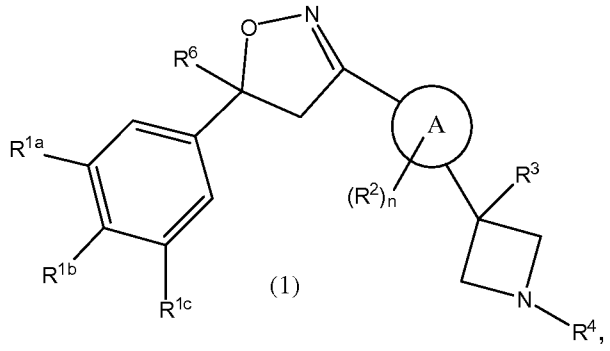
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-methylazetidine-1-carboxamide;

3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-methylazetidine-1-carboxamide;
3-{4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-ethylazetidine-1-carboxamide;
3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}-N-ethylazetidine-1-carboxamide;
3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-methylazetidine-1-carboxamide;
3-(4-{5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-N-cyclopropylazetidine-1-carboxamide;
N-cyclopropyl-3-{4-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
N-cyclopropyl-3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-(2,2,2-trifluoroethyl)azetidine-1-carboxamide;
3-fluoro-N,N-dimethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N,N-dimethylazetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-(3,3,3-trifluoropropyl)azetidine-1-carboxamide;
3-(4-{5-[3,4-dichloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl}phenyl)-3-fluoro-N-oxetan-3-ylazetidine-1-carboxamide;
3-azido-N,N-dimethyl-3-{4-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]phenyl}azetidine-1-carboxamide;
2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
2-(1-acetyl-3-fluoroazetidin-3-yl)-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;

5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-[3-fluoro-1-(3,3,3-trifluoropropanoyl)azetidin-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-propionylazetidin-3-yl)benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-isobutyrylazetidin-3-yl)benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-glycoloylazetidin-3-yl)benzonitrile;
2-(1-butyryl-3-fluoroazetidin-3-yl)-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
2-[1-(cyclobutylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
2-[1-(cyclopentylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-[3-fluoro-1-(methoxyacetyl)azetidin-3-yl]benzonitrile;
2-[1-(cyclopropylacetyl)-3-fluoroazetidin-3-yl]-5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-(3-fluoro-1-pentanoylazetidin-3-yl)benzonitrile;
5-[5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-{3-fluoro-1-[(methylthio)acetyl]-azetidin-3-yl}benzonitrile;
2-[1-(cyclopropylcarbonyl)-3-fluoroazetidin-3-yl]-5-[5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]pyridine;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1-oxidothietan-3-yl)methanone;
(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)(1,1-dioxidothietan-3-yl)methanone;
1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropane-1-thione;
(1-(3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropylidene)cyanamide;

(1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-azetidin-1-yl)-2-methanesulfonyl-ethanone; and
1-(3-{4-[5-(3,4-Dichloro-5-trifluoromethyl-phenyl)-5-trifluoromethyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone,
stereoisomers thereof, pharmaceutical and veterinarily acceptable salts thereof.

6. A pharmaceutical or veterinary composition comprising a therapeutic amount of a compound of Formula (1)



(1)

wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_0-C_3alkylC_3-C_6 cycloalkyl, C_1-C_6haloalkoxy, -C(O)NH_2, -SF_5, or –$S(O)_pR$;

R^2 is halo, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, nitro, hydroxyl, -C(O)NR^aR^b, C_2-C_6alkenyl, C_2-C_6alkynyl, -$S(O)_pR$, or -OR;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, -C(O)NH_2, nitro, -SC(O)R, -C(O)NR^aR^b, C_0-C_3alkylNR^aR^4, -$NR^aNR^bR^4$, -NR^aOR^b, -ONR^aR^b, N_3, -NHR^4, -OR, or -$S(O)_pR$;

R^4 is hydrogen, C_1-C_6alkyl, C_0-C_6alkylC_3-C_6cycloalkyl, -C(O)R^5, -C(S)R^5, -C(O)NR^aR^5, -C(O)C(O)NR^aR^5, -$S(O)_pR^c$, -$S(O)_2NR^aR^5$, -C(NR^7)R^5, -C(NR^7)NR^aR^5, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle;

R^5 is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_0-C_6alkylC_3-C_6cycloalkyl, C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle;

R^6 is cyano, C_1-C_6alkyl, C_1-C_6haloalkyl, -C(O)NR^aR^b, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-C_6haloalkenyl, or C_2-C_6haloalkynyl;

R^7 is hydrogen, C_1-C_6alkyl, hydroxyl, cyano, nitro, -$S(O)_pR^c$, or C_1-C_6alkoxy;

R is C_1-C_6alkyl or C_3-C_6cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1-C_6alkyl, or C_0-C_3alkylC_3-C_6cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_0-C_3alkylphenyl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or -$S(O)_pR$;

R^c is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkylC_3-C_6cycloalkyl, C_0-C_3alkylC_3-C_6cycloalkyl, C_0-C_3alkylphenyl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -$S(O)_pR$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^b$, -SCN, or –$C(O)NR^aR^b$;

each of R^4 and R^5 C_1-C_6alkyl or C_0-C_6alkylC_3-C_6cycloalkyl can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_1-C_6haloalkyl, -$S(O)_pR^c$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^c$, -SCN, or –$C(O)NR^aR^b$; and

wherein R^4 and R^5 C_0-C_6alkylphenyl, C_0-C_6alkylheteroaryl, or C_0-C_6alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from cyano, halo, oxo, =S, $=NR^7$, hydroxyl, C_1-C_6alkoxy, C_1-C_6alkyl, C_1-C_6haloalkyl, -SH, -$S(O)_pR$, and C_1-C_6haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

p is the integer 0, 1, or 2;

and pharmaceutically or veterinarily acceptable salts thereof.

7. The pharmaceutical or veterinary composition of claim 6 further comprising a pharmaceutically or veterinarily acceptable excipient, diluent, or carrier.

8. The pharmaceutical or veterinary composition of claim 6 or 7 further comprising at least one additional veterinary agent.

9. The pharmaceutical or veterinary composition of claim 8 wherein said additional veterinary agent is selected from the group consisting of abamectin, ivermectin, avermectin, moxidectin, emamectin, eprinomectin, selamectin, doramectin, nemadectin, albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfenbendazole, oxibendazole, parbendazole, tetramisole, levamisole, pyrantel pamoate, oxantel, morantel, indoxacarb, closantel, triclabendazole, clorsulon, refoxanide, niclosamide, praziquantel, epsiprantel, 2-desoxoparaherquamide, pyripole, pyrafluprole, lufenuron, spiromesifen, tebufenozide, spinosad, spinetoram, imidacloprid, dinotefuran, metaflumizone, thibendiamide, chlorantraniliprole, indoxacarb, pyridalyl, pyrimidifen, pyrifluquinazon, milbemycin oxime, milbemycin, DEET, demiditraz, amitraz, fipronil, insect growth regulator, permethrin, and pyrethrin, or mixtures thereof.

10. The pharmaceutical or veterinary composition of Claim 9 wherein said additional veterinary agent is milbemycin oxime.

11. The pharmaceutical or veterinary composition of Claim 9 wherein said additional veterinary agent is moxidectin.

12. Use of a compound in any one of Claims 1-11 for preparing a medicament.

13. Use of a compound of any one of Claims 1 to 6 in the manufacture of a medicament for the treatment or control of a parasitic infection or infestation in an animal comprising administering said medicament to the animal.

14. The use according to claim 13 wherein the animal is a companion animal or livestock.

15. The use according to claim 13 wherein the companion animal is dog.

16. The use according to claim 13 wherein livestock is cattle.

17. The use according to claim 13 wherein the animal is a bird.

18. The use according to claim 13 wherein the animal is a fish.

19. The use according to any one of claims 13 to 18 wherein the compound is administered topically, orally, or by injection.

20. The use according to any one of claims 13-18 wherein the compound is admininstered topically.

21. The use according to any one of claims 13-18 wherein the compound is administered orally.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/053355

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 C07D413/14 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 A01N

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/075459 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; PATEL KANU MAGANBHAI [US]; PAHU) 5 July 2007 (2007-07-05) page 1, line 9 - line 21 page 106 - page 113; examples 1-214 claim 1	1-21
Y	WO 2008/019760 A1 (BAYER CROPSCIENCE AG [DE]; MIHARA JUN [JP]; MURATA TETSUYA [JP]; YAMAZ) 21 February 2008 (2008-02-21) page 1, line 4 - line 8 page 56 - page 67 claim 1	1-21

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

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"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
10 October 2011	19/10/2011

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

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/053355

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 2010/020522 A1 (SYNGENTA PARTICIPATIONS AG [CH]; SYNGENTA LTD [GB]; CASSAYRE JEROME YV) 25 February 2010 (2010-02-25) page 1, line 1 - line 11 page 62 - page 67; compounds A1-H4 claim 1	1-21
Y	WO 2010/020521 A1 (SYNGENTA PARTICIPATIONS AG [CH]; PITTERNA THOMAS [CH]; EL QACEMI MYRIE) 25 February 2010 (2010-02-25) page 1, line 1 - line 12 page 71 - page 87; compounds A1-B4 claim 1	1-21

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/053355

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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DERIVADOS DE ISOXAZOLINA COMO AGENTES ANTIPARASITARIOS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a derivados de isoxazolina que tienen actividad parasiticida. Los compuestos de interés son derivados de isoxazolina sustituidos con fenilazetidinas, naftilazetidinas o heteroarilazetidinas. La invención también se refiere a composiciones y procedimientos de uso de los mismos.

ANTEDECENTES

Existe una necesidad de agentes antiparasitarios mejorados para su uso con mamíferos y en particular existe una necesidad de insecticidas y acaricidas mejorados. Además existe una necesidad de productos orales y tópicos mejorados con administración conveniente que contengan uno o más de tales agentes antiparasitarios que puedan usarse para tratar eficazmente ectoparásitos, tales como insectos (por ejemplo, pulgas, piojos y moscas) y acáridos (por ejemplo, ácaros y garrapatas). Tales productos serían particularmente útiles para el tratamiento de animales de compañía, tales como gatos, perros, llamas y caballos, y ganado, tal como vacas, bisontes, cerdos, ovejas y cabras.

Los compuestos actualmente disponibles para tratamiento insecticida y acaricida de animales de compañía y ganado no siempre demuestran buena actividad, buena rapidez de acción o una larga duración de acción. La mayoría de los tratamientos contienen compuestos químicos peligrosos que pueden tener graves consecuencias, incluyendo letalidad de ingestión accidental. A las personas que aplican estos agentes generalmente se les recomienda limitar su

exposición. Se han usado collares y etiquetas de mascotas para superar algunos problemas, pero estos son susceptibles de masticación, ingestión y efectos toxicológicos al mamífero. Por lo tanto, los tratamientos actuales consiguen diversos grados de éxito que dependen parcialmente de la toxicidad, procedimiento de administración y eficacia. Actualmente, algunos agentes se están haciendo ineficaces debido a resistencia parasitaria.

Se ha desvelado en la técnica que los derivados de isoxazolina tienen actividad insecticida y acaricida. Por ejemplo, los documentos WO2007/105814 (US2009/0156643), WO2008/122375 y WO2009/035004 enumeran ciertas amidas ligadas con alquileno. Además, el documento WO2007/075459 desvela fenil isoxazolinas sustituidas con heterociclos de 5 a 6 miembros. Sin embargo, ninguna de estas indicaciones ejemplifica una fenil azetidina sustituida con isoxazolina, ni indica la técnica anterior que tales compuestos serían útiles contra un espectro de especies parasitarias, independientemente de las etapas del ciclo vital morfológicas, en animales.

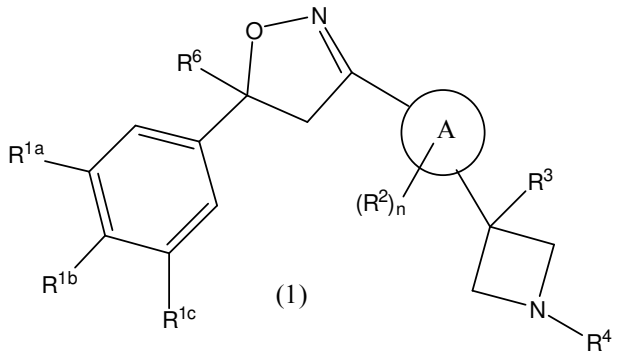
A pesar de la disponibilidad de agentes antiparasitarios de amplio espectro eficaces, sigue habiendo una necesidad de un producto más seguro, conveniente, eficaz y respetuoso con el medio ambiente que supere la amenaza siempre presente del desarrollo de resistencia.

La presente invención supera una o más de las diversas desventajas de las propiedades de los compuestos existentes o mejora éstas. En particular la presente invención desarrolla nuevas fenil azetidinas sustituidas con isoxazolina que demuestran tales propiedades.

SUMARIO

La presente invención proporciona compuestos de Fórmula (I) y Fórmula

(XX), estereoisómeros de los mismos, sales farmacéuticamente o veterinariamente aceptables de los mismos, que actúan como parasiticidas, en particular, ectoparasiticidas; que pueden usarse por lo tanto para tratar infección e infestación por acáridos e insectos en animales. Además, la invención contempla el control y prevención de endoparásitos en animales. La presente invención también contempla el control y tratamiento de enfermedades portadas por garrapatas, por ejemplo, enfermedad de Lyme, anaplasmosis canina y bovina, erliquiosis canina, rickettsiosis canina, babesiosis bovina y canina, aborto bovino epizoótico y teileriosis. Por lo tanto, de acuerdo con la invención, se proporciona un compuesto de Fórmula (I)



(1)

en la que

A es fenilo, naftilo o heteroarilo en la que dicho heteroarilo contiene de 1 a 4 heteroátomos seleccionados cada uno de ellos independientemente entre N, O y S;

cada uno de R^{1a}, R^{1b} y R^{1c} es independientemente hidrógeno, halo, hidroxilo, ciano, nitro, alquilo C_1-C_6, haloalquilo C_1-C_6, alcoxi C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, haloalcoxi C_1-C_6, -$C(O)NH_2$, -SF_5 o -$S(O)_pR$;

R^2 es halo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, nitro, hidroxilo, -$C(O)NR^aR^b$, alquenilo C_2-C_6, alquinilo C_2-C_6, -$S(O)_pR$ u -OR;

R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -$C(O)NH_2$, nitro, -SC(O)R, -$C(O)NR^aR^b$, alquil C_0-$C_3NR^aR^4$, -$NR^aNR^bR^4$, -NR^aOR^b, -ONR^aR^b, N_3, -NHR^4, -OR o -$S(O)_pR$;

R^4 es hidrógeno, alquilo C_1-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, -$C(O)R^5$, -$C(S)R^5$, -$C(O)NR^aR^5$, -$C(O)C(O)NR^aR^5$, -$S(O)_pR^c$, -$S(O)_2NR^aR^5$, -$C(NR^7)R^5$, -$C(NR^7)NR^aR^5$, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6;

R^5 es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6;

R^6 es ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, -$C(O)NR^aR^b$, alquenilo C_2-C_6, alquinilo C_2-C_6, haloalquenilo C_2-C_6 o haloalquinilo C_2-C_6;

R^7 es hidrógeno, alquilo C_1-C_6, hidroxilo, ciano, nitro, -$S(O)_pR^c$ o alcoxi C_1-C_6;

R es alquilo C_1-C_6 o cicloalquilo C_3-C_6, cada uno opcionalmente sustituido con al menos un halo;

R^a es hidrógeno, alquilo C_1-C_6 o alquil C_0-C_3-cicloalquilo C_3-C_6; en la que alquilo y alquilcicloalquilo están opcionalmente sustituidos con ciano o al menos un sustituyente halo;

R^b es hidrógeno, alquilo C_1-C_6, cicloalquilo C_3-C_6, fenilalquilo C_0-C_3, heteroarilalquilo C_0-C_3 o heterocicloalquilo C_0-C_3, cada uno opcionalmente sustituido, cuando sea químicamente posible, con al menos un sustituyente seleccionado entre hidroxilo, ciano, halo o -$S(O)_pR$;

R^c es alquilo C_1-C_6, haloalquilo C_1-C_6, haloalquil C_1-C_6-cicloalquilo C_3-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, fenilalquilo C_0-C_3, heteroarilalquilo C_0-C_3 o heterocicloalquilo C_0-C_3, cada uno opcionalmente sustituido con al menos un

sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, -$S(O)_pR$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^b$, -SCN o -$C(O)NR^aR^b$;

cada uno de R^4 y R^5 alquilo C_1-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6 puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, -$S(O)_pR^c$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^c$, -SCN o -$C(O)NR^aR^b$; y

donde el resto R^4 y R^5 fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6 puede estar además opcionalmente sustituido con al menos un sustituyente seleccionado entre ciano, halo, oxo, =S, =NR^7, hidroxilo, alcoxi C_1-C_6, alquilo C_1-C_6, haloalquilo C_1-C_6, -SH, -$S(O)_pR$ y haloalcoxi C_1-C_6;

n es el número entero 0, 1 ó 2, y cuando n es 2, cada R^2 puede ser idéntico o diferente entre sí; y

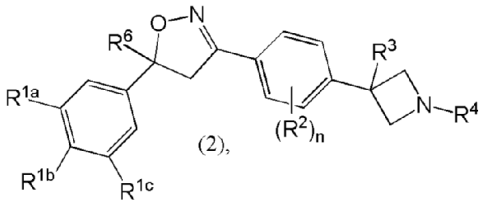
p es el número entero 0, 1 ó 2;

estereoisómeros de los mismos, y sales farmacéutica y veterinariamente aceptables de los mismos.

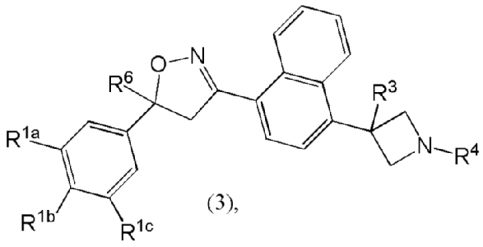
En otro aspecto de la invención, A es fenilo, naftilo, piridinilo, pirimidinilo, pirazolilo, imidazolil pirrolilo, furanilo, tiofenilo, triazolilo, tetrazolilo, tiazolilo, isoxazolilo, oxazolilo, oxadiazolilo, tiadiazolilo, piridazinilo, pirazinilo, benzofuranilo, benzotiofenilo, indolilo, bencimidazolilo, indazolilo, benzotriazolilo, tieno[2,3-c]piridina, tieno[3,2-b]piridina y benzo[1,2,5]tiadiazol. En otro aspecto de la invención, A es fenilo, naftilo, piridinilo, pirimidinilo, pirazolilo, triazolilo, tetrazolilo, tiazolilo, isoxazolilo, benzofuranilo, benzotiofenilo, indolilo y benzo[1,2,5]tiadiazol. En otro aspecto de la invención,

A es fenilo, naftilo, piridinilo, pirazolilo, triazolilo, isoxazolilo, benzofuranilo y benzo[1,2,5]tiadiazol. En otro aspecto de la invención, A es fenilo, naftilo, piridinilo, pirazolilo y benzo[1,2,5]tiadiazol. En otro aspecto de la invención, A es fenilo, piridinilo, naftilo o benzo[1,2,5]tiadiazol. En otro aspecto de la invención A es fenilo o piridinilo. En otro aspecto de la invención A es fenilo. En otro aspecto de la invención A es piridinilo. En otro aspecto de la invención, A es naftilo. En otro aspecto más de la invención, A es benzo[1,2,5]tiadiazol.

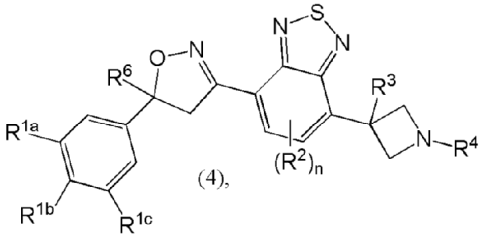
En otro aspecto de la invención son compuestos de Fórmula (2), (3), (4), (5) y (6)



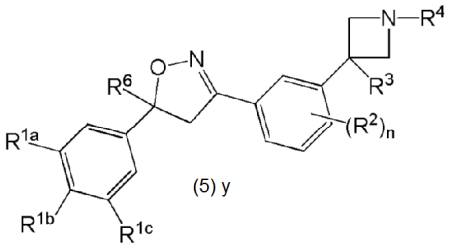
(2),



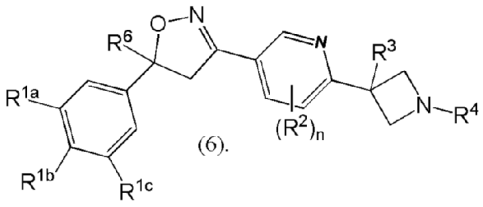
(3),



(4),

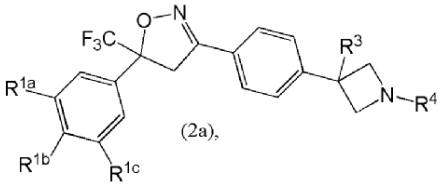


(5) y

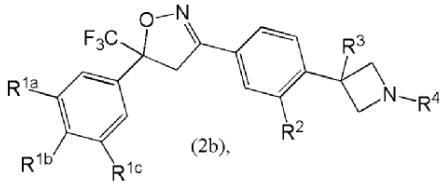


(6).

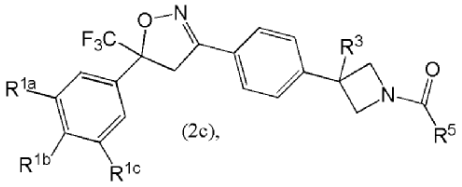
En otro aspecto más de la invención son compuestos de Fórmula (2a), (2b), (2c), (2d), (2e), (2f), (3a), (4a), (4b), (5a), (6a) y (6b).



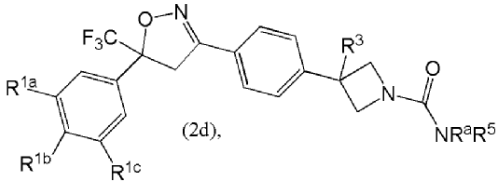
(2a),



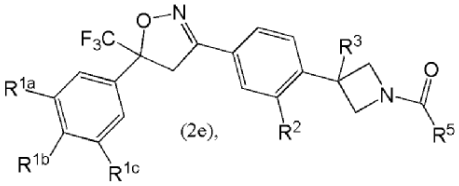
(2b),



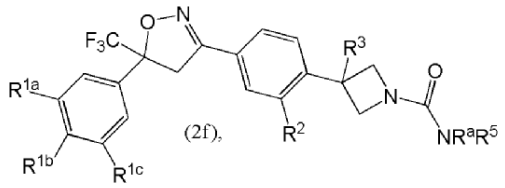
(2c),



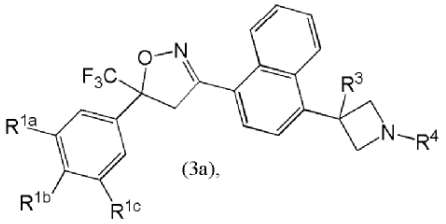
(2d),



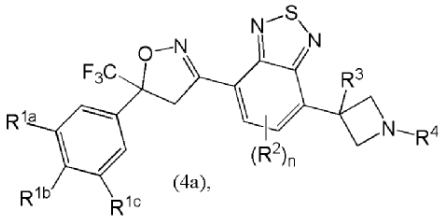
(2e),



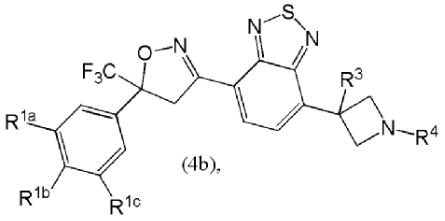
(2f),



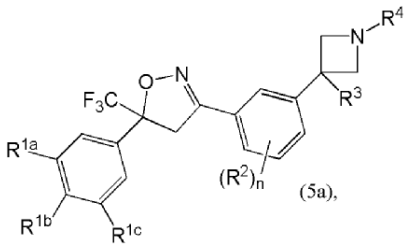
(3a),



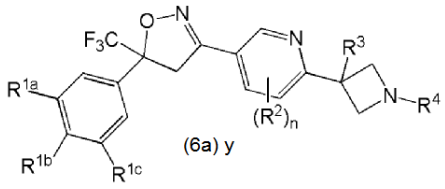
(4a),



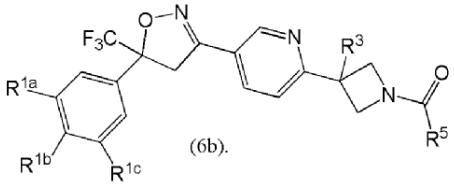
(4b),



(5a),



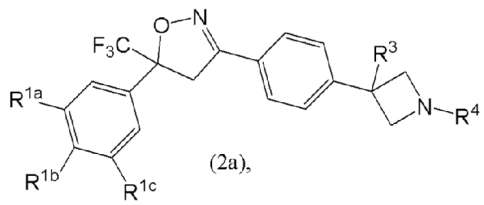
(6a) y



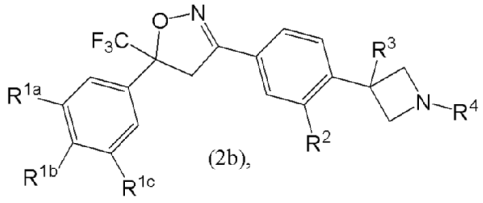
(6b).

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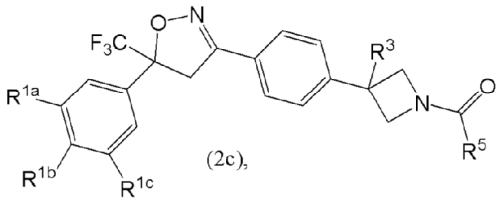
(2b), (2c), (2d), (6a) y (6b).



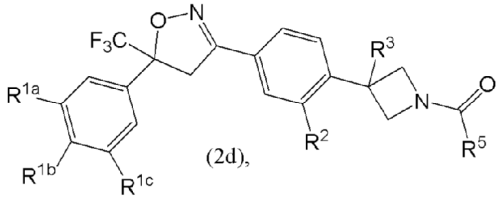
(2a),



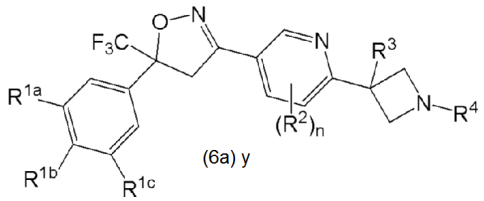
(2b),



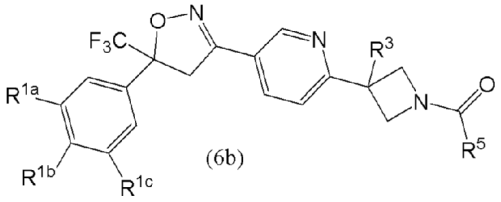
(2c),



(2d),

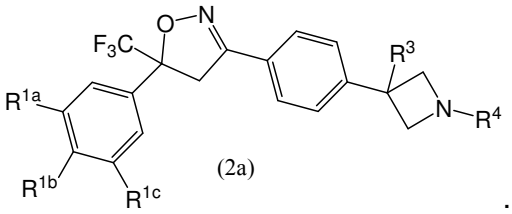


(6a) y



(6b)

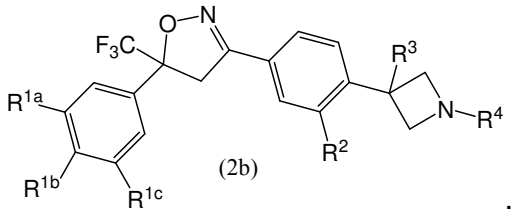
En otro aspecto más de la invención son compuestos de Fórmula (2a)



(2a)

.

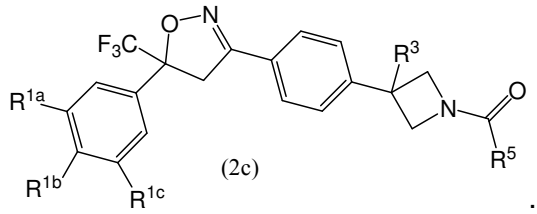
En otro aspecto más de la invención son compuestos de Fórmula (2b)



(2b)

.

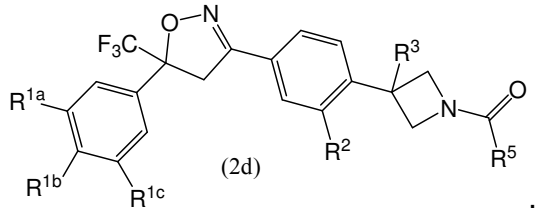
En otro aspecto más de la invención son compuestos de Fórmula (2c)



(2c)

.

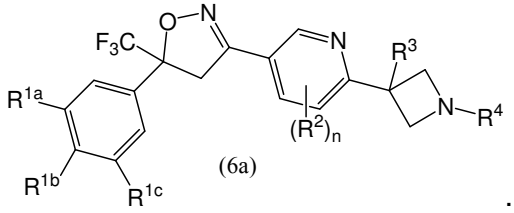
En otro aspecto más de la invención son compuestos de Fórmula (2d)



(2d)

.

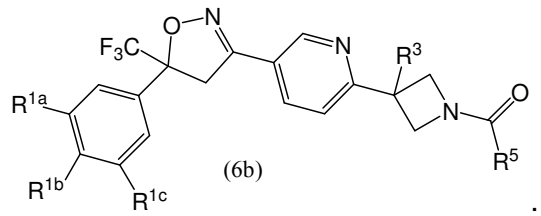
En otro aspecto más de la invención son compuestos de Fórmula (6a)



(6a)

.

En otro aspecto más de la invención son compuestos de Fórmula (6b)



(6b)

.

En otro aspecto de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -$S(O)_pR$ y -SF_5. En otro aspecto más de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, halo, hidroxilo, ciano, haloalquilo C_1-C_6, y alquil C_0-C_3-cicloalquilo C_3-C_6. En otro aspecto más de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, halo, hidroxilo, ciano y haloalquilo C_1-C_6. En otro aspecto más de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, flúor, cloro, bromo, ciano y haloalquilo C_1-C_6. En otro aspecto más de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, flúor, cloro, bromo, y haloalquilo C_1-C_6. En otro aspecto más de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, flúor, cloro, bromo y -CF_3. En otro aspecto más de la invención, cada uno de R^{1a}, R^{1b} y R^{1c} se seleccionan independientemente entre hidrógeno, flúor, cloro y -CF_3.

En otro aspecto más de la invención, el número entero de n de $(R^2)_n$ es 2, Cuando el número entero n es 2, entonces cada R^2 puede ser idéntico o diferente entre sí. En otro aspecto más de la invención, el número entero n de $(R^2)_n$ es 1. En otro aspecto más de la invención, el número entero n de $(R^2)_n$ es 0.

En otro aspecto más de la invención, R^2 se selecciona entre halo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, hidroxilo, -C(O)NR^aR^b, alquenilo C_2-C_6 u -OR. En otro aspecto más de la invención, R^2 se selecciona entre halo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, hidroxilo, -C(O)NR^aR^b u -OR. En otro aspecto más de la invención, R^2 se selecciona entre halo, ciano, alquilo C_1-C_6, -C(O)NR^aR^b, o hidroxilo. En otro aspecto más de la invención, R^2 se selecciona entre halo, ciano, -C(O)NR^aR^b, o hidroxilo. En otro aspecto más de la invención, R^2 se selecciona entre ciano o -C(O)NR^aR^b o hidroxilo. En otro aspecto más de la invención, R^2 se selecciona entre ciano. En otro aspecto más de la invención, R^2 se selecciona entre -C(O)NR^aR^b.

En otro aspecto de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -C(O)NH_2, -SC(O)R, -C(O)NR^aR^b, alquil C_0-$C_3NR^aR^4$, -$NR^aNR^bR^4$, -NR^aOR^b, -ONR^aR^b, N_3, -NHR^4, -OR o -$S(O)_pR$. En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -C(O)NH_2, -C(O)NR^aR^b, alquil C_0-$C_3NR^aR^4$, -$NR^aNR^bR^4$, -NR^aOR^b, -ONR^aR^b, N_3, -NHR^4 o -$S(O)_pR$. En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -C(O)NH_2, -C(O)NR^aR^b, alquil C_0-$C_3NR^aR^4$, -$NR^aNR^bR^4$, -NHR^4, N_3 o -$S(O)_pR$. En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -C(O)NH_2, -C(O)NR^aR^b, -NHR^4, N_3 o -$S(O)_pR$. En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, -C(O)NH_2 o N_3.

En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo,

ciano, alquilo C_1-C_6, haloalquilo C_1-C_6 o N_3. En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6 o N_3. En otro aspecto más de la invención, R^3 es hidrógeno, halo, hidroxilo, ciano o N_3. En otro aspecto más de la invención, R^3 es hidrógeno, flúor, cloro, bromo, N_3, hidroxilo o ciano. En otro aspecto más de la invención, R^3 es hidrógeno, flúor, N_3, hidroxilo o ciano. En otro aspecto más de la invención, R^3 es hidrógeno. En otro aspecto más de la invención, R^3 es flúor. En otro aspecto más de la invención, R^3 es cloro. En otro aspecto más de la invención, R^3 es hidroxilo. En otro aspecto más de la invención, R^3 es ciano. En otro aspecto más de la invención, R^3 es N_3.

En otro aspecto de la invención, R^4 es alquilo C_1-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, -$C(O)R^5$, -$C(S)R^5$, -$C(O)NR^aR^5$, -$C(O)C(O)NR^aR^5$, -$S(O)_pR^c$, -$S(O)_2NR^aR^5$, -$C(NR^7)R^5$, -$C(NR^7)NR^aR^5$, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6; donde cada uno de R^4 y R^5 alquilo C_1-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6 puede estar opcional e independientemente sustituido como se describe en el presente documento, y donde cada uno de los sustituyentes R^a, R^c, R^4 y R^5 puede estar opcional e independientemente sustituido como se describe en el presente documento. En otro aspecto más de la invención, R^4 es -$C(O)R^5$, -$C(O)NR^aR^5$, -$S(O)_pR^c$, -$C(S)R^5$, -$S(O)_2NR^aR^5$, -$C(NR^7)R^5$ o -$C(NR^7)NR^aR^5$, y donde cada uno de los sustituyentes R^a, R^c y R^5 puede estar opcional e independientemente sustituido como se describe en el presente documento.

En otro aspecto más de la invención, R^4 es -$C(O)R^5$ o -$C(O)NR^aR^5$, y donde cada uno de los sustituyentes R^a y R^5 puede estar opcional e independientemente sustituido como se describe en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es hidrógeno, alquilo C_1-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6, donde dicho R^5 alquilo C_1-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6 puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, $-S(O)_pR^c$, -SH, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, -SCN o $-C(O)NR^aR^b$, donde dicho resto R^5 fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6 puede estar además opcionalmente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, alcoxi C_1-C_6, alquilo C_1-C_6, haloalquilo C_1-C_6, -SH, $-S(O)_pR$ y haloalcoxi C_1-C_6. Los sustituyentes R^a y R^c también están opcionalmente sustituidos con al menos un sustituyente como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es hidrógeno, alquilo C_1-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, o heteroarilalquilo C_0-C_6, donde dichos restos alquil C_0-C_6-cicloalquilo C_3-C_6 o C_0-C_6alquilheteroarilo están opcionalmente sustituidos como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es metilo, etilo, propilo, isopropilo, isobutilo, *n*-butilo, *t*-butilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2$-ciclopropilo, $-CH_2$-ciclobutilo, $-CH_2$-ciclopentilo, $-(CH_2)_2$-ciclopropilo, $-(CH_2)_2$-ciclobutilo, $-(CH_2)_2$-ciclopentilo, pirazolilo, $-CH_2$-pirazolilo, $-(CH_2)_2$-pirazolilo, piridinilo, $-CH_2$-piridinilo, $-(CH_2)_2$-piridinilo, donde el alquilo (por ejemplo, metilo, etilo y propilo), cicloalquilo (por ejemplo, ciclopropilo y ciclobutilo) o alquilcicloalquilo (por ejemplo, $-CH_2$-ciclopropilo y -

$(CH_2)_2$-ciclobutilo) pueden estar opcional e independientemente sustituidos como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es metilo, etilo, propilo, isopropilo, isobutilo, *n*-butilo, *t*-butilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2$-ciclopropilo, $-CH_2$-ciclobutilo, $-CH_2$-ciclopentilo, $-(CH_2)_2$-ciclopropilo, $-(CH_2)_2$-ciclobutilo, $-(CH_2)_2$-ciclopentilo, pirazolilo, $-CH_2$-pirazolilo, $-(CH_2)_2$-pirazolilo, piridinilo, $-CH_2$-piridinilo, $-(CH_2)_2$-piridinilo, donde el alquilo (por ejemplo, metilo, etilo y propilo), cicloalquilo (por ejemplo, ciclopropilo y ciclobutilo) o alquilcicloalquilo (por ejemplo, $-CH_2$-ciclopropilo y $-(CH_2)_2$-ciclobutilo) puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, metoxi, $-CF_3$, etoxi, $-S(O)_pR$, $-SCH_3$, $-SCH_2CH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$, -NHciclopropilo, -NHciclobutilo, $-NHCH_2$ciclopropilo, $-NHCH_2$ciclobutilo, $-NR^aC(O)R^b$ o $-C(O)NH_2$.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es metilo, etilo, propilo, isopropilo, isobutilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2$-ciclopropilo, $-CH_2$-ciclobutilo, $-CH_2$-ciclopentilo, pirazolilo, $-CH_2$-pirazolilo, piridinilo, $-CH_2$-piridinilo, donde el alquilo (por ejemplo, metilo, etilo e isopropilo), cicloalquilo (por ejemplo, ciclopropilo y ciclobutilo) o alquilcicloalquilo (por ejemplo, $-CH_2$-ciclopropilo) puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, $-CF_3$, $S(O)_pR$, metoxi, etoxi, $-SCH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, -NHciclopropilo, -NHciclobutilo, -NHC(O)H o $-C(O)NH_2$.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es metilo, etilo, propilo, isopropilo, isobutilo, ciclopropilo, ciclobutilo,

ciclopentilo, -CH_2-ciclopropilo, -CH_2-ciclobutilo, -CH_2-ciclopentilo, pirazolilo, -CH_2-pirazolilo, piridinilo, -CH_2-piridinilo, donde el alquilo (por ejemplo, metilo, etilo e isopropilo), cicloalquilo (por ejemplo, ciclopropilo y ciclobutilo) o alquilcicloalquilo (por ejemplo, -CH_2ciclopropilo) puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, -CF_3, metoxi, -SCH_3, $S(O)_pR$, -NH_2, -$NHCH_3$, -$NHCH_2CH_3$, -NHciclopropilo, -NHC(O)H o -$C(O)NH_2$.

En otro aspecto más de la invención, cuando R^4 es -$C(O)R^5$, entonces R^5 es oxetano, tiatano, azetidina, tetrahidrofurano, tetrahidrotiofeno, pirrolidina, -CH_2-oxetano, -CH_2-tiatano, -CH_2-azetidina o -CH_2-tetrahidrofurano, cada uno de los cuales está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, cuando R^4 es -$C(O)R^5$, entonces R^5 es oxetano, tiatano, azetidina, tetrahidrofurano, tetrahidrotiofeno, -CH_2-oxetano, -CH_2-tiatano o -CH_2-azetidina, cada uno de los cuales está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, cuando R^4 es -$C(O)R^5$, entonces R^5 es oxetano, tiatano, azetidina, -CH_2-oxetano, -CH_2-tiatano o -CH_2-azetidina, cada uno de los cuales está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, cuando R^4 es -$C(O)R^5$, entonces R^5 es oxetano, tiatano o azetidina, cada uno de los cuales está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, cuando R^4 es -$C(O)R^5$, entonces R^5 es -CH_2-oxetano, -CH_2-tiatano o -CH_2-azetidina, cada uno de los cuales está opcionalmente sustituido como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es -$C(O)R^5$, entonces

R^5 es pirazol, imidazol, isoxazol, oxazol, isotiazol, tiazol, triazol, piridina, piridazina, pirazina o pirimidina, cada uno de los cuales está opcionalmente sustituido como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)R^5$, entonces R^5 es alquilo C_1-C_6, alquenilo C_2-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6, donde cada uno de alquilo C_1-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6 está opcionalmente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, $-S(O)_pR^c$, alcoxi C_1-C_6, $-S(O)_pNR^aR^b$ o $-SC(O)R^c$; pirazol, piridina, oxazol, piridazina, triazol, azetidina, tiatano, donde cada resto heterociclo o heteroarilo está opcionalmente sustituido adicionalmente con al menos un sustituyente seleccionado entre flúor, hidroxilo, metilo y oxo;

donde p, R^a, R^b y R^c son como se definen en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)NR^aR^5$, entonces R^a es hidrógeno, metilo, etilo, propilo, isopropilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2$-ciclopropilo, $-CH_2$-ciclobutilo, $-CH_2$-ciclopentilo, $-(CH_2)_2$-ciclopropilo, $-(CH_2)_2$-ciclobutilo o $-(CH_2)_2$-ciclopentilo; donde el alquilo (por ejemplo metilo y propilo), cicloalquilo (por ejemplo, ciclopropilo y ciclopentilo) o el alquilcicloalquilo (por ejemplo, $-CH_2$-ciclopropilo, $-CH_2$-ciclopentilo y $-(CH_2)_2$ciclobutilo) están opcionalmente sustituidos con ciano o al menos un sustituyente halo; y R^5 es como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es $-C(O)NR^aR^5$, entonces R^a es hidrógeno, metilo, etilo, propilo, isopropilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2$-ciclopropilo, $-CH_2$-ciclobutilo, $-CH_2$-ciclopentilo; donde el alquilo (por ejemplo metilo y propilo), cicloalquilo (por ejemplo, ciclopropilo y ciclopentilo), o el alquilcicloalquilo (por ejemplo, $-CH_2$-ciclopropilo

y -CH_2-ciclopentilo) están opcionalmente sustituidos con ciano o al menos un sustituyente halo; y R^5 es como se define en el presente documento.

En otro aspecto más de la invención, cuando R^4 es -$C(O)NR^aR^5$, entonces R^a es hidrógeno o metilo y R^5 se selecciona entre hidrógeno, metilo, etilo, propilo, ciclopropilo y heterocicloalquilo C_0-C_6, donde cada uno del resto alquilo y heterocicloalquilo está opcionalmente sustituido como se describe en el presente documento.

En otro aspecto más de la invención, cuando R^4 es -$S(O)_pR^c$, el número entero p es 2 y R^c es como se define en el presente documento, y dicho sustituyente R^c está opcionalmente sustituido con al menos un sustituyente como se define en el presente documento. En otro aspecto más de la invención, cuando R^4 es -$S(O)_pR^c$, el número entero p es 2, R^c es alquilo C_1-C_6 opcionalmente sustituido con al menos un sustituyente como se define en el presente documento. En otro aspecto más de la invención, cuando R^4 es -$S(O)_pR^c$, el número entero p es 2, R^c es alquilo C_1-C_6 opcionalmente sustituido con al menos un sustituyente seleccionado entre ciano o halo. En otro aspecto más de la invención, cuando R^4 es -$S(O)_pR^c$, el número entero p es 2 y R^c es alquilo C_1-C_6.En otro aspecto más de la invención, cuando R^4 es -$S(O)_pR^c$, el número entero p es 2 y R^c es metilo, etilo, propilo, o isopropilo. En otro aspecto más de la invención, cuando R^4 es -$S(O)_pR^c$, el número entero p es 2 y R^c es metilo o etilo.

En otro aspecto más de la invención, R^6 es ciano, alquilo C_1-C_6, haloalquilo C_1-C_6 o -$C(O)NH_2$. En otro aspecto más de la invención, R^6 es ciano, alquilo C_1-C_6 o haloalquilo C_1-C_6. En otro aspecto más de la invención, R^6 es ciano, metilo, etilo o haloalquilo C_1-C_6. En otro aspecto más de la

invención, R^6 es ciano, metilo o haloalquilo C_1-C_6. En otro aspecto más de la invención, R^6 es ciano o haloalquilo C_1-C_6. En otro aspecto más de la invención, R^6 es haloalquilo C_1-C_6. En otro aspecto más de la invención, R^6 es $-CF_3$, $-CHF_2$, $-CH_2F$ y $-CF_2Cl$. En otro aspecto más de la invención, R^6 es $-CF_3$, $-CHF_2$ y $-CH_2F$. En otro aspecto más de la invención, R^6 es $-CF_3$.

En otro aspecto más de la invención, R es metilo, etilo, propilo, isopropilo, ciclopropilo, ciclobutilo, o ciclopentilo. En otro aspecto más de la invención, R es metilo, etilo, isopropilo, ciclopropilo o ciclobutilo.

En otro aspecto más de la invención, R^a es hidrógeno, metilo, etilo, propilo, isopropilo o isobutilo, cada resto alquilo está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, R^a es hidrógeno, metilo, etilo, propilo o isopropilo, cada resto alquilo está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, R^a es hidrógeno, metilo o etilo, cada alquilo está opcionalmente sustituido como se define en el presente documento.

En otro aspecto más de la invención, R^a es hidrógeno, metilo, etilo, propilo, isopropilo, isobutilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2$-ciclopropilo o $-CH_2$-ciclobutilo, cada resto alquilo, cicloalquilo y alquilcicloalquilo está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, R^a es hidrógeno, metilo, etilo, propilo, isopropilo, ciclopropilo, ciclobutilo, $-CH_2$-ciclopropilo o $-CH_2$-ciclobutilo, cada resto alquilo, cicloalquilo y alquilcicloalquilo está opcionalmente sustituido como se define en el presente documento. En otro aspecto más de la invención, R^a es hidrógeno, metilo, etilo, isopropilo, ciclopropilo, ciclobutilo, $-CH_2$-ciclopropilo o $-CH_2$-ciclobutilo, cada resto alquilo, cicloalquilo y alquilcicloalquilo está

opcionalmente sustituido como se define en el presente documento.

En otro aspecto de la invención, R^b es hidrógeno, alquilo C_1-C_6, cicloalquilo C_3-C_6, fenilalquilo C_0-C_3 o heteroarilalquilo C_0-C_3. En otro aspecto más de la invención, R^b es hidrógeno, alquilo C_1-C_6, cicloalquilo C_3-C_6 o heteroarilalquilo C_0-C_3. En otro aspecto más de la invención, R^b es hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6. En otro aspecto más de la invención, R^b es hidrógeno, metilo, etilo, isopropilo, propilo, isobutilo, ciclopropilo o ciclobutilo.

En otro aspecto de la invención, son compuestos de Fórmula (1) seleccionados entre:

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona;

ciclopropil(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

3-fluoro-N-metil-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida;

N-etil-3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida;

N-ciclopropil-3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida;

ciclopropil(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

N-ciclopropil-3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)butan-1-ona;

2-ciclopropil-1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

3-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-oxopropanonitrilo;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metoxietanona;

ciclobutil(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

N-ciclopropil-3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-

3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona;

ciclobutil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona;

3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

N-ciclopropil-3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-hidroxiazetidin-1-carboxamida;

N-ciclopropil-3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-hidroxiazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-hidroxiazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

ciclopropil(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

2-Ciclopropil-1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

3-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-oxopropanonitrilo;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metoxietanona;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)propan-1-ona;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-

fluoroazetidin-1-il)butan-1-ona;

5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,5-bis(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-acetil-3-fluoroazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanonitrilo;

1-[(3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]ciclopropanol;

1-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]ciclopropanol;

3-{4-[3-fluoro-1-(metoxiacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-1-isobutirilazetidin-3-ol;

1-butiril-3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-3-ol;

5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[3-(4-{5-[3,5-bis(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetanol;

5-[3-cloro-5-(trifluorometil)fenil]-3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanamida;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanamida;

1-[(3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

5-(3,5-diclorofenil)-3-{4-[3-fluoro-1-(3-metilbutanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-propionilazetidin-3-ol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1H-pirazol-3-ilcarbonil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

4-{2-[3-(4-{5-[3,5-bis(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il}fenil)-3-fluoroazetidin-1-il]-2-oxoetil}piridina;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-acetil-3-fluoroazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanonitrilo;

4-[(3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]piridina;

5-[3,5-bis(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(ciclopropilcarbonil)-3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol;

(3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

2-(1-(ciclopropanocarbonil)-3-fluoroazetidin-3-il)-5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)benzonitrilo;

5-(3-cloro-5-(trifluorometil)fenil)-3-(4-(3-fluoro-1-(metilsulfonil)azetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-1-(ciclopropanocarbonil)azetidin-3-carbonitrilo;

1-(ciclopropanocarbonil)-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-carbonitrilo;

1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

2-metil-1-(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

Ciclopropil(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

Ciclopropil(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona;

1-(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona;

1-isobutiril-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol;

3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetanol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-diclorofenil)-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

1-[(3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

5-(3,5-diclorofenil)-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-acetilazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butirilazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butirilazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]-2-oxoetanol;

1-{[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]carbonil}ciclopropanol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]-3-oxopropanonitrilo;

1-{[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]carbonil}ciclopropanol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butirilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

1-[(3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

3-[4-(1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

1-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(3,3-difluoroazetidin-1-il)carbonil]-3-fluoroazetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-(3,3,3-trifluoropropanoil)azetidin-3-ol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(4-metil-1,3-oxazol-5-il)carbonil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

N-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]formamida;

4-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]piridazina;

1-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]-1H-1,2,4-triazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfonil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1H-pirazol-1-ilacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1,3-oxazol-5-ilcarbonil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[1-(2,2-difluoropropanoil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

1-{[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]carbonil}azetidin-3-ol;

1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-ol;

3-[4-(1-but-3-enoil-3-fluoroazetidin-3-il)fenil]-5-(3,5-dicloro-4-fluorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol;

2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-N,N-dimetil-2-oxoetanosulfonamida;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-{[(trifluorometil)tio]acetil}azetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(2-metoxipropanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(2,2-difluorociclopropil)carbonil]-3-fluoroazetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-3-oxopropan-1-ol;

(2S)-4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol;

4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol;

3-{4-[3-cloro-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[3-cloro-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3-clorofenil)-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[5-(3-cloro-4,5-difluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-(ciclopropilcarbonil)-azetidin-3-ol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-difluoro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

(2S)-1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-1-oxopropan-2-ol;

(2R)-1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-1-oxopropan-2-ol;

(2S)-4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfinil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[3-azido-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(3-azido-1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

etanotioato de S-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetilo];

5-(3-fluorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3-clorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,4-diclorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-5-[3-(trifluorometil)fenil]-4,5-dihidroisoxazol;

5-(3-cloro-5-fluorofenil)-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,4-difluorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(ciclopropilcarbonil)-3-{4-[(5R)-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

{[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]sulfonil}acetonitrilo;

1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-3-metanosulfonil-propan-1-ona;

1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-(2,2,2-trifluoro-etanosulfonil)-etanona;

Dimetilamida del ácido 2-(3-{4-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-oxo-etanosulfónico;

2-Bencenosulfonil-1-(3-{4-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-etanona;

1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-metanosulfonil-propan-1-ona;

(1-Ciclopropanocarbonil-3-{4-[5-(3,4-dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-3-il)-amida del ácido ciclopropanocarboxílico;

(3-Amino-3-{4-[5-(3,4-dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-ciclopropil-metanona;

3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

N-ciclopropil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

N-ciclopropil-3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-hidroxi-N-propilazetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-hidroxi-N,N-dimetilazetidin-1-carboxamida;

N-etil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-metilazetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-metilazetidin-1-carboxamida;

3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-etilazetidin-1-carboxamida;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-etilazetidin-1-carboxamida;

3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-metilazetidin-1-carboxamida;

3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-ciclopropilazetidin-1-carboxamida;

N-ciclopropil-3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

N-ciclopropil-3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-(2,2,2-trifluoroetil)azetidin-1-carboxamida;

3-fluoro-N,N-dimetil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N,N-dimetilazetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-(3,3,3-trifluoropropil)azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-oxetan-3-ilazetidin-1-carboxamida;

3-azido-N,N-dimetil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

2-(1-acetil-3-fluoroazetidin-3-il)-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-[3-

fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-propionilazetidin-3-il)benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-isobutirilazetidin-3-il)benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-glicoloilazetidin-3-il)benzonitrilo;
2-(1-butiril-3-fluoroazetidin-3-il)-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;
2-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;
2-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-[3-fluoro-1-(metoxiacetil)azetidin-3-il]benzonitrilo;
2-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-pentanoilazetidin-3-il)benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-{3-fluoro-1-[(metiltio)acetil]-azetidin-3-il}benzonitrilo;
2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]piridina;
(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropano-1-tiona;

(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

(1-(3-Fluoro-3-{4-[5-(3,4,5-tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-2-metanosulfonil-etanona; y

1-(3-{4-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-metanosulfonil-etanona,

estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) los que se muestra que tienen datos biológicos en al menos uno de los bio-ensayos con un valor ED^{100}, LD^{100}, LD^{90} y/o ED^{80} de ≤1 μg/ml o 1 μg/mosca y se seleccionan entre los Ejemplos 1-60, 65-70, 72-77, 82, 84-85, 87, 89, 91, 95-101, 103-104, 106-107, 109-110, 113, 116-117, 119-121, 123-126, 128-133, 135-143, 145-146, 148, 152-155, 158, 160-165, 167-171, 173-176, 187-188, 197-199 y 200-224, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) los que se muestra que tienen datos biológicos en al menos uno de los bio-ensayos con un valor ED^{100}, LD^{100}, LD^{90} y/o ED^{80} de ≤0,3 μg/ml o ≤0,3 μg/mosca y se seleccionan entre los Ejemplos 1-17, 19-30, 32-54, 56-60, 65-70, 72-74, 76-77, 82, 84, 87, 95-99, 103-104, 117, 131, 133, 135-143, 145-146, 148, 152-155,

158, 160-161, 165, 167-171, 173-175, 187-188, 202-204, 206, 209-221 y 223, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) los que se muestra que tienen datos biológicos en al menos uno de los bio-ensayos con un valor ED^{100}, LD^{100}, LD^{90} y/o ED^{80} de ≤0,1 μg/ml o ≤0,1 μg/mosca y se seleccionan entre los Ejemplos 1-17, 19-21, 24, 26-30, 32-34, 36-48, 50-54, 56-60, 65-70, 72-74, 76-77, 84, 87, 95-99, 103-104, 117, 131, 133, 135-137, 139-143, 145-146, 148, 152-155, 158, 160, 165, 168-171, 173-175, 188, 202, 206, 209-213, 215-221 y 223, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) los que se muestra que tienen datos biológicos en al menos uno de los bio-ensayos con un valor ED^{100}, LD^{100}, LD^{90} y/o ED^{80} de ≤0,03 μg/ml y se seleccionan entre los Ejemplos 1-17, 19-21, 26-28, 32-34, 36-38, 40-48, 50-54, 56, 59-60, 65-66, 68, 70, 72-74, 76, 84, 95-99, 103, 131, 133, 135, 141-143, 145-146, 155, 158, 165, 168-169, 171, 173-175, 202, 206, 209-210, 212-213, 215-216, 218-219 y 221, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) los que se muestra que tienen datos biológicos en al menos uno de los bio-ensayos con un valor ED^{100}, LD^{100}, LD^{90} y/o ED^{80} de ≤0,01 μg/ml o ≤0,01 μg/mosca y se seleccionan entre los Ejemplos 1, 5, 10-12,16, 19-21, 26-28, 33-34, 38, 40, 47, 50, 52, 54, 60, 84, 95, 99, 146, 168-169, 173-175, 202 y 221, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los

mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) los que se muestra que tienen datos biológicos en al menos uno de los bio-ensayos con un valor ED^{100}, LD^{100}, LD^{90} y/o ED^{80} de ≤0,003 μg/ml y se seleccionan entre los Ejemplos 11, 19, 40, 169 y 175, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) seleccionados entre:

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfonil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-ol;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol; y

(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona,

estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, son compuestos de Fórmula (1) seleccionados entre:

2,2-dicloro-1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)-3-fluoroazetidin-1-il)-2-fluoro-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-(metiltio)propan-1-ona

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-(metilsulfonil)propan-1-ona;

(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(tietan-3-il)metanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoro-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-2-(metilsulfonil)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)propan-1-ona;

(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-(metilsulfonil)ciclopropil)metanona;

5-(3,5-dicloro-4-fluorofenil)-3-(4-(3-fluoro-1-(1,1,1,3,3,3-hexafluoropropan-2-il)azetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3-difluoropropan-1-ona;

2-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-N-metil-2-oxoetanosulfonamida;

2-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-N-isopropil-2-oxoetanosulfonamida;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(3-hidroxiazetidin-1-il)etanona;

1-(3-(4-(5-(3,5-dicloro-4-hidroxifenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(tietan-2-il)metanona;

N-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-il)acetamida;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-mercapto-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoro-2-hidroxi-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-hidroxi-2,2-dimetilpropan-1-ona;

3-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2,2-dimetil-3-oxopropanonitrilo;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3-difluoropropan-1-ona;

Etanotioato de S-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-ilo);

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-2-(metiltio)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-2-(metilsulfonil)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropano-2-sulfonamida;

1-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-il)urea;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona

(E)-N-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)-cianamida;

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona; (3-Fluoro-3-{4-[5-(3,4,5-tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-

3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3-Cloro-4-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{4-[5-trifluorometil-5-(4-trifluorometil-fenil)-4,5-dihidro-isoxazol-3-il]-

fenil}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3,4-Difluoro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3-Cloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-

fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;
(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;
(E)-N-(1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;
(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;
(3-{4-[5-(3-cloro-5-fluorofenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;
(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{4-[5-trifluorometil-5-(3,4,5-trifluorofenil)-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-

dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropilideno)cianamida;

2-(1-(ciclopropanocarbonil)-3-fluoroazetidin-3-il)-5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)benzonitrilo; y

ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona, estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención son compuestos de Fórmula (1) seleccionados entre:

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)metanona;

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;
(3-{5-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;
(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;
(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;
(E)-N-(1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;
1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropan-1-ona;
ciclopropil(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)propan-1-ona;
1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metiltio)etanona;
1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{5-[5-(3,4,5-tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)metanona;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-

il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(4-Cloro-3-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-

piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{5-[5-trifluorometil-5-(3-trifluorometil-fenil)-4,5-dihidro-isoxazol-3-il]-

piridin-2-il}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)metanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3,4-Difluoro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-

il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3-Cloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-

il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3-Cloro-5-fluorofenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)-1,2-diazetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-fluoro-3-{5-[5-trifluorometil-5-(3,4,5-trifluorofenil)-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-

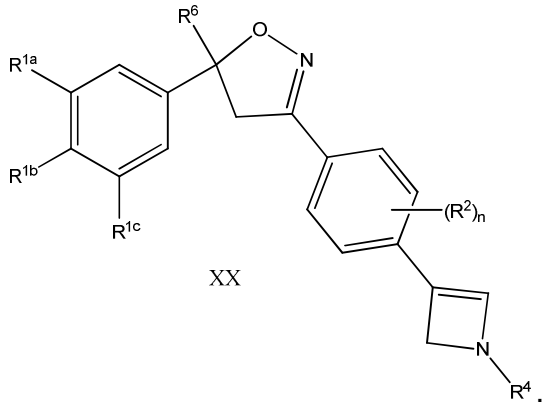
il)piridin-2-il)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona; y

(E)-N-(1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropilideno)cianamida,

estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

En otro aspecto de la invención, es un compuesto de Fórmula (XX)



XX.

En otro aspecto más de la invención es una composición que comprende a) un compuesto de Fórmula (XX), estereoisómeros del mismo, o una sal veterinaria o farmacéuticamente aceptable del mismo, y (b) un excipiente, diluyente o vehículo veterinaria o farmacéuticamente aceptable. Las variables R^{1a}, R^{1b}, R^{1c}, R^2, R^4, R^6 y n son como se definen en el presente documento. Preferentemente, la composición comprende una cantidad terapéuticamente eficaz de un compuesto de Fórmula (XX), un estereoisómero del mismo o una sal veterinaria o farmacéuticamente aceptable del mismo, y un excipiente, diluyente o vehículo veterinaria o farmacéuticamente aceptable.

En otro aspecto de la invención, es una composición veterinaria o

farmacéutica que comprende a) un compuesto de Fórmula (1) o Fórmula (XX), estereoisómeros del mismo, o una sal veterinaria o farmacéuticamente aceptable del mismo, y (b) un excipiente, diluyente o vehículo veterinaria o farmacéuticamente aceptable. Preferentemente, la composición comprende una cantidad terapéuticamente eficaz de un compuesto de Fórmula (1) o Fórmula (XX), un estereoisómero del mismo, o una sal veterinaria o farmacéuticamente aceptable del mismo, y un excipiente, diluyente o vehículo veterinaria o farmacéuticamente aceptable.

La composición puede comprender al menos un agente veterinario adicional. Los agentes veterinarios adicionales preferidos incluyen endoparasiticidas, endectocidas, ectoparasiticidas, insecticidas y anthelmínticos.

En otro aspecto más de la invención está el uso de un compuesto de Fórmula (I) o Fórmula (XX) para la preparación de un medicamento.

En otro aspecto más de la invención está un procedimiento para tratar una infección o infestación parasitaria en un animal que incluye la etapa de administrar a dicho animal, que necesite dicho tratamiento, una cantidad terapéuticamente eficaz de un compuesto de la presente invención, estereoisómero del mismo o sal veterinariamente o farmacéuticamente aceptable del mismo. Los compuestos de Fórmula (1) y Fórmula (XX), estereoisómeros de los mismos, sales farmacéuticamente o veterinariamente aceptables de los mismos o composiciones de los mismos pueden administrarse por vía oral, vía tópica, vía intramuscular, vía subcutánea y por inyección intraperitoneal. Preferentemente, el animal es un mamífero. Más preferentemente, el mamífero es un animal de compañía o ganado.

Preferentemente, el animal de compañía es un perro, gato o caballo. Preferentemente, el ganado es bovino, porcino u ovino. Preferentemente, el animal es un ave, más preferentemente, el ave es ave de corral. Preferentemente el animal es un pez. Los compuestos de la presente invención, y composiciones de los mismos, pueden administrarse al animal por vía oral, tópica y por inyección intramuscular, intraperitoneal y subcutánea. Preferentemente, los compuestos de la presente invención, y composiciones de los mismos, pueden administrarse al animal por vía oral o vía tópica.

En otro aspecto más de la invención está un procedimiento para tratar una infección o infestación parasitaria en un animal que incluye la etapa de administrar a dicho animal que necesite dicho tratamiento, una cantidad terapéuticamente eficaz de un compuesto de Fórmula (1) o Fórmula (XX), estereoisómero del mismo o sal farmacéuticamente o veterinariamente aceptable del mismo, en combinación con al menos un agente veterinario adicional. Los compuestos de Fórmula (1) o Fórmula (XX), estereoisómeros de los mismos, sales veterinariamente o farmacéuticamente aceptables de los mismos, solos, con un agente veterinario adicional o composición de los mismos, pueden administrarse al animal por vía oral, vía tópica o por inyección (intramuscular, intraperitoneal o subcutánea). Los agentes veterinarios preferidos incluyen endoparasiticidas, endectocidas, ectoparasiticidas, insecticidas y antihelmínticos.

Los compuestos de la presente invención solos o en combinación con un agente veterinario adicional, pueden administrarse como (a) una composición veterinaria sencilla que comprende un compuesto de la presente invención, estereoisómero del mismo, sal farmacéuticamente o veterinariamente

aceptable del mismo y, opcionalmente, al menos un agente veterinario adicional como se describe en el presente documento y un excipiente, diluyente o vehículo veterinariamente o farmacéuticamente aceptable; o (b) dos composiciones veterinarias separadas que comprenden (i) una primera composición que comprende un compuesto de la presente invención, estereoisómero del mismo, sal veterinariamente o farmacéuticamente aceptable del mismo y un excipiente, diluyente o vehículo farmacéuticamente o veterinariamente aceptable y (ii) una segunda composición que comprende al menos un agente veterinario adicional, como se describe en el presente documento y un excipiente, diluyente o vehículo veterinariamente o farmacéuticamente aceptable. Las composiciones veterinarias o farmacéuticas pueden administrarse simultáneamente o secuencialmente y en cualquier orden.

En otro aspecto de la invención están composiciones que comprenden un compuesto de Fórmula (1), estereoisómeros del mismo, sal farmacéutica o veterinaria del mismo, opcionalmente, al menos un agente veterinario adicional, que es útil para el control y tratamiento de parásitos en animales.

Todas las publicaciones de patente, patentes y documentos de prioridad indicados en el presente documento se incorporan por referencia en sus totalidades.

DEFINICIONES

Para los fines de la presente invención, como se describe y reivindica en el presente documento, se definen los siguientes términos y expresiones como se indica a continuación:

"Agente o agentes veterinarios adicionales" como se describe en el

presente documento, a menos que se indique otra cosa, se refiere a otros compuestos y productos veterinarios o farmacéuticos que proporcionan una cantidad terapéuticamente eficaz de dichos agentes que son útiles para el tratamiento de una infección parasitaria en un animal, como se describe en el presente documento.

"Alcoxi", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a un resto de oxígeno que tiene un sustituyente alquilo adicional. La porción alquilo (es decir, el resto alquilo) de un grupo alcoxi tiene la misma definición que se indica a continuación. Los ejemplos no limitantes incluyen:

$-OCH_3$, $-OCH_2CH_3$ y similares.

"Alquilo", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a radicales alcano de hidrocarburo monovalente saturados de fórmula general C_nH_{2n+1}. El radical alcano puede ser lineal o ramificado y puede estar sin sustituir o sustituido. Por ejemplo, el término "alquilo (C_1-C_6)" se refiere a un grupo alifático monovalente, lineal o ramificado que contiene de 1 a 6 átomos de carbono. Los ejemplos no exclusivos de grupos alquilo (C_1-C_6) incluyen, pero sin limitación metilo, etilo, propilo, isopropilo, *sec*-butilo, *t*-butilo, *n*-propilo, *n*-butilo, *i*-butilo, *s*-butilo, *n*-pentilo, 1-metilbutilo, 2-metilbutilo, 3-metilbutilo, neopentilo, 3,3-dimetilpropilo, 2-metilpentilo, hexilo y similares. El resto alquilo puede estar unido al resto químico por uno cualquiera de los átomos de carbono de la cadena alifática. Los grupos alquilo están opcionalmente sustituidos como se describe en el presente documento.

"Alquenilo" como se usa en el presente documento, a menos que se

indique otra cosa, se refiere a una cadena hidrocarburo alifático lineal o ramificada que tiene de 2 a 6 átomos de carbono y que contiene al menos un doble enlace carbono-carbono (por ejemplo -C=C- o -C=CH_2). Los ejemplos no exclusivos de alquenilo incluyen: etenilo, 1-propenilo, 2-propenilo, isopropenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-pentenilo y similares.

"Alquinilo" como se usa en el presente documento, a menos que se indique otra cosa, se refiere a una cadena de hidrocarburo alifática lineal o ramificada que tiene de 2 a 6 átomos de carbono y que contiene al menos un triple enlace carbono-carbono (por ejemplo, -C≡C- o -C≡CH). Los ejemplos no exclusivos de alquinilo incluyen: etinilo, 2-propinilo, 1-metil-2-propinilo, 2-butinilo, 3-butinilo, 2-metil-3-butinilo y similares.

"Animal", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a un animal individual que es un mamífero, ave o pez. Específicamente, mamífero se refiere a un animal vertebrado que es un ser humano o no humano, que son miembros de la clase taxonómica Mammalia. Los ejemplos no exclusivos de mamíferos no humanos incluyen animales de compañía y ganado. Los ejemplos no exclusivos de un animal de compañía incluyen: perro, gato, llama, cabra y caballo. Los animales de compañía preferidos son perro, gato y caballo. Es más preferido el perro. Se prefiere igualmente un gato o caballo. Los ejemplos no exclusivos de ganado incluyen: cerdos, camellos, conejos, cabras, ovejas, ciervos, uapitis, ganado bovino y bisontes. El ganado preferido es el bovino. Se prefieren igualmente cerdos. Específicamente, ave se refiere a un animal vertebrado de la clase taxonómica Aves. Las aves tienen plumas, tienen alas, son bípedas, endotérmicas y ponedoras de huevos. Los ejemplos no exclusivos de aves

incluyen, aves de corral (por ejemplo, pollos, pavos, patos y gansos), todos los cuales también se denominan en el presente documento como aves. Específicamente, pez se refiere a la clase taxonómica Chondrichthyes (peces cartilaginosos, por ejemplo, tiburones y rayas) y Osteichthyes (peces óseos) que viven en el agua, tienen agallas o la piel cubierta de moco, para poder respirar, aletas, y pueden tener escamas. Los ejemplos no exclusivos de peces incluyen tiburón, salmón, trucha, corégono, bagre, tilapia, lubina, atún, fletán, rodaballo, lenguado, platija, lubina rayada, anguilas, pez limón, mero y similares.

"Compuestos de la presente invención", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a compuestos de Fórmula (1) o Fórmula (XX), estereoisómeros de los mismos y sales veterinaria o farmacéuticamente aceptables de los mismos.

"Cicloalquilo", como se usa en el presente documento, a menos que se indique otra cosa, incluye restos alquilo carbocíclico completamente saturado o parcialmente saturado. Los ejemplos no limitantes de cicloalquilos parcialmente saturados incluyen: ciclopropeno, ciclobuteno, ciclohepteno, cicloocteno, ciclohepta-1,3-dieno y similares. Los cicloalquilos preferidos son anillos monocíclicos saturados de 3 a 6 miembros que incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. El grupo cicloalquilo puede estar unido al resto químico mediante uno cualquiera de los átomos de carbono en el anillo carbocíclico. Los grupos cicloalquilo están opcionalmente sustituidos con al menos un sustituyente. Adicionalmente, cuando se usan en palabras compuestas, tales como alquilcicloalquilo, dicho resto alquilo y cicloalquilo tiene el mismo significado que se define en el presente documento y pueden estar

unidos al resto químico mediante uno cualquiera de los átomos de carbono de la cadena alifática. Los ejemplos de "alquilcicloalquilo" incluyen, metilciclopropano (-CH_2-ciclopropano), etilciclopropano (-CH_2CH_2-ciclopropano), metilciclobutano (-CH_2-ciclobutano), etilciclobutano (-CH_2CH_2-ciclobutano), metilciclohexano (-CH_2-ciclohexano) y similares. Los cicloalquilos están opcionalmente sustituidos como se describe en el presente documento.

"Halógeno" o "halo", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a flúor, cloro, bromo y yodo. Además, cuando se usan en palabras compuestas, tales como "haloalquilo", "haloalcoxi", "haloalquenilo" o "haloalquinilo", dicho alquilo, alcoxi, alquenilo y alquinilo pueden estar parcialmente o completamente sustituidos con átomos de halógeno que pueden ser el mismo o diferentes y dicho resto alquilo, alcoxi, alquenilo y alquinilo tiene el mismo significado que se ha indicado anteriormente y puede estar unido al resto químico mediante uno cualquiera de los átomos de carbono de la cadena alifática. Los ejemplos de "haloalquilo" incluyen F_3C-, $ClCH_2$-, CF_3CH_2- y CF_3CCl_2- y similares. El término "haloalcoxi" se define de forma análoga al término "haloalquilo". Los ejemplos de "haloalcoxi" incluyen CF_3O-, CCl_3CH_2O-, $HCF_2CH_2CH_2O$- y CF_3CH_2O- y similares. El término "haloalquenilo" se define de forma análoga al término "haloalquilo", con la excepción de que la cadena alifática contiene al menos un doble enlace carbono-carbono. Los ejemplos de "haloalquenilo" incluyen $CF_3C=C$-, $CCl_3C=C$-, $HCF_2C=C$- y $CF_3C=CC$- y similares. El término "haloalquinilo" se define de forma análoga al término "haloalquilo", con la excepción de que la cadena alifática contiene al menos un triple enlace carbono-carbono. Los ejemplos de "haloalquinilo" incluyen $CF_3C\equiv C$-, $CCl_3C\equiv C$-,

$HCF_2C{\equiv}C$- y $CF_3C{\equiv}CC$- y similares.

"Heterociclo", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a un anillo monocíclico parcialmente saturado o saturado de 3 a 6 miembros que contiene uno o más heteroátomos seleccionados cada uno de ellos independientemente entre N, O o S, preferentemente de uno a cuatro heteroátomos. Los ejemplos no exclusivos de heterociclo incluyen oxiranilo, tiaranilo, aziridinilo, oxetanilo, tiatanilo, azetidinilo, tetrahidrofurano, tetrahidrotiofeno, pirrolidinilo, tetrahidropiranilo, piperidinilo, piperazinilo, tetrahidropiridinilo, 2H-azirina, 2,3-dihidro-azeto, 3,4-dihidro-2H-pirrol y similares. El grupo heterociclo puede estar unido al resto químico mediante uno cualquiera de los átomos de carbono o heteroátomos (por ejemplo, N, O y S) en el anillo monocíclico. Los heterociclos están opcionalmente sustituidos como se describe en el presente documento.

"Heteroarilo" o "Het", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a un anillo monocíclico aromático de 5 a 6 miembros o un anillo aromático condensado de 8 a 10 miembros donde dicho resto de anillo monocíclico y condensado contiene uno o más heteroátomos seleccionados cada uno de ellos independientemente entre N, O o S, preferentemente de uno a cuatro heteroátomos. Los ejemplos no exclusivos de heteroarilos monocíclicos incluyen pirrolilo, furanilo, tiofenilo, pirazolilo, imidazolilo, triazolilo, tetrazolilo, tiazolilo, isoxazolilo, oxazolilo, oxadiazolilo, tiadiazolilo, piridinilo, piridazinilo, pirimidinilo, pirazinilo y similares. Los ejemplos no exclusivos de heteroarilos condensados incluyen: benzofuranilo, benzotiofenilo, indolilo, bencimidazolilo, indazolilo, benzotriazolilo, tieno[2,3-c]piridina, tieno[3,2-b]piridina, benzo[1,2,5]tiadiazol y similares. El grupo

heteroarilo puede estar unido al resto químico mediante uno cualquiera de los átomos de carbono o heteroátomos (por ejemplo, N, O y S) en el anillo monocíclico o condensado. Los heteroarilos están opcionalmente sustituidos como se describe en el presente documento.

"Opcionalmente sustituido", se usa en el presente documento de forma intercambiable con la expresión sustituido o sin sustituir. A menos que se indique otra cosa, un grupo opcionalmente sustituido puede tener un sustituyente en cada posición sustituible del grupo, y cada sustitución es independiente de la otra. Un grupo opcionalmente sustituido también puede no tener sustituyentes. Por lo tanto, la expresión "opcionalmente sustituido con al menos un sustituyente" significa que el número de sustituyentes puede variar de cero hasta un número de posiciones disponibles para sustitución.

"Parásito o parásitos", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a endoparásitos y ectoparásitos. Los endoparásitos son parásitos que viven dentro del cuerpo de su huésped e incluyen helmintos (por ejemplo, trematodos, cestodos y nematodos) y protozoos. Los ectoparásitos son organismos del filo Arthropoda (por ejemplo, arácnidos, insectos y crustáceos (por ejemplo, copépodos-piojo de mar) que se alimentan a través de o sobre la piel de su huésped. Los arácnidos preferidos del orden Acarina, por ejemplo, garrapatas y ácaros. Los insectos preferidos son mosquitos pequeños, pulgas, mosquitos, moscas mordedoras (mosca de establo, mosca de los cuernos, moscardones, tábanos y similares) y piojos. Los compuestos de la presente invención preferidos pueden usarse para el tratamiento de parásitos, es decir, el tratamiento de una infección o plaga parasitaria.

"Cantidad terapéuticamente eficaz", como se usa en el presente documento, a menos que se indique otra cosa, se refiere a una cantidad de los compuestos de la presente invención que (i) tratan la infección o plaga parasitaria particular, (ii) atenúa, mejora o elimina uno o más síntomas de la infección o plaga parasitaria particular, o (iii) evita o retrasa la aparición de uno o más síntomas de la infección o plaga parasitaria particular descrita en el presente documento.

"Tratamiento", "tratar" y similares, como se usa en el presente documento, a menos que se indique otra cosa, se refiere a invertir, aliviar o inhibir la infección, plaga o afección parasitaria. Como se usa en el presente documento, estos términos también incluyen, dependiendo de la afección del mamífero, evitar la aparición de un trastorno o afección, o de síntomas asociados con un trastorno o afección, incluyendo reducir la gravedad de un trastorno o afección o síntomas asociados con los mismos antes de la aflicción con dicha infección o plaga. Por lo tanto, el tratamiento puede referirse a la administración de los compuestos de la presente invención a un mamífero que en el momento de la administración no está afectado con la infección o plaga. El tratamiento también incluye evitar la reaparición de una infección o plaga o de síntomas asociados con los mismos, así como referencias a "control" (por ejemplo, matar, repeler, expulsar, incapacitar, disuadir, eliminar, mitigar, minimizar y erradicar).

"Veterinariamente aceptable" como se usa en el presente documento, a menos que se indique otra cosa, indica que la sustancia o composición debe ser químicamente y/o toxicológicamente compatible, con los demás ingredientes que comprenden una formulación, composición y/o el mamífero que se va a

tratar con la misma. El término "farmacéuticamente" aceptable tiene el mismo significado que el indicado para "veterinariamente" aceptable.

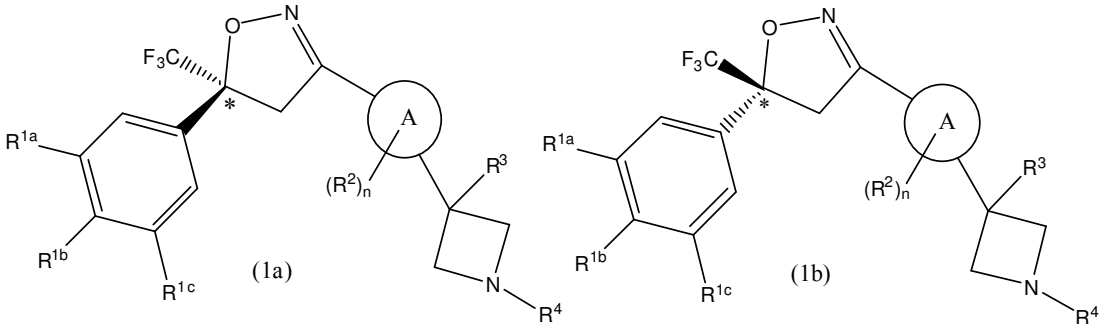
El símbolo "∿∿∿" como se usa en el presente documento, a menos que se indique otra cosa, se refiere a un punto de unión.

DESCRIPCIÓN DETALLADA

La presente invención proporciona compuestos de Fórmula (1), estereoisómeros de los mismos, así como composiciones veterinarias que son útiles como agentes antiparasitarios para animales y aves, en particular, compuestos que actúan como ectoparasiticidas. Además, la presente invención proporciona compuestos de Fórmula (XX), estereoisómeros de los mismos, así como composiciones veterinarias que son útiles como agentes antiparasitarios para animales y aves, en particular, compuestos que actúan como ectoparasiticidas.

Los compuestos de la presente invención pueden sintetizarse mediante rutas sintéticas que incluyen procedimientos análogos a los bien conocidos en la técnica química, particularmente a la luz de la descripción contenida en el presente documento. Generalmente, los materiales de partida están disponibles en fuentes comerciales, tales como Aldrich Chemicals (Milwaukee, Wis.) o se preparan fácilmente usando procedimientos bien conocidos por los expertos en la técnica (por ejemplo, preparados mediante procedimientos descritos generalmente en Louis F. Fieser y Mary Fieser, "Reagents for Organic Synthesis", 1; 19, Wiley, Nueva York (1967, 1999 ed.), o Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlín, incluyendo suplementos (también disponibles mediante la base de datos online de Beilstein)).

Los compuestos de esta invención pueden existir en forma de uno o más estereoisómeros. Los diversos estereoisómeros incluyen enantiómeros, diastereómeros y atropisómeros. Un experto en la técnica apreciará que un estereoisómero puede ser más activo y/o puede mostrar efectos beneficiosos cuando se enriquecen con respecto a los demás estereoisómeros o cuando se separan de los demás estereoisómeros. Además, el experto en la técnica sabe cómo separar, enriquecer y/o preparar selectivamente dichos estereoisómeros. Los compuestos de la invención pueden estar presentes en forma de una mezcla de estereoisómeros, estereoisómeros individuales o como una forma individual ópticamente activa. Por ejemplo, dos posibles enantiómeros de Fórmula 1 se representan como Fórmula 1a y Fórmula Ib que incluyen el centro quiral de isoxazolina identificado con un asterisco (*). Las representaciones moleculares elaboradas en el presente documento siguen convencionales para la representación estereoquímica.



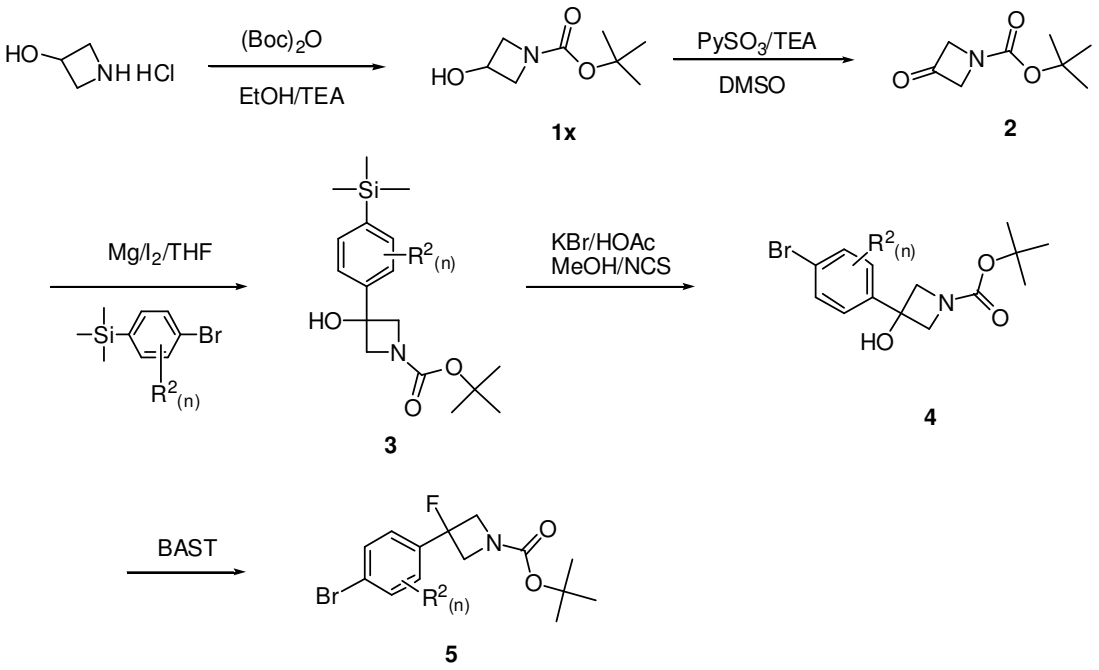
Para fines ilustrativos, los esquemas de reacción representados a continuación demuestran rutas potenciales para sintetizar intermedios y compuestos clave de la presente invención. Para una descripción más detallada de las etapas de reacción individuales, véase la sección de Ejemplos que se muestra a continuación. Los expertos en la técnica apreciarán que pueden usarse otros materiales de partida, reactivos y rutas sintéticas

adecuadas para sintetizar los intermedios y compuestos de la presente invención y una diversidad de derivados de los mismos. Además, muchos de los compuestos preparados mediante los procedimientos descritos a continuación pueden modificarse adicionalmente a la luz de esta divulgación usando la química convencional. Los Esquemas 1-17 representan los procedimientos generales útiles para la preparación de compuestos de la presente invención. Sin embargo, se entenderá que la invención, como se describe por completo en el presente documento y como se enumera en las reivindicaciones, no pretende limitarse por los detalles de los siguientes esquemas o modos de preparación.

En los Esquemas y Ejemplos que se indican a continuación, los siguientes catalizadores/reactivos incluyen: N,N-dimetil formamida (DMF); N-N-dimetilsulfóxido (DMSO); N-cloro-succinimida (NCS); N-bromo-succinimida (NBS); etanol (EtOH); metanol (MeOH); tetrahidrofurano (THF); trietilamina (TEA); acetonitrilo (CH_3CN, ACN); *n*-BuOH (n-butanol); hidróxido de litio (LiOH); hidrazina (H_2NNH_2); bicarbonato potásico ($KHCO_3$); carbonato potásico (K_2CO_3); éter dietílico (Et_2O); carbonato sódico (Na_2CO_3); hidroxilamina (NH_2OH); ácido sulfúrico (H_2SO_4); cloruro de amonio (NH_4Cl); diclorometano (CH_2Cl_2); ácido clorhídrico (HCl); ácido trifluoroacético (TFA); metil *terc*-butil éter (MTBE); acetato potásico (KOAc); alcohol isopropílico (IPA); *n*-butil litio (n-BuLi); trietilamina (Et_3N); acetato de etilo (EtOAc); acetato sódico (NaOAc); cloruro de bis (trifenilfosfina)paladio II ($PdCl_2(PPh_3)_2$) de Strem; hexafluorofosfato de N,N,N',N'-Tetrametil-O-(7-azabenzotriazol-1-il)uronio (HATU); 1-hidroxibenzotriazol hidrato (HOBt); dicarbonato de di-*terc*-butilo (Boc_2O); carbonildiimidazol (CDI); trióxido de dietilaminoazufre (DAST); 2,2'-

azobis(2-metilpropionitrilo) (AIBN); fluoruro de tetrabutilamonio (TBAF); trifluoruro de bis(2-metoxietil)aminoazufre (BAST); carbonato de *terc*-butilo (Boc); trióxido de piridina azufre ($PySO_3$); trifenilfosfina paladio ($Pd(PPh_3)_4$); 4-dimetilaminopiridina (DMAP); hexametildisilazida (KHMDS); (2,2,6,6-tetrametilpiperidin-1-il)oxilo (TEMPO); e hidruro de diisobutilaluminio (DIBAL-H).

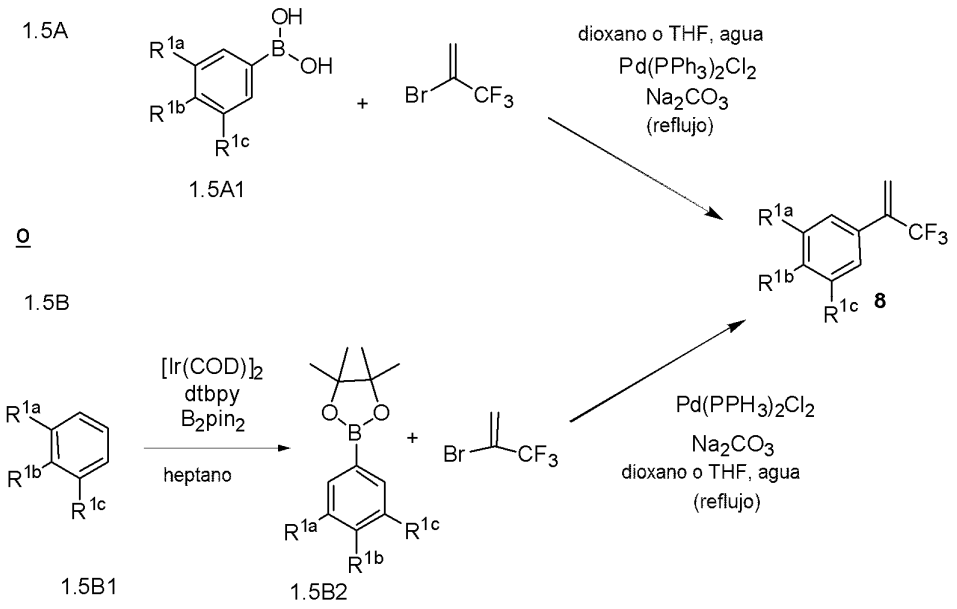
Esquema 1



R^2 y n son como se definen en el presente documento.

Las fenil azetidinas pueden prepararse como se muestra en el Esquema 1. La protección Boc de clorhidrato de hidroxiazetidina seguido de oxidación del grupo hidroxilo dio la cetoazetidina **2.** Este puede condensarse con bromoaril silanos mediante la formación del reactivo arilo de Grignard y la posterior condensación con la cetona para proporcionar la silil fenil azetadina **3.** El reemplazo del silano con bromo se realizó por tratamiento con bromuro potásico en ácido acético para dar la bromofenil azetidina deseada **4.** La fluoración de la hidroxiazetidina **4** puede realizarse por tratamiento con BAST para proporcionar **5.**

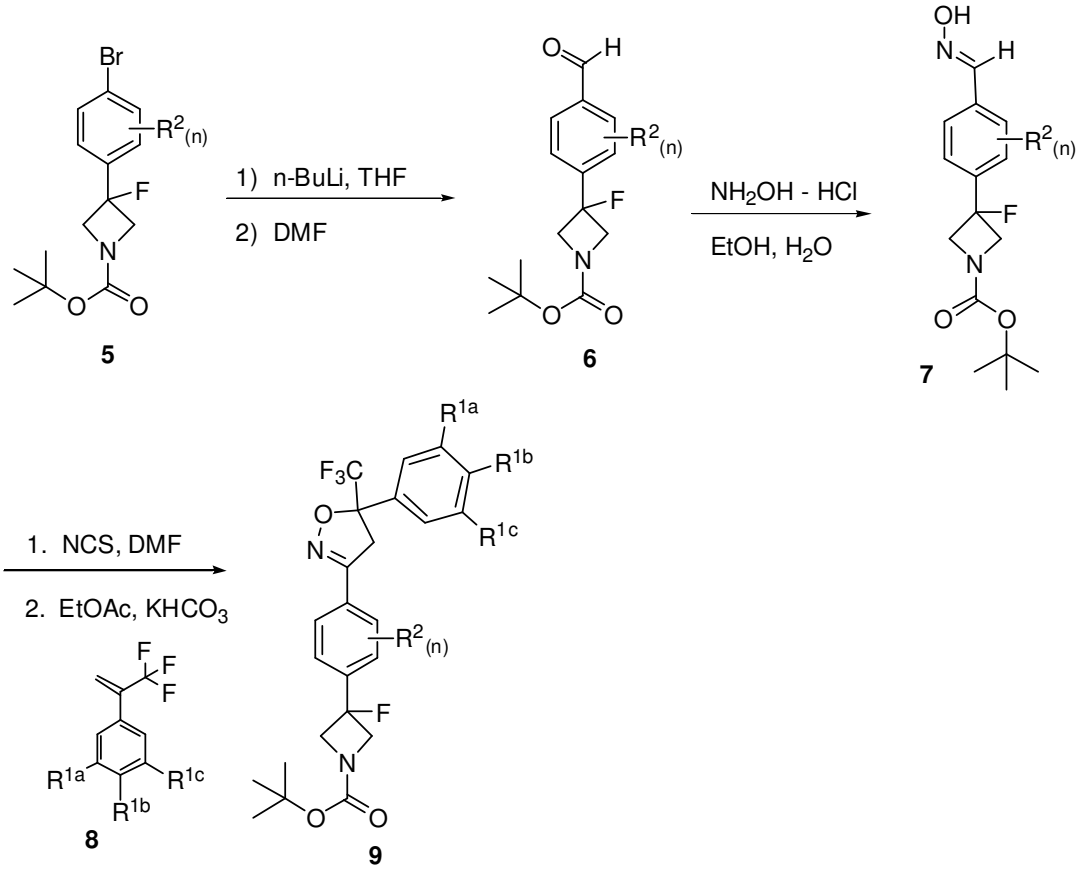
Esquema 1.5



R^{1a}, R^{1b} y R^{1c} son como se definen en el presente documento.

Las aril olefinas (**8**) pueden prepararse de acuerdo con el Esquema 1.5. Los organoboratos necesarios pueden prepararse en forma de intermedios de éster de boronato (1.5B2) a partir de procedimientos bibliográficos (*Org. Lett*. 2007, *9*, 761-764) o adquirirse como ácidos borónicos (1.5A1), tales como ácido 3,5-dicloroborónico de Aldrich. Los compuestos del intermedio 1.5A1 o 1.5B2 pueden añadirse a dioxano o THF y agua seguido de 2-bromo-3,3,3-trifluoropropeno, carbonato potásico y cloruro de bis (trifenilfosfina)paladio II para proporcionar los compuestos del intermedio (**8**).

Esquema 2



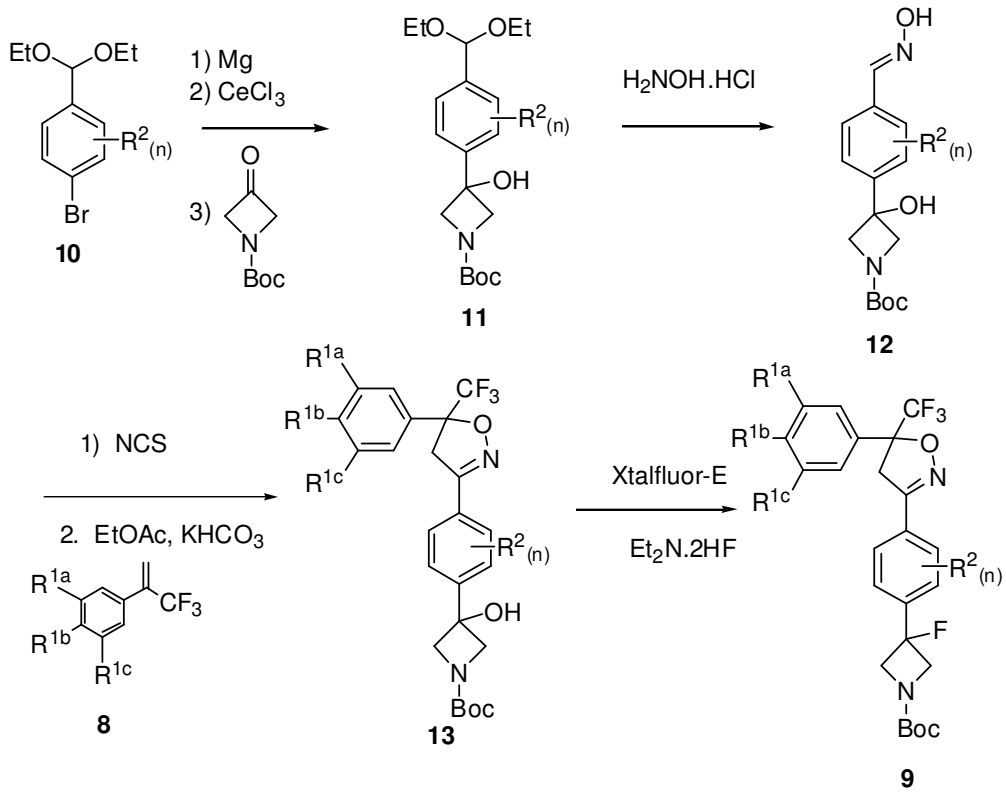
R^{1a}, R^{1b}, R^{1c}, R^2 y n son como se definen en el presente documento.

El Esquema 2 describe la preparación de isoxazolinas a partir de los bromuros de arilo o aril aldehídos. A partir de la bromofenil azetidina **5**, el intercambio halógeno-metal seguido de inactivación con DMF proporciona el aril aldehído **6** que también puede prepararse mediante otros procedimientos (Esquemas 3 y 4). El aldehído se condensa con hidroxilamina para proporcionar la oxima **7.** A partir de la oxima, el anillo de isoxazolina puede prepararse en un procedimiento de un solo paso, dos etapas. El tratamiento de la oxima con N-clorosuccinimida proporciona la clorooxima que experimenta [3+2] ciclación con aril olefinas **8** para proporcionar la isoxazolina **9.** Estas

etapas también pueden hacerse como reacciones por separado. La retirada del grupo protector Boc en la azetidina puede realizarse por tratamiento con ácido trifluoroacético.

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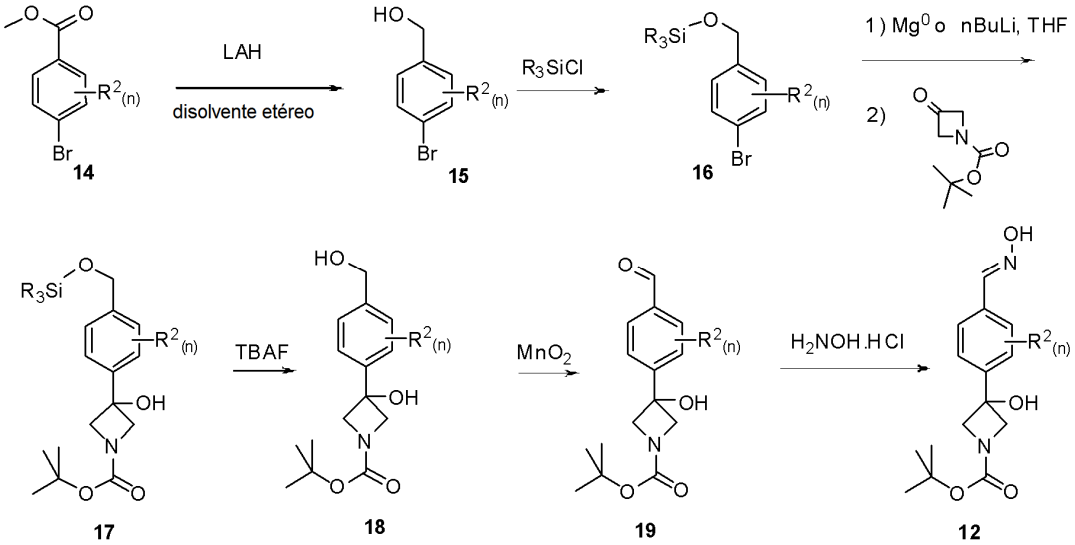
Esquema 3



R^{1a}, R^{1b}, R^{1c}, R^2 y n son como se definen en el presente documento.

Una síntesis alternativa de las azetidinas protegidas con Boc se muestra en el Esquema 3. La reacción de 4-bromobenzaldehído dietilacetal **10** con metal Mg o iPrMgCl seguido de $CeCl_3$ proporciona un reactivo organometálico que se añade a la 3-azetidinona N-protegida. La condensación con hidroxilamina, la cloración y la ciclación como se describen en el Esquema 2 proporcionan la isoxazolina **13.** La fluoración del grupo hidroxilo puede conseguirse por reacción con Xtafluor-E.

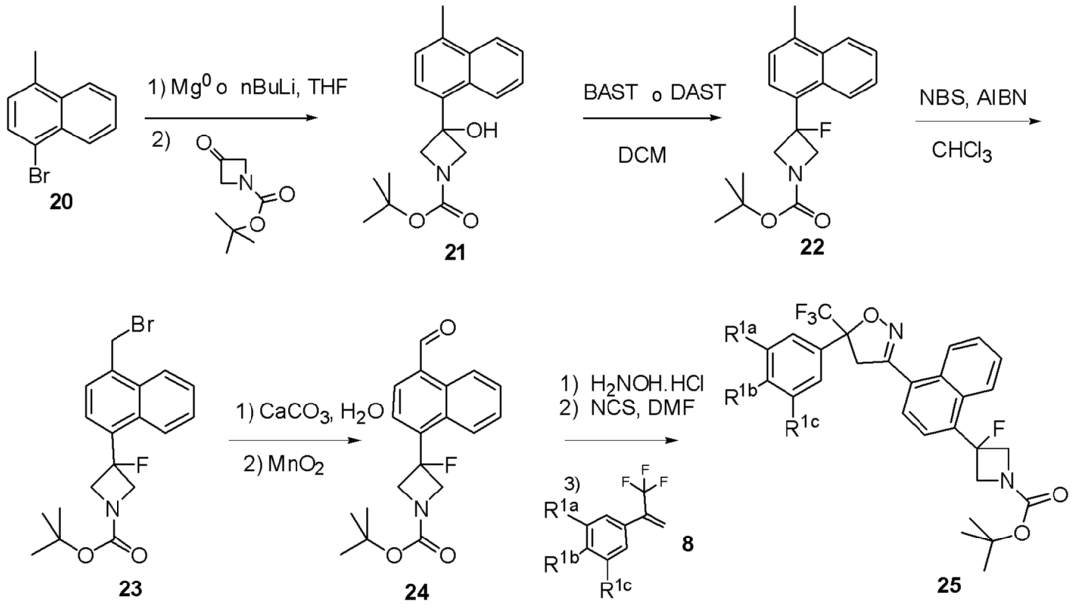
Esquema 4



R^2 y n son como se definen en el presente documento.

Como alternativa, las fenil azetidinas pueden prepararse de bromo aril ésteres o bromoaril metanoles como se muestra en el Esquema 4. La reducción del aril éster con hidruro de litio y aluminio proporciona el aril metanol **15** que puede protegerse como un silano. La formación del reactivo de arilo de Grignard con intercambio metálico de magnesio o halógeno proporciona el anión de arilo que puede condensarse con la azetidinona N-protegida **2** para dar la aril azetidina **17.** La desprotección del alcohol y la oxidación proporcionan la formil fenilazetidina **19** que puede someterse a condensación con hidroxilamina para proporcionar la oxima **12.**

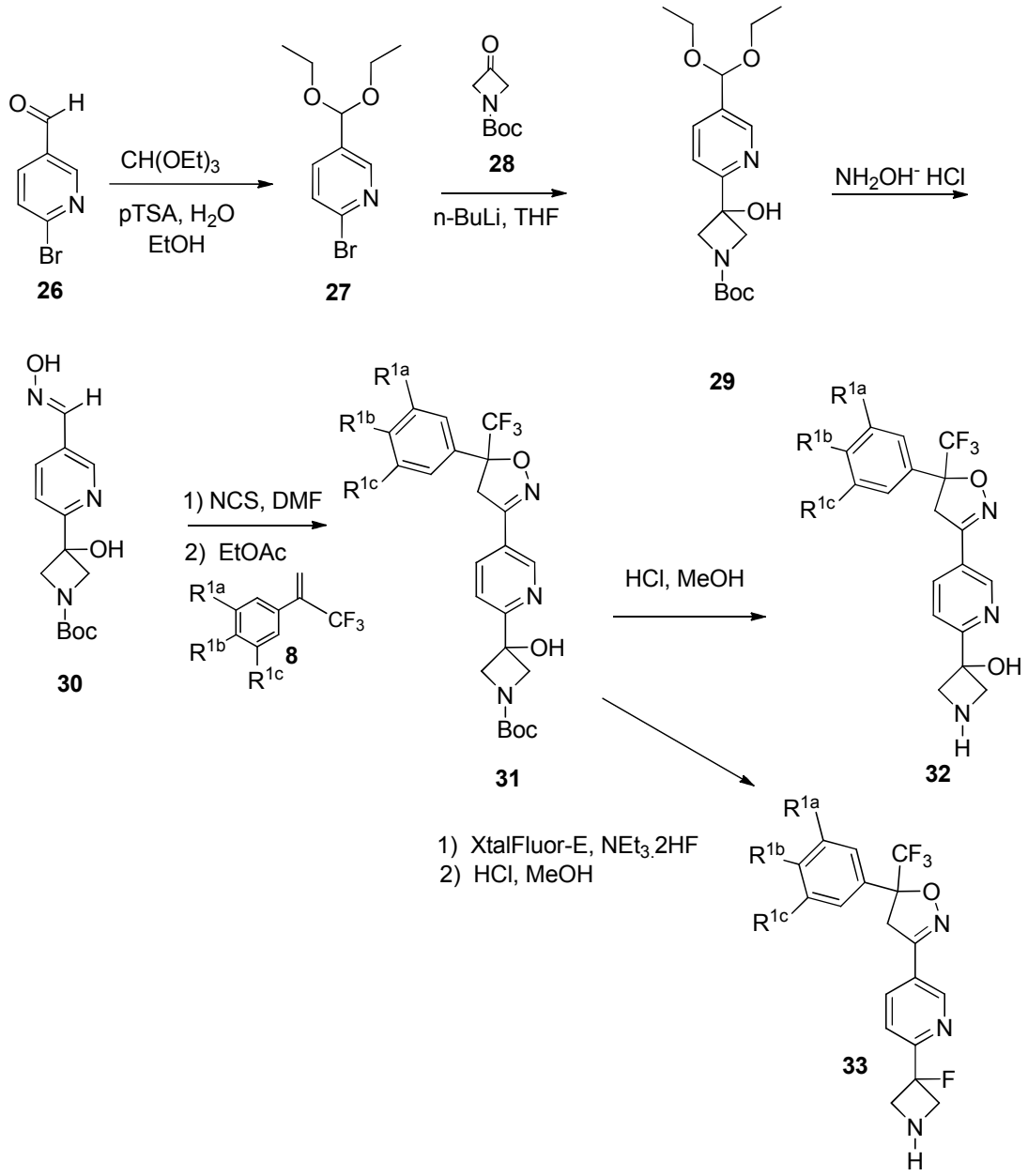
Esquema 5



R^{1a}, R^{1b} y R^{1c} son como se definen en el presente documento.

De una forma similar, los compuestos en los que el anillo central fenilo se reemplaza con grupos arilo o heteroarilo condensados pueden prepararse como se muestra en el Esquema 5 para la serie naftilo. Las naftil azetidinas deseadas pueden prepararse a partir de 1-bromo-4-metilnaftaleno como se muestra en el Esquema 5. El intercambio de halógeno-metales o la formación del reactivo de Grignard del bromonaftaleno **20** proporcionan el anión de naftilo que puede condensarse con cetoazetidina **2** para dar la naftil azetidina **21.** La fluoración del alcohol resultante puede realizarse por tratamiento con BAST, DAST o Xtafluor-E para dar la fluoroazetidina **22.** La bromación del grupo metilo seguido de hidroxilación y oxidación proporciona el aldehído deseado **24** que puede experimentar la formación, cloración y ciclación de oxima como se describe en el Esquema 2 para proporcionar las isoxazolinas **25.**

Esquema 6

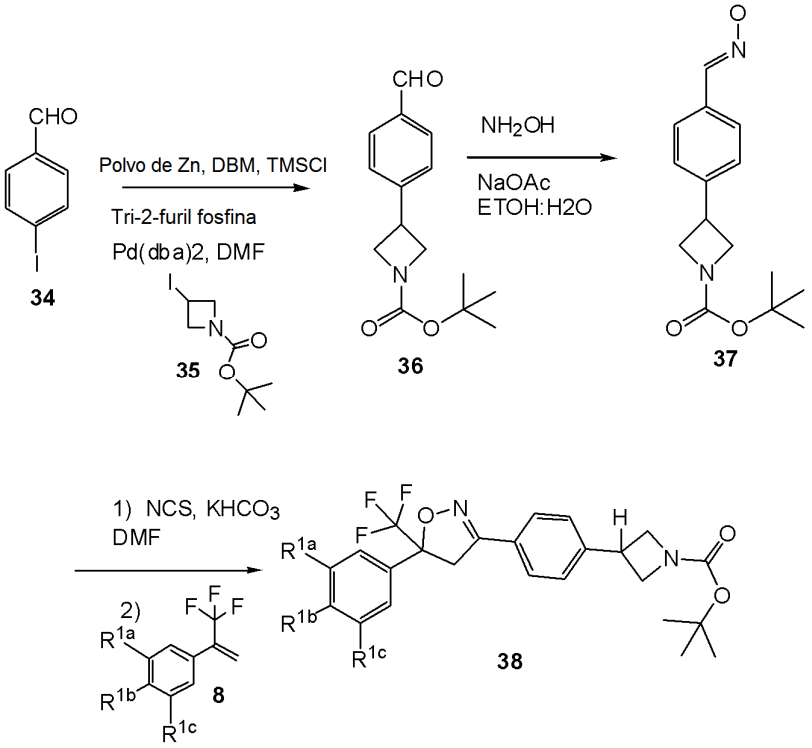


R^{1a}, R^{1b} y R^{1c} son como se definen en el presente documento.

Los compuestos en los que el anillo central fenilo se reemplaza con grupos heteroarilo pueden prepararse como se muestra en el Esquema 6 para

la serie piridilo. La formación del dietilacetal puede realizarse con formiato de etilo. El tratamiento de la yodopiridina **27** con *n*-BuLi proporciona el reactivo organometálico que se añade a la 3-azetidinona N-protegida **28.** La condensación del aldehído enmascarado resultante con hidroxilamina seguido de cloración y ciclación proporciona la isoxazolina **31.** El grupo protector benzhidrilo puede retirarse por hidrogenación o tratamiento con cloroformiato de cloroetilo para proporcionar la hidroxiazetidina **32** o como alternativa, la hidroxiazetidina **31** puede fluorarse por tratamiento con XtaFluor-E seguido de una desprotección similar para proporcionar la fluoroazetidina **33.**

Esquema 7

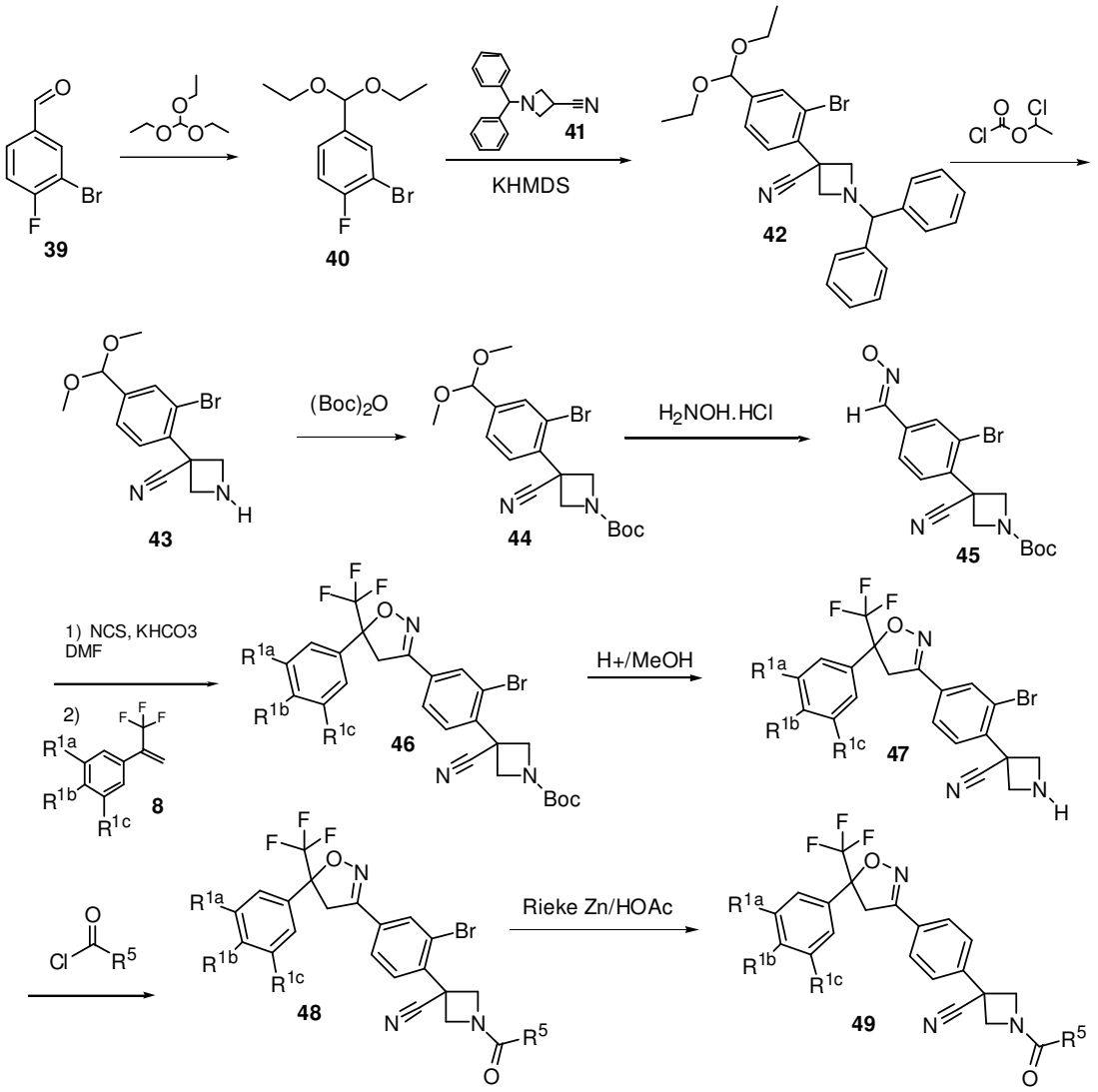


R^{1a}, R^{1b} y R^{1c} son como se definen en el presente documento.

El sustituyente en el anillo azetidina puede eliminarse como se muestra

en el Esquema 7. Una reacción de acoplamiento cruzado catalizado con paladio/cinc del yodoaldehído **34** con la yodoazetidina N-protegida **35** proporciona la fenil azetidina **36.** Este aldehído puede experimentar condensación con hidroxilamina, cloración y ciclación como se describe en el Esquema 2 para dar el compuesto hidruro **38.**

Esquema 8

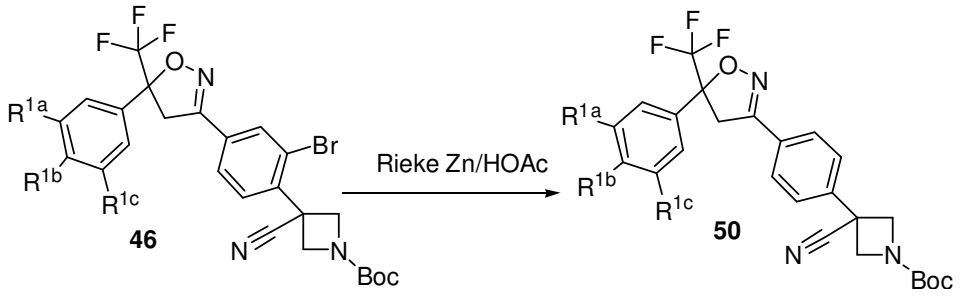


R^{1a}, R^{1b} y R^{1c} son como se definen en el presente documento.

La incorporación de un nitrilo como el sustituyente axial de la fluoroazetidina puede realizarse como se muestra en el Esquema 8. A partir del aldehído **39**, puede realizarse la formación del acetal con formiato de etilo. Después, el aril flúor puede experimentar desplazamiento por el anión de 1-benzhidrilazetidin-3-carbonitrilo para dar la fenilazetidina **42.** La desprotección

del grupo benzhidrilo seguido de protección de nuevo con Boc anhídrido proporciona la N-Boc fenilazetidina **44.** Este aldehído enmascarado puede experimentar condensación con hidroxilamina, cloración y ciclación como se describe en el Esquema 2 para dar las isoxazolinas **46.** La retirada del grupo protector Boc y la acilación de la amina resultante dan las amidas de isoxazolina **48.** El bromo en el anillo fenilo puede retirarse por tratamiento con Reike Zinc en ácido acético para dar las isoxazolinas **49.**

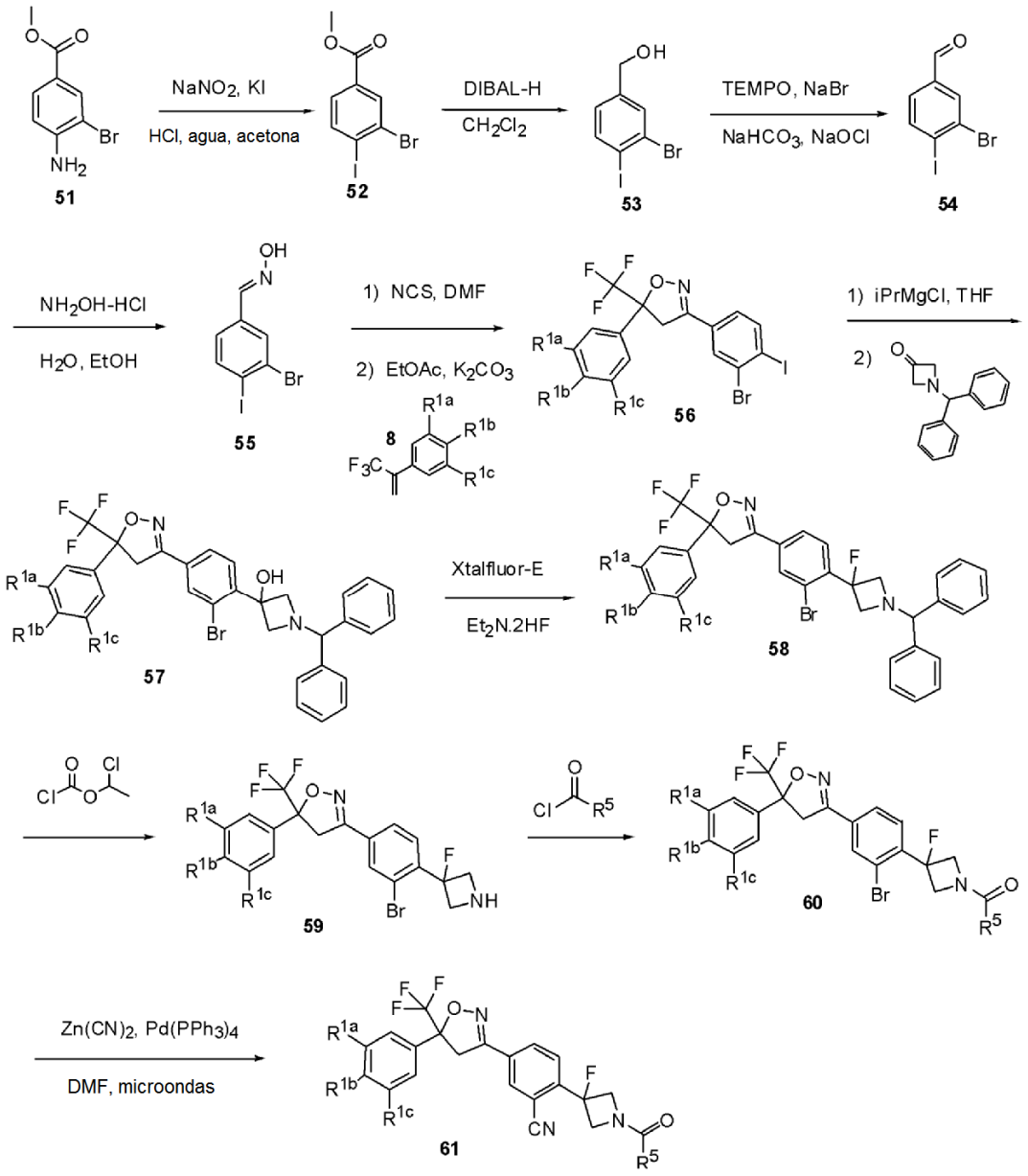
Esquema 9



R^{1a}, R^{1b} y R^{1c} son como se definen en el presente documento.

El bromo en el anillo fenilo puede retirarse en etapas anteriores en la secuencia para formar una plantilla susceptible de síntesis paralela de amidas, aminas, ureas y similares.

Esquema 10

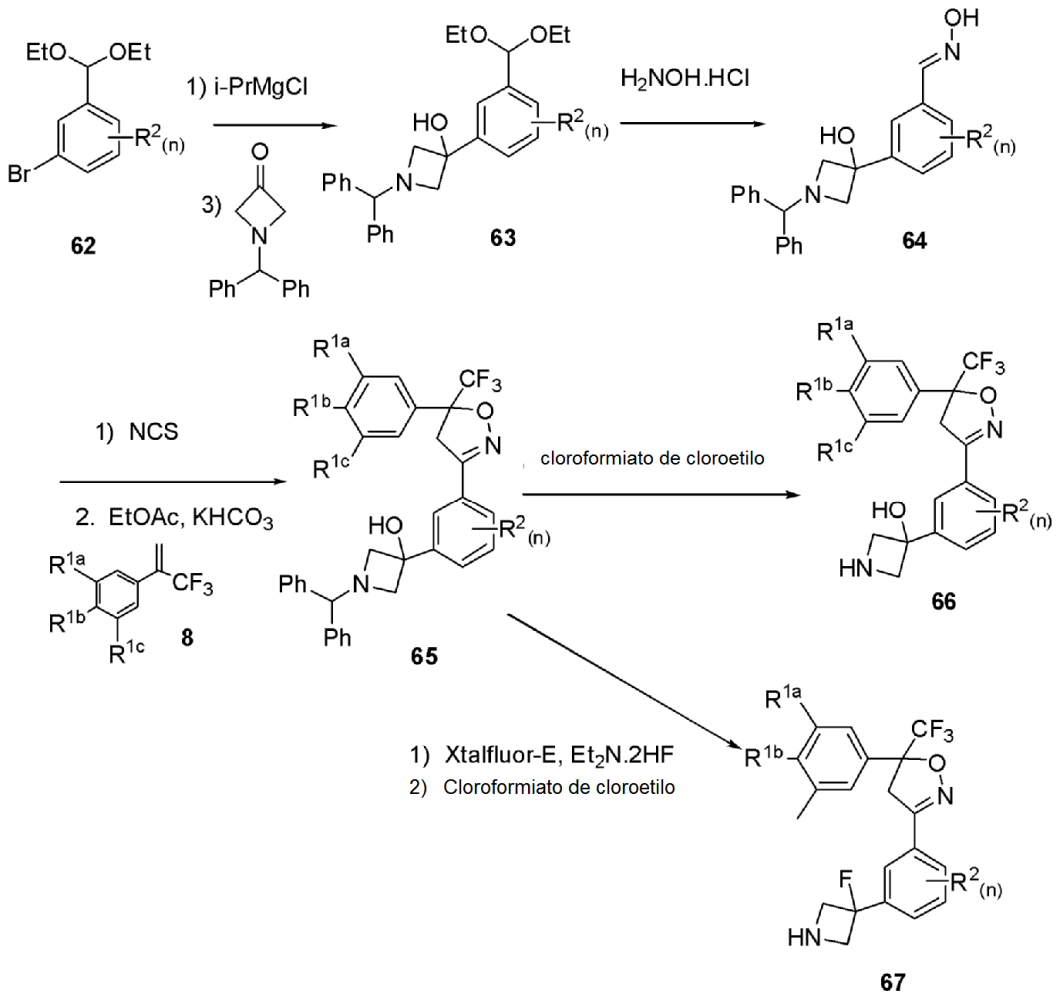


R^{1a}, R^{1b}, R^{1c} y R^5 son como se definen en el presente documento.

La identidad del sustituyente R^2 puede alterarse por la elección del material de partida o por la interconversión de sustituyentes en el anillo arilo

como se muestra en el Esquema 10. El éster de yodo **52** puede prepararse por tratamiento del amino éster **51** con nitrito sódico y yoduro potásico. La reducción del éster para dar el alcohol con hidruro de diisobutilaluminio seguido de oxidación con TEMPO proporciona el yodoaldehído **54.** Este aldehído puede experimentar condensación hidroxilamina, cloración y ciclación como se describe en el Esquema 2 para dar la isoxazolina **56.** La formación de Grignard usando iPrMgCl se da selectivamente con el yodo y el organometálico resultante se añade a la azetidinona N-protegida para proporcionar la fenilazetidina **57.** La fluoración de la azetidina puede realizarse con Xtafluor-E. La retirada del grupo protector benzhidrilo con cloroformiato de cloroetilo y la acilación de la amina resultante con cloruro de ácidos o anhídridos (o el acoplamiento con los ácidos orgánicos deseados) proporcionan las fenilazetidina amidas **60.** En este punto, el bromo del anillo fenilo puede experimentar interconversión en otros grupos funcionales (es decir nitrilo como se muestra) por acoplamientos cruzados catalizados por metales. Como alternativa, **58** puede convertirse en un nitrilo a través de una reacción de acoplamiento cruzado con paladio seguido de protección y acilación de benzhidral para formar los productos finales **61.**

Esquema 11

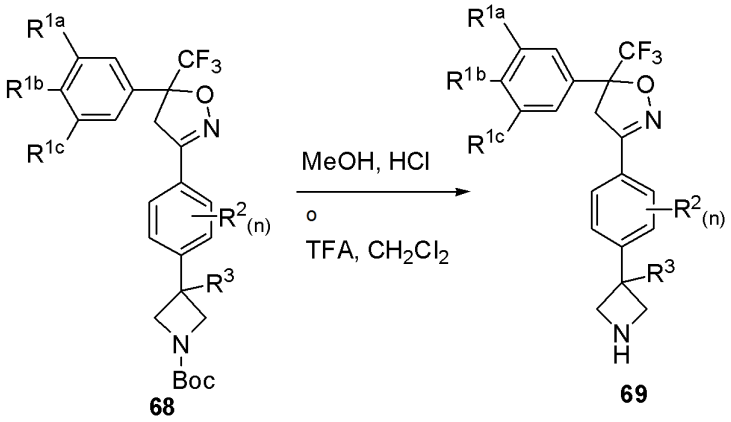


R^{1a}, R^{1b}, R^{1c}, R^2 y n son como se definen en el presente documento.

Los análogos en los que el anillo azetidina está en la posición meta con respecto a la isoxazolina puede prepararse a partir de derivados de 3-bromobenzaldehído como se muestra en el Esquema 11. El tratamiento del bromoaldehído **62** con i-PrMgCl proporciona el reactivo organometálico que se añade a la azetinona N-protegida para proporcionar la hidroxiazetidina **63.** Este aldehído enmascarado puede experimentar condensación con hidroxilamina,

cloración y ciclación como se describe en el Esquema 2 para proporcionar la isoxazolina **65.** La desprotección o la fluoración con cloroformiato de cloroetilo seguido de desprotección proporcionan las aminas requeridas (**66** y **67**) que pueden funcionalizarse para dar las amidas, ureas, aminas y sulfonamidas deseadas como se describe a continuación.

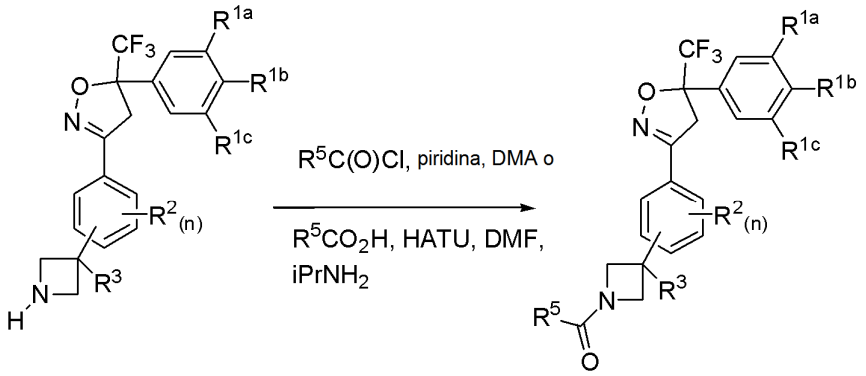
Esquema 12



R^{1a}, R^{1b}, R^{1c}, R^2, R^3 y n son como se definen en el presente documento.

La retirada del grupo protector Boc en las azetidinas en los esquemas anteriores (por ejemplo, las estructuras **9, 25, 38, 50**) puede realizarse por tratamiento con HCl en metanol o con ácido trifluoroacético en diclorometano.

Esquema 13

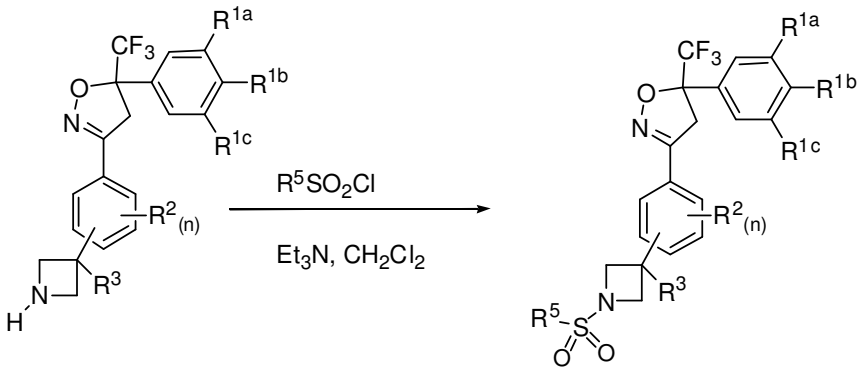


70 **71**

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^5 y n son como se definen en el presente documento.

Los análogos de amida del anillo azetidina pueden prepararse como se muestra en el Esquema 13. La acilación del anillo azetidina puede realizarse por reacción de la azetidina **70** con un cloruro de ácido en piridina/DMA o mediante una condensación con un ácido carboxílico usando un agente de condensación, tal como HATU o HOBt.

Esquema 14

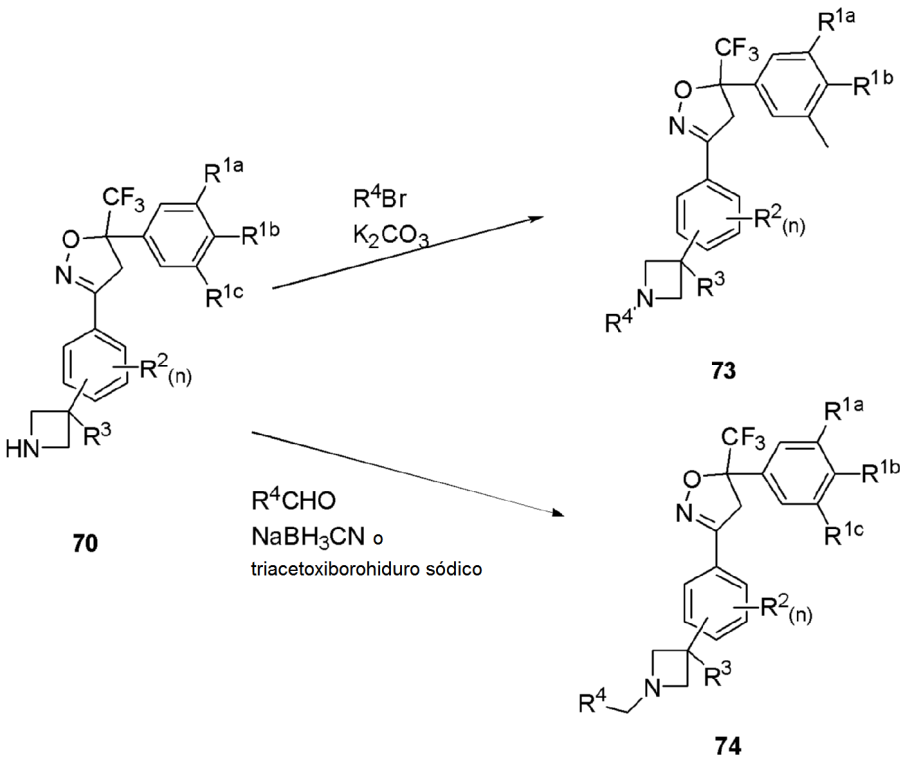


70 **72**

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^5 y n son como se definen en el presente documento.

Los análogos de sulfonamida del anillo azetidina pueden prepararse como se muestra en el Esquema 14. La reacción de azetidina **70** con cloruros de sulfonilo en presencia de trietilamina puede dar las sulfonamidas deseadas.

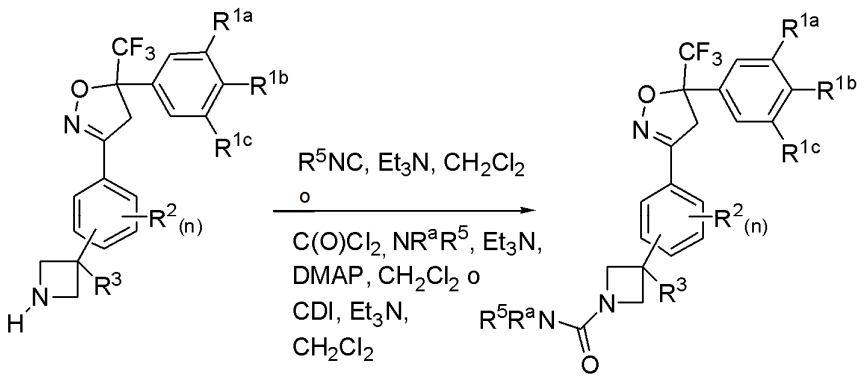
Esquema 15



R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4 y n son como se definen en el presente documento.

Los compuestos en los que R^4 es alquilo o alquilo sustituido pueden prepararse a partir de la azetidina **70** mediante química de alquilación convencional o por aminación reductora con los aldehídos correspondientes como se muestra en el Esquema 15.

Esquema 16

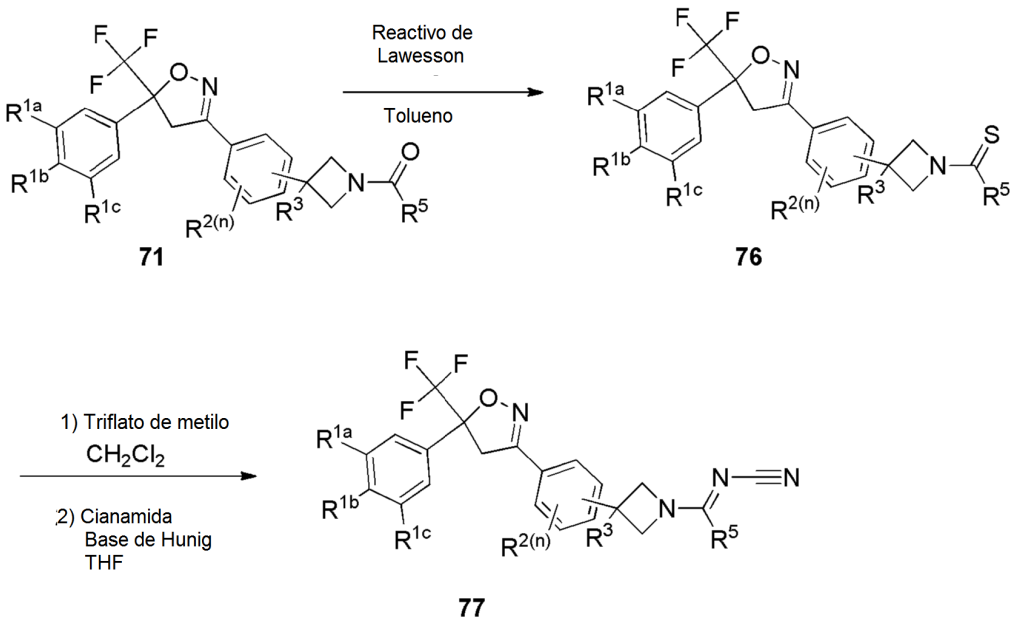


70 **75**

R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^a, R^5 y n son como se definen en el presente documento.

Los análogos de urea pueden prepararse como se muestra en el Esquema 16. La reacción de la azetidina **70** con un isocianato o cloruro de carbamoílo preformado en presencia de una base de amina terciaria proporciona las ureas.

Esquema 17



71 **76** **77**

La tioamida **76** puede prepararse por tratamiento de la amida **71** con el reactivo de Lawesson en tolueno a reflujo. Puede añadirse triflato de metilo a la tioamida **76** en un disolvente, tal como CH_2Cl_2 para formar un intermedio de tioimidato en forma de una solución. La cianamida y la base de Hunig en THF pueden añadirse posteriormente directamente a la solución de tioimidato para proporcionar la cianamida **77.**

Un experto en la materia reconocerá que, en algunos casos, después de la introducción de un reactivo dado como se representa en los esquemas, puede ser necesario realizar etapas sintéticas de rutina adicionales no descritas en detalle para completar la síntesis de compuestos de Fórmula (1) o Fórmula (XX).

La presente invención incluye todos los compuestos de Fórmula (1) y Fórmula (XX) marcados con isótopos veterinariamente aceptables en las que uno o más átomos se reemplazan por átomos que tienen el mismo número

atómico, pero una masa atómica o número másico diferente de la masa atómica o número másico que se encuentra normalmente en la naturaleza.

Ejemplos de isótopos adecuados para su inclusión en los compuestos de la presente invención incluyen isótopos de hidrógeno, tales como ^{2}H y ^{3}H, carbono, tales como ^{11}C, ^{13}C y ^{14}C, cloro, tales como ^{36}Cl, flúor, tales como ^{18}F, yodo, tales como ^{123}I e ^{125}I, nitrógeno, tales como ^{13}N y ^{15}N, oxígeno, tales como ^{15}O, ^{17}O y ^{18}O, y azufre, tales como ^{35}S.

El experto en la materia apreciará que los compuestos de la presente invención pueden fabricarse mediante procedimientos distintos de los que se describen en el presente documento que se incorporan en el presente documento por referencia, mediante la adaptación de los procedimientos descritos en el presente documento y/o la adaptación de los procedimientos conocidos en la técnica, por ejemplo la técnica descrita en el presente documento, o usando libros de texto convencionales, tales como "Comprehensive Organic Transformations-A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 o ediciones posteriores).

Los compuestos de Fórmula (1) y Fórmula (XX) son útiles como agentes ectoparasitarios y endoparasitarios, por lo tanto otra realización de la presente invención es una composición veterinaria farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de Fórmula (1) o Fórmula (XX), estereoisómero del mismo y un excipiente, diluyente o vehículo veterinariamente o farmacéuticamente aceptable. Los compuestos de la presente invención (incluyendo las composiciones y procedimientos usados en ella) también pueden usarse en la preparación de un medicamento para las aplicaciones terapéuticas descritas en el presente documento.

Una formulación típica se prepara mezclando un compuesto de Fórmula (1) o Fórmula (XX) con un vehículo, diluyente o excipiente. Los vehículos, diluyentes o excipientes adecuados se conocen bien para los expertos en la materia e incluyen materiales tales como carbohidratos, ceras, polímeros solubles y/o hinchables en agua, materiales hidrófilos o hidrófobos, gelatina, aceites, disolventes, agua y similares. El vehículo, diluyente o excipiente particular usado dependerá del medio y fin para el que se aplica el compuesto de la presente invención. Los disolventes se seleccionan generalmente basándose en disolventes reconocidos por los expertos en la materia como seguros para administrarse a un animal. Las formulaciones también pueden incluir uno o más tampones, agentes estabilizantes, tensioactivos, agentes humectantes, agentes lubricantes, emulsionantes, agentes de suspensión, conservantes, antioxidantes, agentes opacificantes, emolientes, adyuvantes de procesamiento, colorantes, edulcorantes, agentes perfumantes, agentes saporíferos y otros aditivos conocidos para proporcionar una presentación elegante del fármaco (es decir, un compuesto de la presente invención o composición veterinaria del mismo) o ayudar en la preparación del producto veterinario o farmacéutico (es decir, medicamento).

Las formulaciones pueden prepararse usando procedimientos de disolución y mezclado convencionales. Tales composiciones y procedimientos para su preparación pueden encontrarse, por ejemplo en 'Remington's Veterinary Sciences', 19ª Edición (Mack Publishing Company, 1995; y "Veterinary Dosage Forms: Tablets, Vol. 1", por H. Lieberman y L. Lachman, Marcel Dekker, N. Y., 1980 (ISBN 0-8247-6918-X). Por ejemplo, la sustancia farmacológica a granel (es decir, compuesto de la presente invención o forma

estabilizada del compuesto (por ejemplo, complejo con un derivado de ciclodextrina u otro agente de formación de complejos conocido)) se disuelve en un disolvente adecuado en presencia de uno o más excipientes adicionales. Los compuestos de la presente invención se formulan normalmente en formas de dosificación veterinarias o farmacéuticas para proporcionar una forma de dosificación fácilmente controlable para administración. Los compuestos de la presente invención también pueden mezclarse con pienso animal.

Los compuestos pueden administrarse solos o en una formulación apropiada para el uso específico previsto, la especie de animal huésped particular a tratar y el parásito implicado. Generalmente se administrarán como una formulación en asociación con una o más sales, excipientes, diluyentes o vehículos farmacéuticamente o veterinariamente aceptables. El término “excipiente”, “diluyente” o “vehículo” se usa en el presente documento para describir cualquier ingrediente distinto de los compuestos de Fórmula (1) o Fórmula (XX) o cualquier agente antiparasitario adicional. La selección de excipiente, diluyente o vehículo dependerá en gran medida de factores tales como el modo particular de administración, el efecto del excipiente, vehículo o diluyente en la solubilidad y estabilidad, la naturaleza de la forma de dosificación y la especie animal.

Los procedimientos por los que los compuestos de la presente invención pueden administrarse incluyen administración oral, tópica e inyectable (subcutánea, intraperitoneal e intramuscular). El procedimiento preferido de administración de los compuestos de Fórmula (1) o Fórmula (XX) es en forma de dosificación sólida oral o forma de dosificación líquida oral. Se prefiere igualmente la administración tópica.

Los compuestos de Fórmula (1) o Fórmula (XX) pueden administrarse por vía oral mediante cápsula, embolada, comprimido, polvos, pastillas, pastillas masticables, multi y nanoparticulados, geles, solución sólida, películas, pulverizaciones, forma líquida o mezclados con la comida. La administración oral es el procedimiento preferido de administración y como tal es deseable desarrollar compuestos de Fórmula (1) o Fórmula (XX) activos que sean particularmente adecuados para tales formulaciones. Tales formulaciones pueden emplearse como rellenos en cápsulas duras o blandas, comprimidos o caramelos masticables y normalmente comprenden un vehículo, por ejemplo, agua, etanol, polietilenglicol, N-metilpirrolidiona, propilenglicol, metilcelulosa o un aceite adecuado y uno o más agentes emulsionantes y/o agentes de suspensión. Las formas líquidas incluyen suspensiones, soluciones, jarabes, pociones y elixires. Las formulaciones líquidas también pueden prepararse por la reconstitución de un sólido, por ejemplo, a partir de un sobre. Las pociones orales se preparan habitualmente disolviendo o suspendiendo el principio activo en un medio adecuado. Pueden prepararse mezclas de pienso para ganado y peces. Las formulaciones orales pueden comprender de aproximadamente 0,5 mg/kg a 50 mg/kg de un compuesto de Fórmula (1) o Fórmula (XX) y preferentemente aproximadamente de 1 mg/kg a 30 mg/kg de un compuesto de Fórmula (1) o Fórmula (XX). Dependiendo de la especie huésped tratada y el parásito que se trata, pueden realizarse ajustes de dosis.

Los compuestos pueden administrarse por vía tópica a la piel o la mucosa es decir por vía dérmica o transdérmica. Este es un procedimiento preferido de administración y como tal es deseable desarrollar compuestos de Fórmula (1) o Fórmula (XX) activos que sean particularmente adecuados para

tales formulaciones, por ejemplo, formas líquidas. Las formulaciones típicas para este fin incluyen epicutáneas, de punteado, de multipunteado, en franjas, en crestas, extensión en rodillo, inmersión, pulverización, cremas, champú, formulación el polvo, geles, hidrogeles, lociones, soluciones, espuma cremosa, pomadas, polvos de uso externo, apósitos, espumas, películas, parches cutáneos, obleas, implantes, esponjas, fibras, vendas y microemulsiones. También pueden usarse liposomas. Los vehículos típicos incluyen alcohol, agua, aceite mineral, vaselina líquida, vaselina blanca, glicerina, N-metil formamida, glicol monometil éteres, polietilenglicol, propilenglicol y similares. Pueden incorporarse potenciadores de la penetración, véase, por ejemplo, J Pharm Sci, 88 (10), 955-958 por Finnin y Morgan (octubre de 1999). Las formulaciones epicutáneas o de punteado pueden prepararse disolviendo los principios activos en un vehículo transportador líquido aceptable tal como butil digol, parafina líquida o un éster no volátil, opcionalmente con la adición de un componente volátil tal como propan-2-ol o un glicol éter. Como alternativa, las formulaciones epicutáneas, de punteado o pulverización pueden prepararse por encapsulación, para dejar un resto de agente activo en la superficie del animal. Este efecto puede asegurar que los compuestos de Fórmula (1) o Fórmula (XX) tengan persistencia aumentada de acción y sean más duraderos, por ejemplo pueden ser más resistentes al agua. Las formulaciones tópicas de la combinación contemplada en el presente documento pueden comprender de aproximadamente 0,5 mg/kg a 50 mg/kg de un compuesto de Fórmula (1) y preferentemente de aproximadamente 1 mg/kg a 10 mg/kg de un compuesto de Fórmula (1) o Fórmula (XX). Las composiciones adecuadas para la aplicación del punteo de acuerdo con la invención pueden prepararse por medios de

mezcla convencionales. El volumen de la composición aplicada puede ser de aproximadamente 0,5 ml/kg a 5 ml/kg y preferentemente de aproximadamente 1 ml/kg a 3 ml/kg. De forma similar, puede ajustarse la dosis.

Los compuestos de la presente invención también pueden administrarse por vía tópica mediante una matriz de soporte, por ejemplo, una resina sintética o natural, plástico, tela, cuero u otro sistema polimérico tal en forma de un collar o marca auricular. Dicho collar o marca auricular puede estar revestido, impregnado, estratificado, por cualquier medio de modo que proporcione una cantidad veterinariamente o farmacéuticamente aceptable de un compuesto de la presente invención solo o con un excipiente, diluyente o vehículo veterinariamente o farmacéuticamente aceptable y opcionalmente un agente veterinario adicional o sal veterinariamente o farmacéuticamente aceptable del mismo.

Pueden añadirse agentes a las formulaciones de la presente invención para mejorar la persistencia de tales formulaciones en la superficie del animal al que se aplican, por ejemplo para mejorar su persistencia en el pelaje del animal. Se prefiere particularmente incluir tales agentes en una formulación que va a aplicarse como una formulación epicutánea o de punteado. Los ejemplos de tales agentes incluyen copolímeros acrílicos y en particular copolímeros acrílicos fluorinados. Un reactivo adecuado particular es el reactivo de marca registrada “Foraperle” (Redline Products Inc, Texas, Estados Unidos). Ciertas formulaciones tópicas pueden incluir aditivos desagradables al gusto para minimizar la exposición oral.

Pueden prepararse formulaciones inyectables en forma de una solución estéril, que pueden contener otras sustancias, por ejemplo suficientes sales o

glucosa para hacer a la solución isotónica con la sangre. Los vehículos líquidos aceptables incluyen aceites vegetales tales como aceite de sésamo, glicéridos tales como triacetina, ésteres tales como benzoato de bencilo, miristato de isopropilo y derivados de ácidos grasos de propilenglicol, así como disolventes orgánicos tales como pirrolidin-2-ona y formal de glicerol. Las formulaciones se preparan disolviendo o suspendiendo compuestos de la presente invención solos o con un agente veterinario adicional en el vehículo líquido de modo que la formulación final contenga de aproximadamente el 0,01 al 50 % en peso de los principios activos, preferentemente de aproximadamente el 0,01 % al aproximadamente 10 % en peso de los principios activos.

Los dispositivos adecuados para inyección incluyen inyectores de aguja (incluyendo microaguja), inyectores sin aguja y técnicas de infusión. Las formulaciones cutáneas son normalmente soluciones acuosas que pueden contener excipientes tales como sales, carbohidratos y agentes tamponantes (preferentemente a un pH de 3 a 9), pero, para algunas aplicaciones, pueden formularse de forma más adecuada como una solución no estéril o como una forma en polvo seco a usar junto con un vehículo adecuado tal como agua estéril sin pirógenos. La preparación de formulaciones subcutáneas en condiciones estériles, por ejemplo, por liofilización, puede conseguirse fácilmente usando técnicas veterinarias convencionales bien conocidas por los expertos en la materia. La solubilidad de los compuestos de Fórmula (1) o Fórmula (XX) usados en la preparación de soluciones subcutáneas puede aumentarse mediante el uso de técnicas de formulación apropiadas, tales como la incorporación de agentes potenciadores de la solubilidad.

Tales formulaciones se preparan de una manera convencional de

acuerdo con la práctica veterinaria o médica convencional. Además, estas formulaciones variarán con respecto al peso del compuesto activo contenido en ellas, dependiendo de la especie del animal huésped a tratar, la gravedad y el tipo de infección o infestación y el peso corporal del animal.

Para peces, los compuestos de la presente invención pueden formularse para administración oral mediante mezcla con el pienso. Por ejemplo, los compuestos de la presente invención pueden formularse en un producto alimentario (por ejemplo, gránulos) que pueden dispersarse fácilmente para los peces como un agente alimentario. Además, puede administrarse un compuesto de la presente invención por vía tópica sumergiendo al pez en un ambiente acuoso que contiene al menos uno de los compuestos de la presente invención. Por ejemplo, los peces pueden trasferirse a un tanque para tratamiento o hacer que pasen de una zona de retención a otra. Los compuestos de la presente invención también pueden administrarse directamente al agua que contiene los peces. El compuesto de la presente invención puede estar en cualquier formulación dispersable de modo que tras la introducción en el agua el compuesto se disuelva en la solución. Como alternativa, los compuestos de la presente invención pueden administrarse por inyección. Las vías de inyección preferibles para tratamiento de peces son intraperitoneal o intramuscular. Las formulaciones inyectables incluyen cualquier suspensión líquida, tales como soluciones oleosas, acuosas o emersiones oleosas o acuosas. Los compuestos de la presente invención también pueden coadministrarse con agentes, antígenos, adyuvantes, vehículos, diluyentes o nutrientes adicionales.

Los compuestos de Fórmula (1) y Fórmula (XX) también son activos

contra todas las etapas o etapas individuales del desarrollo de parásitos animales que muestran sensibilidad normal, así como los que muestran resistencia a parasiticidas usados ampliamente.

Como se describe en el presente documento, los compuestos de la presente invención pueden administrarse solos o en combinación con al menos un agente veterinario adicional que incluye insecticidas, acaricidas, antihelmínticos, fungicidas, nematocidas, antiprotozoarios, bactericidas y reguladores del crecimiento para formar un agente multicomponente que proporciona un espectro aún más amplio de utilidad veterinaria. Por lo tanto, la presente invención también se refiere a una composición que comprende una cantidad eficaz de un compuesto de Fórmula (1), un estereoisómero del mismo y una cantidad eficaz de al menos un agente veterinario adicional y puede comprender adicionalmente uno o más de un excipiente, diluyente o vehículo veterinariamente o farmacéuticamente aceptable.

Las siguiente lista de agentes veterinarios adicionales junto con los compuestos de la presente invención pueden usarse pretende ilustrar las posibles combinaciones, pero no imponer ninguna limitación. Los ejemplos no limitantes de agentes veterinarios adicionales incluyen: amitraz, arilpirazoles como se indica en las publicaciones WO1998/24767 y WO2005/060749, amino acetonitrilos, antihelmínticos (por ejemplo, albendazol, cambendazol, fenbendazol, flubendazol, mebendazol, octadepsipéptidos, oxfendazol, oxibendazol, parahercuamida (2-desoxoparahercuamida, dercuantel), parbendazol, piperazinas, pracicuantel, tiabendazol, tetramisol, triclabendazol, levamisol, pamoato de pirantel, oxantel, morantel y similares), indoxacarb y derivados del mismo, avermectinas (por ejemplo, abamectina, doramectina,

emamectina, eprinomectina, ivermectina, moxidectina, selamectina y similares), milbemicina, oxima de milbemicina, DEET, demiditraz, dietilcarbamazina, fipronil, reguladores del crecimiento de insectos (por ejemplo, hidropreno, quinopreno, metopreno, piriproxifeno y similares), metaflumizona, niclosamida, permetrina, piretrinas, espinosad y formamidinas (por ejemplo, demiditraz, amitraz y similares). En ciertos casos, combinaciones de un compuesto de Fórmula (1) o Fórmula (XX) con un agente o agentes veterinarios adicionales pueden dar como resultado un efecto mayor que el aditivo. Reducir la cantidad de principios activos liberados en el ambiente mientras se asegura el control eficaz del parásito siempre es deseable.

Puede ser deseable administrar un compuesto de la presente invención, estereoisómeros del mismo, solo o en una composición que comprende un excipiente, diluyente o vehículo veterinariamente aceptable, por ejemplo, para el fin de tratar una infección o infestación parasitaria particular o afección asociada con la misma. Está dentro del alcance de la presente invención que dos o más composiciones veterinarias, al menos una de las cuales contiene un compuesto de Fórmula (1) o Fórmula (XX) de acuerdo con la invención y la otra, un agente veterinario adicional, puedan combinarse convenientemente en forma de un kit adecuado para coadministración de las composiciones.

Los compuestos de la presente invención (incluyendo las composiciones y procedimientos usados en la misma) también pueden usarse en la preparación de un medicamento para las aplicaciones terapéuticas descritas en el presente documento.

Los compuestos de la presente invención, estereoisómeros de los mismos y composiciones que comprenden una cantidad terapéuticamente

eficaz de un compuesto de Fórmula (1) o Fórmula (XX) y un excipiente, diluyente o vehículo veterinariamente aceptable son útiles como parasiticidas (endo y ecto parásitos) para el control y tratamiento de infecciones o infestaciones manifestadas por dicho parásito en un animal. Los compuestos de la presente invención tienen utilidad como un ectoparasiticida, en particular, como un acaricida e insecticida. Pueden, en particular, usarse en los campos de medicina veterinaria, cría de ganado, piscifactoría y el mantenimiento de la salud pública: contra acáridos e insectos que son parásitos en vertebrados, particularmente vertebrados de sangre caliente, incluyendo animales de compañía, ganado y aves. Los compuestos de la presente invención son también parasiticidas para peces de sangre fría. Algunos ejemplos no limitantes de parásitos acáridos e insectos incluyen: garrapatas (por ejemplo, *Ixodes spp., Rhipicephalus spp., Boophilus spp., Amblyomma spp., Hyalomma spp., Haemaphysalis spp., Dermacentor spp., Ornithodorus spp.*, y similares); ácaros (por ejemplo, *Dermanyssus spp., Sarcoptes spp., Psoroptes spp., Chorioptes spp., Demodex spp.*, y similares); piojos masticadores y chupadores (por ejemplo, *Damalinia spp., Linognathus spp.*, y similares); pulgas (por ejemplo, *Siphonaptera spp., Ctenocephalidas spp.*, y similares); y moscas y mosquitos mordedores (por ejemplo, *Tabanidae spp., Haematobia spp., Stomoxys spp., Dermatobia spp., Simuliidae spp., Ceratopogonidae spp., Psychodidae spp.*, y similares). En otro ejemplo, pueden tratarse ectoparásitos del orden crustáceo copépodo, más particularmente del género Lepeophtheirus (especialmente el piojo del salmón, *Lepeoptheirus salmonis*) y/o Caligus (por ejemplo, *C. elongates*, *C.rogercreysii*, *C. teres*, *C. flexispina*, y similares), particularmente piojos marinos, con un compuesto de la presente invención. Los compuestos

de la invención también pueden usarse para el tratamiento de endoparásitos, por ejemplo, filarias, nemátodos, anquilostomas, tricocéfalos y céstodos.

Los compuestos de la presente invención y composiciones que comprenden compuestos de la presente invención junto con al menos un agente veterinario adicional son de particular valor en el control de ectoparásitos, endoparásitos e insectos que son perjudiciales para, o extienden o actúan como vectores de enfermedades en, animales. Los ectoparásitos, insectos y endoparásitos que pueden tratarse con una combinación de compuestos de Fórmula (1) o Fórmula (XX) y un agente veterinario adicional incluyen los que se han descrito anteriormente en el presente documento e incluyendo helmintos del filo platelmintos (por ejemplo, tremátodos, eucestoda y cestoda) y nematelmintos (por ejemplo, nemátodos).

Cualquiera de los compuestos de la presente invención, o una combinación adecuada de un compuesto de la presente invención y, opcionalmente, con al menos un agente veterinario adicional puede administrarse directamente al animal y/o indirectamente aplicándolo al ambiente local en el que resida el animal. La administración directa incluye poner en contacto con la piel, pelo o plumas de un sujeto animal o ave el compuesto o compuestos, por alimentación o inyectando los compuestos en el mamífero o el ave.

Los compuestos de Fórmula (1) o Fórmula (XX), estereoisómeros de los mismos y combinaciones con al menos un agente veterinario adicional, como se describe en el presente documento, son de valor para el tratamiento y control de las diversas etapas del ciclo de vida de los insectos y parásitos incluyendo etapas de huevo, ninfa, larva, juvenil y adulta.

La presente invención también se refiere a un procedimiento para administrar un compuesto de la presente invención solo o en combinación con al menos un agente veterinario adicional y opcionalmente un excipiente, diluyente o vehículo veterinariamente o farmacéuticamente aceptable, a animales con buena salud que comprende la aplicación a dicho animal para reducir o eliminar el potencial de infección o infestación parasitaria humana de parásitos portados por el animal y para mejorar el ambiente en el que el animal y el ser humano habitan.

Las reacciones expuestas a continuación se hicieron generalmente a una presión positiva de argón o nitrógeno o con un tubo de secado, a temperatura ambiente (a menos que se indique otra cosa), en disolventes anhidros, y los matraces de reacción se equiparon con un tapón de caucho para la introducción de sustratos y reactivos mediante una jeringa. Los objetos de cristal se secaron al horno y/o se secaron con calor. La cromatografía de cada fina analítica (TLC) se realizó usando placas con el fondo recubierto previamente con gel de sílice 60 F 254 y se eluyó con proporciones de disolvente apropiadas (v/v). Las reacciones se ensayaron por TLC o CLEM y terminaron como se determinó por el consumo del material de partida. La visualización de las placas TLC se hizo con luz UV (254 nM de longitud de onda) o con un disolvente de visualización de TLC apropiado y activado con calor. La cromatografía ultrarrápida en columna (Still y col., J. Org. Chem. 43, 2923, (1978) se realizó usando gel de sílice (RediSep Rf) o diversos sistemas de MPLC, tal como un sistema de purificación Biotage o ISCO.

Pueden usarse procedimientos y/o técnicas convencionales de separación y purificación conocidas por un experto en la técnica para aislar los

compuestos de la presente invención, así como los diversos intermedios relacionados con los mismos. Dichas técnicas serán bien conocidos por un experto en la técnica y pueden incluir, por ejemplo, todos los tipos de cromatografía (cromatografía líquida de alto rendimiento (HPLC), cromatografía en columna usando absorbentes comunes, tales como gel de sílice, y cromatografía de capa fina (TLC), recristalización y técnicas de extracción diferencial (es decir, líquido-líquido).

Las estructuras de compuestos en los ejemplos que se indican a continuación se confirmaron por uno o más de los siguientes procedimientos: espectroscopia de resonancia magnética de protones y espectroscopia de masas. Los espectros de resonancia magnética de protones (RMN ^{1}H) se determinaron usando un espectrómetro Bruker que funciona a una intensidad de campo de 400 megahertzios (MHz). Los desplazamientos químicos se indicaron en partes por millón (PPM, δ) campo abajo a partir de un patrón de tetrametilsilano interno. Los datos de espectros de masas (EM) se obtuvieron usando un espectrómetro de masas Agilent con ionización química a presión atmosférica. Procedimiento: Acquity HPLC con cromatografía realizada en una columna Waters BEH C18 (2,1 x 50 mm, 1,7 µm) a 50 ºC. La fase móvil será un gradiente binario de acetonitrilo (que contenía ácido trifluoroacético al 0,1 %) y agua (5-100 %).

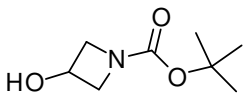
Las realizaciones de la presente invención se ilustran mediante los siguientes Ejemplos. Sin embargo, se entenderá que las realizaciones de la invención no se limitan a los detalles específicos de estos Ejemplos, ya que se conocerán otras variaciones de los mismos, o serán evidentes a la luz de la presente divulgación, para un experto en la técnica.

EJEMPLOS

Un experto en la técnica también reconocerá que los compuestos de Fórmula (1) o Fórmula (XX) y los intermedios descritos en el presente documento pueden someterse a diversas reacciones electrófilas, nucleófilas, radicales, organometálicas, de oxidación y reducción para añadir sustituyentes o modificar los sustituyentes existentes.

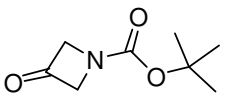
Los siguientes ejemplos proporcionan una descripción más detallada de las condiciones del procedimiento. Sin embargo, se entenderá que la invención, como se describe completamente en el presente documento y como se enumera en las reivindicaciones, no pretende limitarse por los detalles de los siguientes esquemas o modos de preparación.

Preparación 1: 3-hidroxiazetidin-1-carboxilato de *terc*-butilo



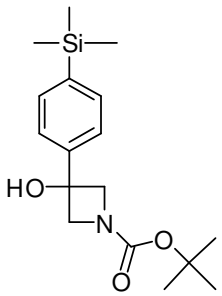
A una solución agitada fría (0 ºC) de clorhidrato de 3-hidroxiazetidina (75 g, 0,68 mol) en etanol (1300 ml) se le añadió trietilamina (208 g/280 ml, 2,05 mol) seguido de Boc_2O (164 g, 0,75 mol). La solución resultante se agitó a temperatura ambiente durante 16 horas. El análisis por CG/EM de la mezcla de reacción reveló la reacción completa. Los volátiles se retiraron al vacío, el residuo se diluyó con EtOAc (1300 ml) y se lavó con ácido cítrico al 10 % (700 ml), agua (700 ml) y salmuera (700 ml). Los extractos orgánicos se secaron sobre sulfato sódico, se filtraron y se concentraron, dando el producto deseado (100,8 g, rendimiento del 85 %). RMN ^1H ($CDCl_3$) δ 4,6 (m, 1 H), 4,2 (m, 2 H), 3,8 (m, 2 H), 1,4 (s, 9 H).

Preparación 2: 3-oxoazetidin-1-carboxilato de *terc*-butilo



Un matraz de 3 bocas de 5 l equipado con un agitador mecánico, un termopar, un embudo de adición y una entrada de nitrógeno se cargó con Py-SO_3 (277 g, 1,74 mol) y DMSO (900 ml) y se enfrió a 10 ºC en un baño de hielo. Se añadió TEA (177 g/244 ml, 1,74 mol). Se añadió lentamente mediante un embudo de adición una solución de 3 hidroxiazetidin-1-carboxilato de *terc*-butilo (Preparación 1, 100,8 g, 0,58 mol) en DMSO (500 ml) a 10 ºC. La reacción se agitó a temperatura ambiente durante una noche. El análisis por CG/EM de la mezcla de reacción reveló que la reacción se había completado. La reacción se interrumpió con salmuera (1 l). Los productos sólidos se filtraron y la fase acuosa se extrajo con acetato de etilo (3 x 1 l). Los extractos orgánicos combinados se lavaron con $NaHCO_3$ acuoso saturado (1,5 l) y salmuera (1,5 l), se secaron sobre sulfato sódico, filtraron y se concentraron, dando el producto deseado (94 g, rendimiento del 95 %). RMN ^1H ($CDCl_3$) δ 4,6 (s, 4 H), 1,4 (s, 9 H).

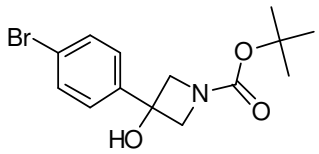
Preparación 3: 3-hidroxi-3-(4-(trimetilsilil)fenil)azetidin-1-carboxilato de *terc*-butilo



Un matraz de 3 bocas de 2 l equipado con un agitador mecánico, un termopar, un embudo de adición y una entrada de nitrógeno se cargó con (4-

bromofenil)trimetilsilano (80,4 g, 0,35 mol), THF (600 ml), Mg (8,5 g) e I_2 (cantidad catalítica). La suspensión se calentó a reflujo a 68 ºC durante 1,5 horas hasta que todo el magnesio desapareció. La solución se enfrió a 0 ºC en un baño de hielo. Después, se añadió lentamente mediante un embudo de adición una solución de 3-oxoazetidin-1-carboxilato de *terc*-butilo (Preparación 2, 30 g, 0,17 mol) en THF (200 ml). La solución se agitó a 0 ºC durante 3 horas. El análisis por CL/EM indicó la formación del producto deseado. La reacción se interrumpió con salmuera a 0 ºC. La fase acuosa se extrajo con EtOAc (2 x 800 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron, dando el producto deseado (47,4 g, rendimiento del 84 %). RMN ^{1}H ($CDCl_3$) δ 7,3 (d, 2 H), 7,2 (d, 2 H), 4,0 (d, 2 H), 3,9 (d, 2 H), 2,9 (s, 1 H), 1,2 (s, 9 H), 0,0 (s, 9 H).

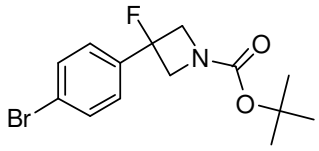
Preparación 4: 3-(4-bromofenil)-3-hidroxiazetidin-1-carboxilato de *terc*-butilo



Una mezcla de 3-hidroxi-3-(4-(trimetilsilil)fenil)azetidin-1-carboxilato de *terc*-butilo (Preparación 3, 45 g, 0,14 mol) y KBr (25 g, 0,21 mol) en ácido acético (1 l) y MeOH (100 ml) se calentó a 60 ºC durante 20 minutos. Después, a la mezcla de reacción se le añadió N-clorosuccinimida (22,4 g, 0,17 mol) y se agitó a 60 ºC durante 2 horas. El análisis por CL/EM indicó que la reacción se había completado (solo el pico de producto). Después de enfriar a temperatura ambiente, la mezcla se vertió en hielo-agua (1 l). La mezcla se extrajo con $CHCl_3$ (2 x 800 ml). Los extractos orgánicos combinados se lavaron con NaOH 3 M (2 x 600 ml), agua (600 ml), se secaron sobre sulfato sódico, se filtraron y

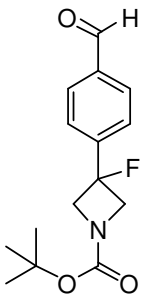
se concentraron. El producto en bruto se lavó con éter, proporcionando el producto deseado (35 g, rendimiento del 76 %). RMN ^{1}H ($CDCl_3$) δ 7,5 (d, 2 H), 7,4 (d, 2 H), 4,2 (s, 4 H), 3,4 (s, 1 H), 1,4 (s, 9 H).

Preparación 5: 3-(4-bromofenil)-3-fluoroazetidin-1-carboxilato de *terc*-butilo



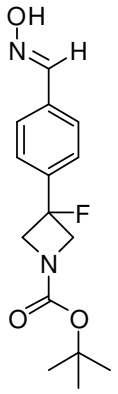
Se enfrió 3-(4-bromofenil)-3-hidroxiazetidin-1-carboxilato de *terc*-butilo (Preparación 4, 25 g, 0,076 mol) en CH_2Cl_2 (500 ml) a -78 ºC. A esta suspensión se le añadió lentamente BAST (20,2 g, 0,09 mol) mediante un embudo de adición. La temperatura de la reacción se elevó de -78 ºC a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante una noche. El análisis por CL/EM indicó que la reacción se había completado. La reacción se interrumpió con una solución acuosa saturada de $NaHCO_3$ (500 ml) y NaOH 1 M (500 ml). La fase acuosa se extrajo con CH_2Cl_2 (2 x 800 ml). Los extractos orgánicos combinados se lavaron con ácido cítrico acuoso (2 x 700 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron, proporcionando el producto deseado en forma de un sólido de color castaño (24,4 g, rendimiento del 97 %). RMN ^{1}H ($CDCl_3$) δ 7,5 (d, 2 H), 7,3 (d, 2 H), 4,4 (m, 2 H), 4,2 (m, 2 H), 1,4 (s, 9 H).

Preparación 6: 3-fluoro-3-(4-formilfenil)azetidin-1-carboxilato de *terc*-butilo



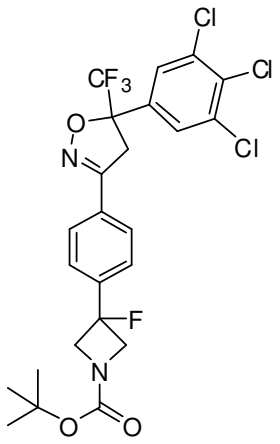
A una solución de 3-(4-bromofenil)-3-fluoroazetidin-1-carboxilato de *terc*-butilo (Preparación 5, 1,0 g, 3 mmol) en THF (10 ml) a -78 ºC se le añadió lentamente *n*-BuLi (2,1 ml de una solución 1,6 M en hexanos). La reacción se agitó a -78 ºC durante 15 minutos al mismo tiempo que se le añadió DMF (0,5 ml, 6 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora más. Se añadió NH_4Cl acuoso saturado (10 ml) y la fase acuosa se extrajo con éter (2 x 10 ml). Las fases orgánicas combinadas se secaron (Na_2SO_4) y se concentraron al vacío. El producto en bruto se sometió a cromatografía sobre sílice (columna de 12 g) usando un gradiente de EtOAc al 0-30 %/hexanos en una realización de 12 minutos. Rendimiento de 460 mg. Tiempo de reacción de CL/EM = 3,004 minutos; EM calculado para ($C_{15}H_{18}FNO_3$) 279,127, observado 180,2 M-BOC. RMN ^1H ($CDCl_3$) δ 10,0 (s, 1 H), 8,0 (d, 2 H), 7,7 (d, 2 H), 4,5 (m, 2 H), 4,2 (m, 2 H), 1,6 (s, 9 H).

Preparación 7: 3-fluoro-3-(4-((hidroxiimino)metil)fenil)azetidin-1-carboxilato de *terc*-butilo



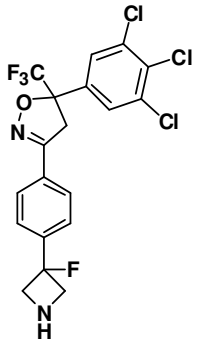
A una solución de 3-fluoro-3-(4-formilfenil)azetidin-1-carboxilato de *terc*-butilo (Preparación 6, 460 mg, 1,65 mmol) en etanol (30 ml) se le añadieron $NH_2OH \cdot HCl$ (127 mg, 1,8 mmol) y agua (2,5 ml). La solución se calentó a 50 ºC durante 1 hora y después se dejó en agitación a temperatura ambiente durante 2 horas. Los reactivos se concentraron al vacío para retirar el etanol. Al residuo restante se le añadió agua (5 ml) y se extrajo con EtOAc (2 x 10 ml). Las fases orgánicas combinadas se secaron (Na_2SO_4) y se concentraron al vacío, proporcionando el intermedio en forma de un sólido. Rendimiento 485 mg. RMN ^1H ($CDCl_3$) δ 8,17 (s, 1 H), 7,65 (d, 2 H), 7,50 (d, 2 H), 5,32 (s, 1 H), 4,37-4,50 (m, 2 H), 4,28 (m, 2 H), 1,45-1,55 (m, 9 H). Tiempo de retención de CL/EM = 2,926 minutos; EM calculado para ($C_{15}H_{19}FN_2O_3$) 294,13, observado 195,0 M-Boc.

Preparación 8: 3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxilato de *terc*-butilo



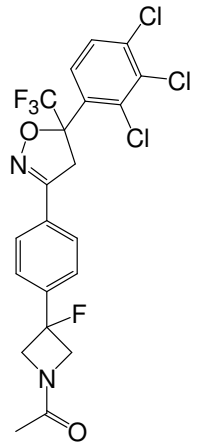
A una solución en DMF (8 ml) de 3-fluoro-3-(4-((hidroxiimino)metil)-fenil)azetidin-1-carboxilato de *terc*-butilo (Preparación 7, 486 mg, 1,65 mmol) se le añadió en dos porciones NCS (232 mg, 1,65 mmol) durante 10 minutos. La reacción se agitó a temperatura ambiente durante una noche. La reacción se diluyó con EtOAc (8 ml) y se añadió 1,2,3-tricloro-5-(1,1,1-trifluoroprop-2-en-2-il)benceno (546 mg, 1,98 mmol) seguido de bicarbonato potásico (248 mg, 2,48 mmol). La reacción se agitó a temperatura ambiente durante 3 días. La reacción se concentró al vacío. El residuo se repartió entre EtOAc (50 ml) y agua (50 ml). La fase acuosa se extrajo con EtOAc (3 x 50 ml). Las fases orgánicas combinadas se secaron y se condensaron. El material en bruto se absorbió sobre sílice y se sometió a cromatografía sobre una columna de sílice de 40 g eluyendo con un gradiente de EtOAc al 0 %-40 %/hexanos durante 20 minutos. Las fracciones que contenían el material deseado se combinaron y se concentraron, produciendo 526 mg de un sólido de color blanco. RMN ^{1}H ($CDCl_3$) δ 7,74 (d, 2 H), 7,67 (s, 2 H), 7,56 (d, 2 H), 4,39-4,51 (m, 2 H), 4,24 (m 2 H), 4,12 (d, 1 H), 3,72 (d, 1 H), 1,5 (s, 9 H).

Preparación 9: 3-(4-(3-fluoroazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol



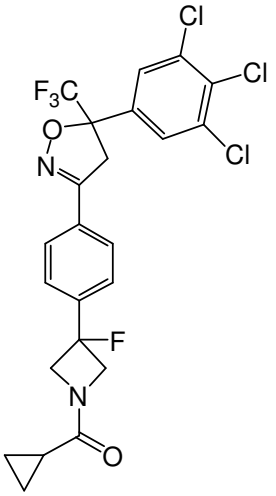
A una solución de 250 mg de 3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxilato de *terc*-butilo (Preparación 8) en 2 ml de CH_2Cl_2 se le añadió 1 ml de ácido trifluoroacético. La reacción se agitó durante una noche a una presión positiva de nitrógeno. La reacción se concentró. El residuo se repartió entre EtOAc y $NaHCO_3$ acuoso saturado. La fase acuosa se extrajo 2 veces con EtOAc (20 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se condensaron, produciendo 188 mg de una película. El análisis por TLC mostró muchas más puntos polares. El producto en bruto se llevó a las siguientes reacciones. EM calculado para ($C_{19}H_{13}Cl_3F_4N_2O$) 466,00, observado 467,9 M+H

Ejemplo 1: 1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona



A una solución de 3-(4-(3-fluoroazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 9, 94 mg) en 2 ml de CH_2Cl_2 se le añadió piridina (0,05 ml) seguido de cloruro de acetilo (31 mg). La reacción se dejó en agitación a temperatura ambiente durante 1 hora. Se añadió agua (3 ml). La reacción se diluyó con 3 ml de CH_2Cl_2, se agitó durante 30 minutos y se vertió a través de un extracto de fase. La fase de CH_2Cl_2 se recogió y se concentró. El producto en bruto de la reacción se absorbió sobre sílice y se sometió a cromatografía sobre una columna de sílice de 12 g eluyendo con un gradiente de EtOAc al 50 %/hexanos a EtOAc al 100 %/hexanos, produciendo 90 mg del compuesto deseado en forma de una espuma de color blanco. RMN ^1H ($CDCl_3$) δ 7,76 (d, 2 H). 7,67 (s, 2 H), 7,56 (d, 2 H), 4,71-4,31 (m, 4 H), 4,12 (d, 1 H), 3,72 (d, 1 H), 2,01 (s, 3 H). Tiempo de retención de CL/EM = 3,591 minutos; EM calculado para ($C_{21}H_{15}Cl_3F_4N_2O_2$) 509,714, observado 511 M+H.

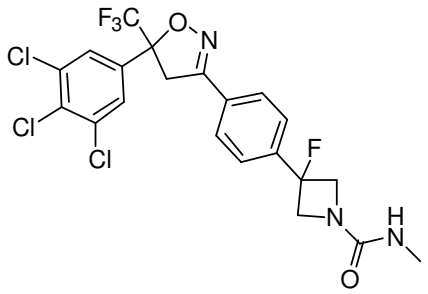
Ejemplo 2: ciclopropil(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona



A una solución del 3-(4-(3-fluoroazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 9, 94 mg) en 2 ml de CH_2Cl_2 se

le añadió piridina (0,05 ml) seguido de cloruro de ciclopropancarbonilo (31 mg). La reacción se dejó en agitación a temperatura ambiente durante 1 hora. Se añadió agua (10 ml). La reacción se diluyó con 10 ml más de CH_2Cl_2, se agitó durante 30 minutos a temperatura ambiente y después se pasó a través de un tubo de separación de fases. La fase de CH_2Cl_2 se recogió y se condensó. El material en bruto se absorbió sobre sílice y se sometió a cromatografía en una columna de sílice de 12 g, eluyendo con un gradiente de EtOAc al 20 %/hexano a EtOAc al 80 %/hexano. Las fracciones que contenían el material deseado se combinaron y se concentraron. A la película resultante se le añadió Et_2O (~½ ml). La colocación del matraz a alto vacío durante una noche dio como resultado la formación del producto en forma de una espuma de color blanco (87 mg). RMN ^1H ($CDCl_3$) δ ppm 7,76 (d, 2 H), 7,67 (s, 2 H), 7,58 (d, 2 H), 4,8-4,7 (m, 1 H), 4,6-4,2 (m, 3 H), 4,12 (d, 1 H), 3,72 (d, 1 H), 1,5-1,4 (m, 1 H), 1,08 (m, 2 H), 0,86 (m, 2 H). Tiempo de retención de CL/EM = 3,710 minutos, EM calculado para ($C_{23}H_{17}Cl_3F_4N_2O_2$) 534,03, observado 535,0 M+H.

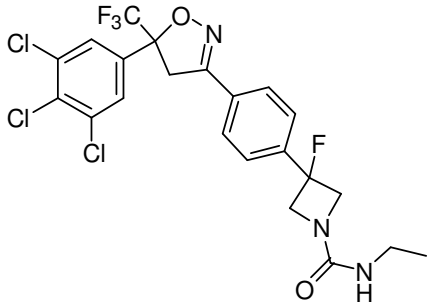
Ejemplo 3: 3-fluoro-N-metil-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida



El compuesto se preparó usando un procedimiento similar al del Ejemplo 2 usando isocianato de metilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 124 mg (94 %). RMN ^1H ($CDCl_3$) δ 7,73 (d, 2 H), 7,66 (s, 2 H),

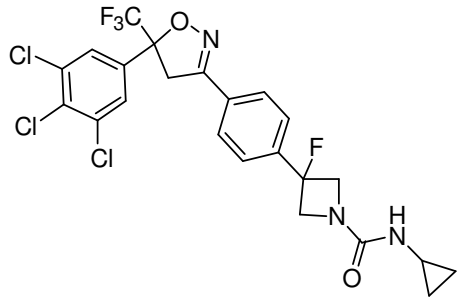
7,56 (d, 2 H), 4,49-4,40 (m, 2 H), 4,28-4,17 (m, 3 H), 4,10 (d, 1 H), 3,70 (d, 1 H), 2,86 (d, 3 H). Tiempo de retención de CL/EM = 3,559 minutos, EM calculado para ($C_{21}H_{16}Cl_3F_4N_3O_2$) 523,02, observado 524,0 M+H.

Ejemplo 4: N-etil-3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida



El compuesto se preparó usando un procedimiento similar al del Ejemplo 2 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 130 mg (96 %). RMN ^{1}H ($CDCl_3$) δ 7,73 (d, 2 H), 7,66 (s, 2 H), 7,56 (d, 2 H), 4,49-4,38 (m, 2 H), 4,27-4,15 (m, 3 H), 4,10 (d, 1 H), 3,70 (d, 1 H), 3,31 (m, 2 H), 1,18 (t, 3 H). Tiempo de retención de CL/EM = 3,638 minutos, EM calculado para ($C_{22}H_{18}Cl_3F_4N_3O_2$) 537,04, observado 538,0 M+H.

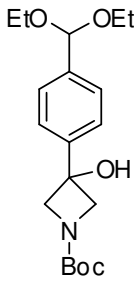
Ejemplo 5: N-ciclopropil-3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida



El compuesto se preparó usando un procedimiento similar al del Ejemplo 2 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo.

Rendimiento de 130 mg (94 %). RMN ^{1}H ($CDCl_3$) δ 7,73 (d, 2 H), 7,66 (s, 2 H), 7,56 (d, 2 H), 4,55-4,40 (m, 3 H), 4,28-4,19 (m, 2 H), 4,10 (d, 1 H), 3,70 (d, 1 H), 2,65 (m, 1 H), 0,78 (m, 2 H), 0,55 (m, 2 H). Tiempo de retención de CL/EM = 3,647 minutos, EM calculado para ($C_{23}H_{18}Cl_3F_4N_3O_2$) 549,04, observado 550,0 M+H.

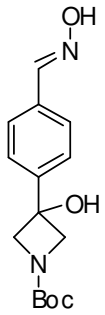
Preparación 10: 3-(4-(dietoximetil)fenil)-3-hidroxiazetidin-1-carboxilato de *terc*-butilo



Se suspendió cloruro de cerio (71,4 g, 290 mmoles) en tetrahidrofurano (600 ml), se calentó a 65 ºC durante 2,5 horas y después se enfrió a temperatura ambiente. En un matraz separado, se disolvió 4-bromobenzaldehído dietilacetal (100 g, 386 mmoles) en tetrahidrofurano (750 ml). Se añadieron limaduras de magnesio (5,9 g, 241 mmoles) y dibromoetano (0,5 ml) y la mezcla se calentó a reflujo durante 2,5 horas, hasta que todo el magnesio había reaccionado. El calentamiento se retiró y la solución de Grignard se enfrió en un baño de hielo. La suspensión de cloruro de cerio/tetrahidrofurano se enfrió en un baño de hielo a 0 ºC. La solución de Grignard se añadió en porciones y la mezcla se agitó a 0 ºC durante 45 minutos. Se añadió en porciones N-(t-butoxicarbonil)azetidinona (41,3 g, 241 mmoles) disuelta en tetrahidrofurano (200 ml) y la reacción se dejó en agitación a 0 ºC durante 30 minutos. La reacción se interrumpió con una solución

saturada de carbonato sódico (500 ml) y después se diluyó con acetato de etilo (2000 ml). La fase orgánica se lavó con agua (3 x 500 ml), se separó, se secó sobre sulfato de magnesio anhidro, se filtró y se evaporó a sequedad, dando un aceite de color amarillo que pesaba 120 g que se purificó usando cromatografía de fase normal (600 g de una columna de SiO_2, cargada como una solución en 25 ml de diclorometano, gradiente lineal de *terc*-butil metil éter al 10 % en *n*-heptano a *terc*-butil metil éter al 100 % durante 60 minutos, 150 ml/minutos, fracciones de 55 ml usando el método "Threshold OR Slope"), dando un aceite de color amarillo claro con un peso de 65 g, cuya RMN sugería que era el producto de acetal deseado. RMN ^{1}H ($CDCl_3$) δ ppm: 7,50 (4H), 5,50 (1H), 4,15 (2H), 4,30 (2H), 3,55 (4H), 1,50 (9H), 1,25 (6H); m/z (IEN) 252 $[M+H-Boc]^+$.

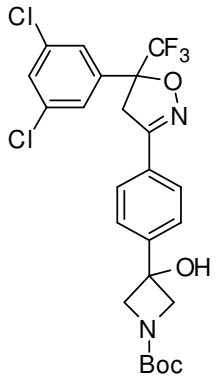
Preparación 11: (E) 3-hidroxi-3-(4-((hidroxiimino)metil)fenil)-azetidin-1-carboxilato de *terc*-butilo



El producto de la Preparación 10 (54 g, 195 mmoles) se disolvió en metanol (800 ml) y agua (400 ml). Se añadió en porciones clorhidrato de hidroxilamina (14 g, 200 mmoles) y la mezcla se agitó a temperatura ambiente durante 60 minutos. La mezcla de reacción se evaporó para retirar el exceso de metanol. El resto acuoso se extrajo con acetato de etilo (3000 ml), se separó, se secó sobre sulfato de magnesio anhidro, se filtró y se evaporó a sequedad, dando un jarabe espeso de color amarillo con un peso de 49 g. RMN ^{1}H

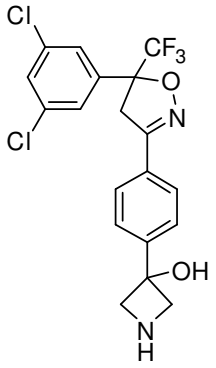
($CDCl_3$) δ ppm: 8,15 (1H), 7,60 (2H), 7,50 (2H), 4,20 (4H), 1,52 (9H); m/z (IEN) 193 $[M+H-Boc]^+$.

Preparación 12: 3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-carboxilato de *terc*-butilo



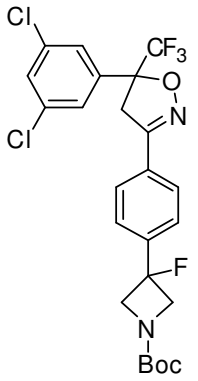
El producto de la Preparación 11 (56 g, 192 mmoles) se disolvió en acetato de etilo (1000 ml) y se agitó a temperatura ambiente. Se añadió en porciones N-clorosuccinimida (29,9 g, 224 mmoles). Después de 60 minutos, a la mezcla de reacción se le añadió bicarbonato potásico (57,5 g, 575 mmoles), agua (5 ml) y 1,3-dicloro-2-fluoro-5-(3,3,3-trifluoroprop-1-en-2-il)benceno (49,7 g, 192 mmoles). La mezcla se agitó durante una noche a temperatura ambiente. La reacción se interrumpió con agua (750 ml), se diluyó con acetato de etilo (1500 ml), las fases se agitaron para disolver todos los sólidos, la fase orgánica se secó sobre sulfato de magnesio anhidro, se filtró y se evaporó, dando una suspensión (aproximadamente 1 litro en volumen). Se añadieron hexanos (1 litro), la mezcla se agitó y se filtró, dando una torta de filtro de color blanco que se lavó con a 300 ml más de hexanos y se secó en la bomba, dando un sólido de color blanco con un peso de 52 g. RMN ^1H (DMSO-D6) δ ppm: 7,80 (2H), 7,75 (2H), 7,62 (2H), 4,32 (2H), 4,05 (4H), 1,40 (9H); m/z (IEN) 449 $[M+H-Boc]^+$, 547 $[M-H]^+$

Preparación 13: 3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol



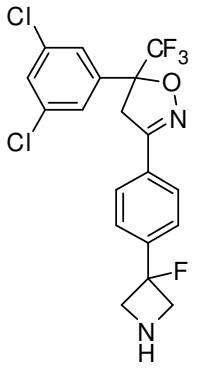
A una suspensión del producto de la Preparación 12 (52 g, 95 mmoles) en metanol (650 ml) se le añadió ácido clorhídrico acuoso concentrado (38 ml). La mezcla se calentó con agitación. A aproximadamente 50 ºC, la suspensión comenzó a disolverse-formando una solución a reflujo. Después del calentamiento a reflujo durante 2 horas, la reacción se enfrió a temperatura ambiente y se evaporó a presión reducida seguido de tolueno, dando un sólido de color blanco que se suspendió con tolueno (1000 ml) y se filtró a presión reducida. La torta de filtro se lavó con hexanos (500 ml) y después se secó en la estufa de vacío a 50 ºC, dando un sólido de color blanco con un peso de 42 g. RMN ^{1}H (DMSO-D6) δ ppm: 7,80 (6H), 4,30 (4H), 4,12 (2H); m/z (IEN) 449 $[M+H]^+$, 447 $[M-H]^+$

Preparación 14: 3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxilato de *terc*-butilo



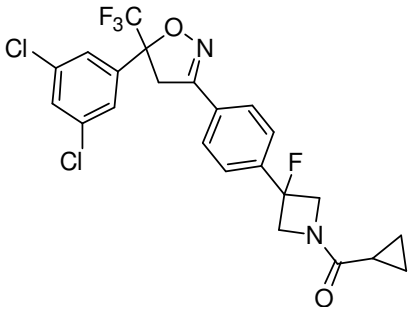
Referencia: J. Org. Chem. 2010, 75, 3401-3411. Se disolvió trifluorhidrato de trietilamina (5,3 g, 32,8 mmoles) en diclorometano (97 ml). Se añadió trietilamina (2,3 ml, 16,4 mmoles) y la solución se enfrió a -78 ºC. A la mezcla enfriada se le añadieron XtalFluor-E (5,6 g, 24,6 mmoles) y después el producto de la Preparación 12 (9 g, 16,4 mmoles). Esto dio como resultado una suspensión espesa. La refrigeración se retiró y la mezcla se dejó calentar a temperatura ambiente, con agitación. La suspensión se disolvió, dando una solución de color pardo claro. Después de agitar a temperatura ambiente, durante una noche, la reacción se interrumpió mediante la adición de una solución acuosa saturada de carbonato sódico (100 ml) y diclorometano (100 ml). Después, las capas se separaron. La fase orgánica se secó sobre sulfato de magnesio anhidro, se filtró y se evaporó a sequedad, dando un aceite de color pardo con un peso de 9 g. RMN ^{1}H ($CDCl_3$) δ ppm: 7,75 (2H), 7,60 (2H), 7,55 (2H), 4,45 (2H), 4,25 (2H), 4,15 (1H), 3,70 (1H), 1,50 (9H); m/z (IEN) 451 $[M+H\text{-}Boc]^+$, 549 $[M\text{-}H]^+$

Preparación 15: 5-(3,5-diclorofenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol



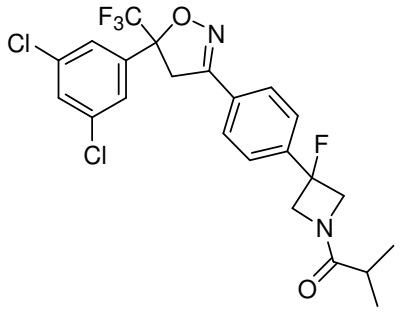
A una solución de 3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxilato de *terc*-butilo (Preparación 14) en metanol (10 ml) se le añadió una solución metanólica de HCl (10 ml de 1,25 M). La mezcla de reacción se calentó a 65 ºC durante 1,5 horas. La reacción se concentró mediante un evaporador rotatorio, produciendo un aceite viscoso. Se añadió CH_2Cl_2 y se formó un precipitado. Los volátiles se retiraron a presión reducida, produciendo 573 mg del compuesto del título en forma de un sólido de color blanco. RMN ^{1}H (DMSO-d_6) δ 9,8-9,6 (s a, 2 H) 7,9-7,8 (m, 3 H), 7,75 (d, 2 H), 7,63 (d, 2 H), 4,64-4,29 (m, 6 H).). Tiempo de retención de CL/EM = 3,039 minutos, EM calculado para ($C_{19}H_{14}Cl_2F_4N_2O$) 432,04, observado 433,0 M+H.

Ejemplo 6: ciclopropil(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona



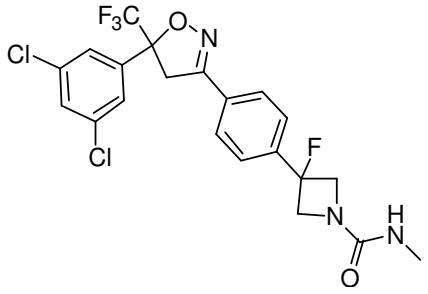
A una solución del 5-(3,5-diclorofenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 15, 65 mg) en 2 ml de CH_2Cl_2 se le añadió trietil amina (50 µl) seguido de cloruro de ciclopropancarbonilo (19 mg). La reacción se dejó en agitación a temperatura ambiente durante 30 minutos. Se añadió agua (5 ml). La reacción se diluyó con 5 ml más de CH_2Cl_2, se agitó durante 5 minutos a temp. ambiente y después se pasó a través de un tubo de separación de fases. La fase de CH_2Cl_2 se recogió y se condensó. El material en bruto se absorbió sobre sílice y se sometió a cromatografía en una columna de sílice de 12 g, eluyendo con un gradiente de acetato de etilo del 0 % al 100 % en heptano. Las fracciones que contenían el material deseado se combinaron y se concentraron. A la película resultante se le añadió Et_2O (~½ ml). Colocar el matraz a alto vacío durante una noche dio como resultado la formación de una espuma de color blanco. Rendimiento de 67 mg (98 %) del producto deseado. RMN ^1H ($CDCl_3$) δ ppm 7,76 (d, 2 H), 7,63-7,51 (s, 4 H), 7,45 (s, 1 H), 4,8-4,7 (m, 1 H), 4,6-4,3 (m, 3 H), 4,12 (d, 1 H), 3,74 (d, 1 H), 1,6-1,4 (m, 1 H), 1,07 (m, 2 H), 0,86 (m, 2 H). Tiempo de retención de CL/EM = 3,654 minutos, EM calculado para ($C_{23}H_{18}Cl_2F_4N_2O_2$) 500,07, observado 501,0 M+H.

Ejemplo 7: 1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona



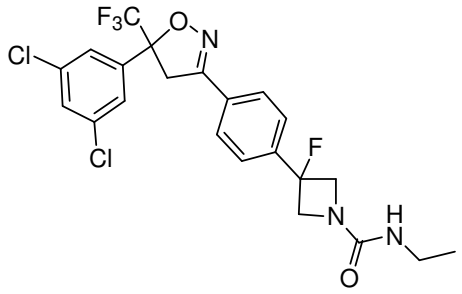
El compuesto se preparó usando un procedimiento similar al del Ejemplo 6 usando cloruro de isobutiroílo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 146 mg (95 %). RMN ^{1}H ($CDCl_3$) δ 7,76 (d, 2 H), 7,58-7,51 (m, 4 H), 7,45 (m, 1 H), 4,71-4,58 (m, 1 H), 4,56-4,32 (m 3 H), 4,12 (d, 1 H), 3,73 (d, 1 H), 2,53 (m, 1 H), 1,22-1,14 (m, 6 H). Tiempo de retención de CL/EM = 3,660 minutos, EM calculado para ($C_{23}H_{20}Cl_2F_4N_2O_2$) 502,08, observado 503,0 M+H.

Ejemplo 8: 3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida



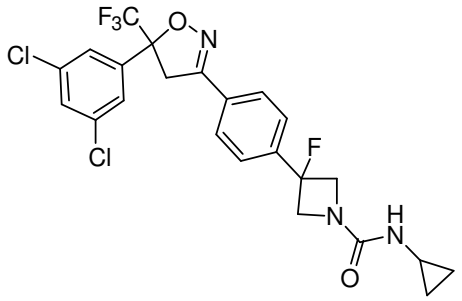
El compuesto se preparó usando un procedimiento similar al del Ejemplo 6 usando isocianato de metilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 118 mg (96 %). RMN ^{1}H ($CDCl_3$) δ 7,73 (d, 2 H), 7,61-7,51 (m, 4 H), 7,44 (m, 1 H), 4,50-4,39 (m, 2 H), 4,28-4,16 (m, 3 H), 4,10 (d, 1 H), 3,71 (d, 1 H), 2,87 (d, 3 H). Tiempo de retención de CL/EM = 2,965 minutos, EM calculado para ($C_{21}H_{17}Cl_2F_4N_3O_2$) 489,06, observado 490,0 M+H.

Ejemplo 9: 3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida



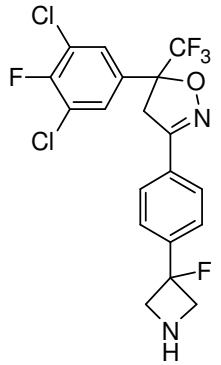
El compuesto se preparó usando un procedimiento similar al del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 123 mg (97 %). RMN ^{1}H ($CDCl_3$) δ 7,73 (d, 2 H), 7,59-7,50 (m, 4 H), 7,44 (m, 1 H), 4,50-4,38 (m, 2 H), 4,27-4,14 (m, 3 H), 4,10 (d, 1 H), 3,71 (d, 1 H), 3,31 (m, 2 H), 1,18 (t, 3 H). Tiempo de retención de CL/EM = 3,018 minutos, EM calculado para ($C_{22}H_{19}Cl_2F_4N_3O_2$) 503,08, observado 504,0 M+H.

Ejemplo 10: N-ciclopropil-3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida



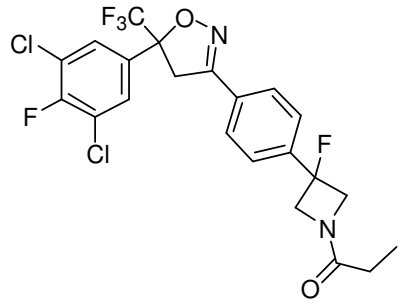
El compuesto se preparó usando un procedimiento similar al del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 124 mg (96 %). RMN ^{1}H ($CDCl_3$) δ 7,73 (d, 2 H), 7,58-7,51 (m, 4 H), 7,44 (m, 1 H), 4,55-4,39 (m, 3 H), 4,29-4,19 (m, 2 H), 4,10 (d, 1 H), 3,71 (d, 1 H), 2,65 (m, 1 H), 0,77 (m, 2 H), 0,55 (m, 2 H). Tiempo de retención de CL/EM = 3,026 minutos, EM calculado para ($C_{23}H_{19}Cl_2F_4N_3O_2$) 515,08, observado 516,0 M+H.

Preparación 16: 5-(3,5-dicloro-4-fluorofenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol



El producto se preparó de acuerdo con los procedimientos de la Preparación 12, 14 y 15 usando 1,3-dicloro-2-fluoro-5-(3,3,3-trifluoroprop-1-en-2-il)benceno. RMN ^{1}H (DMSO-d_6) δ 10,0-9,6 (s a, 2 H) 7,9-7,7 (m, 6 H), 4,68-4,24 (m, 6 H). Tiempo de retención de CL/EM = 3,020 minutos, EM calculado para ($C_{19}H_{13}Cl_2F_5N_2O$) 450,03, observado 450,9 M+H.

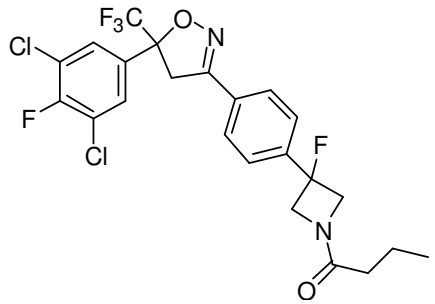
Ejemplo 11: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)propan-1-ona



El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando cloruro de propionilo en lugar de cloruro de ciclopropancarbonilo. RMN ^{1}H ($CDCl_3$) δ 7,74 (d, 2 H), 7,60 (d, 2 H), 7,54 (d, 2 H), 4,66-4,30 (m, 4 H), 2,22 (m, 1 H), 1,19 (m, 3 H). Tiempo de

retención de CL/EM = 3,611 minutos, EM calculado para ($C_{22}H_{17}Cl_2F_5N_2O_2$) 506,6, observado 507,0 M+H.

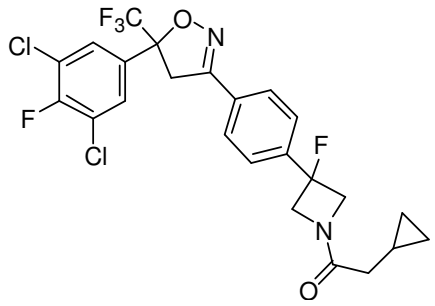
Ejemplo 12: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)butan-1-ona



A una solución de ácido butírico (50 mg) en DMF (5 ml) se le añadió HATU (200 mg) y después trietil amina (150 µl). La solución resultante se agitó a temperatura ambiente durante 15 minutos y después se añadió en una porción clorhidrato de 5-(3,5-dicloro-4-fluorofenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 16, 100 mg). La reacción se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró al vacío y el residuo se repartió entre agua (10 ml) y CH_2Cl_2 (10 ml). La fase orgánica se recogió y se condensó. El material en bruto se absorbió sobre sílice y se sometió a cromatografía en una columna de sílice de 12 g, eluyendo con un gradiente de acetato de etilo del 0 % al 100 % en heptano. Las fracciones que contenían el material deseado se combinaron y se concentraron. A la película resultante se le añadió Et_2O (~½ ml). Colocar el matraz a alto vacío durante una noche dio como resultado la formación de una espuma de color blanco. Rendimiento de 86 mg (80 %). RMN ^1H ($CDCl_3$) δ 7,75 (d, 2 H), 7,61 (d, 2 H), 7,55 (d, 2 H), 4,68-4,33 (m, 4 H), 4,12 (d, 1 H), 3,72 (d, 1 H), 2,19 (m, 2 H), 1,73 (m, 2 H), 1,01 (m, 3 H). Tiempo de retención de CL/EM

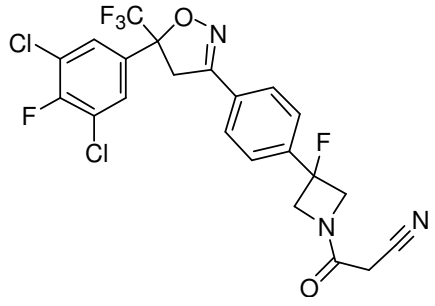
= 3,688 minutos, EM calculado para ($C_{23}H_{19}Cl_2F_5N_2O_2$) 520,07, observado 521,0 M+H.

Ejemplo 13: 2-ciclopropil-1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona



El compuesto se preparó a partir del compuesto de la Preparación 16 de acuerdo con el método del Ejemplo 12 usando ácido ciclopropil acético en lugar de ácido butírico. Rendimiento de 73 mg (67 %). RMN ^1H ($CDCl_3$) δ 7,74 (d, 2 H), 7,60 (d, 2 H), 7,54 (d, 2 H), 4,67-4,33 (m, 4 H), 4,10 (d, 1 H), 3,70 (d, 1 H), 2,03 (m, 2 H), 1,09 (m, 1 H), 0,61 (m, 2 H), 0,20 (m, 2 H). Tiempo de retención de CL/EM = 3,694 minutos, EM calculado para ($C_{24}H_{19}Cl_2F_5N_2O_2$) 532,07, observado 533,0 M+H.

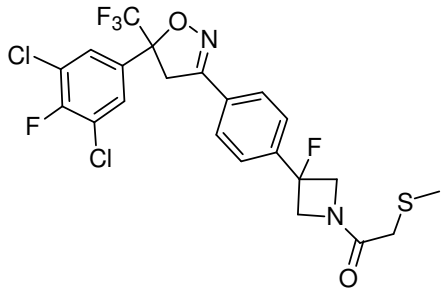
Ejemplo 14: 3-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-oxopropanonitrilo



El compuesto se preparó a partir del compuesto de la Preparación 16 de acuerdo con el método del Ejemplo 12 usando ácido cianoacético en lugar de

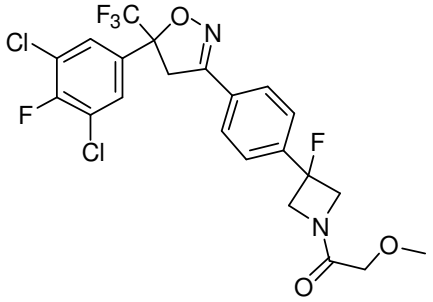
ácido butírico. Rendimiento de 88 mg (55 %). RMN ^{1}H ($CDCl_3$) δ 7,77 (d, 2 H), 7,60 (d, 2 H), 7,55 (d, 2 H), 4,79 (m, 1 H), 4,71-4,40 (m, 3 H), 4,11 (d, 1 H), 3,71 (d, 1 H), 3,40 (s, 2 H). Tiempo de retención de CL/EM = 3,533 minutos, EM calculado para ($C_{22}H_{14}Cl_2F_5N_3O_2$) 517,04, observado 539,9 M+H+Na^+.

Ejemplo 15: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona



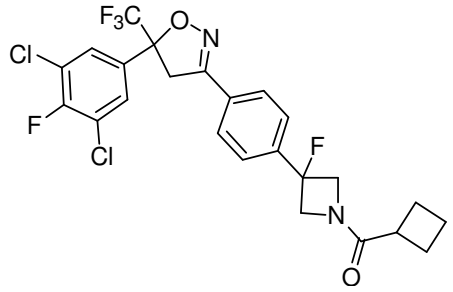
El compuesto se preparó a partir del compuesto de la Preparación 16 de acuerdo con el método del Ejemplo 12 usando ácido 2-(metiltio)acético en lugar de ácido butírico. Rendimiento de 208 mg (94 %). RMN ^{1}H ($CDCl_3$) δ 7,75 (d, 2 H), 7,60 (d, 2 H), 7,55 (d, 2 H), 4,72 (m, 1 H), 4,61-4,34 (m, 3 H), 4,11 (d, 1 H), 3,71 (d, 1 H), 3,15 (s, 2 H) , 2,26 (s, 3 H). Tiempo de retención de CL/EM = 3,637 minutos, EM calculado para ($C_{22}H_{17}Cl_2F_5N_2O_2S$) 538,03, observado 538,9 M+H+.

Ejemplo 16: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metoxietanona



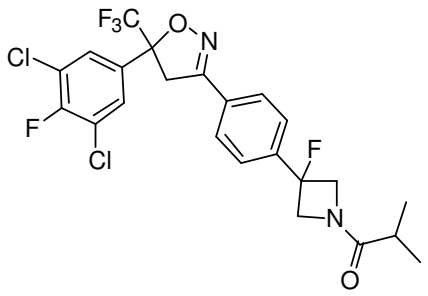
El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando cloruro de metoxi acetilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 114 mg (88 %). RMN ^{1}H ($CDCl_3$) δ 7,74 (d, 2 H), 7,60 (d, 2 H), 7,54 (d, 2 H), 4,82-4,68 (m, 1 H), 4,66-4,34 (m, 3 H), 4,15-4,04 (m, 3 H), 3,71 (d, 1 H), 3,42 (s, 3 H). Tiempo de retención de CL/EM = 3,543 minutos, EM calculado para ($C_{22}H_{17}Cl_2F_5N_2O_3$) 522,05, observado 523,0 M+H.

Ejemplo 17: ciclobutil(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona



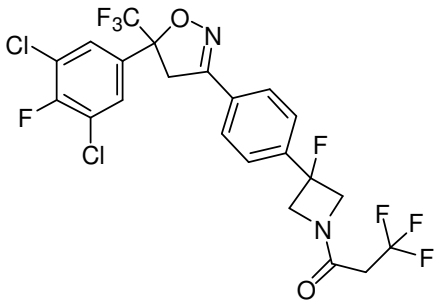
El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando cloruro de ciclobutanocarbonilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 115 mg (88 %). RMN ^{1}H ($CDCl_3$) δ 7,73 (d, 2 H), 7,59 (d, 2 H), 7,51 (d, 2 H), 4,59-4,26 (m, 4 H), 4,10 (d, 1 H), 3,71 (d, 1 H), 3,12 (m, 1 H), 2,38 (m, 2 H), 2,16 (m, 2 H), 2,07-1,87 (m, 2 H). Tiempo de retención de CL/EM = 3,743 minutos, EM calculado para ($C_{24}H_{19}Cl_2F_5N_2O_2$) 532,07, observado 533,0 M+H.

Ejemplo 18: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona



El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando cloruro de isobutiroílo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 166 mg (90 %). RMN ^{1}H ($CDCl_3$) δ 7,74 (d, 2 H), 7,60 (d, 2 H), 7,53 (d, 2 H), 4,70-4,29 (m, 4 H), 4,10 (d, 1 H), 3,71 (d, 1 H), 2,51 (m, 1 H), 1,17 (m, 6 H). Tiempo de retención de CL/EM = 3,685 minutos, EM calculado para ($C_{23}H_{19}Cl_2F_5N_2O_2$) 520,07, observado 521,0 M+H.

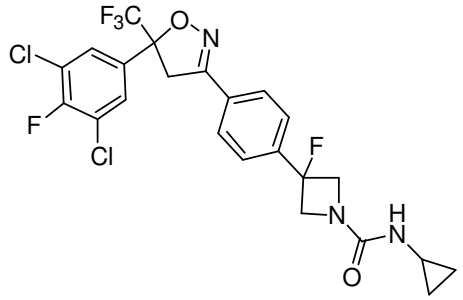
Ejemplo 19: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona



El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando cloruro de 3,3,3-trifluoropropanoílo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 96 mg (70 %). RMN ^{1}H ($CDCl_3$) δ 7,76 (d, 2 H), 7,60 (d, 2 H), 7,53 (d, 2 H), 4,76-4,65 (m, 1 H), 4,61-4,38 (m, 3 H), 4,10 (d, 1 H), 3,71 (d, 1 H), 3,09 (m, 2 H). Tiempo de retención de CL/EM = 3,712 minutos, EM calculado para

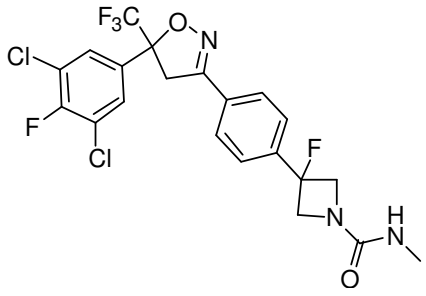
($C_{22}H_{14}Cl_2F_8N_2O_2$) 560,03, observado 561,0 M+H.

Ejemplo 20: N-ciclopropil-3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 126 mg (94 %). RMN ^1H ($CDCl_3$) δ 7,73 (d, 2 H), 7,60 (d, 2 H), 7,56 (d, 2 H), 4,56-4,39 (m, 3 H), 4,29-4,18 (m, 2 H), 4,10 (d, 1 H), 3,70 (d, 1 H), 2,65 (m, 1 H), 0,78 (m, 2 H), 0,55 (m, 2 H). Tiempo de retención de CL/EM = 3,233 minutos, EM calculado para ($C_{23}H_{18}Cl_2F_5N_3O_2$) 533,07, observado 534,0 M+H.

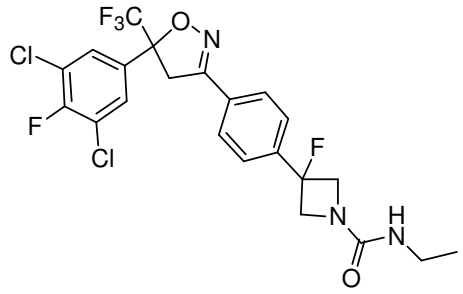
Ejemplo 21: 3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando isocianato de metilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 44 mg (94 %). RMN ^1H

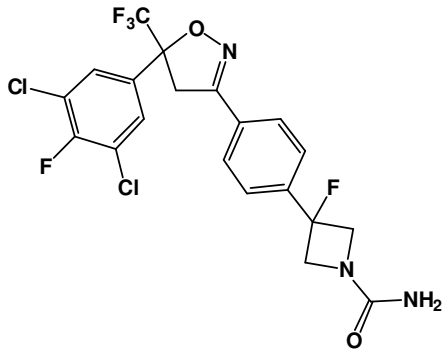
($CDCl_3$) δ 7,71 (d, 2 H), 7,59-7,53 (m, 4 H), 4,45 (d, 1 H), 4,39 (d, 1 H), 4,23 (d, 1 H), 4,21 (d, 1 H), 4,24-4,17 (m, 3 H), 4,08 (d, 1 H), 3,68 (d, 1 H), 2,83 (d, 3 H). Tiempo de retención de CL/EM = 3,001 minutos, EM calculado para ($C_{21}H_{16}Cl_2F_5N_3O_2$) 507, observado 508 M+H.

Ejemplo 22: 3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida



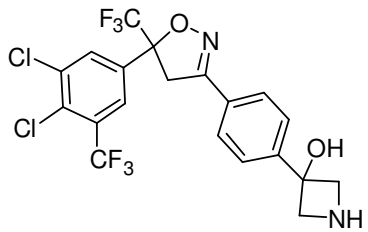
El compuesto se preparó a partir del compuesto de la preparación 16 de acuerdo con el método del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 44 mg (91 %). RMN ^1H ($CDCl_3$) δ 7,71 (d, 2 H), 7,59-7,53 (m, 4 H), 4,44 (d, 1 H), 4,39 (d, 1 H), 4,24-4,17 (m, 3 H), 4,08 (d, 1 H), 3,68 (d, 1 H), 3,33-3,26 (m, 2 H), 1,16 (t, 3 H). Tiempo de retención de CL/EM = 3,531 minutos, EM calculado para ($C_{22}H_{18}Cl_2F_5N_3O_2$) 521, observado 522 M+H.

Ejemplo 23: 3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida



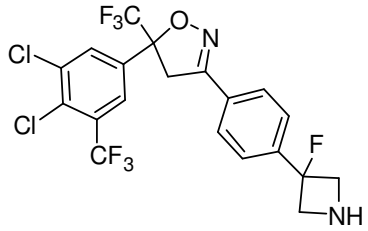
Se añadió trietilamina (0,070 ml, 0,492 mmol) a una suspensión de sal clorhidrato de azetidina (Preparación 16, 0,200 g, 0,410 mmol) en CH_2Cl_2 (5 ml). Posteriormente, se añadió isocianato de trimetilsililo (0,308 ml, 2,05 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante una noche. Se añadió una solución acuosa saturada de Na_2CO_3 (5 ml) y la mezcla de reacción se agitó durante 5 minutos. La fase orgánica se separó, se lavó con salmuera y se secó (Na_2SO_4 anhidro). El disolvente se evaporó a presión reducida, produciendo un sólido de color blanquecino. El residuo se purificó por cromatografía [sistema Teledyne Isco CombiFlash Rf, cartucho de 24 g de gel de sílice RediSep Rf, CH_2Cl_2 a CH_2Cl_2-MeOH (95:5) durante un gradiente de elución de 10 CV], proporcionando el compuesto deseado purificado en forma de un sólido de color blanco (0,089 g, 44 %). T_r de CL/EM = 3,378 minutos, *m/z* 494 $[M+H]^+$

Preparación 17: 3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol



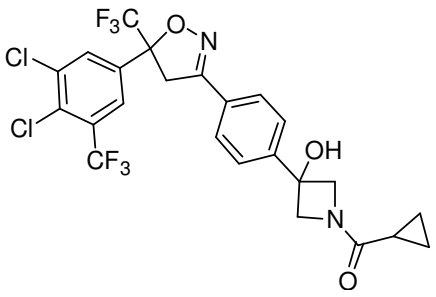
Se preparó de acuerdo con los procedimientos de la Preparación 12 y la Preparación 13 usando 1,2-dicloro-3-(trifluorometil)-5-(3,3,3-trifluoroprop-1-en-2-il)benceno.

Preparación 18: 5-(3,4-dicloro-5-(trifluorometil)fenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol.



Se preparó de acuerdo con los procedimientos de las Preparaciones 12, 14 y 15 usando 1,2-dicloro-3-(trifluorometil)-5-(3,3,3-trifluoroprop-1-en-2-il)benceno. RMN ^{1}H (DMSO-d_6) δ ppm: 8,20 (1H), 7,93 (1H), 7,86 (2H), 7,75 (2H), 4,62-4,36 (6H); m/z (CI) 501 ([M+H]$^+$.

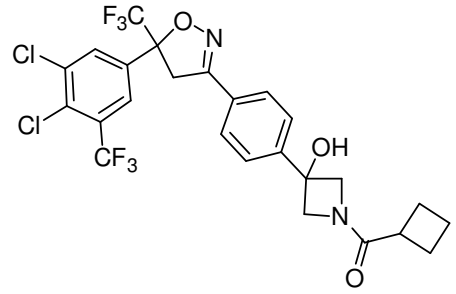
Ejemplo 24: ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona



El compuesto se preparó a partir del compuesto de la preparación 17 de acuerdo con el método del Ejemplo 6 usando cloruro de ciclopropilcarboxilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 112 mg (88 %). RMN ^{1}H ($CDCl_3$) δ 7,96 (d, 1 H), 7,85 (d, 1 H), 7,71 (m, 2 H), 7,62 (m, 2 H), 4,51 (m, 2 H), 4,29 (m, 2 H), 4,16 (d, 1 H), 3,95 (s, 1 H), 3,73 (d, 1 H), 1,47 (m, 1 H), 1,01

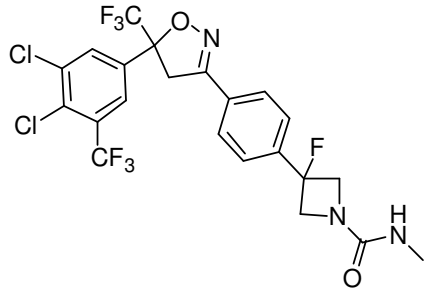
(m, 2 H), 0,82 (m, 2 H). Tiempo de retención de CL/EM = 3,564 minutos, EM calculado para ($C_{24}H_{18}Cl_2F_6N_2O_3$) 566,06, observado 567,0 M+H.

Ejemplo 25: ciclobutil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona



El compuesto se preparó a partir del compuesto de la preparación 17 de acuerdo con el método del Ejemplo 6 usando cloruro de ciclobutanocarbonilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 111 mg (85 %). RMN ^{1}H ($CDCl_3$) δ 7,96 (d, 1 H), 7,85 (d, 1 H), 7,70 (m, 2 H), 7,58 (m, 2 H), 4,37-4,21 (m, 4 H), 4,15 (m, 1 H), 4,04 (d, 1 H), 3,72 (m, 1 H), 3,10 (m, 1 H), 2,33 (m, 2 H), 2,12 (m, 2 H), 2,06-1,83 (m, 2 H). Tiempo de retención de CL/EM = 3,650 minutos, EM calculado para ($C_{25}H_{20}Cl_2F_6N_2O_3$) 580,08, observado 581,0 M+H.

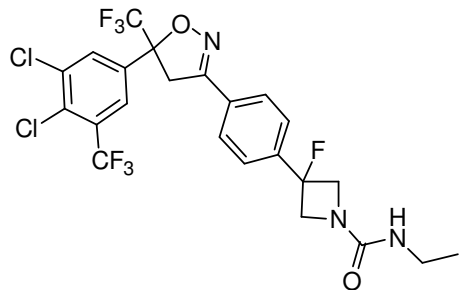
Ejemplo 26: 3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la preparación 18 de

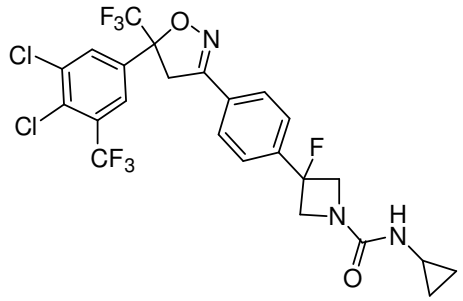
acuerdo con el método del Ejemplo 6 usando isocianato de metilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 132 mg (94 %). RMN ^{1}H ($CDCl_3$) δ 7,96 (m, 1 H), 7,85 (m, 1 H), 7,73 (d, 2 H), 7,57 (d, 2 H), 4,50-4,39 (m, 2 H), 4,28-4,11 (m, 4 H), 3,72 (d, 1 H), 2,86 (d, 3 H). Tiempo de retención de CL/EM = 3,090 minutos, EM calculado para ($C_{22}H_{16}Cl_2F_7N_3O_2$) 557,05, observado 558,0 M+H.

Ejemplo 27: 3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida



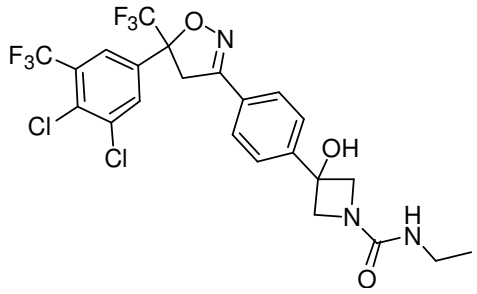
El compuesto se preparó a partir del compuesto de la preparación 18 de acuerdo con el método del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 141 mg (98 %). RMN ^{1}H ($CDCl_3$) δ 7,96 (m, 1 H), 7,85 (m, 1 H), 7,74 (d, 2 H), 7,57 (d, 2 H), 4,49-4,38 (m, 2 H), 4,27-4,11 (m, 4 H), 3,72 (d, 1 H), 3,31 (m, 2 H), 1,18 (t, 3 H). Tiempo de retención de CL/EM = 3,133 minutos, EM calculado para ($C_{23}H_{18}Cl_2F_7N_3O_2$) 571,01, observado 572,0 M+H.

Ejemplo 28: N-ciclopropil-3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la preparación 18 de acuerdo con el método del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 142 mg (97 %). RMN ^{1}H ($CDCl_3$) δ 7,96 (m, 1 H), 7,85 (m, 1 H), 7,74 (d, 2 H), 7,56 (d, 2 H), 4,55-4,38 (m, 3 H), 4,29-4,19 (m, 2 H), 4,16 (d, 1 H), 3,72 (d, 1 H), 2,64 (m, 1 H), 0,78 (m, 2 H), 0,55 (m, 2 H). Tiempo de retención de CL/EM = 3,152 minutos, EM calculado para ($C_{24}H_{18}Cl_2F_7N_3O_2$) 583,07, observado 584,0 M+H.

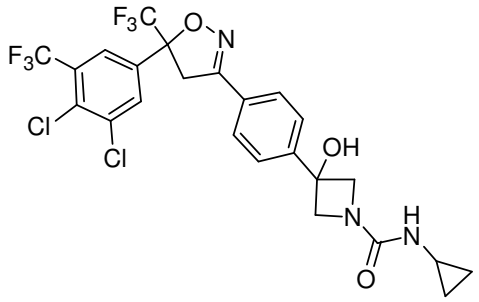
Ejemplo 29: 3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-hidroxiazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la preparación 17 de acuerdo con el método del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 50 mg (94 %). RMN ^{1}H ($CDCl_3$) δ 7,94 (s, 1 H), 7,83 (s, 1 H), 7,68 (d. 2 H), 7,62 (d, 2 H) 4,21-4,11 (m, 6 H), 3,90 (s, 1H), 3,70 (d, 1 H), 3,26 (c, 2H), 1,13 (t, 3 H). Tiempo de retención de CL/EM = 3,179 minutos, EM calculado para ($C_{23}H_{19}Cl_2F_6N_3O_3$) 569,

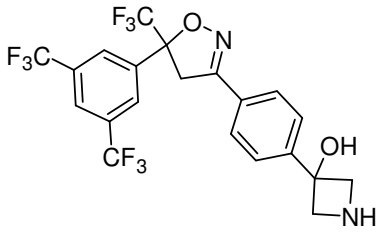
observado 570 M+H.

Ejemplo 30: N-ciclopropil-3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la preparación 17 de acuerdo con el método del Ejemplo 6 usando cloruro de ciclopropancarbonilo. Rendimiento de 51 mg (94 %). RMN ^{1}H ($CDCl_3$) δ 7,94 (s, 1 H), 7,83 (s, 1 H), 7,68 (d, 2 H), 7,62 (d, 2 H), 4,49 (s, 1 H) 4,23-4,18 (m, 4 H), 4,13 (d, 1 H), 3,70 (d, 1 H), 3,3,8 (s, 1 H), 2,63-2,59 (m, 1 H), 0,76-0,72 (m, 2 H), 0,53-0,49 (m, 2 H). Tiempo de retención de CL/EM = 3,481 minutos, EM calculado para ($C_{24}H_{19}Cl_2F_6N_3O_3$) 581, observado 582 M+H.

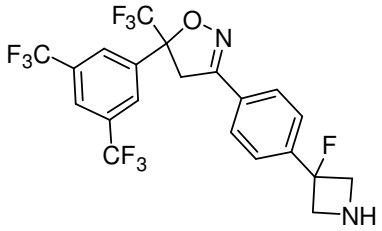
Preparación 19: 3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol



Se preparó de acuerdo con los procedimientos de la Preparación 12 y la Preparación 13 usando 1,3-bis(trifluorometil)-5-(3,3,3-trifluoroprop-1-en-2-il)benceno.

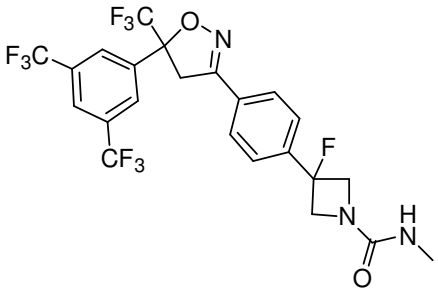
Preparación 20: 5-(3,5-bis(trifluorometil)fenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-

(trifluorometil)-4,5-dihidroisoxazol.



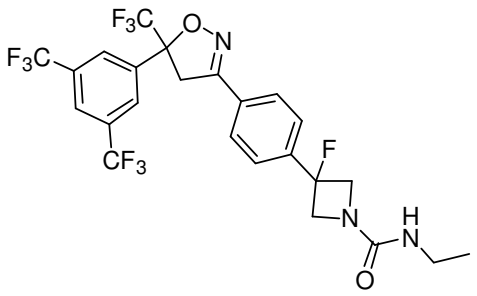
Se preparó de acuerdo con los procedimientos de las Preparaciones 12, 14 y 15 usando 1,3-bis(trifluorometil)-5-(3,3,3-trifluoroprop-1-en-2-il)benceno. RMN ^{1}H (DMSO-d_6) δ ppm: 8,36 (1H), 8,22 (2H), 7,87 (2H), 7,76 (2H), 4,62-4,42 (6H); m/z (CI) 501 ([M+H]$^+$.

Ejemplo 31: 3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida



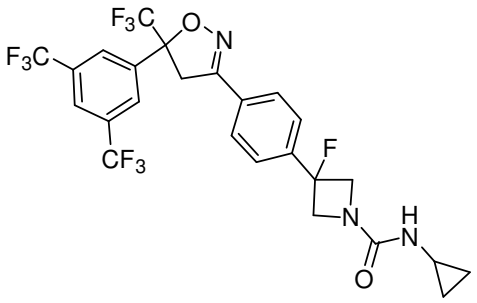
El compuesto se preparó a partir del compuesto de la Preparación 20 de acuerdo con el método del Ejemplo 6 usando isocianato de metilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 131 mg (94 %). RMN ^{1}H ($CDCl_3$) δ 8,10 (s, 2 H), 7,98 (s, 1 H), 7,75 (d, 2 H), 7,57 (d, 2 H), 4,50-4,39 (m, 2 H), 4,28-4,17 (m, 4 H), 3,76 (d, 1 H), 2,86 (d, 3 H). Tiempo de retención de CL/EM = 3,015 minutos, EM calculado para ($C_{23}H_{17}F_{10}N_3O_2$) 557,12, observado 558,0 M+H.

Ejemplo 32: 3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la Preparación 20 de acuerdo con el método del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 131 mg (92 %). RMN ^{1}H ($CDCl_3$) δ 8,10 (s, 2 H), 7,98 (s, 1 H), 7,75 (d, 2 H), 7,57 (d, 2 H), 4,50-4,39 (m, 2 H), 4,27-4,16 (m, 4 H), 3,76 (d, 1 H), 3,31 (m, 2 H), 1,18 (t, 3 H). Tiempo de retención de CL/EM = 3,089 minutos, EM calculado para ($C_{24}H_{19}F_{10}N_3O_2$) 571,13, observado 572,0 M+H.

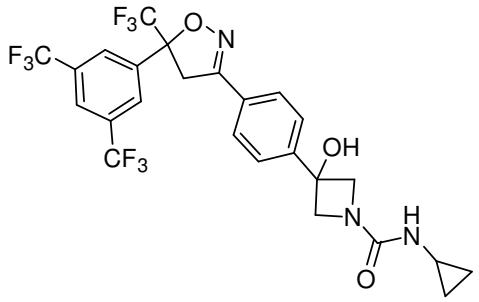
Ejemplo 33: 3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-fluoroazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la Preparación 20 de acuerdo con el método del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 141 mg (96 %). RMN ^{1}H ($CDCl_3$) δ 8,10 (s, 2 H), 7,98 (s, 1 H), 7,75 (d, 2 H), 7,57 (d, 2 H), 4,55-4,39 (m, 3 H), 4,28-4,18 (m, 3 H), 3,77 (d, 1 H), 2,65 (m, 1 H), 0,78 (m, 2 H), 0,55 (m, 2 H). Tiempo de retención de CL/EM = 3,086 minutos, EM calculado para

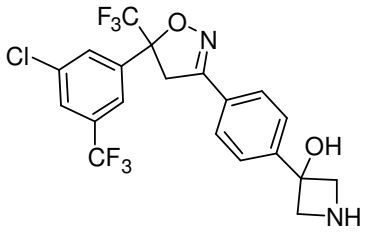
($C_{25}H_{19}F_{10}N_3O_2$) 583,13, observado 584,0 M+H.

Ejemplo 34: 3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-hidroxiazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la Preparación 19 de acuerdo con el método del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 119 mg (89 %). RMN ^{1}H ($CDCl_3$) δ 8,10 (s, 2 H), 7,97 (s, 1 H), 7,71 (m, 2 H), 7,64 (m, 2 H), 4,57 (d, 1 H), 4,28-4,16 (m, 6 H), 3,77 (d, 1 H), 2,61 (m, 1 H), 0,74 (m, 2 H), 0,52 (m, 2 H). Tiempo de retención de CL/EM = 2,989 minutos, EM calculado para ($C_{25}H_{20}F_9N_3O_3$) 581,14, observado 582,0 M+H.

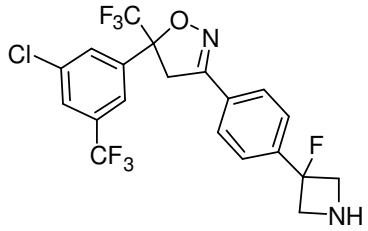
Preparación 21: 3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol



Se preparó de acuerdo con los procedimientos de la Preparación 12 y la Preparación 13 usando 1-cloro-3-(trifluorometil)-5-(3,3,3-trifluoroprop-1-en-2-il)benceno.

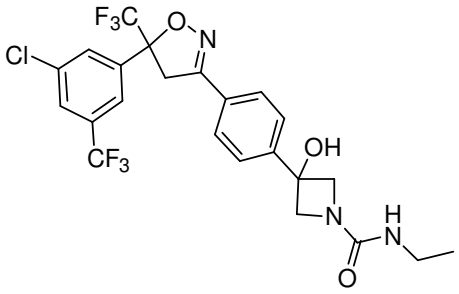
Preparación 22: 5-(3-cloro-5-(trifluorometil)fenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-

5-(trifluorometil)-4,5-dihidroisoxazol.



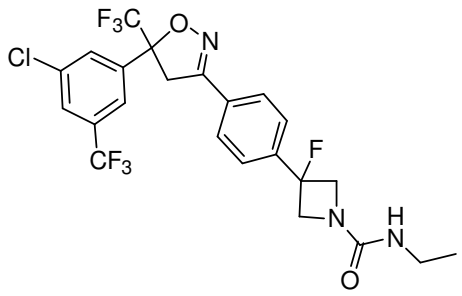
Se preparó de acuerdo con los procedimientos de las Preparaciones 12, 14 y 15 usando 1-cloro-3-(trifluorometil)-5-(3,3,3-trifluoroprop-1-en-2-il)benceno. . RMN ^{1}H (DMSO-d_6) δ ppm: 8,10 (1H), 7,99 (1H), 7,87-7,85 (3H), 7,75 (2H), 4,62-4,37 (6H); m/z (CI) 467 ([M+H]$^+$.

Ejemplo 35: 3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-hidroxiazetidin-1-carboxamida



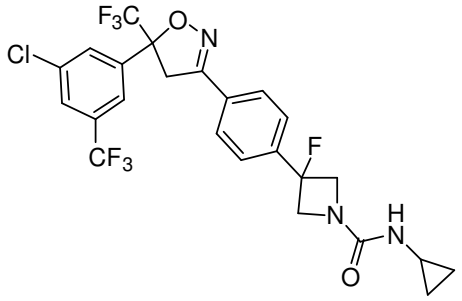
El compuesto se preparó a partir del compuesto de la Preparación 21 de acuerdo con el método del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 121 mg (90 %). RMN ^{1}H ($CDCl_3$) δ 7,84 (s, 1 H), 7,77 (m, 1 H), 7,74-7,68 (m, 3 H), 7,66-7,62 (m, 2 H), 4,22-4,13 (m, 6 H), 3,74 (d, 1 H), 3,30 (m, 2 H), 1,16 (t, 3 H). Tiempo de retención de CL/EM = 3,312 minutos, EM calculado para ($C_{23}H_{20}ClF_6N_3O_3$) 535,11, observado 536,0 M+H.

Ejemplo 36: 3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la Preparación 22 de acuerdo con el método del Ejemplo 6 usando isocianato de etilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 133 mg (99 %). RMN ^{1}H ($CDCl_3$) δ 7,84 (s, 1 H), 7,79-7,68 (m, 4 H), 7,57 (d, 2 H), 4,49-4,38 (m, 2 H), 4,27-4,12 (m, 4 H), 3,74 (d, 1 H), 3,32 (m, 2 H), 1,18 (t, 3 H). Tiempo de retención de CL/EM = 3,571 minutos, EM calculado para ($C_{23}H_{19}ClF_7N_3O_2$) 537,11, observado 538,0 M+H.

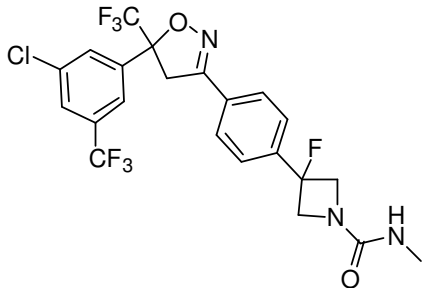
Ejemplo 37: 3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-fluoroazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la Preparación 22 de acuerdo con el método del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 131 mg (95 %). RMN ^{1}H ($CDCl_3$) δ 7,83 (s, 1 H), 7,79-7,68 (m, 4 H), 7,56 (d, 2 H), 4,55-4,39 (m, 3 H), 4,29-4,20 (m, 2 H), 4,16 (d, 1 H), 3,74 (d, 1 H), 2,65 (m, 1 H), 0,78 (m, 2 H), 0,55 (m, 2 H). Tiempo de retención de CL/EM = 3,574 minutos, EM calculado

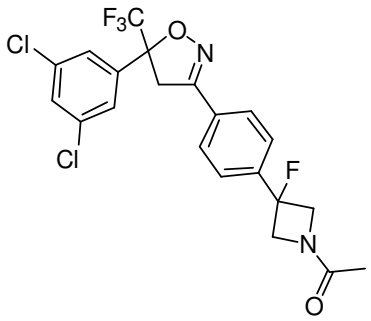
para ($C_{22}H_{17}ClF_7N_3O_2$) 549,11, observado 550,0 M+H.

Ejemplo 38: 3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida



El compuesto se preparó a partir del compuesto de la Preparación 22 de acuerdo con el método del Ejemplo 6 usando isocianato de metilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento de 126 mg (96 %). RMN ^1H ($CDCl_3$) δ 7,83 (s, 1 H), 7,79-7,68 (m, 4 H), 7,57 (d, 2 H), 4,50-4,39 (m, 2 H), 4,28-4,12 (m, 4 H), 3,74 (d, 1 H), 2,86 (d, 3 H). Tiempo de retención de CL/EM = 3,487 minutos, EM calculado para ($C_{22}H_{17}ClF_7N_3O_2$) 523,09, observado 524,0 M+H.

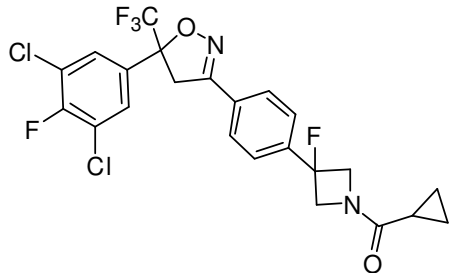
Ejemplo 39: 1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona



A una solución de 5-(3,5-diclorofenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 15, 200 mg, 0,462 mMol) en diclorometano (3 ml) se le añadió trietilamina (0,192 ml) seguido de anhídrido

acético (50,2 µl). La reacción se dejó en agitación a temperatura ambiente durante una noche. La solución se diluyó con agua y se dejó en agitación durante 10 minutos. La mezcla se pasó a través de un separador de fases ISCO. Se vertió una corriente de nitrógeno sobre los productos orgánicos y después se colocaron a alto vacío para formar una espuma de color blanco de 200 mg (rendimiento del 91 %). RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 2,01 (s, 3 H) 3,73 (d, 1 H) 3,92 (cd, 1 H) 4,12 (d, 1 H) 4,32-4,56 (m, 3 H) 4,59-4,70 (m, 1 H) 7,46 (t, 1 H) 7,52-7,59 (m, 4 H) 7,76 (d, 2 H), Tiempo de retención de CL/EM = 3,510 min; EM calculado para ($C_{21}H_{16}Cl_2F_4N_2O_2$) 474,052, observado 475,0 M+H.

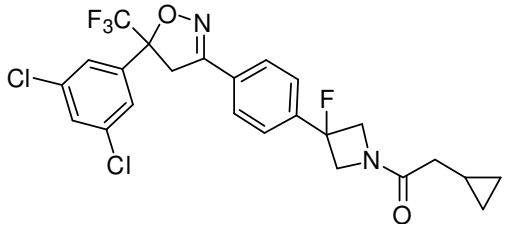
Ejemplo 40: ciclopropil(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona



El compuesto se preparó a partir del compuesto de la Preparación 16 de acuerdo con el método del Ejemplo 6 usando isocianato de ciclopropilo en lugar de cloruro de ciclopropancarbonilo. Rendimiento: 87 % de un sólido vítreo. RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 0,85 (t, Hz, 2 H) 1,06 (dd, 2 H) 1,42-1,51 (m, 1 H) 3,71 (d, 1 H) 4,11 (d, 1 H) 4,28-4,82 (m, 4 H) 7,53-7,64 (m, 4 H) 7,75 (d, 2 H) Tiempo de retención de CL/EM = 3,675 minutos; EM calculado para ($C_{23}H_{17}Cl_2F_5N_2O_2$) 518,059, observado 519 M+H.

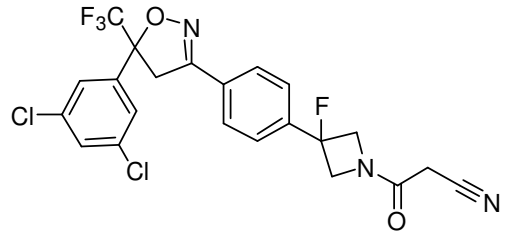
Ejemplo 41: 2-Ciclopropil-1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona



El compuesto se preparó a partir del compuesto de la preparación 15 de acuerdo con el método del Ejemplo 12 usando ácido 2-ciclopropilacético en lugar de ácido butírico. RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm -0,04-0,04 (m, 2 H) 0,41 (d, 2 H) 0,86-0,92 (m, 1 H) 1,95 (d, 2 H) 3,51 (d, 1 H) 3,90 (d, 1 H) 4,12-4,46 (m, 4 H) 7,24 (t, 1 H) 7,30-7,37 (m, 4 H) 7,54 (d, 2 H), Tiempo de retención de CL/EM = 3,682 minutos; EM calculado para ($C_{24}H_{20}Cl_2F_4N_2O_2$) 514,084, observado 515,0 $[M+H]^+$.

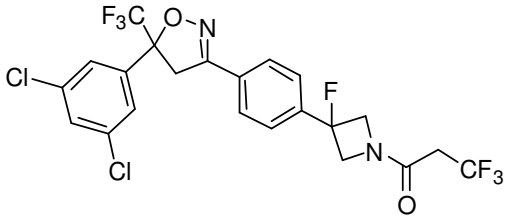
Ejemplo 42: 3-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-oxopropanonitrilo



El compuesto se preparó a partir del compuesto de la preparación 15 de acuerdo con el método del Ejemplo 12 usando ácido 2-cianoacético en lugar de ácido butírico, proporcionando un sólido vítreo. RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 3,41 (s, 1 H) 3,73 (d, 1 H) 4,12 (d, 1 H) 4,41-4,72 (m, 4 H) 4,76-4,86 (m, 1 H) 7,46 (t, 1 H) 7,54-7,58 (m, 4 H) 7,78 (d, 2 H); EM calculado para ($C_{22}H_{15}Cl_2F_4N_3O_2$) 499,048, observado 500,0 $[M+H]^+$.

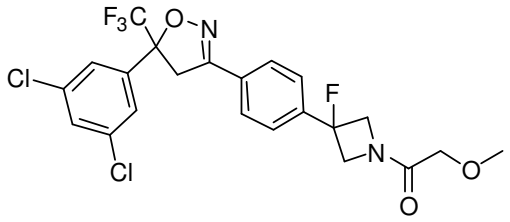
Ejemplo 43: 1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona



El compuesto se preparó a partir del compuesto de la Preparación 15 de acuerdo con el método del Ejemplo 6 usando cloruro de 3,3,3-trifluoropropanoílo en lugar de cloruro de ciclopropancarbonilo. RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 3,09 (c, 2 H) 3,64 (d, 1 H) 4,10 (d, 1 H) 4,39-4,63 (m, 4 H) 7,37 (t, 1 H) 7,44-7,46 (m, 4 H) 7,76 (d, 2 H); EM calculado para ($C_{22}H_{15}Cl_2F_7N_2O_2$) 543,266, observado 544,0 $[M+H]^+$.

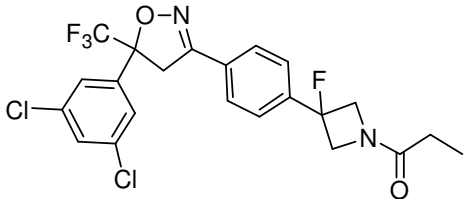
Ejemplo 44: 1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metoxietanona



El compuesto se preparó a partir del compuesto de la Preparación 15 de acuerdo con el método del Ejemplo 6 usando cloruro de 2-metoxiacetilo en lugar de cloruro de ciclopropancarbonilo, proporcionando un sólido de color blanco. RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 3,44 (s, 3 H) 3,73 (d, 1 H) 4,09-4,14 (m, 3 H) 4,37-4,63 (m, 3 H) 4,65-4,85 (m, 1 H) 7,43-7,49 (m, 1 H) 7,51-7,60 (m, 4 H) 7,76 (d, 2 H); EM calculado para ($C_{22}H_{18}Cl_2F_4N_3O_3$) 505,295, observado m/z (IEN) 506,0 $[M+H]^+$.

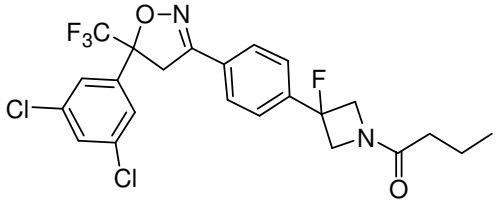
Ejemplo 45: 1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)-3-fluoroazetidin-1-il)propan-1-ona



El compuesto se preparó a partir del compuesto de la Preparación 15 de acuerdo con el método del Ejemplo 6 usando cloruro de propionilo en lugar de cloruro de ciclopropancarbonilo, proporcionando un sólido de color blanco RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 1,14-1,25 (m, 3 H) 2,24 (m, 2 H) 3,73 (d, 1 H) 4,11 (d, 1 H) 4,32-4,67 (m, 4 H) 7,46 (t, 1 H) 7,52-7,60 (m, 4 H) 7,76 (d, 2 H); EM calculado para ($C_{22}H_{18}Cl_2F_4N_2O_2$) 489,296, observado m/z (IEN) 490,0 $[M+H]^+$.

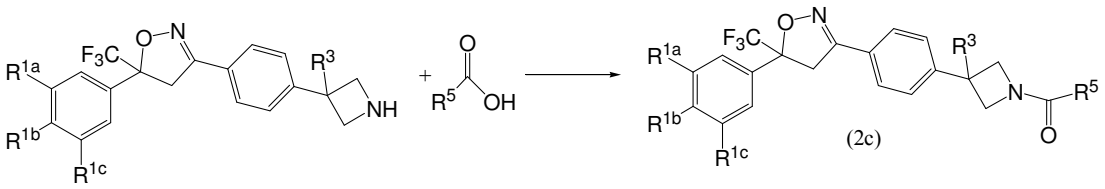
Ejemplo 46: 1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)butan-1-ona



El compuesto se preparó a partir del compuesto de la Preparación 15 de acuerdo con el método del Ejemplo 6 usando cloruro de butirilo en lugar de cloruro de ciclopropancarbonilo, proporcionando un sólido de color blanco. RMN ^{1}H (400 MHz, $CDCl_3$-*d*) δ ppm 1,01 (t, 3 H) 1,73 (m, 2 H) 2,19 (m, 2 H) 3,73 (d, 1 H) 4,11 (d, 1 H) 4,33-4,66 (m, 4 H) 7,46 (t, 1 H) 7,53-7,58 (m, 4 H) 7,76 (d, 2 H); EM calculado para ($C_{23}H_{20}Cl_2F_4N_2O_2$) 503,323, observado m/z (IEN) 503,0 $[M+H]^+$.

Ejemplos 47-82

Los Ejemplos en la Tabla 1 que se indica a continuación se prepararon en las siguientes condiciones



La isoxazolin fenil azetidina (0,05 mmol) se disolvió en dimetil formamida (0,5 ml). Ésta se añadió al respectivo ácido (0,2 mmol) seguido de una solución de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (0,10 mmol) en dimetil formamida (0,5 ml) y Et_3N (0,5 mmol). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró por destilación al vacío y el producto en bruto se purificó por HPLC preparativa. (Waters, Gemini NX C18 21 x 100 mm 5 µm, fase móvil A = TFA al 0,1 % en H_2O, fase móvil B = acetonitrilo, gradiente lineal al 30 % de B al 100 % en 8 minutos, mantenimiento durante 1 minuto, 20 ml/minuto, picos recogidos por masa). Los tiempos de retención (TR) indicados a continuación se obtuvieron con el siguiente procedimiento analítico: Agilent 1200, Columna = Gemini NX C18 4,6 x 50 mm 3 µm, fase móvil A = TFA al 0,1 % en H_2O, fase móvil B = acetonitrilo, gradiente lineal al 30 % de B al 100 % en 5 minutos, mantenimiento durante 1 minuto, 1,5 ml/minuto.

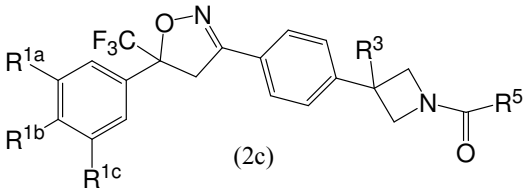
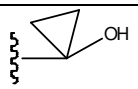
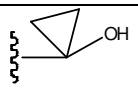
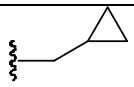
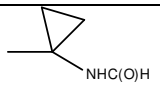
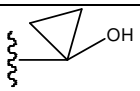
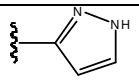
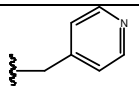
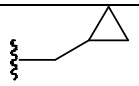
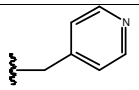


Tabla 1

Ejemplo Nº	R^{1a}	R^{1b}	R^{1c}	R^3	R^5	m/z (IEN) [M+H]+	TR (minutos)
47	CF_3	H	CF_3	F	ciclobutilo	583	4,66
48	CF_3	H	CF_3	F	ciclopropilo	569	4,45
49	CF_3	H	CF_3	F	isopropilo	571	4,55
50	CF_3	H	Cl	F	propilo	538	4,55
51	CF_3	H	Cl	F	etilo	524	4,34
52	CF_3	H	Cl	F	metilo	510	4,07
53	CF_3	H	Cl	F	$-CH_2CN$	535	4,21
54	Cl	H	Cl	F		517	3,98
55	Cl	F	Cl	F		535	4,04
56	Cl	Cl	Cl	F	$-CH_2OCH_3$	539	4,43
57	Cl	Cl	CF_3	OH	isopropilo	569	8,75
58	Cl	Cl	CF_3	OH	propilo	569	8,77
59	CF_3	H	CF_3	F		583	4,55
60	CF_3	H	CF_3	F	$-CH_2OH$	559	3,83
61	CF_3	H	Cl	F	$-CH_2SCH_3$	556	4,44
62	CF_3	H	Cl	F	ciclobutilo	550	4,66
63	CF_3	Cl	Cl	F	$-CH_2C(O)NH_2$	586	5,15
64	Cl	F	Cl	F		562	3,71

65	Cl	Cl	Cl	F		551	4,29
66	Cl	H	Cl	F	isobutilo	517	9,61
67	Cl	Cl	Cl	F	$-CH_2SCH_3$	555	9,59
68	Cl	F	Cl	OH	etilo	505	7,76
69	CF_3	H	Cl	F	ciclopropilo	536	4,44
70	Cl	F	Cl	F		545	4,03
71	CF_3	H	CF_3	F		620	2,75
72	CF_3	H	Cl	F		550	4,53
73	CF_3	Cl	Cl	F	etilo	557	7,31
74	CF_3	Cl	Cl	F	ciclopropilo	569	7,58
75	CF_3	Cl	Cl	F	metilo	543	6,67
76	CF_3	Cl	Cl	F	isopropilo	571	7,84
77	CF_3	Cl	Cl	F	$-CH_2CN$	568	6,72
78	Cl	Cl	Cl	F		572	7,40
79	CF_3	H	CF_3	F	etilo	557	4,36
80	CF_3	Cl	Cl	F	ciclopentilo	597	8,66
81	CF_3	Cl	Cl	F	$-CH_2SCH_3$	589	7,56
82	Cl	F	Cl	OH	ciclopropil	517	8

〰〰〰〰〰〰es el punto de unión, TR = tiempo de retención

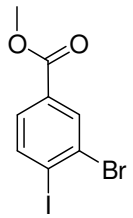
Los siguientes nombres de la IUPAC para los Ejemplos (47-82) de la

Tabla 1 incluyen: 5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (47); 5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (48); 5-[3,5-bis(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (49); 3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (50); 5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (51); 3-[4-(1-acetil-3-fluoroazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (52); 3-[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanonitrilo (53); 1-[(3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]ciclopropanol (54); 1-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]ciclopropanol (55); 3-{4-[3-fluoro-1-(metoxiacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (56); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-1-isobutirilazetidin-3-ol (57); 1-butiril-3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-3-ol (58); 5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (59); 2-[3-(4-{5-[3,5-bis(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetanol (60); 5-[3-cloro-5-(trifluorometil)fenil]-3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (61); 5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclobutilcarbonil)-3-fluoroazetidin-

3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (62); 3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanamida (63); 3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanamida (64); 1-[(3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol (65); 5-(3,5-diclorofenil)-3-{4-[3-fluoro-1-(3-metilbutanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (66); 3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (67); 3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-propionilazetidin-3-ol (68); 5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (69); 5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1H-pirazol-3-ilcarbonil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (70); 4-{2-[3-(4-{5-[3,5-bis(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetil}piridina (71); 5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (72); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (73); 3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (74); 3-[4-(1-acetil-3-fluoroazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (75); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (76); 3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-

3-fluoroazetidin-1-il]-3-oxopropanonitrilo (77); 4-[(3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]piridina (78); 5-[3,5-bis(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (79); 3-{4-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (80); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (81); y 1-(ciclopropilcarbonil)-3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol (82).

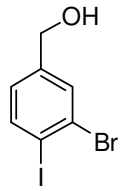
Preparación 23: 3-bromo-4-yodobenzoato de metilo



Una solución de éster metílico del ácido 4-amino-3-bromo-benzoico (5,0 g, 22,0 mmol de Aldrich) en acetona (35 ml) se trató con HCl 6 M (35 ml). La solución se enfrió a 0 ºC y se trató gota a gota con $NaNO_2$ (1,84 g, 26,1 mmol) disuelto en 10 ml de agua. Después de agitar durante 2 horas a 0 ºC, la reacción se trató lentamente con yoduro potásico (5,47 g, 32,6 mmol) disuelto en 20 ml de agua. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc (2 x 150 ml). La fase orgánica combinada se secó (Na_2SO_4) y se concentró al vacío. El residuo se sometió a cromatografía (columna de 80 g Redi-Sep) eluyendo de heptano al 100 % a 20:80 de

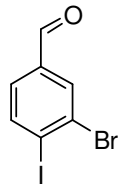
EtOAc:heptano, proporcionando el intermedio (4,1 g, 55 %) en forma de un sólido. RMN ^{1}H ($CDCl_3$): 8,27 (1H), 7,98 (1H), 7,64 (1H), 3,94 (3H).

Preparación 24: (3-bromo-4-yodofenil)metanol



Una solución de 3-bromo-4-yodobenzoato de metilo (Preparación 23, 4,3 g, 12,6 mmol) en CH_2Cl_2 se enfrió, en una atmósfera de N_2, a -78 ºC. A la solución se le añadió lentamente DIBAL-H, que se agitó a -78 ºC durante 45 minutos y después se dejó alcanzar la temperatura ambiente. Después, la mezcla de reacción se diluyó con HCl 1 M (40 ml) y se agitó durante 30 minutos. La reacción se diluyó con más cantidad de agua y se extrajo con CH_2Cl_2. La fase orgánica se secó (Na_2SO_4) y se concentró al vacío, proporcionando el intermedio (3,2 g, 82 %) en forma de un sólido. RMN ^{1}H ($CDCl_3$): 7,85 (1H), 7,67 (1H), 7,02 (1H), 4,65 (2H), 1,76 (1H, OH).

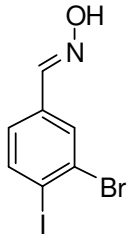
Preparación 25: 3-bromo-4-yodobenzaldehído



Una solución de (3-bromo-4-yodofenil)metanol (Preparación 24, 3,1 g, 9,9 mmol) en CH_2Cl_2/agua (2:1, 225 ml) se trató con $NaHCO_3$ (915 mg, 10,9 mmol), NaBr (1060 mg, 10,2 mmol) y un radical libre de TEMPO (40 mg, 0,2 mmol). La mezcla resultante se enfrió a 0 ºC y se añadió gota a gota una solución de NaOCl (0,8 ml, acuosa al 10 %). La mezcla de reacción se dejó

alcanzar la temperatura ambiente mientras se agitaba. Después de 30 min, el análisis por mostró aproximadamente una conversión del 50 % a un punto menos polar. La secuencia se repitió usando el mismo equivalente de reactivos. El análisis por TLC a 25:75 de EtOAc:heptano todavía mostraba material de partida sin reaccionar. La mezcla de reacción se separó y la fase orgánica se trató con 1,0 x peryodinano de Dess-Martin (2,1 g, 4,9 mmol) mientras se agitaba. Después de 10 minutos, el análisis por TLC mostró la conversión completa a un punto menos polar. La fase orgánica se lavó con $NaHCO_3$ sat., se secó sobre Na_2SO_4, se filtró y se evaporó, dando un sólido de color naranja. El material en bruto se sometió a cromatografía (columna de 80 g Redi-Sep) eluyendo de heptano al 100 % a 50:50 de EtOAc/heptano, dando el intermedio (2,7 g, 87 %) en forma de un sólido de color blanco. RMN ^1H ($CDCl_3$): 9,94 (1H), 8,10 (2H), 7,50 (1H).

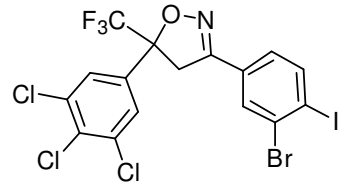
Preparación 26: (*E/Z*)-3-bromo-4-yodobenzaldehído oxima



A una solución de 3-bromo-4-yodobenzaldehído (Preparación 25, 1000 mg, 3,2 mmol) en EtOH (50 ml) se le añadieron $NH_2OH.HCl$ (345 mg, 4,8 mmol) y agua (10 ml). La reacción se calentó a 50 ºC durante 1 hora y después se dejó en agitación durante 18 horas a temperatura ambiente. La mezcla de reacción se concentró al vacío para retirar EtOH. Al residuo se le añadió agua y se extrajo con EtOAc (2 x 75 ml). La fase orgánica combinada se secó (Na_2SO_4) y se concentro al vacío, proporcionando el intermedio (1035 mg, 98

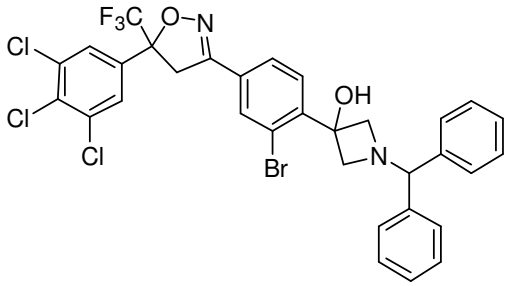
%) en forma de un vidrio. M/z (CI) = 326 $[M+H]^+$.

Preparación 27: 3-(3-bromo-4-yodofenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol



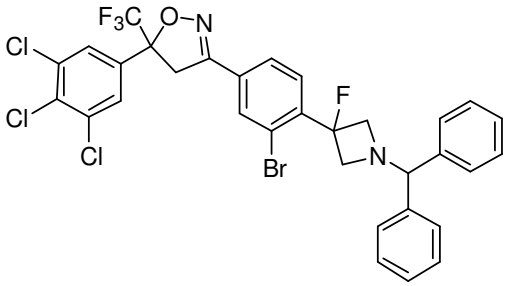
A una solución en DMF (25 ml) de (*E/Z*)-3-bromo-4-yodobenzaldehído oxima (1000 mg, 3,1 mmol) se le añadió en porciones NCS (Preparación 26, 500 mg, 3,7 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. El análisis TLC a 50:50 de EtOAc:heptano mostró un punto ligeramente menos polar, sin material de partida. La mezcla de reacción se diluyó con EtOAc (100 ml) y se lavó con agua (2 x 50 ml). La fase orgánica se secó sobre sulfato sódico y se concentró, dando el intermedio de clorooxima (1056 mg, 96 %) en forma de un sólido. Después, a una solución de acetato de etilo (70 ml) de la clorooxima (1000 mg, 2,8 mmol) y 1,2,3-tricloro-5-(1,1,1-trifluoroprop-2-en-2-il)benceno (765 mg, 2,8 mmol) se le añadió bicarbonato potásico (310 mg, 3,1 mmol). La mezcla se dejó en agitación a temperatura ambiente durante al menos 48 horas. La mezcla de reacción se filtró y se concentró al vacío. El residuo se sometió a cromatografía (columna de 80 g Redi-Sep) eluyendo de heptano al 100 % a 20:80 de EtOAc:heptano, proporcionando el intermedio (1,53 g, 92 %) en forma de un sólido. RMN ^{1}H ($CDCl_3$): 7,95 (1H), 7,88 (1H), 7,65 (2H), 7,33 (1H), 4,07 (1H), 3,67 (1H).

Preparación 28: 1-benzhidril-3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol



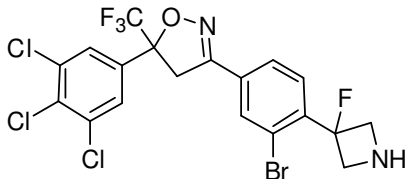
En un matraz secado al horno que contenía 3-(3-bromo-4-yodofenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 27, 1000 mg, 1,67 mmol) en THF (25 ml) a -40 ºC se le añadió lentamente cloruro de isopropil magnesio (1,7 ml de una solución 2,0 M). La reacción se agitó a aprox. -40 ºC durante 1,5 en una atmósfera de nitrógeno. Se añadió lentamente 1-benzhidrilazetidin-3-ona (520 mg en 4 ml de THF). La reacción se agitó a -40 ºC durante 30 minutos más y se dejó calentar a temperatura ambiente. La agitación se continuó durante 2 horas a temperatura ambiente. La reacción se interrumpió con NH_4Cl saturado y se extrajo con EtOAc (2 x 75 ml). La fase orgánica combinada se secó (Na_2SO_4) y se concentró al vacío. El material en bruto se sometió a cromatografía (columna de 40 g Redi-Sep) eluyendo de heptano al 100 % a 60:40 de EtOAc:heptano, recogiendo el intermedio (615 mg, 52 %) en forma de un vidrio. RMN ^1H ($CDCl_3$): 7,87 (1H), 7,66-7,63 (3H), 7,45 (4H), 7,36-7,21 (7H), 4,39 (1H), 4,07 (1H), 3,73-3,58 (5H), 3,06 (1H); m/z (CI) 711 ($[M+H]^+$.

Preparación 29: 3-(4-(1-benzhidril-3-fluoroazetidin-3-il)-3-bromofenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol



Se disolvieron trifluorhidrato de trietilamina (0,3 ml, 1,7 mmol) y trietilamina (0,11 ml, 0,8 ml) en diclorometano (30 ml) y se enfriaron a -78 ºC. A la mezcla enfriada se le añadió XtalFluor-E (310 mg, 1,4 mmol) y después 1-benzhidril-3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol (Preparación 28, 600 mg, 0,8 mmol). La refrigeración se retiró y la mezcla se dejó calentar a temperatura ambiente con agitación durante 2 horas. La reacción se vertió en una solución acuosa saturada de carbonato sódico (100 ml) y la fase orgánica se separó, se secó sobre sulfato sódico anhidro, se filtró y se evaporó a sequedad. El material en bruto se sometió a cromatografía (columna de 40g Redi-Sep) eluyendo de heptano al 100 % a 20:80 de EtOAc:heptano, proporcionando el intermedio (523 mg, 87 %) en forma de un vidrio. RMN ^{1}H ($CDCl_3$) δ ppm: 7,90 (1H), 7,69-7,66 (3H), 7,47-7,21 (11H), 4,46 (1H), 4,08 (1H), 3,90-3,66 (5H); m/z (CI) 713 ($[M+H]^+$.

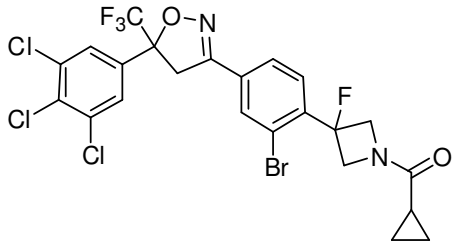
Preparación 30: 3-(3-bromo-4-(3-fluoroazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol



A una solución de 3-(4-(1-benzhidril-3-fluoroazetidin-3-il)-3-bromofenil)-5-

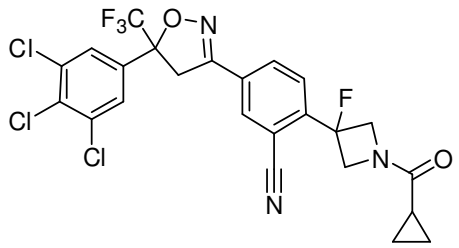
(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 29, 515 mg, 0,76 mmol) en MeCN/DCM (5:1, 60 ml) a 0 ºC se le añadió cloroformiato de 1-cloroetilo (275 µl, 2,5 mmol). La reacción se calentó a reflujo durante 3 horas y después se dejó enfriar a temperatura ambiente mientras se agitaba durante 18 horas. Después, la mezcla de reacción se concentró al vacío, se disolvió de nuevo en MeOH anhidro (50 ml) y se calentó a reflujo durante 1 hora. La reacción se enfrió, se concentró a presión reducida, y al residuo se le añadió éter dietílico. El precipitado resultante se filtró, se aclaró con éter dietílico y se secó al aire, proporcionando el intermedio (365 mg, 87 %) en forma de un sólido. m/z (CI) 713 ($[M+H]^+$.

Ejemplo 83: (3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona



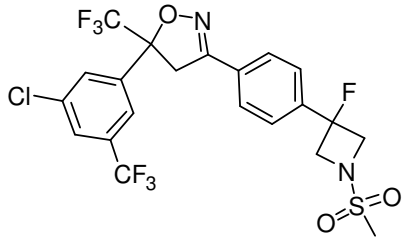
Se preparó a partir del compuesto de la Preparación 30, de acuerdo con el método del Ejemplo 6. RMN ^1H ($CDCl_3$) δ ppm: 7,98 (1H), 7,71 (1H), 7,66 (2H), 7,53 (1H), 4,96-4,46 (4H), 4,09 (1H), 3,70 (1H), 1,49 (1H), 1,11-0,77 (4H); m/z (CI) 615 ($[M+H]^+$.

Ejemplo 84: 2-(1-(ciclopropanocarbonil)-3-fluoroazetidin-3-il)-5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)benzonitrilo



A una solución de (3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona (Ejemplo 83, 35 mg, 0,06 mmol) en DMF se le añadió ZnCN (15 mg, 0,12 mmol) y la reacción se desgasificó con una purga de N_2. Se añadió $Pd(PPh_3)_4$ (4 mg, 0,003 mmol) y la mezcla de reacción se calentó por irradiación de microondas a 150 ºC durante 15 minutos. Después, la mezcla de reacción se diluyó con agua y se extrajo con EtOAc (75 ml). La fase orgánica se secó (Na_2SO_4) y se concentró al vacío. El producto en bruto se sometió a cromatografía (columna de 12 g Redi-Sep) eluyendo de heptano al 100 % a 60:40 de EtOAc:heptano, proporcionando el producto final (18 mg, 56 %) en forma de un sólido. RMN ^1H ($CDCl_3$) δ ppm: 8,08 (1H), 8,00 (1H), 7,70 (1H), 7,66 (2H), 4,98-4,52 (4H), 4,12 (1H), 3,73 (1H), 1,49 (1H), 1,10-0,81 (4H); m/z (CI) 560 ($[M+H]^+$.

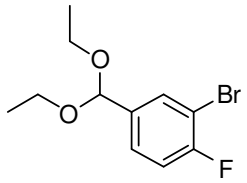
Ejemplo 85: 5-(3-cloro-5-(trifluorometil)fenil)-3-(4-(3-fluoro-1-(metilsulfonil)azetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol



A una solución de 5-(3-cloro-5-(trifluorometil)fenil)-3-(4-(3-fluoroazetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (Preparación 22, 95 mg, 0,2

mmol) en CH_2Cl_2 (5 ml) se le añadieron trietilamina (0,15 ml, 1,1 mmol) y DMAP (5 mg, 0,04 mmol). El contenido se agitó durante 30 minutos al mismo tiempo que se añadió cloruro de mesilo (25 mg, 0,2 mmol) y la reacción se agitó durante 18 horas a temperatura ambiente. Después, la reacción se concentró a ~3 ml en una purga de nitrógeno y se inyectó directamente sobre una columna de 24 g Redi-Sep. El material en bruto se sometió a cromatografía eluyendo de heptano al 100 % a 30:70 de EtOAc:heptano, proporcionando el producto final (95 mg, 94 %) en forma de un sólido. RMN ^1H ($CDCl_3$) δ ppm: 7,85 (1H), 7,79-7,77 (3H), 7,72 (1H), 7,64 (2H), 4,50-4,42, (2H), 4,34-4,27 (2H), 4,18 (1H), 3,76 (1H), 3,03 (3H); m/z (CI) 545 ($[M+H]^+$.

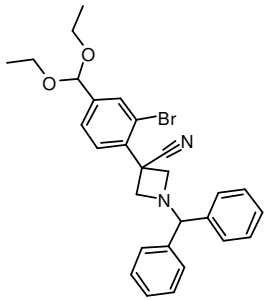
Preparación 31: 2-bromo-4-(dietoximetil)-1-fluorobenceno



Un vial de 10 ml equipado con una barra agitadora se cargó con 1 g de 3-bromo-4-fluoro-benzaldehído, 2 ml de ortoformiato de trietilo y 5 ml de etanol anhidro. Después, se añadieron 50 mg de tribromuro de tetrabutilamonio y la mezcla de reacción se agitó a temperatura ambiente durante una noche. El análisis por TLC mostró una conversión completa a un producto ligeramente menos polar. La reacción bruta se vertió en $NaHCO_3$ y se extrajo con acetato de etilo (2x 25 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se filtraron sobre una capa de sílice. Los disolventes se redujeron al vacío y se aisló un aceite incoloro (1 g). El intermedio de dietil acetal se usa tal cual en la siguiente etapa. Rendimiento del 74 %.

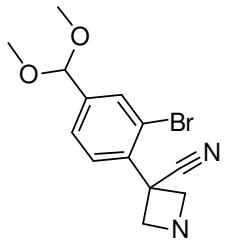
Preparación 32: 1-benzhidril-3-(2-bromo-4-(dietoximetil)fenil)azetidin-3-

carbonitrilo



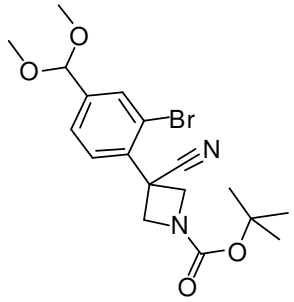
Se disolvieron 2-bromo-4-(dietoximetil)-1-fluorobenceno (Preparación 31, 1 g) y 1-benzhidrilazetidin-3-carbonitrilo (2,7 g) en THF anhidro (4 ml). Después, se añadió de una sola vez KHMDS (2,2 g). La solución se volvió instantáneamente de color pardo oscuro. La reacción se agitó a temperatura ambiente durante una noche. Un análisis por CL-EM confirmó la conversión completa en el producto deseado: [433] ~3,31 minutos y [505] ~3,62 min. Ambos picos corresponden al producto deseado: uno es el aldehído, y el otro es el acetal. La mezcla de reacción bruta se concentró, dando un aceite, se cargó sobre un cartucho de 80 g de SiO_2 y después se eluyó con un gradiente de acetato de etilo al 0-100 % en heptano. Las fracciones deseadas se recogieron y se concentraron al vacío. El aceite resultante se suspendió en metanol, se sonicó durante 30 s, y el polvo de color blanco resultante se filtró y se usó tal cual en la siguiente etapa. Rendimiento del 55 %. CL-EM [505].

Preparación 33: 3-(2-bromo-4-(dimetoximetil)fenil)azetidin-3-carbonitrilo



El producto de la Preparación 32 (500 mg) se disolvió en acetonitrilo, la mezcla de reacción se enfrió a 0 ºC y después se añadió de una sola vez cloroformiato de cloroetilo (0,2 ml). La mezcla de reacción se calentó a reflujo durante 2 horas. El análisis por CL-EM mostró la formación de picos deseada de ~2,329 minutos [339], pero quedó un poco de material de partida. Se añadió otro equivalente de cloroformiato de cloroetilo y la mezcla de reacción se dejó en agitación durante una hora más a reflujo. El análisis por TLC mostró la finalización. La reacción bruta se concentró al vacío, el aceite de color amarillo resultante se disolvió en MeOH y se calentó de nuevo a reflujo durante 30 minutos. El análisis por TLC mostró la conversión completa en un punto inicial. La reacción se concentró, dando un aceite y se añadieron 20 ml de éter dietílico. Después, la goma se sonicó durante 15 minutos, y el sólido se filtró y se analizó. El análisis por CL-EM ([311] ~2,036 min) confirmó el producto deseado, aunque el etilacetal es ahora un metilacetal debido al calentamiento a reflujo en metanol. Se usó como tal en la siguiente etapa. Asumió un rendimiento cuantitativo.

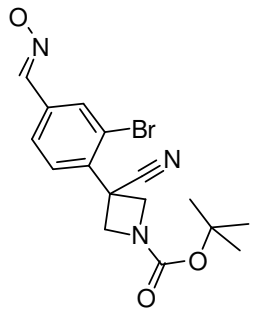
Preparación 34: 3-(2-bromo-4-(dimetoximetil)fenil)-3-cianoazetidin-1-carboxilato de *terc*-butilo



El producto de la Preparación 33 (300 mg) y anhídrido de boc (252 mg) se mezclaron en CH_2Cl_2 (4 ml) y se añadió una base de Hunig (500 µl). La

mezcla de reacción se dejó en agitación a temperatura ambiente durante 1 hora, después se recogió por TLC (50/50 de acetato de etilo/heptano) y mostró la finalización. La mezcla en bruto se concentró, dando un aceite y se sometió a cromatografía sobre una columna de 25 g de SiO_2, eluyendo con un gradiente de acetato de etilo al 0-100 % en heptano. Las fracciones deseadas se recogieron y se concentraron al vacío. El análisis por CL-EM y la RMN confirmaron el producto deseado [m/z 411], usado como tal en la siguiente etapa. Mezcla del aldehído y dimetoxiacetal.

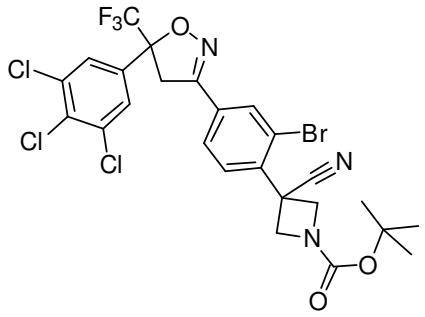
Preparación 35: 3-(2-bromo-4-((hidroxiimino)metil)fenil)-3-cianoazetidin-1-carboxilato de *terc*-butilo



El producto de la Preparación 34 (320 mg) se añadió a 4 ml de MeOH y se añadió 1 ml de agua seguido de clorhidrato de hidroxilamina (85 mg). La mezcla de reacción se agitó a temp. ambiente y después de 30 minutos, el análisis por CL-EM mostró la formación de un nuevo pico de 2,976 minutos, si aislamiento. Después de 60 minutos, el análisis por CL-EM mostró un pequeño progreso por lo que la mezcla se calentó a 65 ºC durante 10 minutos. Ahora, el análisis por CL-EM mostró una conversión limpia en la masa deseada [446] ~3,165 min. La reacción en bruto se concentró hasta un mínimo (suspensión de color blanco) y después se extrajo con acetato de etilo/$NaHCO_3$. La fase de acetato de etilo se secó sobre $MgSO_4$, se filtró y se concentró al vacío, y la

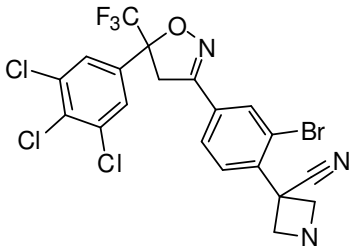
goma resultante se analizó por RMN. Mostró el producto deseado. 300 mg, se usaron como tal en la siguiente etapa.

Preparación 36: 3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-cianoazetidin-1-carboxilato de *terc*-butilo



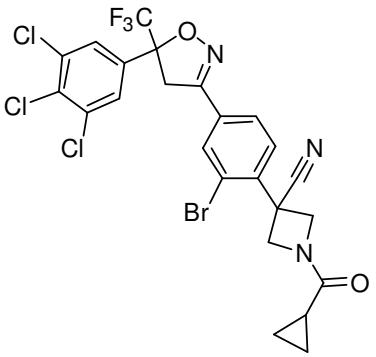
La oxima de la Preparación 35 (130 mg) se mezcló con N-clorosuccinimida (50 mg) en acetato de etilo y la mezcla de reacción se agitó a 55 ºC durante 15 minutos. El análisis por CL-EM conformó la formación del producto deseado (todo el material de partida había desaparecido). A la reacción se le añadió tricloroestireno (95 mg) seguido de $KHCO_3$ (63 mg). La mezcla de reacción se dejó en agitación a temperatura ambiente durante una noche. El análisis por CL-EM mostró la finalización. La mezcla se filtró sobre una fase de $MgSO_4$, y la solución de color amarillo se concentró, produciendo un sólido. El análisis por CL-EM confirmó la masa deseada [553] ~4,059 minutos. El sólido se cargó en una columna de 25 g de sílice y se eluyó con un gradiente de acetato de etilo al 0-100 %/heptano. Las fracciones deseadas se concentraron y se recogió un polvo de color blanco. 95 mg, rendimiento del 46 %.

Preparación 37: 3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-carbonitrilo



El producto de la Preparación 36 (90 mg) se disolvió en metanol anhidro. Se añadió una solución metanólica de HCl (300 µl) y se calentó a 65 ºC. Después de 3 horas, el análisis por CL-EM mostró el producto deseado [m/z 553] ~3,195 min. Después, la mezcla se concentró a sequedad y al sólido se le añadió éter dietílico (6 ml). La suspensión resultante se sonicó durante 10 minutos y después se filtró un polvo fino de color blanco. Se usó como tal en la siguiente etapa. El análisis por CL-EM confirmó el producto deseado [553]. 75 mg. Rendimiento del 98 %.

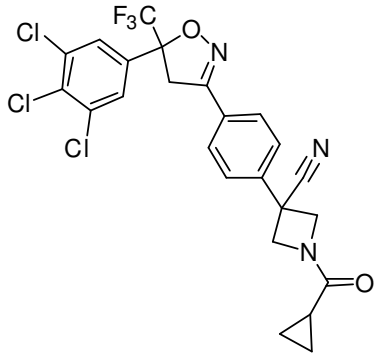
Ejemplo 86: 3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-1-(ciclopropanocarbonil)azetidin-3-carbonitrilo



El producto de la Preparación 37 (75 mg) se disolvió en CH_2Cl_2 (5 ml) y se añadió base de Hunig (74 mg, 97 µl) . La reacción se agitó a temperatura ambiente durante 1 minuto, después se añadió cloruro de ciclopropanocarbonilo (18,4 mg, 16 µl) y la mezcla se agitó durante 15 minutos. El análisis por CL-EM mostró el producto deseado formado [m/z 621] ~3,73

min. La mezcla se concentró y se cargó en una columna de 25 g de SiO_2, y se eluyó con un gradiente de acetato de etilo en heptano (0-50 % sobre 8 CV). Las fracciones deseadas se aislaron y se concentraron al vacío. 60 mg, rendimiento del 62 %. RMN 400 MHz δ ppm: 7,99 (s, 1H), 7,74 (d, 1H), 7,64 (s, 2H), 7,49 (d, 1H), 5,05 (m, 1H), 4,73 (m, 2H), 4,65 (m, 1H), 4,08 (d, 1H), 3,68 (d, 1H), 1,41 (m, 1H), 1,10-1,06 (m, 2H), 0,91-0,86 (m, 2H); CL-EM: [m/z 621] @ 3,73 minutos.

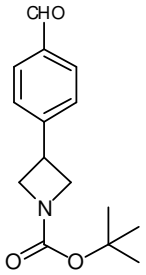
Ejemplo 87: 1-(ciclopropanocarbonil)-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-carbonitrilo



El compuesto del Ejemplo 86 (60 mg) se disolvió en THF (2 ml) y después se añadió gota a gota Rieke Zn en THF (2 ml de una solución 0,7 N). Después, la mezcla se sonicó durante 5 minutos. El análisis por CL-EM (THF + unas gotas de ácido acético) mostró una conversión de aproximadamente el 50 %. Se añadieron 4 equivalentes más de Zn y de nuevo se sometió a sonicación durante 15 minutos. El análisis por CL-EM mostró que la mezcla de reacción había desaparecido en una conversión de aproximadamente el 90 %. Después, se añadieron aproximadamente 200 µl de ácido acético, la mezcla de reacción se agitó durante 2 minutos y después se filtró sobre celite. La solución se concentró al vacío, el aceite restante se disolvió en acetato de etilo, se lavó con

$NaHCO_3$, después se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El aceite restante se purificó por cromatografía de fase inversa. Rendimiento de 55 mg. El análisis por CL-EM confirmó el producto deseado [m/z 542]. RMN 400 MHz δ ppm: 7,78 (d, 2H), 7,67 (d, 2H), 7,66 (s, 2H), 4,99 (m, 1H), 4,71 (m, 1H), 4,53 (m, 1H), 4,39 (m, 1H), 4,10 (d, 1H), 3,71 (d, 1H), 1,45-1,39 (m, 1H), 1,10-1,06 (m, 2H), 0,91-0,86 (m, 2H).

Preparación 38: éster *terc*-butílico del ácido 3-(4-formil-fenil)-azetidin-1-carboxílico:



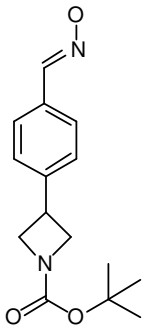
A una suspensión agitada de cinc activado (5,636 g, 86,19 mmol, 2 equivalentes) en DMF seca (20 ml) se le añadió dibromometano disuelto previamente (1,89 g, 10,77 mmol, 0,25 equivalentes) en DMF seca (5 ml) y la mezcla de reacción se calentó a 70°C durante 30 minutos en una atmósfera de nitrógeno. Después de 30 minutos, la reacción se enfrió a temperatura ambiente. A la mezcla de reacción resultante se le añadió clorotrimetilsilano disuelto previamente (1,12 g, 10,77 mmol, y 0,25 equivalentes) en DMF seca (5 ml) y se agitó durante 15 minutos seguido de la adición de 3-Yodo-N-Boc-Azetidina disuelta previamente (15,24 g, 53,86 mmol, 1,25 equiv.) en DMF seca (30 ml) y la mezcla de reacción se calentó a 40 °C durante 30 minutos en una atmósfera de nitrógeno. La mezcla de reacción se sonicó durante 30 minutos, durante la sonicación se suspendió de forma uniforme polvo de cinc para dejar

turbia la mezcla de reacción. A la mezcla de reacción sonicada (Zincato) se le añadió 4-Yodo benzaldehído disuelto previamente (10 g, 43,099 mmol, 1equiv.) en DMF seca (42 ml) seguido de adición de Tri-2-furil fosfina (1,1 g, 4,73 mmol, 0,1 equiv.) y Tris (dibencilideno-acetona) dipaladio (0) (1,18 g, 1,292 mmol, 0,03 equivalentes). La mezcla de reacción resultante se calentó a 70°C durante 18 horas en una atmósfera de nitrógeno. El progreso de la reacción se controló por TLC usando acetato de etilo al 10 % en hexano y se visualizó en luz UV (254 nm). La referencia del nuevo punto y el material de partida fue de 0,3 y 0,7 respectivamente. Después del consumo máximo del material de partida (18 horas), la mezcla de reacción se inactivó con cloruro de amonio saturado (100 ml) y se extrajo mediante acetato de etilo (3 x 100 ml). La fase orgánica combinada se secó sobre sulfato sódico y se concentró al vacío, proporcionando un líquido de color pardo (15 g, en bruto). El compuesto en bruto se purificó por cromatografía en columna usando un gel de sílice tamaño de malla de 100-200. El compuesto deseado se eluyó en acetato de etilo al 10 % en hexanos, proporcionando 6,5 g (57,79 %) de un líquido de color pardo. El RMN ^{1}H y el análisis por CL-EM eran coherentes. RMN ^{1}H (400 MHz, DMSO-d_6) δ: 1,40 (s, 9 H), 3,86-3,89 (m, 3 H), 4,26-4,29 (m, 2 H), 7,57 (d, *J* = 8,04 Hz, 2H), 7,90 (d, *J* = 8,16 Hz, 2H), 9,99 (s, 1 H). CL-EM (m/z): = 262,30 (M+H).

***Activación de cinc: Se agitó polvo de cinc (5 g) con una solución al 10 % de HCl (20 ml) durante 5 minutos a temperatura ambiente y se decantó. Este procedimiento se repitió dos veces, se filtró a través de un embudo Buchner, se lavó con agua (3 x 25 ml), acetona (2 x 20 ml) y se secó bien al vacío, proporcionando cinc activado (2 g).

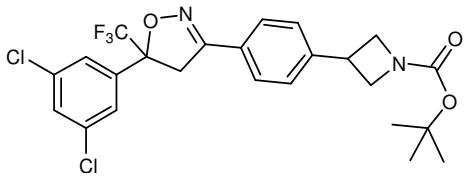
Preparación 39: Éster *terc*-butílico del ácido 3-[4-(hidroxiimino-metil)-fenil]-

azetidin-1-carboxílico



A una suspensión agitada de éster *terc*-butílico del ácido 3-(4-formil-fenil)-azetidin-1-carboxílico (Preparación 38, 6,5 g, 24,904 mmol, 1 equivalentes) en etanol:agua (1:1, 120 ml) se le añadió clorhidrato de hidroxil amina (2,5 g, 37,356 mmol, 1,5 equivalentes) seguido de acetato sódico (3,67 g, 44,82 mol, 1,8 equiv.). La mezcla de reacción resultante se agitó a temperatura ambiente durante 0,5 horas. El progreso de la reacción se controló por TLC usando acetato de etilo al 20 % en hexano y se visualizó en luz UV (254 nm). La referencia de un nuevo punto y el material de partida fue de 0,32 y 0,67 respectivamente. Después del consumo de material de partida, se evaporaron los disolventes a presión reducida y se extrajeron con DCM (3 x 25 ml). La evaporación de los volátiles proporcionó un sólido de color amarillo claro (6,5 g, 94,51 %). El análisis por CL-EM y el RMN ^{1}H eran coherentes. RMN ^{1}H (400 MHz, DMSO-d_6) δ 1,39 (s, 9 H), 3,81 (s ancho, 3 H), 4,42 (s ancho, 2 H), 7,36 (d, J = 8 Hz, 2 H), 7,57 (d, J = 8 Hz, 2 H), 8,12 (s, 1 H), 11,19 (s, 1 H). CL-EM (m/z): = 277,30 (M+H).

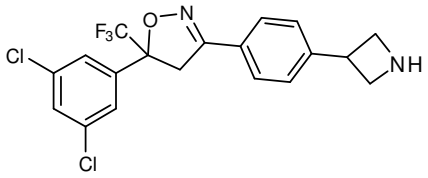
Preparación 40: éster *terc*-butílico del ácido 3-{4-[5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-carboxílico:



A una solución agitada de éster *terc*-butílico del ácido 3-[4-(hidroxiimino-metil)-fenil]-azetidin-1-carboxílico (Preparación 39, 1 g, 3,62 mmol, 1,0 equivalentes) en DMF (6,0 ml) se le añadió NCS (725,26 mg, 5,43 mmol, 1,5 equivalentes) y se calentó a 50°C durante 1 hora. El progreso de la reacción se controló por TLC usando metanol al 5 % en diclorometano. Después del consumo completo del material de partida, la reacción se enfrió a 0 ºC seguido de la adición de carbonato ácido potásico (543,18 mg, 5,43 mmol, 1,5 equivalentes) y una solución disuelta previamente de 1,3-dicloro-5-(1-trifluorometil-vinil)-benceno (1,04 g, 4,345 mmol, 1,2 equivalentes) en DMF (4,0 ml). La reacción resultante se agitó a temperatura ambiente durante 16 horas en una atmósfera de nitrógeno. El progreso de la reacción se controló por TLC usando acetato de etilo al 20 % en hexano y se visualizó en la luz UV (254 nm). La referencia del producto requerido fue de 0,6 y 0,5 para el material de partida. Después del consumo del material de partida, la mezcla de reacción se inactivó con agua (40 ml) y se extrajo con éter dietílico (3 x 50 ml). La fase orgánica combinada se lavó con salmuera (20 ml), se secó sobre sulfato sódico anhidro y se concentró al vacío, proporcionando (1,50 g, en bruto). La purificación adicional por cromatografía en columna (en alúmina neutra) usando acetato de etilo al 10 % en hexano como eluyente proporcionó un sólido de color blanquecino de 1,3 g (69,84 %). El RMN ^{1}H y el análisis por CL-EM eran coherentes. RMN ^{1}H (400 MHz, DMSO-d_6) δ 1,39 (s, 9 H), 3,84 (m, 3 H), 4,25-4,38 (m, 4 H), 7,47 (d, J = 8 Hz, 2 H), 7,62 (d, J = 1 Hz, 2 H), 7,71 (d, J = 8 Hz,

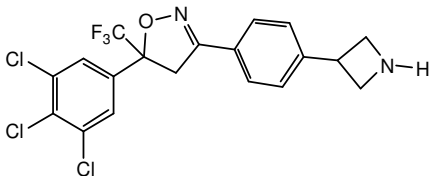
2 H), 7,81 (t, *J* = 2 Hz, 1 H). CL-EM (*m/z*): = 513(M-H).

Preparación 41: Sal clorhidrato de 3-(4-azetidin-3-il-fenil)-5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol



A una solución agitada de éster *terc*-butílico del ácido 3-{4-[5-(3,5-dicloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-carboxílico (Preparación 40, 1 g, 1,94 mmol, 1 equiv.) en MeOH (10 ml) se purgó HCl (g) a 0 ºC durante 0,5 horas y después la mezcla de reacción se calentó a reflujo a 70 ºC durante 0,5 horas. El progreso de la reacción se controló por TLC, después del consumo completo del material de partida, la mezcla de reacción se evaporó a presión reducida a sequedad, dando 1,15 g (en bruto) que se lavó con metil *t*-butil éter (10 ml x 2), proporcionando 1,1 g (95,21 %). El RMN ^{1}H y el análisis por CL-EM eran coherentes. RMN ^{1}H (400 MHz, DMSO-d_6) δ 4,05 (t, *J* = 8 Hz, 2 H), 4,15-4,21 (m, 1 H), 4,24-4,39 (m, 4 H), 7,55 (d, *J* = 8 Hz, 2 H), 7,62 (d, *J* = 1 Hz, 2 H), 7,74 (d, *J* = 8 Hz, 2 H), 7,81 (t, *J* = 2 Hz, 1 H), 8,99 (s a, 2 H). CL-EM (*m/z*): = 415 (M+H).

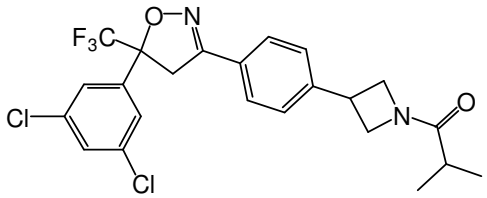
Preparación 42: sal clorhidrato de 3-(4-(azetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol



Se preparó a partir del compuesto de la Preparación 39 usando procedimientos similares a las Preparaciones 40 y 41 usando 1,2,3-tricloro-5-

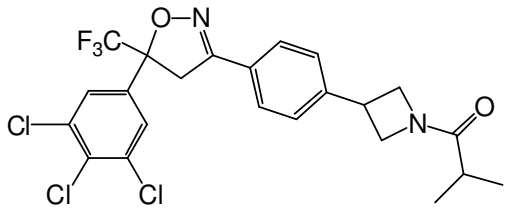
(3,3,3-trifluoroprop-1-en-2-il)benceno en lugar de 1,3-dicloro-5-(3,3,3-trifluoroprop-1-en-2-il)benceno. RMN ^{1}H (400 MHz, DMSO-d_6) δ 4,06 (t, J = 17 Hz, 2 H), 4,15-4,19 (m, 1 H), 4,24-4,29 (m, 2 H), 4,35 (t, J = 18 Hz, 2 H), 7,55 (d, J = 8 Hz, 2 H), 7,74 (d, J = 8 Hz, 2 H), 7,84 (s, 2 H), 9,004 (s a, 2 H). CL-EM (*m/z*): = 488,90 (M+H).

Ejemplo 88: 1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona



El compuesto se preparó a partir del compuesto de la preparación 41 usando un procedimiento similar al del Ejemplo 6 usando cloruro de isobutirilo en lugar de cloruro de ciclopropancarbonilo. RMN ^{1}H (DMSO-d6) δ ppm: 7,81 (1H), 7,72 (2H), 7,63 (2H), 7,49 (2H), 4,59-3,81 (8H), 1,0 (6H); m/z (EN+IQPA Positiva) 485 $[M+H]^+$.

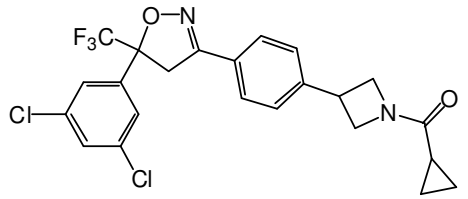
Ejemplo 89: 2-metil-1-(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona



El compuesto se preparó a partir del compuesto de la Preparación 42 usando un procedimiento similar al del Ejemplo 6 usando cloruro de isobutirilo en lugar de cloruro de ciclopropancarbonilo. RMN ^{1}H (DMSO-d6) δ ppm: 7,84 (2H), 7,72 (2H), 7,50 (2H), 4,59-3,84 (8H),1,0 (6H); m/z (EN+IQPA Positiva)

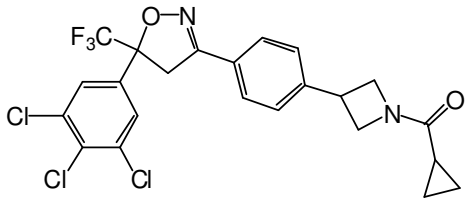
519 $[M+H]^+$.

Ejemplo 90: Ciclopropil(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona



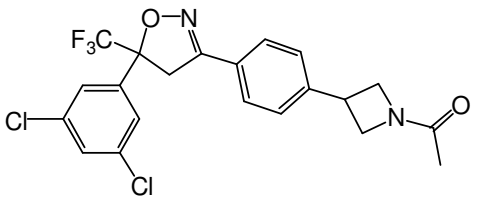
El compuesto se preparó a partir del compuesto de la Preparación 41 usando un procedimiento similar al del Ejemplo 6 usando cloruro de isobutirilo en lugar de cloruro de ciclopropancarbonilo. RMN ^{1}H (DMSO-d6) δ ppm: 7,81 (1H), 7,72 (2H), 7,63 (2H), 7,51 (2H), 4,66-3,16 (8H), 0,72 (4H); m/z (EN+IQPA Positiva) 483 $[M+H]^+$.

Ejemplo 91: Ciclopropil(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona



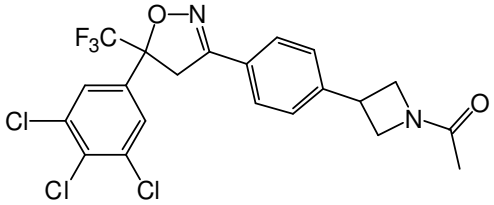
El compuesto se preparó a partir del compuesto de la Preparación 42 usando un procedimiento similar al del Ejemplo 6 usando cloruro de isobutirilo en lugar de cloruro de ciclopropancarbonilo. RMN ^{1}H ($CDCl_3$) δ ppm: 7,84 (2H), 7,71 (2H), 7,51 (2H), 4,69-3,18 (8H), 0,72 (4H); m/z (EN+IQPA Positiva) 517 $[M+H]^+$.

Ejemplo 92: 1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona



El compuesto se preparó a partir del compuesto de la Preparación 41 usando un procedimiento similar al del Ejemplo 1. RMN ^{1}H ($CDCl_3$) δ ppm 7,81 (1H), 7,72 (2H), 7,63 (2H), 7,51 (2H), 4,53-3,80 (7H), 1,80 (3H); m/z (EN+IQPA Positiva) 457 $[M+H]^+$.

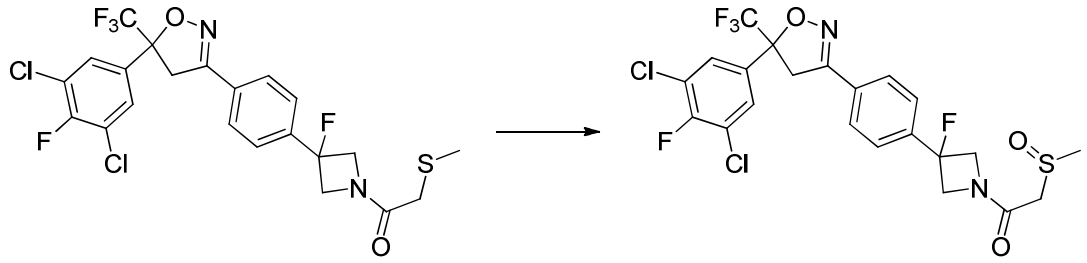
Ejemplo 93: 1-(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona



El compuesto se preparó a partir del compuesto de la Preparación 42 usando un procedimiento similar al del Ejemplo 1. RMN ^{1}H ($CDCl_3$) δ ppm: 7,84 (2H), 7,71 (2H), 7,50 (2H), 4,53-3,83 (7H), 1,80 (3H); m/z (EN+IQPA Positiva) 491 $[M+H]^+$.

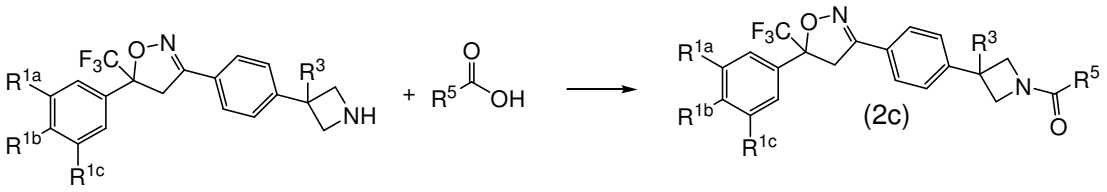
Preparación 43-oxidación de sulfuro a sulfóxido:

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona (Ejemplo 162)



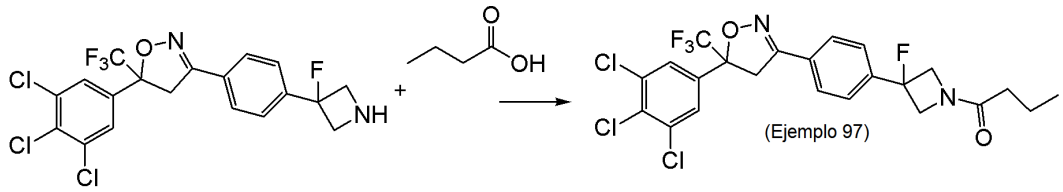
Una solución de (meta)peryodato sódico (49 mg, 0,23 mmol) en 1:1 de metanol/agua (6 ml) se enfrió con un baño de hielo y se añadió gota a gota mediante una pipeta una solución de 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona (102 mg, 0,19 mmol) en metanol (~2 ml). Se formó un precipitado y la reacción se dejó en agitación con el baño de hielo en lugar de calentar lentamente a temperatura ambiente durante una noche. Cuando se completó, la reacción se repartió entre agua (5 ml) y CH_2Cl_2 (5 ml). El producto acuoso se extrajo con más cantidad de CH_2Cl_2 (2 x 5 ml). La fase orgánica se recogió y se condensó. El material en bruto se absorbió sobre sílice y se sometió a cromatografía en una columna de 12 g de sílice, eluyendo con un gradiente de acetato de etilo del 0 % al 100 % en heptano. Las fracciones que contenían el material deseado se combinaron y se concentraron. A la película resultante se le añadió CH_2Cl_2 (~100 µl). Colocar el matraz a alto vacío durante una noche dio como resultado la formación de una espuma de color blanco. Rendimiento de 90 mg (86 %). Tiempo de retención de CL/EM = 3,317 minutos, EM calculado para ($C_{22}H_{17}Cl_2F_5N_2O_3S$) 554,03, observado 555,0 M+H+.

Preparación 44: Acoplamiento amida por química paralela



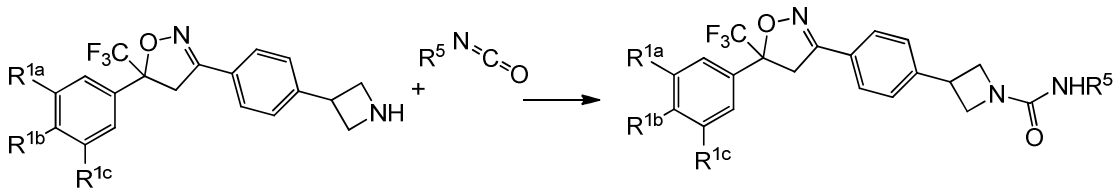
La isoxazolina fenil azetidina (0,05 mmol) se disolvió en dimetil formamida (0,5 ml); se añadió al ácido respectivo (0,1 mmol) seguido de una solución de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-

tetrametiluronio en dimetil formamida (0,5 ml) y trietilamina (0,5 mmol). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró por destilación al vacío, y el producto en bruto se purificó por HPLC preparativa. A continuación se muestra un ejemplo según se preparó por este procedimiento preparativo:



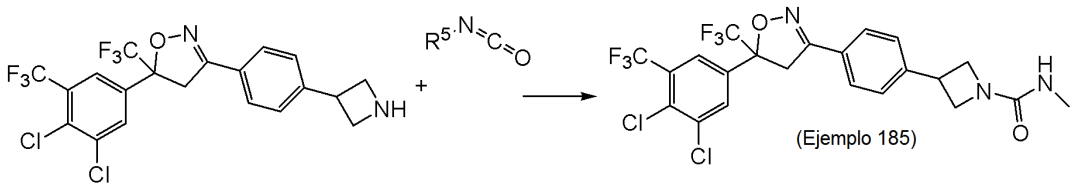
Se disolvió 3-(4-(3-fluoroazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (0,05 mmol) en dimetil formamida (0,5 ml); se añadió a ácido butírico (0,1 mmol) seguido de una solución de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio en dimetil formamida (0,5 ml) y trietilamina (0,5 mmol). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró por destilación al vacío y el producto en bruto se purificó por HPLC preparativa, dando 3,2 mg de 1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)butan-1-ona. MH+ 537; tiempo de retención de 9,83 minutos.

Preparación 45: Formación de urea por química paralela



Una solución de la isoxazolina fenil azetidina (0,05 mmol) en DMF (1 ml)

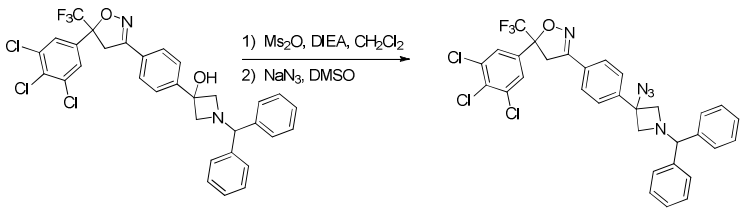
se trató con trietilamina (0,20 mmol). Se añadió una solución del isocianato respectivo (0,055 mmol) en DMF (0,5 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró a presión reducida y el producto en bruto se purificó por HPLC preparativa. A continuación se muestra un ejemplo preparado mediante este procedimiento preparativo:



Se disolvió 3-(4-(azetidin-3-il)fenil)-5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (0,05 mmol) en DMF (1 ml); se añadió trietilamina (0,20 mmol) seguido de una solución isocianatometano. La solución resultante se agitó a temperatura ambiente durante 16 horas. El disolvente se retiró a presión reducida y el producto en bruto se purificó por HPLC preparativa, dando 3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-metilazetidin-1-carboxamida (11,2 mg) MH+ 540,1; tiempo de retención de 6,14 minutos.

Preparación 46: Formación de azido

Pueden prepararse intermedios de azida de acuerdo con el siguiente procedimiento para 3-(4-(3-azido-1-benzhidrilazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (intermedio para el Ejemplo 163).



A una solución de 1,19 gramos (1,88 mmol, 1,0 equiv.) de 1-benzhidril-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ol en 17 ml de CH_2Cl_2 se le añadieron mediante una jeringa 500 µl (2,8 mmol, 1,5 equiv.) de diisopropil-etilamina pura seguido de 438 mg (2,5 mmol, 1,3 equiv.) de un sólido de anhídrido de metilsulfónico. Después de agitar durante 3,5 horas a temperatura ambiente, se puso una alícuota de la mezcla de reacción en 1,0 ml de metanol y se analizó mediante análisis por CL/EM. La cromatografía indicó que el material de partida se había consumido. La reacción se diluyó con 20 ml de CH_2Cl_2 y 20 ml de una solución saturada de $NaHCO_3$. Después de agitar durante 2 horas, las fases se separaron mediante un cartucho separado de fases Biotage. La fase orgánica se concentró a presión reducida, dando 1,29 gramos (rendimiento del 96 %) del intermedio de metanosulfonato de 1-benzhidril-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ilo en forma un sólido de color amarillo claro. Una muestra de 227 de metanosulfonato de 1-benzhidril-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-ilo (0,35 mmol, 1,0 equiv.) y 72,1 mg de azida sódica (1,1 mmol, 3,1 equiv.) se pesaron en un matraz de 100 ml y a éste se le añadieron 3 ml de DMSO anhidro. Después de agitar durante 1,5 horas a temperatura ambiente, la reacción se diluyó con 30 ml de CH_2Cl_2 y 15 ml de una solución saturada de $NaHCO_3$. Después de agitar esta mezcla durante 1 hora, las fases se separaron

mediante un cartucho separador de fases Biotage. La fase de agua se aclaró con más cantidad de CH_2Cl_2 y las fases orgánicas combinadas se concentraron por evaporación usando una corriente de gas N_2. El aceite en bruto resultante se purificó por cromatografía en columna sobre gel de sílice eluyendo con CH_2Cl_2 al 100 %. La evaporación de las fracciones apropiadas dio 144,5 mg de producto, 3-(4-(3-azido-1-benzhidrilazetidin-3-il)fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol, (rendimiento del 63 %) en forma de un sólido vítreo de color amarillo. EM 656 [M+H], tiempo de retención de HPLC: 3,600 minutos.

Preparación 47: Separación quiral de enantiómeros:

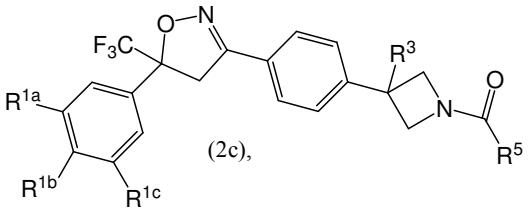
Al igual que un ejemplo para separar un enantiómero individual a partir de una mezcla racémica, se separó el Ejemplo 18 racémico en una columna quiral, proporcionando Ejemplo 177 de acuerdo con la siguiente resolución quiral por HPLC: SFC analítica Berger, columna Chiral IC 4,6 x 250 mm 5µ, fase móvil (A) era CO_2 y la fase móvil (B) era TEA al 0,1 % en metanol. Gradiente lineal al 5 % de B al 65 % de B en 12 minutos, 3 ml/minuto a 100 bar. La SFC preparativa se realizó en un Berger Multigram con una columna IC 30 x 250 mm 5 µ, con fase móvil (A) de CO_2 y fase móvil (B) de metanol, isocrático al 25 % de B, a 100 ml/minuto y 120 bar. El Ejemplo 172 es un enantiómero individual del racemato del Ejemplo 19. El Ejemplo 176 es un enantiómero individual del racemato 24.

Las condiciones de HPLC usadas para obtener los tiempos de retención y las masas de los Ejemplos de las Tablas 2, 3 y 4 se basaron en los siguientes procedimientos. Cada tiempo de retención en las tablas correspondientes se enumera con una "a", "b", "c", "d", "e" o "f". Cada símbolo alfabético se refiere a

condiciones y procedimientos de HPLC por separado. Para el Procedimiento "a", los datos de espectros de masas (EM) se obtuvieron usando un espectrómetro de masas Agilent con ionización química a presión atmosférica. Procedimiento: HPLC Acquity con cromatografía realizada en una columna Waters BEH C18 (2,1 x 50 mm, 1,7 μm) a 50 ºC. La fase móvil era un gradiente binario de agua (que contenía ácido trifluoroacético al 0,1 %) y acetonitrilo (acetonitrilo al 5-100 % en un tiempo de realización de 5 minutos), a 254 nm. Para el Procedimiento "b", el análisis HPLC con cromatografía se realizó en una columna Gemini NX-50 x 4,60 mm, 5 μ. La fase móvil era un gradiente binario de tampón acetato amónico 10 mM (pH = 4,6) y acetonitrilo (gradiente de acetonitrilo al 10-100 % en un tiempo de realización de 12 minutos con un caudal de 1 ml/minuto) a 254 nm. Para el Procedimiento "c", el análisis por HPLC con cromatografía se realizó en una columna Gemini NX-50 x 4,60 mm, 5 μ. La fase móvil era un gradiente binario de tampón acetato amónico 10 mM (pH = 4,6) y acetonitrilo (gradiente de acetonitrilo al 50-100 % en un tiempo de realización de 4,5 minutos con un caudal de 1 ml/minuto) a 254 nm. Para el Procedimiento "d", el análisis por HPLC con cromatografía se realizó en un Waters Alliance 2795 con ZQ MS-ESI+ con una columna Gemini NX C18 4,6 x 100, 5 μ. La fase móvil era un gradiente binario de agua (que contenía ácido trifluoroacético al 0,05 %) y acetonitrilo (gradiente de acetonitrilo al 50-95 % en un tiempo de realización de 12 minutos, caudal 1 ml/min) a 254 nm. Para el Procedimiento "e", el análisis HPLC con cromatografía se realizó en Waters Alliance 2795 con ZQ MS-ESI+ con una columna Gemini NX C18 4,6 x 150, 5 μ. La fase móvil era un gradiente binario de agua (que contenía ácido trifluoroacético al 0,1 %) y acetonitrilo (gradiente de acetonitrilo al 50-95 % en

un tiempo de realización de 12 minutos, caudal 1 ml/min) a 254 nm. Para el Procedimiento "f", la cromatografía de SFC se realizó en una columna Berger 2-EP 5 µm de 4,6 x 250 mm. La fase móvil era un gradiente binario de CO_2 y trietilamina al 0,1 % en MeOH (gradiente al 5-65 % de TEA al 0,1 % en MeOH en un tiempo de realización de 9 minutos, caudal 3 ml/min).

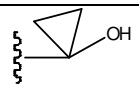
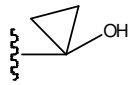
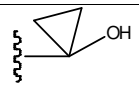
Usando los procedimientos descritos de forma similar en el presente documento, se prepararon y se muestran los compuestos (Ejemplos 94-185) de Fórmula (2c) en la Tabla 2.

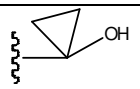
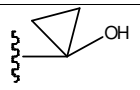
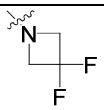
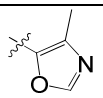
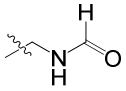
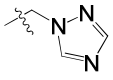


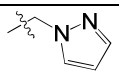
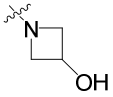
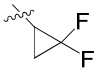
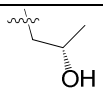
(2c),

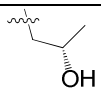
Tabla 2

Ejemplo Nº	**R^{1a}**	**R^{1b}**	**R^{1c}**	**R^3**	**R^5**	**m/z (IEN) [M+H]+**	**Tiempo de retención (minutos)**
94	Cl	Cl	Cl	OH	isopropilo	535	10,05e
95	Cl	Cl	Cl	F	CH_2CF_3	577	11,19e
96	Cl	Cl	Cl	F	CH_2-ciclopropilo	549	11,35e
97	Cl	Cl	Cl	F	propilo	537	9,83d
98	Cl	Cl	Cl	F	isopropilo	537	9,8d
99	Cl	Cl	Cl	F	etilo	523	9,44d

100	CF_3	H	Cl	F	isopropilo	537,1	4,53d
101	CF_3	H	Cl	F	CH_2OH	525,1	3,76d
102	CF_3	H	Cl	F	ciclopentilo	563,1	4,85d
103	CF_3	Cl	Cl	F	propilo	571,1	7,86d
104	Cl	H	Cl	H	etilo	471,1	6,2d
105	Cl	H	Cl	H		499,1	5,27d
106	Cl	H	Cl	H	CH_2OCH_3	487,1	5,62d
107	CF_3	Cl	Cl	H	CH_2-ciclopropilo	565,1	7,69d
108	CF_3	Cl	Cl	H	CH_3	525	7,11d
109	CF_3	Cl	Cl	H	etilo	539,1	7,2d
110	CF3	H	Cl	H	propilo	519,1	6,96d
111	CF_3	Cl	Cl	H	propilo	553,1	7,82d
112	CF_3	Cl	Cl	H	CH_2OH	541	5,53d
113	CF_3	Cl	Cl	H		567,1	6,24d
114	CF_3	Cl	Cl	H	CH_2SCH_3	571	7,42d
115	CF_3	H	Cl	H	CH_2-ciclopropilo	531,1	6,97d
116	CF_3	H	Cl	H	CH_2OCH_3	521,1	5,72d
117	CF_3	Cl	Cl	H	CH_2CN	550	6,72d
118	CF_3	H	Cl	H		533,1	5,39d
119	CF_3	Cl	Cl	H	CH_2OCH_3	555,1	6,58d
120	CF_3	H	Cl	H	etilo	505,1	6,34d
121	Cl	Cl	Cl	H	propilo	519,1	7,82d

122	CF_3	H	Cl	H	isopropilo	519,1	6,94d
123	Cl	Cl	Cl	H		533	6,14d
124	Cl	Cl	Cl	H	etilo	505	7,17d
125	Cl	Cl	Cl	H	CH_2SCH_3	537	7,41d
126	Cl	Cl	Cl	H	CH_2OCH_3	521	6,42d
127	Cl	Cl	Cl	H	CH_2-ciclopropilo	531,1	7,82d
128	Cl	F	Cl	H	CH_2SCH_3	521	6,55d
129	Cl	F	Cl	H	CH_2OCH_3	505,1	5,74d
130	Cl	F	Cl	H		517,1	5,41d
131	Cl	F	Cl	H	etilo	489,1	6,4d
132	Cl	F	Cl	H	isopropilo	503,1	7,03d
133	Cl	F	Cl	F		570	3,674a
134	Cl	F	Cl	OH	CH_2CF_3	559	3,483a
135	CF_3	Cl	Cl	F	CH_2CF_3	611	3,2a
136	Cl	F	Cl	F		560	7,42d
137	Cl	F	Cl	F		536	5,28d
138	Cl	F	Cl	F		557	6,13d
139	Cl	F	Cl	F		560,1	5,7d

140	Cl	F	Cl	F	$CH_2S(O)_2CH_3$	571	6,51d
141	Cl	F	Cl	F		559,1	6,7d
142	Cl	F	Cl	F		546	6,71d
143	Cl	F	Cl	F	CF_2CH_3	543	8,54d
144	CF_3	Cl	Cl	F		600	3,295a
145	Cl	F	Cl	F	$C(OH)(CH_3)_2$	537,1	6,74d
146	Cl	F	Cl	F	$CH_2CH=CH_2$	519,1	7,23d
147	Cl	F	Cl	F	$CH_2S(O)_2N(CH_3)_2$	600	6,99d
148	Cl	F	Cl	F	CH_2SCF_3	592,9	3,54a
149	Cl	F	Cl	F	$CH(OCH_3)CH_3$	537,1	6,93d
150	Cl	F	Cl	F		555	7,32d
151	Cl	F	Cl	F	$CH(CH_3)CH_2OH$	537,1	6,39d
152	Cl	F	Cl	F		537,1	6,43d
153	Cl	F	Cl	F		537,1	6,44d
154	Cl	F	Cl	Cl	ciclopropilo	nd	Nd-a
155	CF_3	Cl	Cl	Cl	ciclopropilo	nd	Nd-a
156	Cl	H	H	F	ciclopropilo	466,90	5,88b
157	Cl	F	F	OH	ciclopropilo	498,80	5,58b

						[M-H]	
158	CF_3	F	F	F	ciclopropilo	534,60 [M-H]	6,16b
159	Cl	F	Cl	F		523	3,419a
160	Cl	F	Cl	F		523	3,406a
161	Cl	F	Cl	F		537	3,414a
162	Cl	F	Cl	F	$CH_2S(O)CH_3$	555	3,317a
163	Cl	Cl	Cl	N_3	ciclopropilo	558	3,176a
164	Cl	Cl	Cl	N_3	etilo	546	3,271a
165	Cl	F	Cl	F	$CH_2SC(O)CH_3$	567	3,604a
166	F	H	H	F	etilo	436,90 [M-H]	2,38c
167	Cl	H	H	F	etilo	455,20	2,60c
168	Cl	Cl	H	F	etilo	486,70 [M-H]	6,11b
169	CF_3	H	H	F	ciclopropilo	498,90 [M-H]	5,90b
170	Cl	H	F	F	ciclopropilo	482,90 [M-H]	5,45b
171	F	F	H	F	ciclopropilo	467,00 [M-H]	2,55c
172^	Cl	F	Cl	F	CH_2CF_3	nd	nd-a

173	Cl	H	Cl	F		516	3,562a
174	Cl	Cl	Cl	F		552	3,667a
175	Cl	F	Cl	F		534,0	3,58a
176^	CF_3	Cl	Cl	OH	ciclopropilo	nd	nd-a
177^	Cl	F	Cl	F	isopropilo	nd	nd-a
178	Cl	F	Cl	F	$CH_2S(O)_2CH_2CN$	596	3,55d
179	Cl	F	Cl	F	$CH_2CH_2S(O)_2CH_3$	585	3,43d
180	Cl	F	Cl	F	$CH_2S(O)_2CH_2CF_3$	639	3,66d
181	Cl	F	Cl	F	$CH_2S(O)_2N(CH_3)_2$	600	3,55d
182	Cl	F	Cl	F	$CH_2S(O)_2$Fenilo	633	3,65d
183	Cl	F	Cl	F	$CHCH_3S(O)_2CH_3$	585	3,51d
184	CF_3	Cl	Cl	NHC(O)-ciclopropilo	ciclopropilo	634	6,315f
185	CF_3	Cl	Cl	NH_2	ciclopropilo	567	6,23f

~~~~~~~~~~ es el punto de unión.

^ representa un enantiómero individual resuelto sobre una columna quiral,

nd = no determinado

Los procedimientos de HPLC a, b, c, d y e son como se definen en el presente documento.

Los siguientes nombres para los Ejemplos (94-185) de la Tabla 2
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incluyen:

1-isobutiril-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol (94); 3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (95); 3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (96); 3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (97); 3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (98); 3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (99); 5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (100); 2-[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetanol (101); 5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (102); 3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (103);

5-(3,5-diclorofenil)-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (104); 1-[(3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol (105); 5-(3,5-diclorofenil)-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (106); 3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (107); 3-[4-(1-acetilazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (108); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(1-

propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (109); 3-[4-(1-butirilazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (110); 3-[4-(1-butirilazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (111); 2-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]-2-oxoetanol (112); 1-{[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]carbonil}ciclopropanol (113); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (114); 5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (115); 5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (116); 3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]-3-oxopropanonitrilo (117); 1-{[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]carbonil}ciclopropanol (118); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (119); 5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (120); 3-[4-(1-butirilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (121); 5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (122); 1-[(3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol (123); 3-[4-(1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (124); 3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol (125); 3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (126); 3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (127); 5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (128); 5-(3,5-dicloro-4-fluorofenil)-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (129); 1-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol (130); 5-(3,5-dicloro-4-fluorofenil)-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (131); 5-(3,5-dicloro-4-fluorofenil)-3-[4-(1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (132); 5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(3,3-difluoroazetidin-1-il)carbonil]-3-fluoroazetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (133); 3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-(3,3,3-trifluoropropanoil)azetidin-3-ol (134); 5-[3,4-dicloro-5-(trifluorometil)fenil]-3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (135); 5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(4-metil-1,3-oxazol-5-il)carbonil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (136); N-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]formamida (137); 4-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]piridazina (138); 1-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]-1H-1,2,4-triazol (139); 5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfonil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (140);

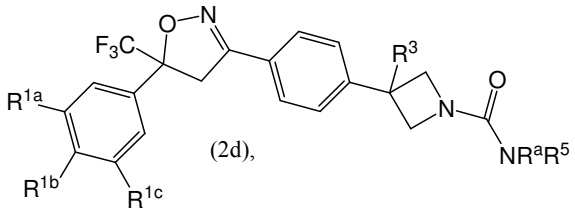
5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1H-pirazol-1-ilacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (141); 5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1,3-oxazol-5-ilcarbonil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (142); 5-(3,5-dicloro-4-fluorofenil)-3-{4-[1-(2,2-difluoropropanoil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (143); 1-{[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]carbonil}azetidin-3-ol (144); 1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-ol (145); 3-[4-(1-but-3-enoil-3-fluoroazetidin-3-il)fenil]-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (146); 2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-N,N-dimetil-2-oxoetanosulfonamida (147); 5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-{[(trifluorometil)tio]acetil}azetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (148); 5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(2-metoxipropanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (149); 5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(2,2-difluorociclopropil)carbonil]-3-fluoroazetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (150); 3-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-3-oxopropan-1-ol (151); (2S)-4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol (152); 4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol (153); 3-{4-[3-cloro-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (154); 3-{4-[3-cloro-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-

(trifluorometil)-4,5-dihidroisoxazol (155); 5-(3-clorofenil)-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (156); 3-{4-[5-(3-cloro-4,5-difluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-(ciclopropilcarbonil)-azetidin-3-ol (157); 3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-difluoro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (158); (2S)-1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-1-oxopropan-2-ol (159); (2R)-1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-1-oxopropan-2-ol (160); (2S)-4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol (161); 5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfinil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol (162); 3-{4-[3-azido-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (163); 3-[4-(3-azido-1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (164); etanotioato de S-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetilo] (165); 5-(3-fluorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (166); 5-(3-clorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (167); 5-(3,4-diclorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (168); 3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-5-[3-(trifluorometil)fenil]-4,5-dihidroisoxazol (169); 5-(3-cloro-5-fluorofenil)-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol (170); 3-{4-[1-

(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,4-difluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (171); 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona (172); 3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (173); 3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (174); 3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol (175); 1-(ciclopropilcarbonil)-3-{4-[(5R)-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol (176); 5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol (177), {[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]sulfonil}acetonitrilo (178), 1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-3-metanosulfonil-propan-1-ona (179), 1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-(2,2,2-trifluoro-etanosulfonil)-etanona (180), dimetilamida del ácido 2-(3-{4-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-oxo-etanosulfónico (181), 2-Bencenosulfonil-1-(3-{4-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-etanona (182), 1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-metanosulfonil-propan-1-ona (183), (1-Ciclopropanocarbonil-3-{4-[5-(3,4-dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-

azetidin-3-il)-amida del ácido ciclopropanocarboxílico (184), y (3-Amino-3-{4-[5-(3,4-dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-ciclopropil-metanona (185).

Usando procedimientos descritos de forma similar en el presente documento, se prepararon y se muestran los compuestos (Ejemplos 186-205) de Fórmula (2d) en la Tabla 3.



(2d),

Tabla 3

Ejemplo Nº	**R^{1a}**	**R^{1b}**	**R^{1c}**	**R^{a}**	**R^{3}**	**R^{5}**	**m/z (IEN) [M+H]+**	**Tiempo de Retención (minutos)**
186	Cl	Cl	Cl	H	F	H	nd	nd a
187	Cl	Cl	Cl	H	H	ciclopropilo	532	6,68d
188	Cl	H	Cl	H	H	ciclopropilo	498,1	5,8d
189	CF_3	Cl	Cl	H	OH	propilo	nd	nd a
190	CF_3	Cl	Cl	metilo	OH	metilo	570	3,0a
191	Cl	Cl	Cl	H	H	etilo	520	6,69d
192	Cl	F	Cl	H	H	metilo	490,1	5,32d
193	CF3	Cl	Cl	H	H	metil o	540,1	6,14d

194	Cl	H	Cl	H	H	etilo	486,1	5,8d
195	Cl	F	Cl	H	H	etilo	504,1	5,94d
196	CF_3	H	Cl	H	H	metilo	506,1	5,32d
197	CF_3	H	Cl	H	H	ciclopropilo	532,1	5,91d
198	Cl	F	Cl	H	H	ciclopropilo	516,1	5,94d
199	CF_3	Cl	Cl	H	H	ciclopropilo	566,1	6,74d
200	CF_3	Cl	Cl	H	F	CH_2CF_3	626	3,461a
201	Cl	Cl	Cl	metilo	F	metilo	538	3,278a
202	CF_3	Cl	Cl	metilo	F	metilo	572	3,422a
203	CF_3	Cl	Cl	H	F	$CH_2CH_2CF_3$	640	3,238a
204	CF_3	Cl	Cl	H	F		600	3,305a
205	Cl	Cl	Cl	metilo	N_3	metilo	561	3,724a

〰〰〰 es el punto de unión

nd = no determinado

Los procedimientos por HPLC a, b, c, d y e son como se definen en el presente documento

Los siguientes nombres de la IUPAC para los Ejemplos (186-205) de la Tabla 3 incluyen:

3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (186); N-ciclopropil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (187); N-ciclopropil-3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (188); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-hidroxi-N-propilazetidin-1-

carboxamida (189); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-hidroxi-N,N-dimetilazetidin-1-carboxamida (190); N-etil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (191); 3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-metilazetidin-1-carboxamida (192); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-metilazetidin-1-carboxamida (193); 3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-etilazetidin-1-carboxamida (194); 3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-etilazetidin-1-carboxamida (195); 3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-metilazetidin-1-carboxamida (196); 3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-ciclopropilazetidin-1-carboxamida (197); N-ciclopropil-3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (198); N-ciclopropil-3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-carboxamida (199); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-(2,2,2-trifluoroetil)azetidin-1-carboxamida (200); 3-fluoro-N,N-dimetil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (201); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N,N-dimetilazetidin-1-carboxamida (202); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-(3,3,3-trifluoropropil)azetidin-1-carboxamida (203); 3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-

3-fluoro-N-oxetan-3-ilazetidin-1-carboxamida (204); y 3-azido-N,N-dimetil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida (205).

Usando procedimientos descritos de forma similar en el presente documento, se prepararon y se muestran los compuestos (Ejemplos 206-218) de Fórmula (2e) en la Tabla 4.

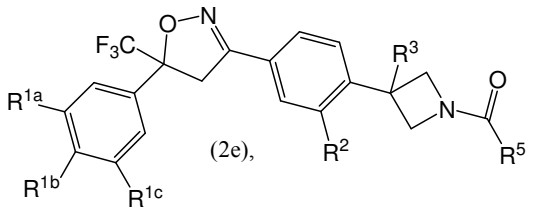


Tabla 4

Ejemplo Nº	**R^{1a}**	**R^{1b}**	**R^{1c}**	**R^2**	**R^3**	**R^5**	**m/z (IEN) [M+H]+**	**Tiempo de Retención (minutos)**
206	Cl	F	Cl	CN	F	ciclopropilo	544	3,573a
207	Cl	F	Cl	CN	F	metilo	518	3,046a
208	Cl	F	Cl	CN	F	CH_2CF_3	586	3,206a
209	Cl	F	Cl	CN	F	etilo	532	3,534a
210	Cl	F	Cl	CN	F	isopropilo	546	3,657a
211	Cl	F	Cl	CN	F	CH_2OH	534	6,19d
212	Cl	F	Cl	CN	F	propilo	546,1	7,17d
213	Cl	F	Cl	CN	F	ciclobutilo	558,1	7,3d

214	Cl	F	Cl	CN	F	ciclopentilo	572,1	7,54d
215	Cl	F	Cl	CN	F	CH_2OCH_3	548	6,74d
216	Cl	F	Cl	CN	F	CH_2-ciclopropilo	558,1	7,15d
217	Cl	F	Cl	CN	F	n-butilo	560,1	7,44d
218	Cl	F	Cl	CN	F	CH_2SCH_3	564	7,02d

Los procedimientos por HPLC a, b, c, d y e son como se definen en el presente documento

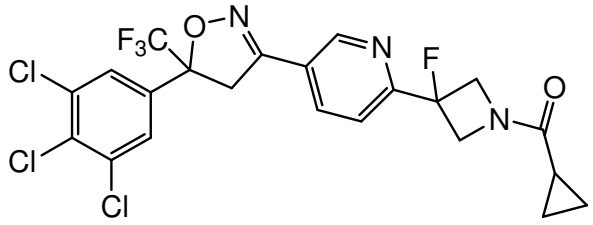
Los siguientes nombres de la IUPAC para los Ejemplos (206-218) de la Tabla 4 incluyen:

2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo (206); 2-(1-acetil-3-fluoroazetidin-3-il)-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo (207); 5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]benzonitrilo (208); 5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-propionilazetidin-3-il)benzonitrilo (209); 5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-isobutirilazetidin-3-il)benzonitrilo (210); 5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-glicoloilazetidin-3-il)benzonitrilo (211); 2-(1-butiril-3-fluoroazetidin-3-il)-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo (212); 2-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo (213); 2-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo (214); 5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-[3-fluoro-1-(metoxiacetil)azetidin-3-il]benzonitrilo (215); 2-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo (216); 5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-pentanoilazetidin-3-il)benzonitrilo (217); y

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-{3-fluoro-1-[(metiltio)acetil]-azetidin-3-il}benzonitrilo (218).

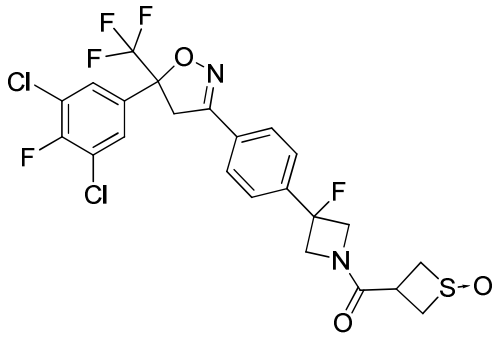
Ejemplo 219: 2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]piridina



Usando los procedimientos que se han descrito anteriormente, se preparó 2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]piridina a partir de 6-bromonicotinaldehído y 3-oxoazetidin-1-carboxilato de *terc*-butilo. EM 533,80[M-H], tiempo de retención de HPLC 6,41 minutos**.** Procedimiento de HPLC "b". RMN ^{1}H (400 MHz, $CDCl_3$) δ 0,79-0,86 (m, 2 H), 1,03-1,05(m, 2 H), 1,44-1,47 (m, 1 H), 3,70 (d, *J* = 16,88 Hz, 1H), 4,10 (d, *J* = 17,28 Hz, 1H), 4,34-4,52 (m, 2 H), 4,61 (dd, *J* = 9,48, 22,36 Hz, 1H), 4,84 (dd, *J* = 9,56, 20,32 Hz, 1H), 7,63 (s, 2H), 7,65 (s, 1H), 8,07-8,11 (m, 1H), 8,85 (s,1 H).

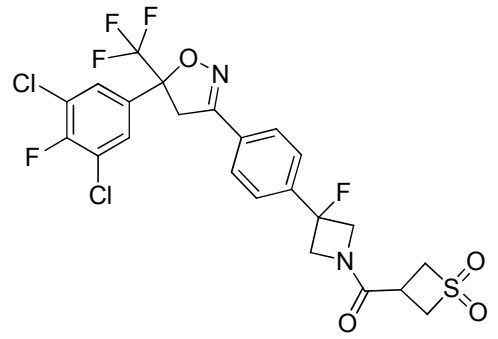
Ejemplo 220: (3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona



El compuesto se preparó a partir del compuesto de la Preparación 16 de acuerdo con el método del Ejemplo 12 usando 1-óxido del ácido tietano-3-carboxílico en lugar de ácido butírico. Rendimiento de 133 mg (70 %). RMN ^{1}H ($CDCl_3$) δ 7,69 (d, 2 H), 7,58 (d, 2 H), 7,47 (m, 2 H), 4,67-4,32 (m, 4 H), 4,09 (d, 1 H), 3,91-3,64 (m, 4 H), 3,60-3,33 (m, 2 H). Tiempo de retención de CL/EM = 3,355 minutos, EM calculado para ($C_{23}H_{17}Cl_2F_5N_2O_3S$) 566,03, observado 567,0 M+H+.

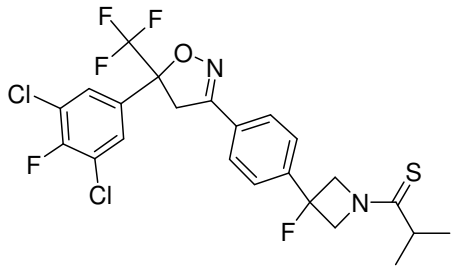
Ejemplo 221: (3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona



Una solución de (3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona (30 mg) en metanol (2 ml) se añadió a una solución de oxona (160 mg) en agua (1

ml) enfriada con un baño de hielo. La reacción se dejó calentar lentamente a temperatura ambiente y después se agitó a temperatura ambiente durante 16 horas. La mayor parte del metanol se retiró a presión reducida y después se extrajo el producto acuoso restante con DCM (2 x 5 ml). La fase orgánica se recogió y se condensó. El material en bruto se absorbió sobre sílice y se sometió a cromatografía en una columna de 4 g de sílice, eluyendo con un gradiente de acetato de etilo del 0 % al 100 % en heptano. Las fracciones que contenían el material deseado se combinaron y se concentraron. Colocar el matraz a alto vacío durante una noche dio como resultado la formación de una espuma de color blanco. Rendimiento de 15,7 mg (51 %). RMN ^{1}H (DMSO-D6) δ 7,82 (m, 4 H), 7,69 (m, 2 H), 4,67 (d, 2 H), 4,46-4,29 (m, 8 H), 3,56-3,43 (m, 1 H). Tiempo de retención de CL/EM = 3,455 minutos, EM calculado para ($C_{23}H_{17}Cl_2F_5N_2O_4S$) 582,02, nd M+H+.

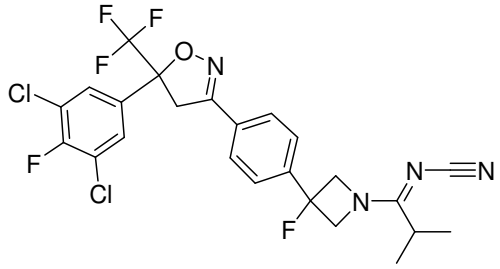
Ejemplo 222: 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropano-1-tiona



Se disolvió 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona (500 mg, 1,9 mmol) en tolueno (35 ml). Se añadió reactivo de Lawesson (790 mg, 1,9 mmol), la mezcla de reacción se calentó a reflujo durante 2 horas, después se enfrió a temperatura ambiente y se dejó en agitación durante una noche. La mezcla de

reacción se filtró y el filtrado se concentró al vacío. El residuo en bruto del filtrado se sometió a cromatografía (columna de 40 g Redi-Sep) eluyendo de heptano al 100 % a 25:75 de EtOAc:heptano, proporcionando el producto (415 mg, 80 %) en forma de un sólido. RMN ^{1}H ($CDCl_3$): 7,77 (2H), 7,61 (2H), 7,54 (2H), 4,68 (4H), 4,12 (1H), 3,72 (1H), 2,88 (1H), 1,28 (6H); m/z (CI) 537 ($[M+H]^+$.

Ejemplo 223: (1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida

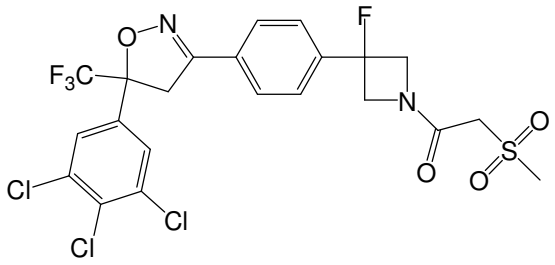


Se disolvió 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropano-1-tiona (325 mg, 0,6 mmol) en CH_2Cl_2 (15 ml) a 0 ºC y se añadió triflato de metilo (130 µl, 1,2 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante 3 horas. Después, la solución se enfrió a 0 ºC y se añadió gota a gota una solución de cianimida (54 mg, 1,2 mmol) y base de Hunig (220 µl, 1,2 mmol) en THF. La reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. A la solución se le añadió agua y la reacción se extrajo con CH_2Cl_2. La fase orgánica se secó (Na_2SO_4) y se concentró al vacío. El material en bruto se sometió a cromatografía (columna de 24 g Redi-Sep) eluyendo de heptano al 100 % a 50:50 de EtOAc:heptano, proporcionando el producto (104 mg, 31 %) en forma de un sólido. RMN ^{1}H ($CDCl_3$): 7,79 (2H), 7,61 (2H), 7,54 (2H), 4,68

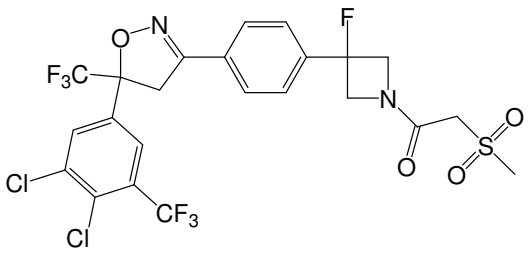
(4H), 4,12 (1H), 3,72 (1H), 3,44 (1H), 1,38 (6H); m/z (CI) 545 ($[M+H]^+$.

Los Ejemplos 224 y 225 se prepararon de acuerdo con los procedimientos y esquemas que se describen en el presente documento.

Ejemplo 224: (1-(3-Fluoro-3-{4-[5-(3,4,5-tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-2-metanosulfonil-etanona



Ejemplo 225: 1-(3-{4-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-metanosulfonil-etanona



Se muestran los datos de RMN para los compuestos seleccionados como se describe en el presente documento en la Tabla 5.

Tabla 5. Datos de RMN para los compuestos seleccionados

Compuesto Nº	Disolvente	RMN ^{1}H (δ ppm)
54	$CDCl_3$	7,76 (d, 2 H), 7,61-7,52 (d, 4 H), 7,46 (t, 1 H), 5,17-4,18 (m, 4 H), 4,12 (d, 1 H), 3,73 (d, 1 H), 2,46 (s, 1 H), 1,43 (c, 2 H), 1,08 (c, 2 H)
55	$CDCl_3$	7,75 (d, 2 H), 7,61 (d, 2 H), 7,57 (m, 2 H), 5,15-4,20

		(m, 4 H), 4,12 (d, 1 H), 3,72 (d, 1 H), 2,95 (s, 1 H), 1,41 (c, 2 H), 1,07 (c, 2 H)
57	$CDCl_3$	7,97 (d, 1 H), 7,87 (d, 1 H), 7,72 (m, 2 H), 7,61 (m, 2 H), 4,49-4,12 (m, 5 H), 3,84-3,69 (m, 2 H), 2,52 (m, 1 H), 1,15 (d, 6 H)
58	$CDCl_3$	7,97 (d, 1 H), 7,86 (d, 1 H), 7,72 (m, 2 H), 7,61 (m, 2 H), 4,46-4,12 (m, 5 H), 4,01 (d, 1 H), 3,74 (m, 1 H), 2,16 (t, 2 H), 1,68 (m, 2 H) 0,98 (t, 3 H)
68	DMSO-d_6	7,82 (d, 2 H), 7,74 (d, 2 H), 7,64 (d, 2 H), 6,53 (s, 1 H), 4,40-4,22 (m, 4 H), 4,03 (m, 2 H), 2,15 (c, 2 H), 1,00 (t, 2 H)
133	$CDCl_3$	7,75 (d, 2 H), 7,61 (d, 2 H), 7,55 (d, 2 H), 4,48 (m, 2 H), 4,38-4,24 (m, 6 H), 4,11 (d, 1 H), 3,72 (d, 1 H)
134	$CDCl_3$	7,72 (d, 2 H), 7,66-7,53 (m, 4 H), 4,56-4,28 (m, 4 H), 4,12 (d, 1 H), 3,90 (s, 1 H), 3,72 (d, 1 H), 3,07 (m, 2 H)
135	$CDCl_3$	7,97 (m, 1 H), 7,86 (m, 1 H), 7,78 (d, 2 H), 7,55 (d, 2 H), 4,78-4,66 (m, 1 H), 4,63-4,39 (m, 3 H), 4,17 (d, 1 H), 3,74 (d, 1 H), 3,11 (m, 2 H)
137	$CDCl_3$	8,29 (d, 1 H), 7,77 (d, 2 H), 7,61 (d, 2 H), 7,55 (d, 2 H), 6,58 (s a, 1 H), 4,73-4,39 (m, 4 H), 4,18-3,93 (m, 3 H), 3,72 (d, 1 H)
140	$CDCl_3$	7,77 (d, 2 H), 7,60 (m, 4H), 4,81 (d, 2 H), 4,57 (m, 1 H), 4,44 (m, 1 H), 4,11 (d, 1 H), 3,90 (s, 2 H), 3,72 (d, 1 H), 3,20 (s, 3 H)

141	$CDCl_3$	7,73 (d, 2 H), 7,64-7,57 (m, 4H), 7,50 (d, 2 H), 6,39 (m, 1 H), 4,96 (m, 2 H), 4,59-4,48 (m, 1 H), 4,46-4,33 (m, 2 H), 4,28-4,17 (m, 1 H), 4,14-4,07 (m, 1 H), 3,71 (d, 1 H)
144	$CDCl_3$	7,96 (m, 1 H), 7,85 (m, 1 H), 7,75 (d, 2 H), 7,58 (d, 2 H), 4,72-7,61 (m, 1 H), 4,49-4,38 (m, 2 H), 4,29-4,19 (m, 4 H), 4,15 (d, 1 H), 3,92-3,87 (m, 2 H), 3,72 (d, 1 H), 2,57 (m, 1 H)
145	$CDCl_3$	7,76 (d, 2 H), 7,61 (d, 2 H), 7,55 (d, 2 H), 4,95-4,33 (m, 4 H), 4,12 (d, 1 H), 3,72 (d, 1 H), 2,99 (s, 1 H), 1,50 (s, 6 H)
153	$CDCl_3$	7,76 (d, 2 H), 7,61 (d, 2 H), 7,55 (d, 2 H), 4,71-4,35 (m, 4 H), 4,34-4,23 (m, 1 H), 4,12 (d, 1 H), 3,72 (d, 2 H), 2,41-2,21 (m, 2 H), 1,28 (d, 3 H)
165	DMSO-d_6	7,85-7,79 (m, 4 H), 7,69 (d, 2 H), 4,82-4,69 (m, 2 H), 4,44-4,30 (m, 4 H), 3,70 (d, 2 H), 2,38 (s, 3 H)
178	$CDCl_3$	7,8 (2H), 7,5-7,7 (4H), 4,2-4,9 (6H), 4,0-4,2 (3H), 3,7 (1H)
179	$CDCl_3$	7,8 (2H), 7,6-7,7 (4H), 4,3-4,8 (4H), 4,0-4,2 (1H), 3,7-3,8 (1H), 3,3-3,6 (2H), 3,05 (3H), 2,7-2,9 (2H)
180		7,8 (2H), 7,5-7,7 (4H), 4,65-4,9 (2H), 4,3-4,65 (2H), (3,9-4,3 (5H), 3,6-3,8 (1H)
181	DMSO-d_6	7,8-7,9 (4H), 7,7 (2H), 4,7-4,9 (2H), 4,3-4,5 (4H), 4,15 (2H), 2,85 (6H)
182	$CDCl_3$	8,0 (2H), 7,7-7,8 (3H), 7,5-7,7 (6H), 4,7-4,9 (2H), 4,3-

		4,6 (2H), 3,9-4,2 (3H), 3,7-3,8 (1H)
183	$CDCl_3$	7,8 (2H), 7,5-7,7 (4H), 4,9-5,2 (1H), 4,3-4,8 (3H), 4,0-4,2 (1H), 3,6-3,9 (2H), 3,0 (3H), 1,7 (3H).
187	$CDCl_3$	7,69-7,64 (m, 4 H), 7,41 (d, 2 H), 4,43-4,34 (m, 3 H), 4,11 (d, 1 H), 3,98 (m, 2 H), 3,86-3,77 (m, 1 H), 3,70 (d, 1 H), 2,68-2,61 (m, 1 H), 0,76 (m, 2 H) 0,54 (m, 2 H)
188	$CDCl_3$	7,67 (m, 2 H), 7,54 (d, 2 H), 7,45 (t, 1 H), 7,41 (d, 2 H), 4,44-4,35 (m, 3 H), 4,10 (d, 1 H), 3,97 (m, 2 H), 3,85-3,76 (m, 1 H), 3,71 (d, 1 H), 2,68-2,60 (m, 1 H), 0,76 (m, 2 H) 0,54 (m, 2 H).
190	$CDCl_3$	7,98 (d, 1 H), 7,87 (d, 1 H), 7,70 (m, 4 H), 4,27 (m, 4 H), 4,17 (d, 1 H), 3,73 (d, 1 H), 3,62 (s, 1 H), 2,92 (s, 6 H)
200	$CDCl_3$	7,97 (s, 1 H), 7,86 (s, 1 H), 7,76 (d, 2 H), 7,56 (d, 2 H), 4,85 (m, 1 H), 4,60-4,43 (m, 2 H), 4,40-4,25 (m, 2 H), 4,18 (d, 1 H), 3,92 (m, 2 H), 3,75 (d, 1 H)
201	$CDCl_3$	7,72 (d, 2 H), 7,66 (s, 2 H), 7,57 (d, 2 H), 4,51-4,41 (m, 2 H), 4,31-4,21 (m, 2 H), 4,10 (d, 1 H), 3,70 (d, 1 H), 2,92 (s, 6 H)
202	$CDCl_3$	7,96 (m, 1 H), 7,85 (m, 1 H), 7,73 (d, 2 H), 7,58 (d, 2 H), 4,51-4,41 (m, 2 H), 4,31-4,21 (m, 2 H), 4,15 (d, 1 H), 3,72 (d, 1 H), 2,92 (s, 6 H)
203	$CDCl_3$	7,96 (m, 1 H), 7,85 (m, 1 H), 7,74 (d, 2 H), 7,56 (d, 2 H), 4,52-4,40 (m, 3 H), 4,29-4,20 (m, 2 H), 4,16 (d, 1

		H), 3,72 (d, 1 H), 3,54 (m, 2 H), 2,46-2,33 (m, 2 H)
204	$CDCl_3$	7,96 (m, 1 H), 7,85 (m, 1 H), 7,75 (d, 2 H), 7,56 (d, 2 H), 5,05-4,92 (m, 3 H), 4,85 (d, 1 H), 4,54-4,47 (m, 3 H), 4,44 (d, 1 H), 4,32-4,22 (m, 2 H), 4,16 (d, 1 H), 3,73 (d, 1 H)
213	$CDCl_3$	8,07 (s, 1 H), 7,99 (m, 1H), 7,68 (m, 1H), 7,60 (d, 2 H), 4,74-4,47 (m, 4 H), 4,11 (d, 1 H),), 3,73 (d, 1 H). 3,14 (m, 1 H), 2,45-2,29 (m, 2 H), 2,27-1,86 (m, 4 H)
216	$CDCl_3$	8,06 (s, 1 H), 7,98 (m, 1 H), 7,68 (m, 1 H), 7,58 (d, 2 H), 4,80-4,48 (m, 4 H), 4,10 (d, 1 H), 3,72 (d, 1 H), 2,15 (d, 2 H), 1,12-1,02 (m, 1 H), 0,59 (m, 2 H), 0,18 (m, 2 H)
224	$CDCl_3$	7,77 (d, 2 H), 7,67 (s, 2 H), 7,59 (d, 2 H), 4,81 (d, 2 H), 4,63-4,38 (m, 2 H), 4,11 (d, 1 H), 3,90 (s, 2 H), 3,72 (d, 1 H), 3,20 (s, 3 H)
225	$CDCl_3$	.97 (m, 1 H), 7,86 (m, 1 H), 7,77 (d, 2 H), 7,59 (d, 2 H), 4,81 (d, 2 H), 4,64-4,39 (m, 2 H), 4,17 (d, 1 H), 3,90 (s, 2 H), 3,73 (d, 1 H), 3,20 (s, 3 H)

Además de los 225 Ejemplos anteriores, los siguientes compuestos pueden prepararse de acuerdo con los Esquemas y preparaciones que se han mencionado anteriormente y se incluyen en el presente documento por la presente invención. Estos compuestos de Fórmula (1) incluyen: 2,2-dicloro-1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona; 1-(3-(4-(5-(3,5-dicloro-4-

fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-fluoro-2-metilpropan-1-ona; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-(metiltio)propan-1-ona; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-(metilsulfonil)propan-1-ona; (3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(tietan-3-il)metanona; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoro-2-metilpropan-1-ona; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-2-(metilsulfonil)propan-1-ona; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)propan-1-ona; (3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-(metilsulfonil)ciclopropil)metanona; 5-(3,5-dicloro-4-fluorofenil)-3-(4-(3-fluoro-1-(1,1,1,3,3,3-hexafluoropropan-2-il)azetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3-difluoropropan-1-ona; 2-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-N-metil-2-oxoetanosulfonamida; 2-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-N-isopropil-2-oxoetanosulfonamida; 1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(3-hidroxiazetidin-1-il)etanona; 1-(3-(4-(5-(3,5-dicloro-4-hidroxifenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(tietan-2-il)metanona;

N-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-il)acetamida;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-mercapto-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoro-2-hidroxi-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-hidroxi-2,2-dimetilpropan-1-ona;

3-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2,2-dimetil-3-oxopropanonitrilo;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3-difluoropropan-1-ona;

Etanotioato de S-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-ilo);

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-2-(metiltio)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-2-(metilsulfonil)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropano-2-sulfonamida;

1-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-il)urea;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;
(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona
(E)-N-(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;
1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;
3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;
1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metiltio)etanona;
1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona; (3-Fluoro-3-{4-[5-(3,4,5-

tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-

il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3-Cloro-4-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{4-[5-trifluorometil-5-(4-trifluorometil-fenil)-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-

il)fenil)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3,4-Difluoro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3-Cloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-

fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{4-[5-(3-cloro-5-fluorofenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(4-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{4-[5-trifluorometil-5-(3,4,5-trifluorofenil)-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-

dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropilideno)cianamida;
2-(1-(ciclopropanocarbonil)-3-fluoroazetidin-3-il)-5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)benzonitrilo;
ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;
ciclopropil(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)metanona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;
(3-{5-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;
(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{5-[5-(3,4,5-tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-

dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;
(E)-N-(1-(3-fluoro-3-(5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropilideno)cianamida;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;
ciclopropil(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)metanona;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;
(3-{5-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;
(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;
(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(4-Cloro-3-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(4-cloro-3-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)propan-1-ona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metiltio)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-Fluoro-3-{5-[5-trifluorometil-5-(3-trifluorometil-fenil)-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-azetidin-1-il)-tietan-3-il-metanona;

(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)(1-oxidotietan-3-il)metanona;

(1,1-dioxidotietan-3-il)(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;

(E)-N-(1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3-(trifluorometil)fenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

ciclopropil(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)metanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3,4-Difluoro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3,4-difluoro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3-Cloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3-cloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfinil)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(metilsulfonil)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-(1H-pirazol-1-il)etanona;

1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;

(3-{5-[5-(3-Cloro-5-fluorofenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-3-fluoro-azetidin-1-il)-tietan-3-il-metanona;

(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;

(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)piridin-2-il)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;

(E)-N-(1-(3-(5-(5-(3-cloro-5-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)piridin-2-il)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;
1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropan-1-ona;
ciclopropil(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona;
3,3,3-trifluoro-1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)propan-1-ona;
1-(3-fluoro-3-(4-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)fenil)-1,2-diazetidin-1-il)-2-(metiltio)etanona;
1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfinil)etanona;
1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(metilsulfonil)etanona;
1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-(1H-pirazol-1-il)etanona;
1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-hidroxi-2-metilpropan-1-ona;
(3-fluoro-3-{5-[5-trifluorometil-5-(3,4,5-trifluorofenil)-4,5-dihidro-isoxazol-3-il]-piridin-2-il}-azetidin-1-il)-tietan-3-il-metanona;
(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)(1-oxidotietan-3-il)metanona;
(1,1-dioxidotietan-3-il)(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)metanona; y
(E)-N-(1-(3-fluoro-3-(5-(5-(trifluorometil)-5-(3,4,5-trifluorofenil)-4,5-dihidroisoxazol-3-il)piridin-2-il)azetidin-1-il)-2-metilpropilideno)cianamida,

estereoisómeros de los mismos y sales farmacéutica y veterinariamente aceptables de los mismos.

ENSAYOS BIOLÓGICOS

La actividad biológica de los compuestos de la presente invención se ensayó frente a pulgas, garrapatas, moscas y/o piojos marinos usando los procedimientos de ensayo descritos posteriormente.

Ensayo de Alimentación de Mosca de los Cuernos (*Haematobia irritans*)

Se disolvieron los compuestos de Fórmula (1) en DMSO y se añadieron alícuotas a sangre bovina con citrato en una placa de Petri recubierta de membrana. Se colocaron aproximadamente diez moscas con cuernos en cada placa de Petri y se recubrieron. Se permitió a las moscas alimentarse en las células sanguíneas tratadas. Las moscas se mantuvieron a aproximadamente 26,67 ºC con un mínimo de aproximadamente 50 % de humedad relativa. Se examinó a las moscas con respecto a caída y mortalidad a aproximadamente 2 y 24 horas. Los datos de puntos finales se registraron como una dosis letal al 90 % (LD^{90}) en μg/ml. En este ensayo, los Ejemplos 8-10, 28, 32-34, 36, 38, 54, 160, 168-69, 171, 209 y 221 demostraron una LD^{90} de ≤ 0,3 μg/ml. Además en este ensayo, los Ejemplos 3-5, 11, 13-16, 20-22, 26-27, 31, 37, 40, 42, 45, 56, 59, 84-85, 87, 95, 99, 117, 137, 141, 145, 148, 152-53, 158, 162, 200, 206-07, 220 y 224 demostraron una LD^{90} de ≤ 1 μg/ml. Además en este ensayo, los Ejemplos 1, 2, 6,12, 46, 60, 65, 69, 77, 98, 108, 112, 133, 135, 138, 140, 142-44, 147, 154, 163, 170, 179, 187, 193, 197, 199, 201-02, 204, 216, 219, 222 y 225 demostraron una LD^{90} de ≤ 3 μg/ml

Ensayo Tópico de Mosca de los Establos (*Stomoxys calcitrans*)

Se disolvieron los compuestos de Fórmula (1) en acetona y se colocó 1

µl en el tórax de una mosca anestesiada (n=10). Se permitió a las moscas que se recuperaran y se incubaron durante 24 horas a temperatura ambiente. Se examinó a las moscas con respecto a caída y mortalidad a las 2 y 24 horas. Los datos de puntos finales se registraron como dosis letal al 90 % (LD^{90}) en µg/mosca. En este ensayo, los Ejemplos 1 y 11 demostraron una LD^{90} de ≤ 0,01 µg/mosca. Además en este ensayo, los Ejemplos 2, 9, 12 y 99 demostraron una LD^{90} de ≤ 0,03 µg/mosca. Además en este ensayo, los Ejemplos 6, 16, 26, 28, 33, 36, 37 y 98 demostraron una LD^{90} de ≤ 0,1 µg/mosca. Además en este ensayo, los Ejemplos 3, 14, 19, 27, 46, 84, 91 y 188 demostraron una LD^{90} de ≤ 1 µg/mosca.

Ensayo de Alimentación de Membrana de Pulga (*Ctenocephalidas felis*) Adulta

Se disolvieron los compuestos de Fórmula (1) en DMSO y se añadieron alícuotas a sangre bovina con citrato en una placa de Petri recubierta con membrana precalentada a 37 ºC. Se colocaron tubos de alimentación que contenían aproximadamente 30-35 pulgas adultas en las placas de Petri. Se permitió a las pulgas alimentarse durante aproximadamente 2 horas. Se observó a las pulgas con respecto a caída y/o muerte a aproximadamente 2 y 24 horas. Se registraron los datos de puntos finales como una dosis letal al 90 % (LD^{90}) en µg/ml. En este ensayo, el Ejemplo 10 demostró una LD^{90} de ≤ 0,03 µg/ml. Además en este ensayo, los Ejemplos 27 y 36 demostraron una LD^{90} de ≤ 0,1 µg/ml. Además en este ensayo, los Ejemplos 4-5, 11, 19, 23, 28, 32-33, 38, 84, 104, 117, 131, 137, 141, 160-161, 167-169, 175, 215-216 y 221 demostraron una LD^{90} de ≤ 0,3 µg/ml. Además, en este ensayo, los Ejemplos 1-3, 6-8, 12-16, 20-22, 26, 31, 37, 40-41, 43, 45-56, 59-60, 68, 72-77, 82, 91, 95-101, 103, 106-107, 109-110, 113, 116, 119-121, 123-126, 128-130, 132-133,

135, 138, 140, 145-146, 148, 152-153, 158, 162-164, 170, 173-174, 176, 197-199, 201-202, 205-210, 212-213, 218-220 y 222-223 demostraron una LD^{90} de ≤ 1 μg/ml. Además en este ensayo, los Ejemplos 17, 24-25, 29-30, 34-35, 39, 42, 44, 57-58, 61-65, 67, 69-70, 79-81, 87, 89, 94, 102, 105, 108, 111-112, 114-115, 118, 122, 127, 134, 136, 139, 142-144, 147, 154-157, 165-166, 171, 179, 186-196, 200, 203-204, 211, 214-215, 217 y 224-225 demostraron una LD^{90} de ≤ 3 μg/ml.

Ensayo de Alimentación de Sangre de Garrapata Blanda (*Ornithidorus turicata*)

Se disolvieron los compuestos de Fórmula (1) en dimetilsulfóxido (DMSO) y se añadieron alícuotas a sangre bovina con citrato en una placa de Petri cubierta con membrana. Se colocó después la placa de Petri en una bandeja de calentamiento. Se colocaron aproximadamente 5 garrapatas de etapa ninfa en la membrana, se cubrieron y se dejó que se alimentaran. Se retiraron las garrapatas alimentadas y se colocaron en una placa de Petri con arena. Se observó a las garrapatas alimentadas a aproximadamente 24, 48 y 72 horas con respecto a parálisis y/o muerte. Los datos de puntos finales se registraron como una ED^{100} y/o una LD^{100} en μg/ml. El control positivo fue fipronil y se usó DMSO para el control negativo. En este ensayo, los Ejemplos 11, 19, 40, 169 y 175 demostraron una ED^{100} de ≤ 0,003 μg/cm^2. Además, en este ensayo, los Ejemplos 2-8, 10-17, 20-21, 26-28, 32-34, 36-38, 41-48, 50-54, 56, 59-60, 65-66, 68, 70, 72-74, 76, 84, 95-99, 103, 131, 133, 135, 141-143, 145-146, 155, 158, 165, 168, 171, 173-174, 202, 206, 209-210, 212-213, 215-216, 218-219 y 221 demostraron una ED^{100} de ≤ 0,03 μg/cm^2. En este ensayo, los Ejemplos 1, 9, 22,-25, 29-31, 35, 39, 49, 55, 57-58, 67, 69, 71, 75, 77, 82, 87, 104, 117, 136-140, 144, 148, 152-154, 160, 170, 187-188, 203-204, 207,

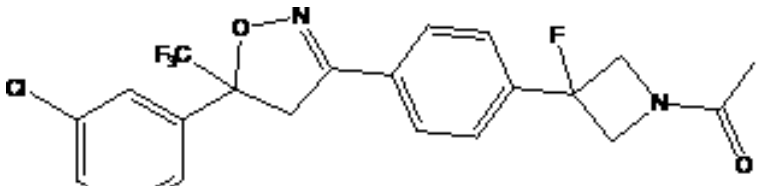
211, 214, 217, 220 y 223 demostraron una ED^{100} de ≤ 0,3 μg/cm^2. Además, en este ensayo, los Ejemplos 18, 89 y 91 demostraron una ED^{100} de ≤1 μg/cm^2. Además, en este ensayo, el Ejemplo 86 demostró una ED^{100} de ≤3 μg/cm^2.

Bioensayo de Copépodos (*Lepeophtheirus salmonis*)

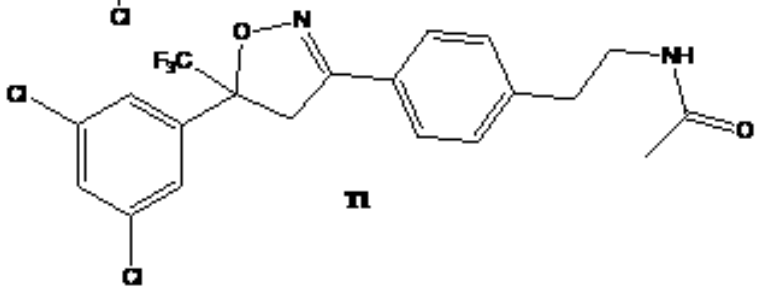
Se disolvieron dos compuestos de Fórmula (1) en agua marina. El control negativo fue agua marina y el control positivo fue benzoato de emamectina. Se expusieron diez piojos del salmón preadultos/adultos durante 24 horas. Se controló a los piojos con respecto a motilidad y se registraron los datos de puntos finales como una concentración eficaz del 100 % (EC^{100}) basándose en inmovilidad. En este ensayo, los Ejemplos 19 y 177 tuvieron un valor de CE^{100} de 50 ppb.

Datos Comparativos: Ensayo de Alimentación de Pulgas

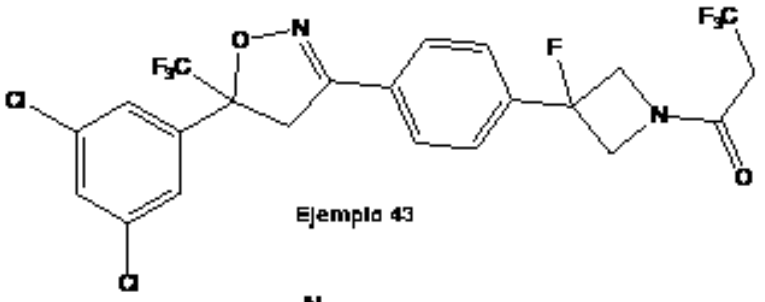
Se ensayaron los compuestos comparadores T1 y T2 en el ensayo de alimentación de pulgas, como se ha descrito anteriormente y se compararon con los Ejemplos 39 y 43, respectivamente. Los compuestos T1 (documento WO2008/122375) y T2 (documento US2009/0156643) representan la técnica ejemplificada más cercana. Los datos representan el periodo de tiempo de 24 horas. Se registraron los datos de puntos finales como unas dosis letal al 90 % (LD^{90}) en μg/ml. En este ensayo, los Ejemplos 39 y 43 tuvieron una LD^{90} de ≤ 3 y ≤ 1 μg/cm^2, respectivamente. Ambos compuestos comparadores T1 y T2 tuvieron valores de LD^{90} de ≥ 30 μg/cm^2.



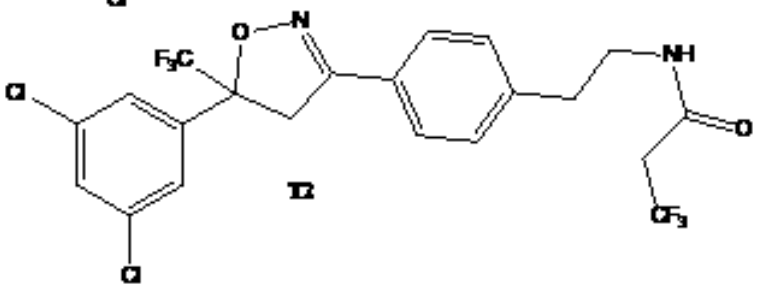
Ejemplo 39



T1



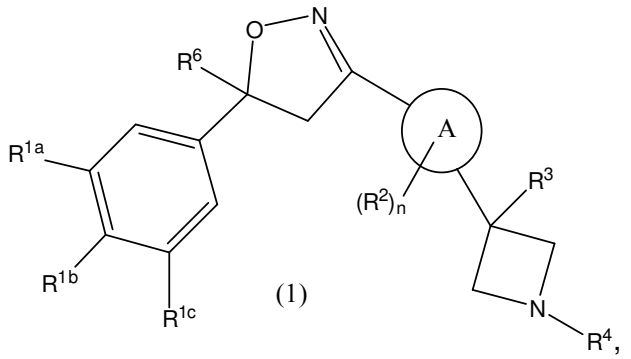
Ejemplo 43



T2

REIVINDICACIONES

1. Un compuesto de Fórmula (1)



(1)

en la que

A es fenilo, naftilo o heteroarilo en donde dicho heteroarilo contiene de 1 a 4 heteroátomos seleccionados cada uno de ellos independientemente entre N, O y S;

cada uno de R^{1a}, R^{1b} y R^{1c} es independientemente hidrógeno, halo, hidroxilo, ciano, nitro, alquilo C_1-C_6, haloalquilo C_1-C_6, alcoxi C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, haloalcoxi C_1-C_6, $-C(O)NH_2$, $-SF_5$ o $-S(O)_pR$;

R^2 es halo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, nitro, hidroxilo, $-C(O)NR^aR^b$, alquenilo C_2-C_6, alquinilo C_2-C_6, $-S(O)_pR$ u $-OR$;

R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, $-C(O)NH_2$, nitro, $-SC(O)R$, $-C(O)NR^aR^b$, alquil C_0-$C_3NR^aR^4$, $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3, $-NHR^4$, $-OR$ o $-S(O)_pR$;

R^4 es hidrógeno, alquilo C_1-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, $-C(O)R^5$, $-C(S)R^5$, $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6;

R^5 es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6;

R^6 es ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, -$C(O)NR^aR^b$, alquenilo C_2-C_6, alquinilo C_2-C_6, haloalquenilo C_2-C_6 o haloalquinilo C_2-C_6;

R^7 es hidrógeno, alquilo C_1-C_6, hidroxilo, ciano, nitro, -$S(O)_pR^c$ o alcoxi C_1-C_6;

R es alquilo C_1-C_6 o cicloalquilo C_3-C_6, cada uno opcionalmente sustituido con al menos un halo;

R^a es hidrógeno, alquilo C_1-C_6 o alquil C_0-C_3-cicloalquilo C_3-C_6; en donde el alquilo y el alquilcicloalquilo están opcionalmente sustituidos con ciano o al menos un sustituyente halo;

R^b es hidrógeno, alquilo C_1-C_6, cicloalquilo C_3-C_6, fenilalquilo C_0-C_3, heteroarilalquilo C_0-C_3 o heterocicloalquilo C_0-C_3, cada uno opcionalmente sustituido, cuando sea químicamente posible, con al menos un sustituyente seleccionado entre hidroxilo, ciano, halo o -$S(O)_pR$;

R^c es alquilo C_1-C_6, haloalquilo C_1-C_6, haloalquil C_1-C_6-cicloalquilo C_3-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, fenilalquilo C_0-C_3, heteroarilalquilo C_0-C_3 o heterocicloalquilo C_0-C_3, cada uno opcionalmente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, -$S(O)_pR$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^b$, -SCN o -$C(O)NR^aR^b$;

cada uno de R^4 y R^5 alquilo C_1-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6 puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, -$S(O)_pR^c$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^c$,

-SCN o -C(O)NR^aR^b; y

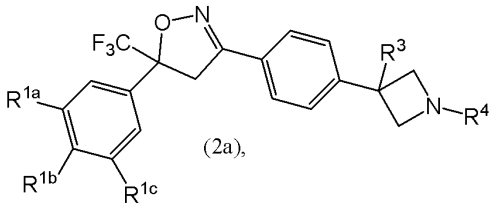
donde los restos R^4 y R^5 fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6 pueden estar además opcionalmente sustituidos con al menos un sustituyente seleccionado entre ciano, halo, oxo, =S, $=NR^7$, hidroxilo, alcoxi C_1-C_6, alquilo C_1-C_6, haloalquilo C_1-C_6, -SH, $-S(O)_pR$ y haloalcoxi C_1-C_6;

n es el número entero 0, 1 ó 2, y cuando n es 2, cada R^2 puede ser idéntico o diferente entre sí; y

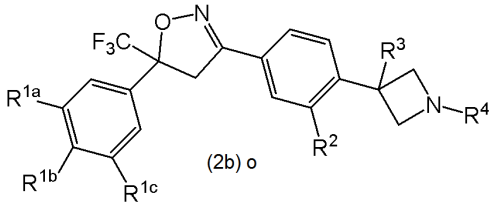
p es el número entero 0, 1 ó 2;

y sales farmacéutica o veterinariamente aceptables de los mismos.

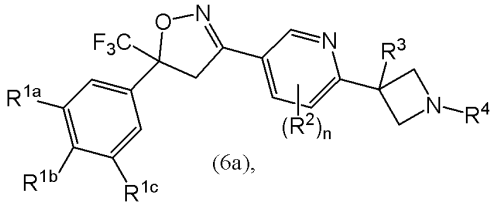
2. El compuesto de la reivindicación 1 que tiene la Fórmula (2a), (2b) o (6a)



(2a),



(2b) o



(6a),

en las que

cada uno de R^{1a}, R^{1b} y R^{1c} se selecciona independientemente entre hidrógeno, halo, hidroxilo y haloalquilo C_1-C_6;

R^2 es halo, ciano, hidroxilo, -C(O)NR^aR^b u -OR; y

R^3 es hidrógeno, halo, hidroxilo, N_3 o ciano;

y sales farmacéutica o veterinariamente aceptables de los mismos.

3. El compuesto de la reivindicación 1 ó 2, en el que

cada uno de R^{1a}, R^{1b} y R^{1c} se selecciona independientemente entre hidrógeno, flúor, cloro, bromo y $-CF_3$;

R^2 es halo, ciano, hidroxilo o $-C(O)NR^aR^b$;

R^3 es hidrógeno, flúor, cloro, hidroxilo, N_3 o ciano; y

R^4 es $-C(O)R^5$, $-C(O)NR^aR^5$, $-S(O)_pR^c$, $-C(S)R^5$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$ o $-C(NR^7)NR^aR^5$, y sales veterinarias de los mismos.

4. El compuesto de una cualquiera de las reivindicaciones 1 a 3, en el que

R^2 es ciano o $-C(O)NR^aR^b$;

R^3 es hidrógeno, flúor, hidroxilo, N_3 o ciano;

R^4 es $-C(O)R^5$, $-C(O)NR^aR^5$ o $-C(NR^7)R^5$; y

sales farmacéutica o veterinariamente aceptables de los mismos.

5. Un compuesto de la reivindicación 1 seleccionado del grupo constituido por:

1-(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona;

ciclopropil(3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

3-fluoro-N-metil-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida;

N-etil-3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)azetidin-1-carboxamida;

N-ciclopropil-3-fluoro-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-carboxamida;

ciclopropil(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

N-ciclopropil-3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)propan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)butan-1-ona;

2-ciclopropil-1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

3-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-oxopropanonitrilo;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-(metiltio)etanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metoxietanona;

ciclobutil(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropan-1-ona;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

N-ciclopropil-3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

ciclopropil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona;

ciclobutil(3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-il)metanona;

3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

N-ciclopropil-3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il)fenil)-N-etil-3-hidroxiazetidin-1-carboxamida;

N-ciclopropil-3-(4-(5-(3,4-dicloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-hidroxiazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3,5-bis(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-hidroxiazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-hidroxiazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-etil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-N-ciclopropil-3-fluoroazetidin-1-carboxamida;

3-(4-(5-(3-cloro-5-(trifluorometil)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoro-N-metilazetidin-1-carboxamida;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

ciclopropil(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)metanona;

2-Ciclopropil-1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)etanona;

3-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3-oxopropanonitrilo;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metoxietanona;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)propan-1-ona;

1-(3-(4-(5-(3,5-Diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)butan-1-ona;

5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,5-bis(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-acetil-3-fluoroazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanonitrilo;

1-[(3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-

fluoroazetidin-1-il)carbonil]ciclopropanol;

1-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]ciclopropanol;

3-{4-[3-fluoro-1-(metoxiacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-1-isobutirilazetidin-3-ol;

1-butiril-3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-3-ol;

5-[3,5-bis(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[3-(4-{5-[3,5-bis(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetanol;

5-[3-cloro-5-(trifluorometil)fenil]-3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanamida;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanamida;

1-[(3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

5-(3,5-diclorofenil)-3-{4-[3-fluoro-1-(3-metilbutanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-propionilazetidin-3-ol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1H-pirazol-3-ilcarbonil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

4-{2-[3-(4-{5-[3,5-bis(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetil}piridina;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-acetil-3-fluoroazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-3-oxopropanonitrilo;

4-[(3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]piridina;

5-[3,5-bis(trifluorometil)fenil]-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-

(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-(4-{3-fluoro-1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(ciclopropilcarbonil)-3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol;

(3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(ciclopropil)metanona;

2-(1-(ciclopropanocarbonil)-3-fluoroazetidin-3-il)-5-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)benzonitrilo;

5-(3-cloro-5-(trifluorometil)fenil)-3-(4-(3-fluoro-1-(metilsulfonil)azetidin-3-il)fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(2-bromo-4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-1-(ciclopropanocarbonil)azetidin-3-carbonitrilo;

1-(ciclopropanocarbonil)-3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-3-carbonitrilo;

1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)-2-metilpropan-1-ona;

2-metil-1-(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)propan-1-ona;

Ciclopropil(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

Ciclopropil(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)metanona;

1-(3-(4-(5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona;

1-(3-(4-(5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)azetidin-1-il)etanona;

1-isobutiril-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol;

3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]-2-oxoetanol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butiril-3-fluoroazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-diclorofenil)-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-

dihidroisoxazol;

1-[(3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

5-(3,5-diclorofenil)-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-acetilazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butirilazetidin-3-il)fenil]-5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butirilazetidin-3-il)fenil]-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

2-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]-2-oxoetanol;

1-{[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]carbonil}ciclopropanol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]-3-oxopropanonitrilo;

1-{[3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-il]carbonil}ciclopropanol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(1-butirilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-[3-cloro-5-(trifluorometil)fenil]-3-[4-(1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

1-[(3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

3-[4-(1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilacetil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(metiltio)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[1-(metoxiacetil)azetidin-3-il]fenil}-5-

(trifluorometil)-4,5-dihidroisoxazol;

1-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-il)carbonil]ciclopropanol;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(3,3-difluoroazetidin-1-il)carbonil]-3-fluoroazetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-(3,3,3-trifluoropropanoil)azetidin-3-ol;

5-[3,4-dicloro-5-(trifluorometil)fenil]-3-{4-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(4-metil-1,3-oxazol-5-il)carbonil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

N-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]formamida;

4-[(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)carbonil]piridazina;

1-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]-1H-1,2,4-triazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfonil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1H-pirazol-1-ilacetil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(1,3-oxazol-5-ilcarbonil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[1-(2,2-difluoropropanoil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

1-{[3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoroazetidin-1-il]carbonil}azetidin-3-ol;

1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-1-oxopropan-2-ol;

3-[4-(1-but-3-enoil-3-fluoroazetidin-3-il)fenil]-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-N,N-dimetil-2-oxoetanosulfonamida;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-{[(trifluorometil)tio]acetil}azetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-{4-[3-fluoro-1-(2-metoxipropanoil)azetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{1-[(2,2-difluorociclopropil)carbonil]-3-fluoroazetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-metil-3-oxopropan-1-ol;

(2S)-4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol;

4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol;

3-{4-[3-cloro-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-(3,5-dicloro-4-fluorofenil)-

5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[3-cloro-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3-clorofenil)-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[5-(3-cloro-4,5-difluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-1-(ciclopropilcarbonil)-azetidin-3-ol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-[3,4-difluoro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

(2S)-1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-1-oxopropan-2-ol;

(2R)-1-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-1-oxopropan-2-ol;

(2S)-4-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-4-oxobutan-2-ol;

5-(3,5-dicloro-4-fluorofenil)-3-(4-{3-fluoro-1-[(metilsulfinil)acetil]azetidin-3-il}fenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[3-azido-1-(ciclopropilcarbonil)azetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-[4-(3-azido-1-propionilazetidin-3-il)fenil]-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

etanotioato de S-[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetilo];

5-(3-fluorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3-clorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

5-(3,4-diclorofenil)-3-[4-(3-fluoro-1-propionilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-5-[3-(trifluorometil)fenil]-4,5-dihidroisoxazol;

5-(3-cloro-5-fluorofenil)-3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,4-difluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-3,3,3-trifluoropropan-1-ona;

3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

3-{4-[1-(azetidin-1-ilcarbonil)-3-fluoroazetidin-3-il]fenil}-5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol;

1-(ciclopropilcarbonil)-3-{4-[(5R)-5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-3-ol;

5-(3,5-dicloro-4-fluorofenil)-3-[4-(3-fluoro-1-isobutirilazetidin-3-il)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol;

{[2-(3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-3-fluoroazetidin-1-il)-2-oxoetil]sulfonil}acetonitrilo;

1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-

fenil}-3-fluoro-azetidin-1-il)-3-metanosulfonil-propan-1-ona;

1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-(2,2,2-trifluoro-etanosulfonil)-etanona;

Dimetilamida del ácido 2-(3-{4-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-oxo-etanosulfónico;

2-Bencenosulfonil-1-(3-{4-[5-(3,5-dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-etanona;

1-(3-{4-[5-(3,5-Dicloro-4-fluoro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-metanosulfonil-propan-1-ona;

(1-Ciclopropanocarbonil-3-{4-[5-(3,4-dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-3-il)-amida del ácido ciclopropanocarboxílico;

(3-Amino-3-{4-[5-(3,4-dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-ciclopropil-metanona;

3-fluoro-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

N-ciclopropil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

N-ciclopropil-3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-hidroxi-N-propilazetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-hidroxi-N,N-dimetilazetidin-1-carboxamida;

N-etil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-

il]fenil}azetidin-1-carboxamida;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-metilazetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-metilazetidin-1-carboxamida;

3-{4-[5-(3,5-diclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-etilazetidin-1-carboxamida;

3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}-N-etilazetidin-1-carboxamida;

3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-metilazetidin-1-carboxamida;

3-(4-{5-[3-cloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-N-ciclopropilazetidin-1-carboxamida;

N-ciclopropil-3-{4-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

N-ciclopropil-3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-(2,2,2-trifluoroetil)azetidin-1-carboxamida;

3-fluoro-N,N-dimetil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N,N-dimetilazetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-(3,3,3-trifluoropropil)azetidin-1-carboxamida;

3-(4-{5-[3,4-dicloro-5-(trifluorometil)fenil]-5-(trifluorometil)-4,5-dihidroisoxazol-3-il}fenil)-3-fluoro-N-oxetan-3-ilazetidin-1-carboxamida;

3-azido-N,N-dimetil-3-{4-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]fenil}azetidin-1-carboxamida;

2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

2-(1-acetil-3-fluoroazetidin-3-il)-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-[3-fluoro-1-(3,3,3-trifluoropropanoil)azetidin-3-il]benzonitrilo;

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-propionilazetidin-3-il)benzonitrilo;

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-isobutirilazetidin-3-il)benzonitrilo;

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-glicoloilazetidin-3-il)benzonitrilo;

2-(1-butiril-3-fluoroazetidin-3-il)-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

2-[1-(ciclobutilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

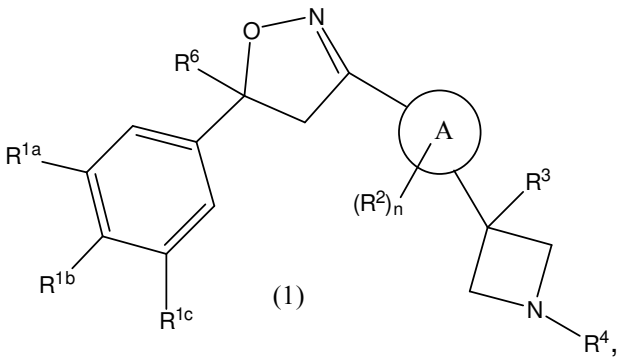
2-[1-(ciclopentilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;

5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-[3-fluoro-1-(metoxiacetil)azetidin-3-il]benzonitrilo;

2-[1-(ciclopropilacetil)-3-fluoroazetidin-3-il]-5-[5-(3,5-dicloro-4-fluorofenil)-5-

(trifluorometil)-4,5-dihidroisoxazol-3-il]benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-(3-fluoro-1-pentanoilazetidin-3-il)benzonitrilo;
5-[5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]-2-{3-fluoro-1-[(metiltio)acetil]-azetidin-3-il}benzonitrilo;
2-[1-(ciclopropilcarbonil)-3-fluoroazetidin-3-il]-5-[5-(3,4,5-triclorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il]piridina;
(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1-oxidotietan-3-il)metanona;
(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)(1,1-dioxidotietan-3-il)metanona;
1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropano-1-tiona;
(1-(3-(4-(5-(3,5-dicloro-4-fluorofenil)-5-(trifluorometil)-4,5-dihidroisoxazol-3-il)fenil)-3-fluoroazetidin-1-il)-2-metilpropilideno)cianamida;
(1-(3-Fluoro-3-{4-[5-(3,4,5-tricloro-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-azetidin-1-il)-2-metanosulfonil-etanona; y
1-(3-{4-[5-(3,4-Dicloro-5-trifluorometil-fenil)-5-trifluorometil-4,5-dihidro-isoxazol-3-il]-fenil}-3-fluoro-azetidin-1-il)-2-metanosulfonil-etanona,
estereoisómeros de los mismos, sales farmacéutica y veterinariamente aceptables de los mismos.

6. Una composición farmacéutica o veterinaria que comprende una cantidad terapéutica de un compuesto de Fórmula (1)



(1)

en la que

A es fenilo, naftilo o heteroarilo en la que dicho heteroarilo contiene de 1 a 4 heteroátomos seleccionados cada uno de ellos independientemente entre N, O y S;

cada uno de R^{1a}, R^{1b} y R^{1c} es independientemente hidrógeno, halo, hidroxilo, ciano, nitro, alquilo C_1-C_6, haloalquilo C_1-C_6, alcoxi C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, haloalcoxi C_1-C_6, $-C(O)NH_2$, $-SF_5$ o $-S(O)_pR$;

R^2 es halo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, nitro, hidroxilo, $-C(O)NR^aR^b$, alquenilo C_2-C_6, alquinilo C_2-C_6, $-S(O)_pR$ u $-OR$;

R^3 es hidrógeno, halo, hidroxilo, ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, $-C(O)NH_2$, nitro, $-SC(O)R$, $-C(O)NR^aR^b$, alquil C_0-$C_3NR^aR^4$, $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3, $-NHR^4$, $-OR$ o $-S(O)_pR$;

R^4 es hidrógeno, alquilo C_1-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, $-C(O)R^5$, $-C(S)R^5$, $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6;

R^5 es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquil C_0-C_6-cicloalquilo C_3-C_6, fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6;

R^6 es ciano, alquilo C_1-C_6, haloalquilo C_1-C_6, $-C(O)NR^aR^b$, alquenilo C_2-

C_6, alquinilo C_2-C_6, haloalquenilo C_2-C_6 o haloalquinilo C_2-C_6;

R^7 es hidrógeno, alquilo C_1-C_6, hidroxilo, ciano, nitro, -$S(O)_pR^c$ o alcoxi C_1-C_6;

R es alquilo C_1-C_6 o cicloalquilo C_3-C_6, cada uno opcionalmente sustituido con al menos un halo;

R^a es hidrógeno, alquilo C_1-C_6 o alquil C_0-C_3-cicloalquilo C_3-C_6; en la que el alquilo y el alquilcicloalquilo están opcionalmente sustituidos con ciano o al menos un sustituyente halo;

R^b es hidrógeno, alquilo C_1-C_6, cicloalquilo C_3-C_6, fenilalquilo C_0-C_3, heteroarilalquilo C_0-C_3 o heterocicloalquilo C_0-C_3, cada uno opcionalmente sustituido, cuando sea químicamente posible, con al menos un sustituyente seleccionado entre hidroxilo, ciano, halo o -$S(O)_pR$;

R^c es alquilo C_1-C_6, haloalquilo C_1-C_6, haloalquil C_1-C_6-cicloalquilo C_3-C_6, alquil C_0-C_3-cicloalquilo C_3-C_6, fenilalquilo C_0-C_3, heteroarilalquilo C_0-C_3 o heterocicloalquilo C_0-C_3, cada uno opcionalmente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, -$S(O)_pR$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^b$, -SCN o -$C(O)NR^aR^b$;

cada uno de R^4 y R^5 alquilo C_1-C_6 o alquil C_0-C_6-cicloalquilo C_3-C_6 puede estar opcional e independientemente sustituido con al menos un sustituyente seleccionado entre ciano, halo, hidroxilo, oxo, alcoxi C_1-C_6, haloalcoxi C_1-C_6, haloalquilo C_1-C_6, -$S(O)_pR^c$, -SH, -$S(O)_pNR^aR^b$, -NR^aR^b, -$NR^aC(O)R^b$, -$SC(O)R^c$, -SCN o -$C(O)NR^aR^b$; y

donde los restos R^4 y R^5 fenilalquilo C_0-C_6, heteroarilalquilo C_0-C_6 o heterocicloalquilo C_0-C_6 pueden estar además opcionalmente sustituidos con al

menos un sustituyente seleccionado entre ciano, halo, oxo, =S, =NR^7, hidroxilo, alcoxi C_1-C_6, alquilo C_1-C_6, haloalquilo C_1-C_6, -SH, -$S(O)_pR$ y haloalcoxi C_1-C_6;

n es el número entero 0, 1 ó 2, y cuando n es 2, cada R^2 puede ser idéntico o diferente entre sí; y

p es el número entero 0, 1 ó 2;

y sales farmacéutica o veterinariamente aceptables de los mismos.

7. La composición farmacéutica o veterinaria de la reivindicación 6 que comprende adicionalmente un excipiente, diluyente o vehículo veterinaria o farmacéuticamente aceptable.

8. La composición farmacéutica o veterinaria de la reivindicación 6 ó 7 que comprende además al menos un agente veterinario adicional.

9. La composición farmacéutica o veterinaria de la reivindicación 8 en la que dicho agente veterinario adicional se selecciona del grupo que consiste en abamectina, ivermectina, avermectina, moxidectina, emamectina, eprinomectina, selamectina, doramectina, nemadectina, albendazol, cambendazol, fenbendazol, flubendazol, mebendazol, oxfenbendazol, oxibendazol, parbendazol, tetramisol, levamisol, pamoato de pirantel, oxantel, morantel, indoxacarb, closantel, triclabendazol, clorsulon, refoxanida, niclosamida, prazicuantel, epsiprantel, 2-desoxoparahercuamida, piripol, piraflupro l, lufenuron, espiromesifen, tebufenozida, espinosad, espinetoram, imidacloprid, dinotefuran, metaflumizona, tibendiamida, clorantraniliprol, indoxacarb, piridalil, pirimidifen, pirifluquinazon, oxima de milbemicina, milbemicina, DEET, demiditraz, amitraz, fipronil, regulador del crecimiento de

insectos, permetrina y piretrina o mezclas de los mismos.

10. La composición farmacéutica o veterinaria de la reivindicación 9 en la que dicho agente veterinario adicional es oxima de milbemicina.

11. La composición farmacéutica o veterinaria de la reivindicación 9 en la que dicho agente veterinario adicional es moxidectina.

12. Uso de un compuesto en una cualquiera de las reivindicaciones 1-11 para preparar un medicamento.

13. Uso de un compuesto de una cualquiera de las reivindicaciones 1 a 6 en la fabricación de un medicamento para el tratamiento o el control de una infección o infestación parasitaria en un animal, que comprende administrar dicho medicamento al animal.

14. El uso de acuerdo con la reivindicación 13 en el que el animal es un animal de compañía o ganado.

15. El uso de acuerdo con la reivindicación 13 en el que el animal de compañía es un perro.

16. El uso de acuerdo con la reivindicación 13 en el que el ganado es ganado vacuno.

17. El uso de acuerdo con la reivindicación 13 en el que el animal es un ave.

18. El uso de acuerdo con la reivindicación 13 en el que el animal es un pez.

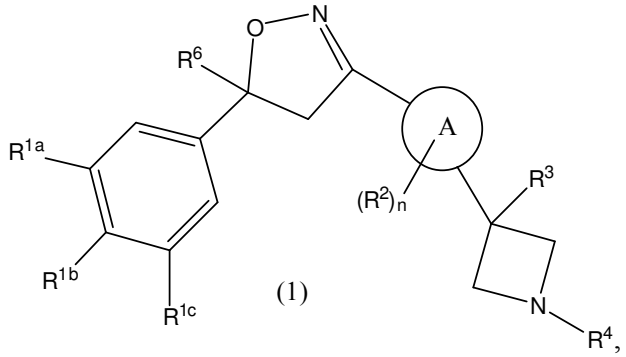
19. El uso de acuerdo con una cualquiera de las reivindicaciones 13 a 18 en el que el compuesto se administra por vía tópica, vía oral o por inyección.

20. El uso de acuerdo con una cualquiera de las reivindicaciones 13 a 18 en el que el compuesto se administra por vía tópica.

21. El uso de acuerdo con una cualquiera de las reivindicaciones 13-18 en el que el compuesto se administra por vía oral.

RESUMEN

La presente invención enumera derivados de azetidina sustituidos con isoxazolina de Fórmula (1)



(1)

estereoisómeros de los mismos, sales veterinariamente aceptables de los mismos, composiciones de los mismos y su uso como un parasiticida en mamíferos y aves. R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^4, R^6 y n son como se describe en el presente documento.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

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

To:

BENSON, Gregg, C.
Pfizer Inc.
Eastern Point Road MS9114
Groton, CT 06340
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
02 November 2012 (02.11.2012)

Applicant's or agent's file reference
PC71703A

IMPORTANT NOTIFICATION

International application No.
PCT/IB2011/053355

International filing date *(day/month/year)*
27 July 2011 (27.07.2011)

1. The following indications appeared on record concerning:

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

Name and Address
PFIZER INC.
235 East 42nd Street
New York, NY 10017
United States of America

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

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

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

Name and Address
AH USA 42 LLC
235 East 42nd Street
New York, NY 10017
United States of America

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

3. Further observations, if necessary:

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

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

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

Facsimile No. +41 22 338 82 70

Authorized officer
Blanc Veronique
e-mail ro.ib@wipo.int
Telephone No. +4122 338 9666

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PC71703A	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/IB2011/053355	International filing date *(day/month/year)* 27/07/2011	(Earliest) Priority Date *(day/month/year)* 05/08/2010
Applicant PFIZER INC.		

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,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), 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. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/053355

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 C07D413/14 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 A01N

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/075459 A2 (DU PONT [US]; LAHM GEORGE PHILIP [US]; PATEL KANU MAGANBHAI [US]; PAHU) 5 July 2007 (2007-07-05) page 1, line 9 - line 21 page 106 - page 113; examples 1-214 claim 1 -----	1-21
Y	WO 2008/019760 A1 (BAYER CROPSCIENCE AG [DE]; MIHARA JUN [JP]; MURATA TETSUYA [JP]; YAMAZ) 21 February 2008 (2008-02-21) page 1, line 4 - line 8 page 56 - page 67 claim 1 -----	1-21

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2011	19/10/2011

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

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/080250 A2 (SYNGENTA PARTICIPATIONS AG [CH]; RENOLD PETER [CH]; ZAMBACH WERNER [CH) 2 July 2009 (2009-07-02) page 1, line 3 - line 9 page 63 - page 66; compounds A1-C4 page 65; compound B1 claim 1	1-21

Y	WO 2010/020522 A1 (SYNGENTA PARTICIPATIONS AG [CH]; SYNGENTA LTD [GB]; CASSAYRE JEROME YV) 25 February 2010 (2010-02-25) page 1, line 1 - line 11 page 62 - page 67; compounds A1-H4 claim 1	1-21

Y	WO 2010/020521 A1 (SYNGENTA PARTICIPATIONS AG [CH]; PITTERNA THOMAS [CH]; EL QACEMI MYRIE) 25 February 2010 (2010-02-25) page 1, line 1 - line 12 page 71 - page 87; compounds A1-B4 claim 1	1-21

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/053355

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/053355

Patent document cited in search report	Publication date	Patent family member(s)	Publication date

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